

# **MODELING THE DYNAMICS OF GONORRHEA WITH OPTIMAL CONTROL**



**Tadele Giza**

**A Thesis Submitted to the Department of Mathematics  
College of Natural Science**

**Presented in Partial Fulfillment of the Requirement for the Degree of  
Master's in Applied Mathematics (Mathematical Modeling)**

**SALALE UNIVERSITY**

**May, 2024  
Fitcha, Ethiopia**

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**Co-advisor: Birke Siyum**

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## APPROVAL OF BOARD OF EXAMINERS

We, the undersigned, members of the board of examiners of the final open defense, Tadele Giza have read and evaluated his thesis entitle ”**Modeling the Dynamics of Gonorrhea With Optimal Control** ” and examined the candidate. This is, therefore, to certify that the thesis has been accepted in partial fulfillment of the requirement of the degree of Master’s in Applied Mathematics (Mathematical Modeling).

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## DECLARATION

I hereby declare that this MSc Thesis is my original work and has not been presented for a degree in any other university, and all sources of material used for this thesis have been duly acknowledged.

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## **ABBREVIATION AND ACRONYMS**

AIDS	Acquired Immunodeficiency Syndrome
DFEP	Disease Free Equilibrium Point
EEP	Endemic Equilibrium Point
EPHI	Ethiopia Public Health Institute
ESI	Early Stage Infected
LSI	Latent Stage Infected
STI	Sexually Transmitted Infections
WHO	World Health Organization

## ABSTRACT

*The aim of this thesis was to formulate a mathematical model of the Gonorrhea disease that included the best possible control measures. First, we proved with great rigor that the solution to the model is bounded and positive within a given domain. We also obtained a basic reproduction number using the next-generation matrix, which is essential for evaluating the dynamics of Gonorrhea. The endemic equilibrium point and the Gonorrhea-free equilibrium of the model equation were found to have both local and global stability. The findings demonstrate that the solution converges to the Gonorrhea-free steady-state if the basic reproduction number is less than one, and this shows that the Gonorrhea-free equilibrium is asymptotically stable. A sensitivity analysis of the model equation on the important parameters was carried out to evaluate their effect on the dynamics of Gonorrhea transmission. We utilized the Pontryagin minimum principle to obtain control measures, such as prevention and treatment strategies to reduce infectious transmission and prevention interventions to protect susceptible individuals, and we extended the model to optimal control. Numerical simulations were used to verify the effectiveness of the suggested models, and sensitivity analysis shed light on their robustness. According to our analysis, prevention strategies are more effective at reducing Gonorrhea outbreaks. Numerical simulations ultimately highlight that the best strategy uses a synergistic application.*

**Keywords:** Gonorrhea, Models, Optimal, Stability, Dynamics.

# CHAPTER 1

## INTRODUCTION

### 1.1 Background of the Study

Infectious diseases have always been a major concern of humanity. Every year, diseases like AIDS, malaria, syphilis, tuberculosis, and gonorrhea claim millions of lives. , and millions more people have the infection. An infectious disease is one that develops when a dangerous pathogen spreads from an infected individual or vector to a new host. There are two types of transmission: direct (where an infectious agent is transferred from the infected individual to the new host, e.g. g. biting, sexual relations, etc. ) or indirect (infectious agent transmission via a vector or contaminated items like food, water, etc.). occur. air, and so forth. A simple infection, which is the invasion and multiplication of different pathogens in the body, such as bacteria, viruses, fungi, and protozoa, can be distinguished from an infectious disease ([Kirkcaldy et al., 2019](#)).

Gonorrhoea is a frequent sexually transmitted illness infection caused by the bacteria *Neisseria gonorrhoeae*. It is a clinical disease caused by Gram-negative *Diplococcus Neisseria* Gonorrhea infection. Gonorrhea is most commonly discovered in the semen and vaginal secretions of infected men and women. The illness mostly affects the mucous membranes of the urethra, endocervix, rectum, pharynx, and conjunctiva.

In 2020, WHO estimated 82.4 million new *N. gonorrhoeae* infections among individuals aged 15 to 49 years. Gonorrhea is most common among vulnerable populations, including males who have sex with men, sex workers, transsexual women, and adolescents and young people in high-burden nations. Getting tested regularly, as recommended by your healthcare physician, and practicing safer sex practices will help minimize your risk of infection ([Mishra et al., 2023](#)).

Usually, seven to fourteen days after exposure, the symptoms appear. On the other hand, some people never have symptoms, and it can take up to six months for them to manifest. The asymptomatic people are still contagious. Compared

to men, women are more likely to be asymptomatic. It is thought that only about 10% of infected males experience symptoms; up to 50% of infected females are supposed to never show any signs. The majority of women who have gonorrhea do not experience any symptoms; those who do often have lower stomach pain, an uncommon vaginal discharge that might be thin or watery, yellow or green, and infrequently, intermenstrual hemorrhage. Men's common symptoms include discomfort or burning when peeing, peculiar discharge from the ends of the penis, and, in some cases, pain in the testes. The discharge might be white, yellow, or green, with pain when passing urine and, in rare cases, tenderness in the testicles ([Chidiac et al.,2023](#)). These are the signs of Gonorrhea; in order to prevent this disease, we must understand its transmission mechanism.

During intercourse, gonorrhea is typically passed from one person to another. The cells of the rectum, cervix, urethra, throat, and infrequently the eyes can harbor bacteria. If someone comes into contact with secretions from an infected person's vagina, throat, urine, or rectum, they could contract gonorrhea. The most common ways to spread the virus are through exchanging sex equipment that haven't been cleaned and through unprotected vaginal, anal, or oral sex. Additionally, gonorrhea can be passed from a pregnant woman to her unborn child during childbirth. The baby's eyes may get inflamed and discharged as a result. Gonorrhea cannot be contracted by kissing, hugging, sharing cups, plates, or silverware, bathing or towel together, or swimming in a pool. From this, it is clear that the transmission mechanisms of gonorrhea disease, so we must prevent ourselves from gonorrhea disease ([Akinboro et al.,2023](#)).

Certain antibiotics can be used to treat and cure gonorrhea. Additionally, sexually active people may become more aware of the signs and gravity of gonorrhea through educational initiatives offered by clinics or the media, prompting those who suspect they may be infected to seek testing and treatment as soon as possible. This program's main component is screening a large number of women for gonorrhea through cultural testing. Many of the culture tests are performed on women who are having a gynecologic examination but do not yet have symp-

toms, even though some of the tests are performed on patients who have visited the clinic with symptoms. Antibiotics such as ciprofloxacin, ofloxacin, ampicillin, azithromycin, cefixime, ceftriaxone, spectinomycin, and ampicillin can be used to treat gonorrhea. One of the most important gonorrhea control strategies is antibiotic therapy. The infections should be cured by the conventional treatment plan ([Owonaro et al.,2023](#)).

In order to better understand and forecast the behavior, effects, and potential outcomes of infectious diseases, mathematical models are extremely useful tools. They are applied in many scientific and medical domains for a variety of tasks, including data interpretation, hypothesis generation, experiment design, disease diagnosis, and decision-making. We are able to conduct thorough analysis and produce quantitative forecasts of disease trends and control strategies by employing mathematical equations to explain the dynamics of disease transmission and intervention effects ([Dunbar,2023](#)). Additionally, it is crucial for improving our comprehension of the dynamics of disease and developing management plans for rapidly spreading infectious diseases when there is no suitable vaccine or antiviral medication. Therefore, mathematical models can offer insight into the intricate dynamics of infection as well as practical preventative measures. In order to identify the parameters that have the greatest influence and are most controllable, it is helpful to develop a mathematical model that helps concentrate thinking on the crucial mechanisms that shape the epidemiology of infectious diseases.

Control and eradication of the organisms responsible for infectious diseases has been a priority for public health officials since the late 1950s. In addition, epidemiology still benefits greatly from mathematical modeling since it offers a better understanding of the underlying mechanisms governing the emergence and resurgence of infectious diseases as well as practical solutions for control ([Hethcote, 2000](#)). According to Hethcote, the ability to comprehend the dynamics of a given disease's transmission, apply the best control strategies, and put logistical policies into place are all necessary for the successful eradication of

these emerging diseases.

Optimal control theory aims to reduce the incidence of disease in particular regions by employing mathematical models to determine the most efficient intervention techniques. To reduce the burden of disease, the theory offers practical tools for organizing and evaluating disease control plans, allowing for the most effective control interventions and resource allocation. The cost of interventions, the dynamics of the disease, and the resources at hand are usually some of the factors that are considered. With the aid of optimal control models, it is also feasible to evaluate the financial viability of different interventions. By considering a number of variables, including quality-adjusted life years gained, the effect on disease reduction, and implementation costs, policy makers can prioritize interventions that maximize health benefits relative to costs. This makes decision-making easier, particularly when resources are scarce. The application of optimal control is vitally important because it is a key tool in identifying the best control strategies to employ in the eradication of diseases.

Reducing gonorrhea in the community necessitates effective control of the disease. To create an efficient control strategy, it is crucial to have knowledge about the incidence and severity of gonorrhea in Ethiopia. The burden of the disease on human mortality has persisted as a concern for the world even in the face of gonorrhea disease control strategies. In Ethiopia and other sub-Saharan African countries, gonorrhea is also a serious problem. Because of this, the primary goal of this study is to develop a mathematical model that analyzes and controls the threshold dynamics of gonorrhea and suggests effective control measures to the people of Ethiopia and Africa as a whole.

## 1.2 Statement of the Problems

Gonorrhea is the second most frequently reported sexually transmitted infection worldwide. The World Health Organization estimates 4 million people contracted gonorrhea for the first time in 2020 ([Barbaric et al.,2022](#)). Many scientists have worked hard to investigate the dynamics of the gonorrhea disease from a variety of perspectives due to this serious illness. For instance, in the research conducted by ([Grad et al.,2018](#); [Tuite et al.,2018](#); [Rönn et al.,2020](#)) examined epidemiological modeling and emphasized the approaches and practicality of researching the dynamics of gonorrhea infection transmission. Beyond the works by those authors, research has been done on the management and prevention of gonorrhea.

However, it is imperative to comprehend the nature of the disease and whether an epidemic is imminent. The community must establish the intervention of disease management and control. But none of the writers have thought about using mathematical models to understand the dynamics of gonorrhea infection and create practical methods for managing the illness. Optimizing control measures while minimizing costs is also essential. A robust mathematical model is required to improve comprehension and pinpoint important variables affecting the dynamics of disease. As such, the following basic questions are the focus of this study:

1. How can mathematical models be applied to accurately represent the dynamics of Gonorrhea infection?
2. What is the purpose of integrating optimal control strategies into the formulated mathematical model of Gonorrhea infection?
3. How can we determine the stability, sensitivity, and recommend the best strategy to reduce the disease from the community?



## **1.3 Objectives of the Study**

### **1.3.1 General Objective**

The general objective of this study is to develop a comprehensive understanding of the dynamics of Gonorrhea infection through mathematical modeling, and to formulate optimal control strategies for mitigating its spread.

### **1.3.2 Specific Objectives**

The specific objectives of the study are to:

1. Construct a mathematical model that accurately describes the dynamics of Gonorrhea infection.
2. Integrate optimal control strategies into the formulated mathematical model of Gonorrhea infection.
3. Conduct sensitivity analyses of evaluate the robustness of optimal control strategies derived from the mathematical model, identifying critical parameters and assessing their impact on disease dynamics.

## **1.4 Significance of the Study**

The proposed study is significant because it has the potential to address important community issues, advance mathematical techniques, and provide practical, precision-driven strategies for managing diseases. In conclusion, the study is critically important in the following ways:

- A more accurate representation of Gonorrhea dynamics is sought by the proposed mathematical model, which incorporates optimal control strategies. To minimize the virus's spread while making the best use of available resources, targeted and efficient control measures must be developed.
- Using optimal control strategies in combination is a novel and sophisticated mathematical technique. Its use in disease modeling is being studied to

further advance mathematical methods and possibly provide insights into a wider range of epidemiological research.

- The study closes a possible research gap in the literature and advances our understanding of gonorrhea dynamics. The results could lead to new discoveries in the area of infectious disease mathematical modeling.
- The study is noteworthy for its ability to convert mathematical conclusions into useful suggestions for medical procedures. This link between theoretical modeling and real-world applications is essential to guaranteeing the study's applicability and impact.

This study also establishes the groundwork for future research directions in optimal control, disease modeling, and the use of mathematical models in epidemiology. This provides opportunities for additional investigation and improvement of mathematical methods for the treatment of gonorrhea.

## **1.5 The Scope of the Study**

With the use of differential equations and optimal control, this study will concentrate on creating a mathematical model and analyzing the dynamics of gonorrhea. The primary governing control strategies based on disease dynamics will be the sole focus of the study.

## **1.6 Expected Outcomes of the Study**

The expected outcomes of the present study include:

- A better understanding of the intricate dynamics of the gonorrhea virus, with an emphasis on how mathematical models help to accurately depict the disease's behavior.
- Identification and improvement of control strategies within the mathematical model, offering suggestions for practical preventative and control measures for gonorrhea outbreaks based on solid evidence.

- Improved forecasting precision for the incidence, severity, and spread of gonorrhea outbreaks, enabling more prompt and focused public health interventions.

## CHAPTER 2

### LITERATURE REVIEW

Numerous investigations into the dynamics and regulation of gonorrhea disease have been carried out utilizing various mathematical models. We reviewed some studies that were conducted in order to develop a mathematical model of infectious disease before looking into the Gonorrhea disease.

The dynamics of gonorrhea infection transmission in Anantapur District, Andhra Pradesh, India, were modeled mathematically in 2013 by Prabhakararao ([Adamu et al., 2018](#)). They assumed that recovery from infection confers permanent immunity when they developed the model, which divided the population into susceptible, infectious, and removed compartments. In terms of its severity among the people living in the Anantapur District, the study's findings indicated that the epidemic does not eventually die out but rather approaches a steady state.

Throughout their work, ([Adamu et al., 2018](#)), they created and examined a deterministic epidemic model to simulate the transmission of gonorrhea. They demonstrated that, in comparison to its continuous counterparts, the discrete-time dynamical system displays far more complex dynamics. Additionally, they performed a stability analysis on their model and found evidence of the existence of fold-flip bifurcations. Their study's findings showed that using male latex condoms can stabilize the system's chaotic vibrations to the point where the number of infected people stays stable and is either negligible or zero, which controls the spread of the illness.

A few studies examined the effect of treatment on the dynamics of infection with *Neisseria gonorrhoea*. The work of Sacrifice, N., is one of them ([Budkaew et al., 2019](#)), where they created a treatment-effect-based mathematical model of the dynamics of gonorrhea and examined the model's dynamics to comprehend the epidemic phenomenon and suggest control measures. Their study's findings demonstrated that a higher treatment rate significantly affects the infectious patient.

A related study conducted by Nana-Kyere et al. ([Kwasi Adu et al.](#)), investigated the treatment effects of a qualitative analysis of *Neisseria gonorrhoea* diseases. Their findings show that gonorrhea can be fatal if the infected individual does not receive the appropriate care because of the host's complications. [Adamu et al.\(2018\)](#) investigated the effects of treatment and natural immunity on the dynamics of *Neisseria gonorrhoeae* disease. According to their research, treating more patients and enhancing their innate immunity can help lower the number of new *Neisseria gonorrhoea* infections in the general population. A deterministic model for the dynamics of gonorrhea transmission and control was created and examined by Fatima S. and Bako, D. in 2019 ([Adediipo et al., 2020](#)). This spread was described by three nonlinear ordinary differential equations. The stability of the model's equilibrium points is examined and determined. It was also calculated what the basic reproduction number was. Both the disease-free equilibrium, in which all infected compartments are zero, and the endemic equilibrium, in which all compartments are greater than zero, are displayed by the model. They found that the Disease Free Equilibrium is locally asymptotically stable for basic reproduction numbers less than or equal to one, and unstable for values greater than or equal to one.

[Adedayo et al. \(2023\)](#) suggested using control individual class into mathematical modeling of the dynamics of gonorrhea infection treatment. The disease-free equilibrium state and the endemic state were attained. The reproduction number was used to establish the disease-free state stability criterion. The Homotopy Perturbation Method was used to solve the model equations. The study's findings indicate that, with a high treatment rate, gonorrhea can be totally eradicated, eliminating both human-to-disease transmission.

In an associated research, [Chen et al. \(2023\)](#) offered a mathematical epidemic model for the investigation of the dynamic dissemination of gonorrhea in society. The model under study provided insight into how early treatment affected the exposed and infectious individuals. For equilibrium points that are endemic and free of disease, local and global stability was examined. According to the

findings, the disease spreads and becomes endemic when the threshold is exceeded, but it dies out when the basic reproduction number is less than unity. Using MAPLE software, they ran numerical simulations to show how early treatment of the disease would affect those who were already infected.

The studies mentioned above have developed mathematical models of gonorrhea transmission dynamics from various perspectives. Some focused on deterministic models while others utilized stochastic models and categorized the population into Susceptible, Infective, and Recovered groups. However, none of these studies addressed the optimal control strategy for managing the transmission of gonorrhea infection within the community. This gap in research has inspired us to conduct this study.

## **CHAPTER 3**

### **RESEARCH METHODOLOGY**

This chapter describes an overview of the study area, study period, data sources, data collection and analysis methodologies, mathematical procedures, and a detailed description of the modified model employed to fulfill the objectives of the study.

#### **3.1 Description of the Study Area**

This study was conducted in Fitcha, North Shewa, Oromia region, Ethiopia. Fitcha, a town situated 110 kilometers from the capital city of Addis Ababa, is located within the North Shewa zone of the Oromia region. The chosen hospitals for this study are in close proximity to Salale University in the North Shewa region of Ethiopia.

#### **3.2 Study Period**

The study carried out in Fitcha, Ethiopia, from January 2024 to June 2024.

#### **3.3 Source of Data**

The study used secondary sources to procure the necessary data for analysis. These sources encompass Fitcha Hospital, the Ethiopian Public Health Institute (EPHI), and WHO situation reports. In the event that the data obtained from these sources is insufficient, supplementary data was taken from published materials.

#### **3.4 Data Analysis**

In the proposed model analysis, we focused on the mathematical and statistical analysis of the datasets employing computational techniques and a numerical algorithm. We used Runge Kutta method within the MATLAB software to scrutinize the data. The ensuing results visually depicted in graphs to probe the influence of the model parameters on the prevalence of Gonorrhea within the

population.

### **3.5 Mathematical Procedure**

In the present study, we constructed a mathematical models using a system of non-linear differential equations that describe the dynamics of Gonorrhea transmission. Firstly, we obtained the model's behavior in order to develop a better understanding of the dynamics of the suggested models. Next, we shown that both models are well-posed within a region that is biologically feasible. The equilibrium points of the model equations was analyzed for both local and global stability using the relevant Lyapunov functions and the Jacobian matrix, respectively. By carefully selecting (and estimating) the system parameter values with MATLAB software. Finally, we extend the formulated model to an optimal control problem. For the extended optimal control model, we plot numerical simulations using an iterative fourth-order Runge-Kutta integration scheme to support the analytical results.



## CHAPTER 4

### MODEL FORMULATION AND ANALYSIS

#### 4.1 Gonorrhea Model Description and Formulation

The model considered the total number of human population  $N$  and categorized into six classes depend on their disease status at time  $t$ . Those are; Susceptible individuals  $S(t)$ , consisting of individuals who are at risk for developing an infection from gonorrhea. Exposed individuals  $E(t)$ , are individuals who are exposed to the gonorrhea. Asymptomatic individuals  $A(t)$ , are asymptomatic gonorrhea infected individuals with no clinical symptoms of infection. Symptomatic individuals  $I(t)$ , are symptomatic gonorrhea infected individuals with clinical symptoms of gonorrhea infection. Treated individuals,  $T(t)$ , are individuals who fail treatment. Recovered individuals,  $R(t)$ , are individuals who recovered from gonorrhea infection.

The population are recruited to susceptible class at a rate  $\Pi$  and subjected to infections at a rate

$$\lambda = \frac{\beta(A(t) + \delta I(t) + \gamma T)}{N}$$

, representing the force of infection due to infectious by individuals with asymptomatic, symptomatic and treated individuals. The modification parameter  $\delta$  and  $\gamma$ , explains the assumed variability implies increase and decrease in the relative infectiousness of individuals in  $I$  and  $T$  classes respectively, in comparison to infected in the  $A$  class and  $\beta$  is the probability that a contact between a susceptible individuals and an infectious individuals will result to an infection. The model also assumed that exposed individuals progress to either asymptomatic class with probability  $(1 - p)\eta$  or to the symptomatic class with probability  $p\eta$ , where  $\eta$  is the per capita rate of becoming infectious. Asymptomatic individuals move forward to symptomatic class after developing the symptom of gonorrhea infection at the rate  $\phi$ . Both asymptomatic and symptomatic individuals are treated at the rate  $\alpha$ . A fraction  $q$ , of treated individuals from the asymptomatic class

will recover and move to the recovery class, while the remaining fraction  $(1 - q)$ , will fail treatment and move to the treated class. A fraction  $\rho$ , of the treated individuals in the symptomatic class, will recover and move to the recovery class, while the remaining fraction  $(1 - \chi\rho)$  will fail treatment and move to the treated class, where  $\chi$  rate of individuals in the symptomatic class in comparison to those in the asymptomatic class. Individuals who recovered in treated class move to recovery class at a rate  $\omega$ . Recovered individuals may revert to the susceptible class after losing their immunity at rate  $\theta$ . All class are subjected to a natural death rate  $\mu$ . However, individuals in asymptomatic, symptomatic and treated individuals who failed treatment of gonorrhea infection are induced to mortality at a rate  $\xi_1, \xi_2$  and  $\xi_3$  respectively. All parameters in the model are non-negative. The schematic diagram of the formulated model is given in Figure 1.

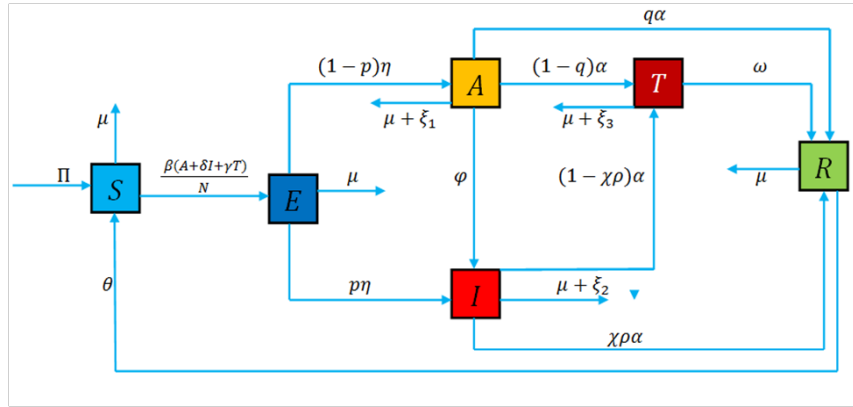


Figure 4.1: Model Diagram of Gonorrhea

Based on the model assumption and schematic diagram, the model equations

are given as follows;

$$\left\{ \begin{array}{l} \frac{dS}{dt} = \Pi + \theta R - \left( \frac{\beta(A(t) + \delta I(t) + \gamma T)}{N} \right) S - \mu S, \\ \frac{dE}{dt} = \left( \frac{\beta(A(t) + \delta I(t) + \gamma T)}{N} \right) S - (\eta + \mu) E, \\ \frac{dA}{dt} = (1 - p)\eta E - (\alpha + \phi + \mu + \xi_1) A, \\ \frac{dI}{dt} = \phi A - (\alpha + \mu + \xi_2) I, \\ \frac{dT}{dt} = (1 - q)\alpha A + (1 - \chi\rho)\alpha I - (\omega + \mu + \xi_3) T, \\ \frac{dR}{dt} = q\alpha A + \chi\rho\alpha I + \omega T - (\theta + \mu) R. \end{array} \right. \quad (4.1)$$

With initial condition  $S(t) \geq 0, E(t) \geq 0, A(t) \geq 0, I(t) \geq 0, T \geq 0$  and  $R(t) \geq 0$ .

Table 4.1: Model Parameter and its Description

Parameters	Description
$\Pi$	Recruitment rate
$\beta$	Probability of contact between a susceptible and an infectious
$\delta$	Modification parameter for Symptomatic individuals
$\gamma$	Modification parameter for Treated individuals
$p$	Probability of Exposed progress to Asymptomatic individuals
$\phi$	Rate of asymptomatic individuals become symptomatic individuals
$\eta$	Per capita rate of becoming infectious
$\alpha$	Treatment rate
$q$	A fraction of treated from the asymptomatic of infection become recover and move to the recovery
$\rho$	A fraction of the treated in the symptomatic of infection become recover and move to the recovery
$\chi$	rate asymptomatic of infection in comparison to the symptomatic of infection
$\omega$	Rate of recovered
$\mu$	Natural death rate
$\theta$	Rate of recovered human become susceptible
$\xi_1$	Rate of asymptomatic infected who failed treatment is to mortality
$\xi_2$	Rate of symptomatic infected who failed treatment is to mortality
$\xi_3$	Rate of treated who failed treatment is to mortality

## 4.2 Basic Properties of Gonorrhea Model

### 4.2.1 Invariant Region

In this section, we obtain a region in which the solutions of model equation (4.1) are uniformly bounded in the proper subsets of  $\Omega \in \mathfrak{R}^{6+}$ . To obtain this, first we considered the total population  $N$  where  $N = S + E + A + I + T + R$ . Then, after differentiating  $N$  both sides with respect to  $t$  and substituting the expression for  $\frac{dS}{dt}, \frac{dE}{dt}, \frac{dA}{dt}, \frac{dI}{dt}, \frac{dT}{dt}, \frac{dR}{dt}$ , and from equation (4.1) we obtained;

$$\frac{dN}{dt} = \Pi - \mu(S + E + A + I + T + R) - \xi_1 A - \xi_2 I - \xi_3 T \quad (4.2)$$

In the absence of mortality due to Gonorrhea ( $\xi_1 = \xi_2 = \xi_3 = 0$ ), then equation (4.2) become;

$$\frac{dN}{dt} \leq \Pi - \mu N \quad (4.3)$$

After solving equation (4.3) by integrating both side by using separable variable and equating it as time tends to infinity, we obtain  $0 \leq N(t) \leq \frac{\Pi}{\mu}$ . Hence, the feasible solution set of model equation (4.1) remains in the region:

$$\Omega = \{(S, E, A, I, T, R) \in \mathfrak{R}^{6+} : N \leq \frac{\Pi}{\mu}\} \quad (4.4)$$

Therefore the model was well posed epidemiologically and mathematically. Hence, it is sufficient to study the dynamics of the model in  $\Omega$

### 4.2.2 Positivity of the Solution

In this section, we assumed that the initial condition of the model is positive, and now we showed all the solution of the model equation (4.1) remain positive for future time if their respective initial values are positive.

**Lemma 1:** Let  $\Omega = \{(S, E, A, I, T, R) \in \mathfrak{R}^{6+}; S(0) \geq 0, E(0) \geq 0, A(0) \geq 0, I(0) \geq 0, T(0) \geq 0 \text{ and } R(0) \geq 0\}$ ; then the solutions of  $\{S, E, A, I, T, R\}$  are positive for all  $t \geq 0$ .

**Proof:** Positivity is verified separately for each of the model  $S(t), E(t), A(t), I(t), R(t), T(t)$ .

**Positivity of  $S(t)$ :** From model equation (4.1) we have:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \left( \frac{\beta(A(t) + \delta I(t) + \gamma T)}{N} \right) S - \mu S + \theta R, \\
\frac{dS}{dt} &\geq - \left( \frac{\beta(A(t) + \delta I(t) + \gamma T)}{N} \right) S - \mu S \text{ by elimination positive term,} \\
\int \frac{dS}{S} &\geq \int - \left( \frac{\beta(A(t) + \delta I(t) + \gamma T)}{N} \right) + \mu dt \text{ by separable variable,} \\
\ln S &\geq - \left( \frac{\beta(A(t) + \delta I(t) + \gamma T)}{N} + \mu \right) t + c, \\
e^{\ln S} &\geq e^{- \left( \frac{\beta(A(t) + \delta I(t) + \gamma T)}{N} + \mu \right) t + c}, \\
S &\geq e^{- \left( \frac{\beta(A(t) + \delta I(t) + \gamma T)}{N} + \mu \right) t} \cdot e^c \text{ where } e^c = S_0, \\
S &\geq S_0 e^{- \left( \frac{\beta(A(t) + \delta I(t) + \gamma T)}{N} + \mu \right) t} \text{ as } t \rightarrow \infty, \\
S &\geq 0.
\end{aligned}$$

**Positivity of  $E(t)$ :** From model equation (4.1) we have:

$$\begin{aligned}
\frac{dE}{dt} &= \left( \frac{\beta(A(t) + \delta I(t) + \gamma T)}{N} \right) S - (\eta + \mu) E, \\
\frac{dE}{dt} &\geq -(\eta + \mu) E \text{ by elimination positive term,} \\
\int \frac{dE}{E} &\geq \int -(\eta + \mu) dt \text{ by separable variable,} \\
\ln E &\geq -(\eta + \mu) t + c, \\
e^{\ln E} &\geq e^{- (\eta + \mu) t + c}, \\
E &\geq e^{- (\eta + \mu) t} \cdot e^c \text{ where } e^c = E_0, \\
E &\geq E_0 e^{- (\eta + \mu) t} \text{ as } t \rightarrow \infty, \\
E &\geq 0.
\end{aligned}$$

**Positivity of  $A(t)$ :** From model equation (4.1) we have:

$$\begin{aligned}
\frac{dA}{dt} &= (1 - p) \eta E - (\alpha + \phi + \mu + \xi_1) A, \\
\frac{dA}{dt} &\geq -(\alpha + \phi + \mu + \xi_1) A \text{ by elimination positive term,} \\
\int \frac{dA}{A} &\geq \int -(\alpha + \phi + \mu + \xi_1) dt \text{ by separable variable,} \\
\ln A &\geq -(\alpha + \phi + \mu + \xi_1) t + c, \\
e^{\ln A} &\geq e^{- (\alpha + \phi + \mu + \xi_1) t + c}, \\
A &\geq e^{- (\alpha + \phi + \mu + \xi_1) t} \cdot e^c \text{ where } e^c = A_0, \\
A &\geq A_0 e^{- (\alpha + \phi + \mu + \xi_1) t} \text{ as } t \rightarrow \infty, \\
A &\geq 0.
\end{aligned}$$

**Positivity of  $I(t)$ :** From model equation (4.1) we have:

$$\begin{aligned}
\frac{dI}{dt} &= \varphi A - (\alpha + \mu + \xi_2)I, \\
\frac{dI}{dt} &\geq -(\alpha + \mu + \xi_2)I \text{ by elimination positive term,} \\
\int \frac{dI}{I} &\geq \int -(\alpha + \mu + \xi_2)dt \text{ by separable variable,} \\
\ln I &\geq -(\alpha + \mu + \xi_2)t + c, \\
e^{\ln I} &\geq e^{-(\alpha + \mu + \xi_2)t + c}, \\
I &\geq e^{-(\alpha + \mu + \xi_2)t} \cdot e^c \text{ where } e^c = I_0, \\
I &\geq I_0 e^{-(\alpha + \mu + \xi_2)t} \text{ as } t \rightarrow \infty, \\
I &\geq 0.
\end{aligned}$$

**Positivity of  $T(t)$ :** From model equation (4.1) we have:

$$\begin{aligned}
\frac{dT}{dt} &= (1 - q)\alpha A + (1 - \chi\rho)\alpha I - (\omega + \mu + \xi_3)T \\
, \frac{dT}{dt} &\geq -(\omega + \mu + \xi_3)T \text{ by elimination positive term,} \\
\frac{dT}{dt} &\geq -(\omega + \mu + \xi_3)T, \\
\int \frac{dT}{T} &\geq \int -(\omega + \mu + \xi_3)dt \text{ by separable variable,} \\
e^{\ln T} &\geq e^{-(\omega + \mu + \xi_3)t + c}, \\
T &\geq e^{-(\omega + \mu + \xi_3)t} \cdot e^c \text{ where } e^c = T_0, \\
T &\geq T_0 e^{-(\omega + \mu + \xi_3)t} \text{ as } t \rightarrow \infty, \\
T &\geq 0.
\end{aligned}$$

**Positivity of  $R(t)$ :** From model equation (4.1) we have:

$$\begin{aligned}
\frac{dR}{dt} &= q\alpha A + \chi\rho\alpha I + \omega T - (\theta + \mu)R, \\
\frac{dR}{dt} &\geq -(\theta + \mu)R \text{ by elimination positive term,} \\
\int \frac{dR}{R} &\geq \int -(\theta + \mu)dt \text{ by separable variable,} \\
\ln R &\geq -(\theta + \mu)t + c, \\
e^{\ln R} &\geq e^{-(\theta + \mu)t + c}, \\
R &\geq e^{-(\theta + \mu)t} \cdot e^c \text{ where } e^c = R_0, \\
R &\geq R_0 e^{-(\theta + \mu)t} \text{ as } t \rightarrow \infty, \\
R &\geq 0.
\end{aligned}$$

The six dimensional solution space shows that all the solutions are positive. Hence, the feasible region containing all the solutions of the system of equations

(4.1) is given by the set;

$$\Omega = \{(S, E, A, I, T, R) \in \mathfrak{R}^6_+ : N \leq \frac{\Pi}{\mu}\}. \quad (4.5)$$

Here the quantities  $S(t), A(t), I(t), T(t)$  and  $R(t)$  are all non-negatives.

### 4.2.3 Gonorrhea Free Equilibrium (DFE)

Gonorrhea free equilibrium points are steady state solutions where there is no Gonorrhea in the population. Absence of Gonorrhea implies that  $E(t) = A(t) = I(t) = R(t) = T(t) = 0$  and the equilibrium points require that the right hand sides of the model equations set equal to zero. These requirements reflect in reducing the model equations (4.1) as;

$$\begin{aligned} \frac{dS}{dt} &= \Pi - \left(\frac{\beta(A(t)+\delta I(t)+\gamma T)}{N}\right)S - \mu S + \theta R = 0 \\ &, \Pi - \left(\frac{\beta(A(t)+\delta I(t)+\gamma T)}{N}\right)S - \mu S = 0 \\ S^0 &= \frac{\Pi}{\mu}. \end{aligned}$$

Thus, the Gonorrhea-free equilibrium point of the model equation in (4.1) above is given by  $E_0 = \{S^0, E^0, A^0, I^0, T^0, R^0\} = \{\frac{\Pi}{\mu}, 0, 0, 0, 0, 0\}$ .

### 4.2.4 The Basic Reproduction Number ( $\mathfrak{R}_0$ )

The basic reproduction number is denoted  $\mathfrak{R}_0$  by and is defined as the expected number of people getting secondary infection among the whole susceptible population. The dominant eigenvalue of the next generation matrix is  $\mathfrak{R}_0$ , which is computed using the next-generation matrix method for the model system (4.1) the associated matrices and for the new infectious terms and the remaining transition terms are respectively given by:

$$F_i = \begin{bmatrix} \left(\frac{\beta(A(t)+\delta I(t)+\gamma T)}{N}\right)S \\ 0 \\ 0 \\ 0 \end{bmatrix}, V_i = \begin{bmatrix} (\eta + \mu)E \\ (\alpha + \phi + \mu + \xi_1)A - (1 - P)\eta E \\ (\alpha + \mu + \xi_2)I - \phi A - \rho \eta E \\ (\omega + \mu + \xi_3)T - (1 - q)\alpha A - (1 - \chi \rho)\alpha I \end{bmatrix}$$

The Jacobian matrices of  $F_i$  and  $V_i$  at the Gonorrhea free equilibrium point take the form respectively as;

$$F = \begin{bmatrix} 0 & \frac{\beta\Pi}{\mu N} & \frac{\beta\delta\Pi}{\mu N} & \frac{\beta\gamma\Pi}{\mu N} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, V = \begin{bmatrix} \eta + \mu & 0 & 0 & 0 \\ -(1-\rho)\eta & \varphi + \alpha + \mu + \xi_1 & 0 & 0 \\ -\rho\eta & -\varphi & \alpha + \mu + \xi_2 & 0 \\ 0 & -(1-q)\alpha & -(1-\chi\rho)\alpha & \varphi + \mu + \xi_3 \end{bmatrix}$$

It can be verified that the matrix  $V$  is non-singular as its determinant  $\det[V]$  is non-zero and after some algebraic computations its inverse matrix is constructed as;

$$V^{-1} = \begin{bmatrix} \frac{1}{a} & 0 & 0 & 0 \\ \frac{-b}{ac} & \frac{1}{c} & 0 & 0 \\ \frac{-b\varphi-dc}{ace} & \frac{\varphi}{ce} & \frac{1}{e} & 0 \\ \frac{b(g\varphi-fe)-cdg}{aceh} & \frac{fe-g\varphi}{ceh} & \frac{-g}{eh} & \frac{1}{h} \end{bmatrix}$$

The product of the matrices  $F$  and  $V^{-1}$  can be computed as:

$$FV^{-1} = \begin{bmatrix} \beta(\frac{-b}{ac} + \delta r + \gamma s) & \beta(\frac{1}{c} + \frac{\delta\varphi}{ce} + \gamma t) & \frac{\beta\delta}{e} & \frac{\beta\gamma}{h} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

Now it is possible to calculate the eigenvalue to determine the basic reproduction number  $\mathfrak{R}_0$  by taking the spectral radius of the matrix  $FV^{-1}$ . Thus, the eigenvalues are computed by evaluating  $\det[FV^{-1} - \lambda I] = 0$  or equivalently solving;

$$FV^{-1} - \lambda = \begin{bmatrix} \beta(\frac{-b}{ac} + \delta r + \gamma s) - \lambda & \beta(\frac{1}{c} + \frac{\delta\varphi}{ce} + \gamma t) & \frac{\beta\delta}{e} & \frac{\beta\gamma}{h} \\ 0 & 0 - \lambda & 0 & 0 \\ 0 & 0 & 0 - \lambda & 0 \\ 0 & 0 & 0 & 0 - \lambda \end{bmatrix} = 0$$

It reduces to the equation for  $\lambda$  as  $\lambda^3[\beta(\frac{-b}{ac} + \delta r + \gamma s) - \lambda]$  giving the four eigen-



values as  $\lambda_1 = [\beta(\frac{-b}{ac} + \delta r + \gamma s)], \lambda_2 = 0, \lambda_3 = 0, \lambda_4 = 0$

Hence, the largest eigenvalue here is  $\lambda_1 = [\beta(\frac{-b}{ac} + \delta r + \gamma t)]$  and is the basic reproductive number. Thus, it can be concluded that the reproduction number of the model is

$$\mathfrak{R}_0 = [\beta(\frac{-b}{ac} + \frac{\delta(-b\phi-dc)}{ace}) + \frac{\gamma(b(g\phi-fe)-cdg)}{aceh}]$$

#### 4.2.5 Local Stability of Gonorrhea Free Equilibrium

In absence of Gonorrhea, the model populations have a unique Gonorrhea free steady state  $E_0$ . To find the local stability of  $E_0$ , the Jacobian of the model equations evaluated at GEF,  $E_0$  is used. It is already shown that the GFE of model (4.1) is given by  $E_0 = \{\frac{\Pi}{\mu}, 0, 0, 0, 0, 0\}$ . Now, the stability analysis of GEF is conducted and the results are presented in the form of theorems and proofs as follows:

**Theorem 1:** The GFE of the system (4.1) is locally asymptotically stable if  $\mathfrak{R}_0 < 1$  and unstable if  $\mathfrak{R}_0 > 1$ .

**Proof:** The begin we start by finding ,the Jacobian matrix J of model at the Gonorrhea free equilibrium  $E_0$  reduces to;

$$J(E_0) = \begin{bmatrix} -\mu & 0 & \beta & \beta\delta & \beta\gamma & 0 \\ 0 & -(\eta + \mu) & \beta & \beta\delta & \beta\gamma & 0 \\ 0 & (1-q)\eta & -(\alpha + \phi + \mu + \xi_1) & 0 & 0 & 0 \\ 0 & \rho\eta & \phi & -(\alpha + \mu + \xi_2) & 0 & 0 \\ 0 & 0 & (1-q)\alpha & (1-\chi\rho)\alpha & -(\omega + \mu + \xi_3) & 0 \\ 0 & 0 & q\alpha & \chi\rho\alpha & \omega & (\theta + \mu) \end{bmatrix}$$

Let  $J_{22} = -(\eta + \mu), J_{33} = -(\alpha + \phi + \mu + \xi_1), J_{44} = -(\alpha + \mu + \xi_2), J_{54} = (1 - \chi\rho)\alpha, J_{55} = -(\omega + \mu + \xi_3), J_{66} = (\theta + \mu)$ . Now, the eigenvalues are required to be found. The characteristic equation  $\det[J(E_0) - \lambda I] = 0$  is expanded and

simplified as follows:

$$J(E_0) - \lambda I = \begin{bmatrix} -\mu - \lambda & 0 & \beta & \beta\delta & \beta\gamma & 0 \\ 0 & J_{22} - \lambda & \beta & \beta\delta & \beta\gamma & 0 \\ 0 & (1-q)\eta & J_{33} - \lambda & 0 & 0 & 0 \\ 0 & \rho\eta & \varphi & J_{44} - \lambda & 0 & 0 \\ 0 & 0 & (1-q)\alpha & J_{54} & J_{55} - \lambda & 0 \\ 0 & 0 & q\alpha & \chi\rho\alpha & \omega & J_{66} - \lambda \end{bmatrix}$$

The first column of Jacobian matrix is all zero except the first entry, which is  $-\mu - \lambda$ . Then, we have the first eigenvalue ;  $\lambda_1 = -\mu$ . The rest of the eigenvalues are computed from the following Jacobian matrix.

$$J(E_0) - \lambda I = \begin{bmatrix} J_{22} - \lambda & \beta & \beta\delta & \beta\gamma & 0 \\ (1-q)\eta & J_{33} - \lambda & 0 & 0 & 0 \\ \rho\eta & \varphi & J_{44} - \lambda & 0 & 0 \\ 0 & (1-q)\alpha & J_{54} & J_{55} - \lambda & 0 \\ 0 & q\alpha & \chi\rho\alpha & \omega & J_{66} - \lambda \end{bmatrix}$$

The fifth column of Jacobian matrix is all zero except the fifth entry, which is  $J_{66} - \lambda$ . Then, we have the second eigenvalue ;  $\lambda_2 = J_{66} = (\theta + \mu)$ . The rest of the eigenvalues are computed from the following Jacobian matrix.

$$J(E_0) - \lambda I = \begin{bmatrix} J_{22} - \lambda & \beta & \beta\delta & \beta\gamma \\ (1-q)\eta & J_{33} - \lambda & 0 & 0 \\ \rho\eta & \varphi & J_{44} - \lambda & 0 \\ 0 & (1-q)\alpha & J_{54} & J_{55} - \lambda \end{bmatrix}$$

The fourth column of Jacobian matrix is all zero except the first and forth entry, which is;

$$J(E_0) - \lambda I = \beta\gamma \begin{bmatrix} (1-q)\eta & J_{33} - \lambda & 0 \\ \rho\eta & \varphi & J_{44} - \lambda \\ 0 & (1-q)\alpha & J_{54} \end{bmatrix}$$

+

$$(J_{55} - \lambda) = \begin{bmatrix} J_{22} - \lambda & \beta & \beta\delta \\ (1-q)\eta & J_{33} - \lambda & 0 \\ \rho\eta & \varphi & J_{44} - \lambda \end{bmatrix}$$

Then, Jacobian matrix obtained as the polynomial function given by;

$$(-(-\mu - \lambda_1))(- (J_{66} - \lambda_2)(J_{11} - \lambda_3)[(1-q)\eta(\varphi J_{54}) - (1-q)\alpha(J_{44} - \lambda_4) - (J_{33} - \lambda)(\rho\eta)(J_{55} - \lambda)] \quad (4.6)$$

From the equation (4.7)

$$\begin{aligned} -(\mu - \lambda_1) &= 0, \\ \lambda_1 &= -\mu, \\ -(J_{66} - \lambda_2) &= 0, \\ \lambda_2 &= -J_{66}, \\ \text{since } (\theta + \mu), \\ \lambda_2 &= -(\theta + \mu), \\ (J_{33} - \lambda_3) &= 0, \\ \lambda_3 &= (J_{33}), \\ \text{since } J_{33} &= -(\alpha + \mu + \varphi + \xi_1), \\ \lambda_3 &= -(\alpha + \mu + \varphi + \xi_1), \\ ((1-q)\eta(\varphi J_{54}) - (1-q)\alpha(J_{44} - \lambda_4)) &= 0, \\ \lambda_4 &= -(1-q)\eta(\varphi) - (1-q), \\ \text{since } J_{55} &= -(\omega + \mu + \xi_3), \\ \lambda_5 &= -(\omega + \mu + \xi_3), \\ \lambda_6 &= -(\alpha + \mu + \xi_2), \end{aligned}$$

all  $\lambda$  are negative. Therefore,  $\mathfrak{R}_0 < 1$  Hence the GFE is locally asymptotically stable in  $\Omega$  if  $\mathfrak{R}_0 < 1$ .

#### 4.2.6 Global Stability of Gonorrhea Free Equilibrium

**Theorem 2:** The Gonorrhea free equilibrium of the system (4.1) is Global asymptotically stable if  $\mathfrak{R}_0 < 1$ .

**Proof.** To establish the stability of the GFE point globally, we first developed the following Lyapunov function defined as;

$$L = A_1 E + A_2 A \quad (4.7)$$

By differentiating the above Lyapunov function with respect to time  $t$ , we obtain,

$$\begin{aligned} \frac{dL}{dt} &= A_1 \frac{dE}{dt} + A_2 \frac{dA}{dt}, \\ &= A_1 \left( \left( \frac{\beta(A(t) + \delta I(t) + \gamma T)}{N} \right) S - (\eta + \mu) E \right) + A_2 (1 - p) \eta E - (\alpha + \phi + \mu + \xi_1), \\ &= A_1 (\phi \delta E) - (\tau + \alpha + \mu + \xi_1) I_e A_1 + A_2 (1 - p) \eta E - (\alpha + \phi + \mu + \xi_1), \\ &= -(\tau + \delta + \mu + \xi_2) A \frac{(\beta \phi \mu + \beta \gamma \phi \alpha)}{(acch)} + \left( \frac{(\beta \gamma \phi)}{(ace)} \right) (\alpha A) \\ &\quad \text{By taking } A_1 = \frac{(\delta \mu \phi \alpha c + \beta \gamma \phi d)}{(acefh)}, A_2 = \left( \frac{(\beta \gamma \phi)}{(ace)} \right), \\ \frac{dL}{dt} &\leq [ -(\mu + \delta + \mu + \xi_2) \frac{(\beta \gamma \phi c + \beta \gamma \phi d)}{(aceh)} + \left( \frac{(\beta \gamma \phi \mu)}{(ace)} \right) ] A, \\ &= \left[ \left( \frac{-aceh}{(\tau + \alpha + \mu + \xi_2)(\beta \gamma \phi \mu e + \beta \gamma \phi ec + \beta \gamma \phi \alpha)} - \frac{(\tau + \alpha + \mu + \xi_2)(\beta \gamma \phi \alpha e + \beta \gamma \phi ec + \beta \gamma \phi \alpha)}{\beta \phi c f + \beta \delta \phi \alpha f - (\beta \gamma \phi \alpha e + \beta \gamma \phi d)} \right) \right. \\ &\quad \left. (- (\tau + \alpha + \mu + \xi_2) \frac{(\alpha \gamma \phi \alpha e + \beta \gamma \phi d)}{(aceh)} + \left( \frac{(\beta \gamma \phi \alpha)}{(ace)} \right) \right], \\ &= \left[ \left( \frac{(\beta \gamma \phi \alpha)}{(ace)} \right) \left( 1 - \frac{\beta \phi + \mu \delta \phi \alpha - (\beta \gamma \phi \alpha e + \beta \mu \phi d)}{(abcf)} \right) \right] A, \\ &= \left[ \left( \frac{(\alpha \mu \phi \alpha)}{(ace)} \right) (1 - \mathfrak{R}_0) \right] A. \end{aligned}$$

Hence, we obtain  $\frac{dL}{dt} < 0$  if  $(\mathfrak{R}_0) < 0$  and  $\frac{dL}{dt} = 0$  if and only if  $A = 0$ . Thus, the singleton set GFE in  $\Omega$  is the dominant compact invariant set in  $(S, E, A, I, T, R)$  :  $\frac{dL}{dt} = 0$ . As a result of LaSalles invariant principle (La Salle, 1976), as  $t$  tends to infinity, every solution that begins in the domain approaches GFE. Thus, if  $\mathfrak{R}_0 < 1$ , the GFE is globally asymptotically stable in  $\Omega$ .

#### 4.2.7 The Endemic Equilibrium

Endemic equilibrium point  $E_1$  is a steady state solution where the Gonorrhea persists in the population. For the existence and uniqueness of endemic equilibrium

$E_1 = \{S^*, E^*, A^*, I^*, T^*, R^*\}$ , its coordinates should satisfy the conditions  $E_1 = \{S^*, E^*, A^*, I^*, T^*, R^*\} \neq 0$  where  $S^* > 0, E^* > 0, A^* > 0, I^* > 0, T^* > 0$  and  $R^* > 0$ . The endemic equilibrium point is obtained by setting left hand sides of equations of the system (4.1) to zero and express each dependent variable in

terms of  $A^*$  at equilibrium point and we obtain;

$$\begin{cases} S^* = \frac{\mu(\beta(A+\delta I+\gamma T)+\Pi)}{\Pi(\Pi+\theta R^*)}, \\ E^* = \frac{S^*\mu(\beta(A(t)+\delta I(t)+\gamma T))}{\Pi(\eta+\mu)}, \\ I^* = \frac{\phi A^*+p\eta E}{\alpha+\mu+\xi_2}, \\ T^* = \frac{(1-q)\alpha A^*+(1-\chi\rho)\alpha I^*}{\omega+\mu+\xi_3}, \\ R^* = \frac{q\alpha A^*+\chi\rho\alpha I^*}{\theta+\mu}. \end{cases} \quad (4.8)$$

From equation (4.15) the endemic equilibrium easily satisfies the following polynomial and  $A^*$  is obtained by solving the equation.

$$A(A^*)^2 + B(A^*) = 0, \quad (4.9)$$

$A = q\alpha\delta\eta, B = \omega + \mu + \xi_3$ . Hence  $A > 0$  and  $B > 0$  whenever  $\mathfrak{R}_0 < 1$ . Solve for  $A^*$ , we have that  $A^* = -\frac{B}{A} < 0$ . From this, we see that, there is no endemic equilibrium for this model. Therefore, this condition shows that it is not possible for backward bifurcation in the model if  $\mathfrak{R}_0 < 1$ .

#### 4.2.8 Global Stability of Endemic Equilibrium

**Theorem 1:** The endemic equilibrium point of the model equation (4.1) is globally asymptotically stable whenever  $\mathfrak{R}_0 > 1$ .

**Proof:** To prove the global asymptotic stability of the endemic equilibrium we use the method of Lyapunov functions.

Define

$$\begin{aligned} \mathbf{L}(S^*, E^*, A^*, I^*, T^*, R^*) = & [S - S^* - S^* \ln(\frac{S}{S^*})] + [E - E^* - E^* \ln(\frac{E}{E^*})] + [A - A^* - A^* \ln(\frac{A}{A^*})] \\ & + [I - I^* - I^* \ln(\frac{I}{I^*})] + [T - T^* - T^* \ln(\frac{T}{T^*})] + [R - R^* - R^* \ln(\frac{R}{R^*})] \end{aligned}$$

By direct calculating the derivative of  $\mathbf{L}$  along the solution (4.1) we have;

$$\begin{aligned} \frac{dL}{dt} = & [\frac{S-S^*}{S}] \frac{dS}{dt} + [\frac{E-E^*}{E}] \frac{dE}{dt} + [\frac{A-A^*}{A}] \frac{dA}{dt} + [\frac{I-I^*}{I}] \frac{dI}{dt} + [\frac{T-T^*}{T}] \frac{dT}{dt} + [\frac{R-R^*}{R}] \frac{dR}{dt}, \\ = & [\frac{S-S^*}{S}] (\Pi - (\frac{\beta(A(t)+\delta I(t)+\gamma T)}{N})S - \mu S + R\theta) \\ & + [\frac{E-E^*}{E}] ((\frac{\beta(A(t)+\delta I(t)+\gamma T)}{N})S - (\eta + \mu)E) \end{aligned}$$

$$\begin{aligned}
& + \left[ \frac{A-A^*}{A} \right] ((1-P)\eta E - (\varphi + \alpha + \mu + \xi_1)A) \\
& + \left[ \frac{I-I^*}{I} \right] (\varphi A - (\alpha + \mu + \xi_2)I) \\
& + \left[ \frac{T-T^*}{T} \right] ((1-q)\alpha A + (1-\chi\rho)\alpha I - (\omega + \mu + \xi_3)T) \\
& + \left[ \frac{R-R^*}{R} \right] (q\alpha A + \chi\rho\alpha I + \omega T - (\theta + \mu)R), \\
& = \left[ 1 - \frac{S^*}{S} \right] \left( \Pi - \left( \frac{\beta(A(t) + \delta I(t) + \gamma T)}{N} \right) S - \mu S + R\theta \right) \\
& + \left[ 1 - \frac{E^*}{E} \right] \left( \left( \frac{\beta(A(t) + \delta I(t) + \gamma T)}{N} \right) S - (\eta + \mu)E \right) \\
& + \left[ 1 - \frac{A^*}{A} \right] ((1-P)\eta E - (\varphi + \alpha + \mu + \xi_1)A) \\
& + \left[ 1 - \frac{I^*}{I} \right] (\varphi A - (\alpha + \mu + \xi_2)I) \\
& + \left[ 1 - \frac{T^*}{T} \right] ((1-q)\alpha A + (1-\chi\rho)\alpha I - (\omega + \mu + \xi_3)T) \\
& + \left[ 1 - \frac{R^*}{R} \right] (q\alpha A + \chi\rho\alpha I + \omega T - (\theta + \mu)R).
\end{aligned}$$

Then collecting positive and negative terms together we obtain

$$\frac{dL}{dt} = M - N,$$

where  $M = [\Pi + \frac{S^*}{N}(\beta(A(t) + \delta I(t) + \gamma T)) + \mu N^* + \theta E^* \eta E + (\varphi + \alpha + \xi_1)A^* + \varphi A + (\alpha + \xi_2)I^* + (1-q)\alpha A + (1-\chi\rho)\alpha I + (\omega + \xi_3)T^* + q\alpha A + \chi\rho\alpha I + \omega T + \theta R^*]$ , and

$$N = [\mu N + \frac{S^*}{S}(\Pi) + \eta E + \frac{E^*(\beta(A(t) + \delta I(t) + \gamma T))}{EN} + (\varphi + \alpha + \xi_1)A + \frac{A^*}{A}(\eta E) + (\varphi + \xi_1) + \alpha A \frac{I^*}{I} + (\omega + \xi_3)T + \frac{T^*}{T}((1-q)\alpha A + (1-\chi\rho)\alpha I) + \theta R + \frac{R^*}{R}(q\alpha A + \chi\rho\alpha I)].$$

Thus if  $M < N$ , then  $\frac{dL}{dt} \leq 0$ . Noting that  $\frac{dL}{dt} = 0$  if and only if  $S = S^*, E = E^*, A = A^*, I = I^*, T = T^*, R = R^*$ . Therefore, the largest compact invariant set  $(S^*, E^*, A^*, I^*, T^*, R^*) \in \Omega : \frac{dL}{dt} = 0$  is the singleton  $E_1$  is the endemic equilibrium of the system (4.1). By LaSalle's invariant principle ([1], 1976), it implies that  $E_1$  is globally asymptotically stable in  $\Omega$  if  $M < N$ .

### 4.3 Sensitivity Analysis of Model Parameters

In this section, we will see the sensitivity analysis of the parameters that found in the model (4.1) those can determine the value of the basic reproduction number. Because those parameters can increasing or decreasing a basic reproduction number ( $\mathcal{R}_0$ ) if their values increases or decreases and vice-versa. So that to identify the parameters that have a high impact on the basic reproduction num-

ber ( $\mathfrak{R}_0$ ) we should have applied the sensitivity analysis. Thus, to find the sensitivity analysis, we followed the technique outlined in and with the developed techniques defined as follows, we will obtain the sensitivity index of all the basic parameters.

**Definition** The normalized forward sensitivity index of  $\mathfrak{R}_0$  that depends differentiable on a parameter  $\mathbf{M}$  is defined as:

$$\eta_M^{\mathfrak{R}_0} = \frac{\partial \mathfrak{R}_0}{\partial M} \times \frac{\mathfrak{R}_0}{M} \quad (4.10)$$

The sensitivity index of  $\mathfrak{R}_0$  in relation to the parameter  $\beta$  is calculated as

$$\begin{aligned} \eta_\beta^{\mathfrak{R}_0} &= \frac{\partial \mathfrak{R}_0}{\partial \beta} \times \frac{\beta}{\mathfrak{R}_0} \\ &= \left[ \frac{-b}{ac} + \frac{\delta(-b\phi-dc)}{ace} + \left( \frac{\gamma(b(g\phi-fe)-cdg)}{aceh} \right) \right] \times \frac{\beta}{\beta \left[ \frac{-b}{ac} + \frac{\delta(-b\phi-dc)}{ace} + \left( \frac{\gamma(b(g\phi-fe)-cdg)}{aceh} \right) \right]} = 1 > 0 \end{aligned}$$

More over, in similar procedure with respect to remaining parameters in basic reproduction number and their sensitivity indices were written in Table 4.2 as follows.

This is described in figure 4.2 as follows;

Table 4.2: Sensitivity indices of parameters

Parameters symbol	Sensitivity index
$\beta$	1
$\omega$	0.432
$\delta$	0.366
$\alpha$	0.0195
$\xi_3$	0.0123
$\xi_2$	0.0000123
$\xi_1$	0.000023
$\mu$	0.1356
$\eta$	-0.313
$\gamma$	-0.169
$\phi$	-0.338
$\chi$	-0.65

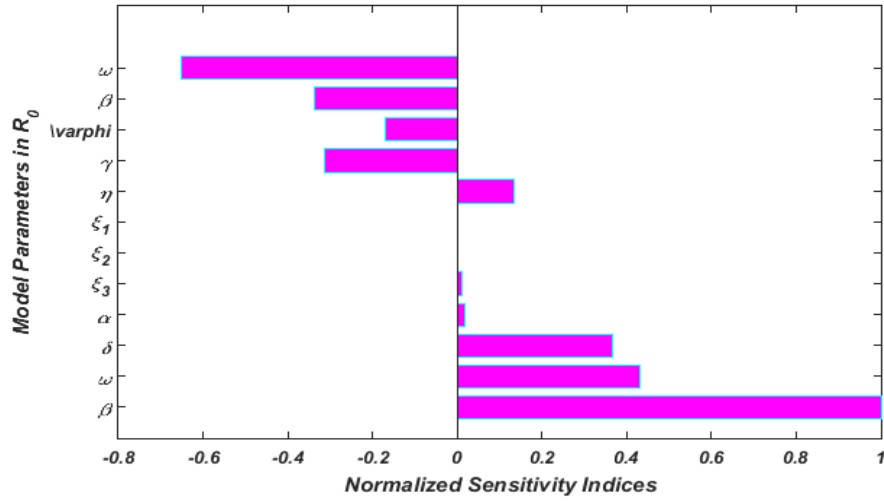


Figure 4.2: Sensitivity indices of basic reproduction number  $\mathfrak{R}_h$

Based on the described sensitivity indices of the basic reproduction number  $\mathfrak{R}_0$  with respect to five basic parameters in Table(4.2). The results showed that the parameters with a positive sensitivity index increased the value of  $\mathfrak{R}_0$  as their values increased, whereas the other parameters remained constant. Furthermore, increasing the values of the parameters with negative indices while keeping the values of the other parameters constant reduces the value of  $\mathfrak{R}_0$ .

#### 4.4 Optimal Control Model Formulation

The aim of this section is to extend model equation (1) into an optimal control problem. The controls defined as follows;

- $u_1$  represents prevention effort that protect susceptible individuals from contracting of Gonorrhea infection,
- $u_2$  represents a screening effort for individuals which are asymptomatic with virus,
- $u_3$  represents treatment effort that minimize infection by treating infectious, implies asymptomatic individuals, symptomatic individuals and treated individuals.



Time is specified and relatively short and is given by  $t \in [0, T]$ ,  $T$  is the terminal time. After incorporating control functions  $u_1(t), u_2(t)$  and  $u_3(t)$  in Gonorrhea model equation (1), we obtain the following state system;

$$\begin{cases} \frac{dS}{dt} = \Pi + R\theta - (1 - u_1)\left(\frac{\beta(A+\delta I+\gamma T)}{N}\right)S - \mu S, \\ \frac{dE}{dt} = (1 - u_1)\left(\frac{\beta(A+\delta I+\gamma T)}{N}\right)S - (\eta + \mu)E, \\ \frac{dA}{dt} = (1 - p)\eta E - (u_2 + \phi)A - (u_3 + \alpha)A - (\mu + \xi_1)A, \\ \frac{dI}{dt} = (u_2 + \phi)A - (u_3 + \alpha)I - (\mu + \xi_3)I, \\ \frac{dT}{dt} = (1 - u_3)(1 - q)\alpha A + (1 - u_3)(1 - \chi\rho\alpha)I - (\omega + \mu + \xi_3)T, \\ \frac{dR}{dt} = (u_3 + q\alpha)A + (u_3 + \chi\rho\alpha)I + \omega T - (\theta + \mu)R. \end{cases} \quad (4.11)$$

Our main objective is to minimize the objective function  $J$  considering the exposed individuals  $E(t)$ , asymptomatic individuals  $A(t)$ , the Symptomatic individuals  $I(t)$ , treated individuals  $T(t)$  and costs of controls  $u_i(t)$ . The optimal control models objective functional (4.11) is given as

$$J(u_1, u_2, u_3) = \underbrace{\min}_{u_1, u_2, u_3} \int_0^{t_f} [M_1 E + M_2 A + M_3 I + M_4 T + \frac{1}{2}(w_1 u_1^2 + w_2 u_2^2 + w_3 u_3^2)] dt \quad (4.12)$$

where  $t_f$  is the terminal time,  $M_1, M_2, M_3$  and  $M_4$  were the weight constants for the exposed individuals, asymptomatic individuals, symptomatic individuals and treatment individuals, respectively, while  $w_1, w_2, w_3$  are weight constants for use controls efforts, respectively. The expression  $\frac{1}{2}(w_i u_i^2)$  represents the cost function that corresponds to the controls  $u_i(t)$  and is quadratic as in the other literature. The objective functional (4.12) is to minimize the exposed individuals  $E(t)$ , asymptomatic individuals  $A(t)$ , symptomatic individuals  $I(t)$ , treated individuals  $T(t)$ , and control costs  $u_i(t)$ . The main point is to compute an a double optimal controls  $u_1^*$ , and  $u_2^*, u_3^*$  Such that;

$$J(u_1^*, u_2^*, u_3^*) = \min J(u_1, u_2, u_3) \quad (4.13)$$

where  $u = (u_1, u_2, u_3) : u_i(t)$  are Lebesgue measurable on  $t \in [0, t_f]$ . Hence, the basic setup of the optimal control problem is to check the existence and uniqueness of the optimal controls and to characterize them.

## 4.5 Optimal Control Problem Analysis

### 4.5.1 Existence of an optimal controls

**Theorem :** Given  $J(u)$  subject to system (4.21) with  $S(0) \geq 0, E(0) \geq 0, A(0) \geq 0, I(0) \geq 0, T(0) \geq 0, R(0) \geq 0$ , then there exists an optimal control  $u^*$  and corresponding  $(S^*, E^*, A^*, I^*, T^*, R^*)$ , that minimizes  $J(u)$  over  $U$ .

Let the control set  $U = [0, 1]^2$ ,  $v = (u_1, u_2, u_3) \in U$ ,  $x = (S^*, E^*, A^*, I^*, T^*, R^*)$  and  $f(t, x, v)$  the right hand side of state system (4.21), is given by

$$f(t, x, v) = \begin{bmatrix} \Pi + \theta R - (1 - u_1) \left( \frac{\beta(A + \delta I + \gamma T)}{N} \right) S - \mu S, \\ (1 - u_1) \left( \frac{\beta(A + \delta I + \gamma T)}{N} \right) S - (\eta + \mu) E, \\ (1 - p) \eta E - (u_2 + \phi) A - (u_3 + \alpha) A - (\mu + \xi_1) A, \\ (u_2 + \phi) A - (u_3 + \alpha) I - (\mu + \xi_2) I, \\ (1 - u_3) (1 - q) \alpha A + (1 - u_3) (1 - \chi \rho \alpha) I - (\omega + \mu + \xi_3) T, \\ (u_3 + q \alpha) A + (u_3 + \chi \rho \alpha) I + \omega T - (\theta + \mu) R. \end{bmatrix}.$$

The proof is based on the following assumption and by Fleming and Rishel's theorem.

1. The set of controls and corresponding state variable is nonempty.
2. The measurable control set is convex and closed.
3. All the right hand sides of equations of the state system is continuous, bounded above by a sum of bounded control and state, and can be written as a linear function of  $u$  with coefficients depending on time and state.
4. The integrand  $g(\phi, u)$  of the objective functional is convex.
5. There exist constants  $c_1, c_2, c_3, c_4 \geq 0$  and  $\rho^* \geq 1$  such that the integrand of the objective functional satisfies  $g(\phi, u) \geq c_1 + c_2 |u_1|^{\rho} + c_3 |u_2|^{\rho} + c_4 |u_3|^{\rho}$

**Proof:**

1.  $U$  is a nonempty set of measurable functions on  $0 \leq T$  with values in real numbers  $\mathbb{R}$ . The system (4.21) has bounded coefficients and hence any solutions are bounded on  $[0, T]$ . The corresponding solutions for the system (4.11) exists.
2. Assume that  $u_1, u_2, u_3 \in U$  such that  $\|u_i\| \leq 1, i = 1, 2$ . Now, let us take any controls  $u_1, u_2 \in U$  and  $\lambda \in [0, 1]$ , then  $0 \leq \lambda u_1 + (1 - \lambda)u_2$ . Additionally, we observe that

$$\|\lambda u_1\| \leq \lambda \|u_1\| \leq \lambda \text{ and } \|(1 - \lambda)u_2\| \leq (1 - \lambda)\|u_2\| \leq (1 - \lambda).$$

Then for any  $\lambda \in [0, 1]$ ,

$$\begin{aligned} & \|\lambda u_1 + (1 - \lambda)u_2\|, \\ & \leq \|\lambda u_1\| + \|(1 - \lambda)u_2\|, \\ & \leq \lambda \|u_1\| + (1 - \lambda)\|u_2\|, \\ & \leq \lambda + (1 - \lambda) = 1. \end{aligned}$$

Hence,  $0 \leq \lambda u_1 + (1 - \lambda)u_2 \leq 1$ , for all  $u_1, u_2 \in U$  and  $\lambda \in [0, 1]$ .

Therefore, the control space  $U = \{u = (u_1, u_2, u_3), 0 \leq u_i \leq u_{i_{max}}, i = 1, 2, 3\}$  and  $t \in [0, T]$  is convex and closed by definition.

3. The integrand in the objective functional, which is a cost function is an affine function. Recall that any affine function is a convex and the sum of a convex function is a convex. Therefore, cost function is convex on  $U$ .
4. Assume that there exists constants  $c_1, c_2, c_3, c_4 \geq 0$  and  $\tau^* \geq 1$  such that  $g(\phi, u)$  satisfies  $g(\phi, u) \geq c_1 + c_2|u_1|^\rho + c_3|u_2|^\rho + c_4|u_3|^\rho$ . Thus, the state variables are being bounded.

Let  $c_1 = \inf_{t \in [0, T]} [M_1 E + M_2 A + M_3 I + M_4 T]$ ,  $c_2 = \frac{w_1}{2}$ ,  $c_3 = \frac{w_2}{2}$ ,  $c_4 = \frac{w_3}{2}$  and  $\rho = 2$  then it follows that

$$g(\varphi, u) \geq c_1 + c_2|u_1|^p + c_3|u_2|^p + c_4|u_3|^p.$$

Thus, this assumption is justified.

#### 4.5.2 Characterization of an optimal control

The optimal control must satisfy the necessary conditions that are formulated by Pontryagins Maximum Principle. This principle converts the system of equations (4.11) and (4.12) into a problem of minimizing point-wise a Hamiltonian (H), with respect to  $u_1(t), u_2(t), u_3(t)$  as

$$\begin{cases} H = [M_1E + M_2A + M_3I + M_4T + \frac{1}{2}(w_1u_1^2 + w_2u_2^2 + w_3u_3^2)] \\ + \lambda_1 \frac{dS}{dt} + \lambda_2 \frac{dE}{dt} + \lambda_3 \frac{dA}{dt} + \lambda_4 \frac{dI}{dt} + \lambda_5 \frac{dT}{dt} + \lambda_6 \frac{dR}{dt} \end{cases} \quad (4.14)$$

It follows that the system of equation (4.11) and equation (4.12) are substituted into a minimized Hamiltonian function with respect to  $u_1, u_2, u_3$ , as given by:

$$\begin{cases} H = [M_1E + M_2A + M_3I + M_4T + \frac{1}{2}(w_1u_1^2 + w_2u_2^2 + w_3u_3^2)] \\ + \lambda_1 [\Pi + R\theta - (1 - u_1)(\frac{\beta(A+\delta I+\gamma T)}{N})S - \mu S] \\ + \lambda_2 [(1 - u_1)(\frac{\beta(A+\delta I+\gamma T)}{N})S - (\eta + \mu)E] \\ + \lambda_3 [(1 - p)\eta E - (u_2 + \varphi)A - (u_3 + \alpha)A - (\mu + \xi_1)A] \\ + \lambda_4 [(u_2 + \varphi)A - (u_3 + \alpha)I - (\mu + \xi_2)I] \\ + \lambda_5 [(1 - u_3)(1 - q)\alpha A + (1 - u_3)(1 - \chi\rho\alpha)I - (\omega + \mu + \xi_3)T] \\ + \lambda_6 [(u_3 + q\alpha)A + (u_3 + \chi\rho\alpha)I + \omega T - (\theta + \mu)R] \end{cases} \quad (4.15)$$

where  $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$  and  $\lambda_6$  are adjoint variables. Next to obtaining the co-state variables by using Pontryagins maximum principle (4.11) with the existence result (4.15), the following theorem is stated:

**Theorem** For given optimal control triples  $(u_1^*, u_2^*, u_3^*)$  and  $(S^*, E^*, A^*, I^*, T^*, R^*)$  of the corresponding state system that minimizes  $J(u_1^*, u_2^*, u_3^*)$  over  $u$  subject to equation (4.1), adjoint variables  $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$  and  $\lambda_6$  are found, holding

the adjoint system.

$$\left\{ \begin{array}{l} \frac{d\lambda_1}{dt} = -(1-u_1)\left(\frac{\beta(A+\delta I+\gamma T)}{N}\right)(\lambda_2-\lambda_1) + \mu\lambda_1, \\ \frac{d\lambda_2}{dt} = -[-(\eta+\mu)\lambda_2 + (1-p)\eta\lambda_3 + M_1], \\ \frac{d\lambda_3}{dt} = -[-(u_2+\varphi)\lambda_3 - (u_3+\alpha)\lambda_3 - (\mu+\xi_1)\lambda_3 + \\ (u_2+\varphi)\lambda_4 + (1-u_3)(1-q)\alpha\lambda_4 + \\ (u_3+q\alpha)\lambda_6 + M_2], \\ \frac{d\lambda_4}{dt} = -[-(u_3+\alpha)\lambda_4 - (\mu+\xi_3)\lambda_4 + \\ (1-u_3)(1-\chi\rho\alpha)\lambda_5 + (u_3+\chi\rho\alpha)\lambda_6 + M_3], \\ \frac{d\lambda_5}{dt} = -[-(\omega+\mu+\xi_3)\lambda_5 + \omega\lambda_6 + M_4], \\ \frac{d\lambda_6}{dt} = -(-(\theta+\mu)\lambda_6). \end{array} \right. \quad (4.16)$$

With transversely conditions

$$\lambda_1(t_f)=\lambda_2(t_f)=\lambda_3(t_f)=\lambda_4(t_f)=\lambda_5(t_f)=\lambda_6(t_f)=0$$

Thus, the optimal control  $u_1^*$ ,  $u_2^*$  and  $u_3^*$  are represented by:

$$\left\{ \begin{array}{l} u_1^* = \min\{1, \max\{0, \frac{\beta(A^*+\delta I+\gamma T)S^*(\lambda_2-\lambda_1)}{w_1 N}\}\}, \\ u_2^* = \min\{1, \max\{0, \frac{A^*(\lambda_3-\lambda_4)}{w_2}\}\}, \\ u_3^* = \min\{1, \max\{0, \frac{A^*(\lambda_3-\lambda_6)+(1-q)\alpha A^*\lambda_3+(1-\chi\rho\alpha)I^*\lambda_5-\lambda_6 I^*}{w_3}\}\}. \end{array} \right. \quad (4.17)$$

**Proof:** To obtain the form of the co-state equations we compute the derivative of the Hamiltonian function (H), equation (4.14), with respect to S, E, A, I, T and R respectively. Then the adjoint or co-state equations obtained are given by;

$$\left\{ \begin{array}{l} \frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S} = -(1-u_1)\left(\frac{\beta(A+\delta I+\gamma T)}{N}\right)(\lambda_2 - \lambda_1) + \mu\lambda_1, \\ \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial E} = -[-(\eta + \mu)\lambda_2 + (1-p)\eta\lambda_3 + M_1], \\ \frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial A} = -[-(u_2 + \phi)\lambda_3 - (u_3 + \alpha)\lambda_3 - (\mu + \xi_1)\lambda_3 + \\ (u_2 + \phi)\lambda_4 + (1-u_3)(1-q)\alpha\lambda_4 + \\ (u_3 + q\alpha)\lambda_6 + M_2], \\ \frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial I} = -[-(u_3 + \alpha)\lambda_4 - (\mu + \xi_3)\lambda_4 + \\ (1-u_3)(1-\chi\rho\alpha)\lambda_5 + (u_3 + \chi\rho\alpha)\lambda_6 + M_3], \\ \frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial T} = -[-(\omega + \mu + \xi_3)\lambda_5 + \omega\lambda_6 + M_4], \\ \frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial R} = -(-(\theta + \mu)\lambda_6). \end{array} \right. \quad (4.18)$$

With transversely conditions

$$\lambda_1(t_f)=\lambda_2(t_f)=\lambda_3(t_f)=\lambda_4(t_f)=\lambda_5(t_f)=\lambda_6(t_f)=0$$

To obtain the control values, we compute the partial derivative of the Hamiltonian, given by:

$$\frac{\partial H}{\partial u_i} = 0$$

Obviously, after derivation of function (H), equation (4.14), with respect to the controls, the result

becomes:

$$\left\{ \begin{array}{l} \frac{\partial H}{\partial u_1} = 0 = w_1 u_1 + \frac{\beta(A+\delta I+\gamma T)\lambda_1 S}{N} - \frac{\beta(A+\delta I+\gamma T)\lambda_2 S}{N}, \\ \frac{\partial H}{\partial u_2} = 0 = w_2 u_2 + \lambda_4 A - \lambda_3 A, \\ \frac{\partial H}{\partial u_3} = 0 = w_2 u_3 - (1-q)\alpha A \lambda_3 - (1-\chi\rho\alpha)I\lambda_5 \\ + \lambda_6 A + \lambda_6 I. \end{array} \right. \quad (4.19)$$

Moreover, solving for the control variables from equation (4.19) we obtain

$$\begin{cases} u_1^* = \min\{1, \max\{0, \frac{\beta(A^* + \delta I + \gamma T)S^*(\lambda_2 - \lambda_1)}{w_1 N}\}\}, \\ u_2^* = \min\{1, \max\{0, \frac{A^*(\lambda_3 - \lambda_4)}{w_2}\}\}, \\ u_3^* = \min\{1, \max\{0, \frac{A^*(\lambda_3 - \lambda_6) + (1-q)\alpha A^*\lambda_3 + (1-\chi\rho\alpha)I^*\lambda_5 - \lambda_6 I^*}{w_3}\}\}. \end{cases} \quad (4.20)$$

Rearranging the solution of equation (4.20) with the boundary condition of each control, we get:

$$\begin{cases} u_1^* = \max\{0, \min\{1, \frac{\beta(A^* + \delta I + \gamma T)S^*(\lambda_2 - \lambda_1)}{w_1 N}\}\}, \\ u_2^* = \max\{0, \min\{1, \frac{A^*(\lambda_3 - \lambda_4)}{w_2}\}\}, \\ u_3^* = \max\{0, \min\{1, \frac{A^*(\lambda_3 - \lambda_6) + (1-q)\alpha A^*\lambda_3 + (1-\chi\rho\alpha)I^*\lambda_5 - \lambda_6 I^*}{w_3}\}\}. \end{cases} \quad (4.21)$$

### 4.5.3 Uniqueness of the optimality system

In order to successively discuss uniqueness of the optimality system we notice that the adjoint system is also linear in  $\lambda_i$  for  $i = 1, 2, 3, 4, 5, 6$  with bounded coefficients. Thus, there exists a  $M > 0$  such that  $|\lambda_i(t)| < M$  for  $i = 1, 2, 3, 4, 5, 6$  on  $[0, T]$ .

**Theorem :** For  $T$  sufficiently small the solution to the optimality system is unique.

## 4.6 Numerical Simulations

In this subsection, numerical simulation study of the autonomous system (4.21) are carried out using the software MATLAB R2015b with ODE45 solver. To conduct the study, a set of physically meaningful values are assigned to the model parameters. These values are either taken from literature or assumed on the basis of reality. Using the parameter values given in Table 5.3 and the initial conditions  $S(0) = 100, E(0) = 60, I_e(0) = 40, I_l(0) = 40, T(0) = 20$  and  $R(0) = 10$  and also coefficients of the state and controls that we used are  $M_1 = 250, M_2 = 250, M_3 = 250, M_4 = 250, w_1 = 100, w_2 = 100, w_3 = 100$  a simulation

study is conducted. Finally, an optimal control strategy is designed and discussed using different control strategies. To solve the optimal controls and states, we use the Runge-Kutta numerical method using MATLAB program. It needs to solve thirteen-state equations and thirteen adjoint equations. For that, first we solve system 2 with a guess for the controls forward in time and then using the transversality conditions as initial values and the adjoint system is solved backward in time using the current iteration solution of the state system.

Table 4.3: Parameter Description and Values

Parameters	Description	Value	Source
$\Pi$	Recruitment rate	1000	Estimated
$\beta$	Probability of contact between a susceptible and an infectious	0.3	Assumed
$\delta$	Modification parameter for Symptomatic individuals	0.35	Estimated
$\gamma$	Modification parameter for Treated individuals	0.25	Assumed
$p$	probability of Exposed progress to Asymptomatic individuals	0.9	Assumed
$\phi$	Rate of asymptomatic individuals become symptomatic individuals	0.9	Assumed
$\eta$	Per capita rate of becoming infectious	0.6849	Assumed
$\alpha$	Treatment rate	0.6849	Assumed
$q$	A fraction of treated from the asymptomatic of infection become recover and move to the recovery	0.9	(Chen et al., 2023)
$\rho$	A fraction of the treated in the symptomatic of infection become recover and move to the recovery	0.9	(Chen et al., 2023)
$\chi$	rate asymptomatic of infection in comparison to the symptomatic of infection	0.6849	(Chen et al., 2023)
$\omega$	Rate of recovered	0.35	Estimated
$\mu$	Natural death rate	0.00548	Estimated
$\theta$	Rate of recovered human become susceptible	0.3	Assumed
$\xi_1$	Rate of asymptomatic infected who failed treatment is to mortality	0.0001	Estimated
$\xi_2$	Rate of symptomatic infected who failed treatment is to mortality	0.0001	Estimated
$\xi_3$	Rate of treated who failed treatment is to mortality	0.0001	Estimated



### Scenario I: Optimal use of Prevention

We simulated the optimality control system by incorporating prevention intervention only to eradicate Gonorrhea infection from the community. Figures 4.3, 4.4, 4.5 and 4.6 shows that an infectious individual goes to zero at the end of the implementation period. Therefore, applying this strategy is effective in eradicating Gonorrhea form the community in a specified period of time.

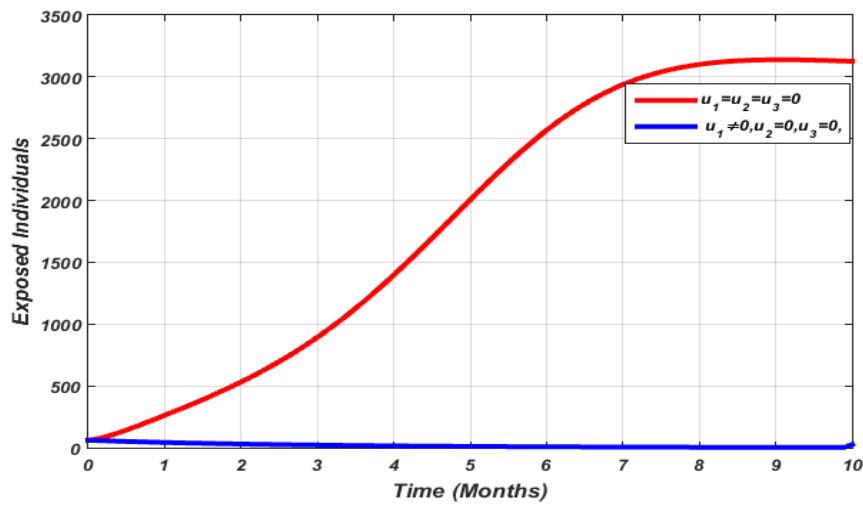


Figure 4.3: Dynamics of Gonorrhea Exposed individuals

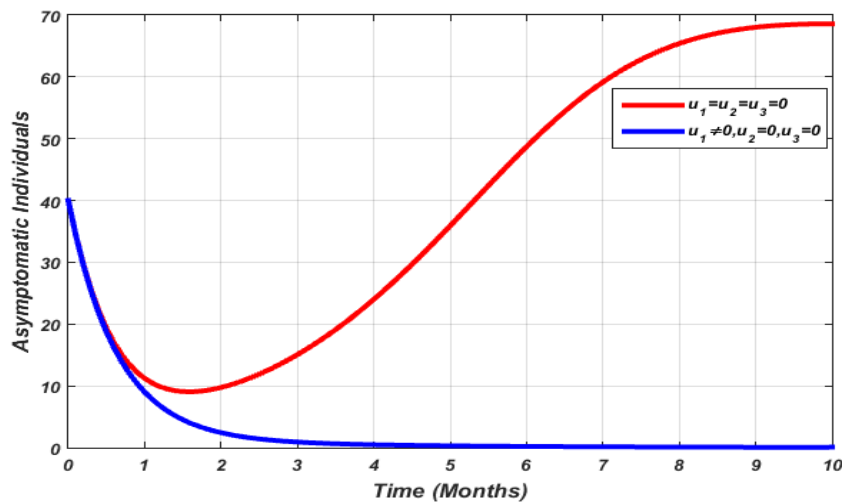


Figure 4.4: Dynamics of Asymptomatic individuals

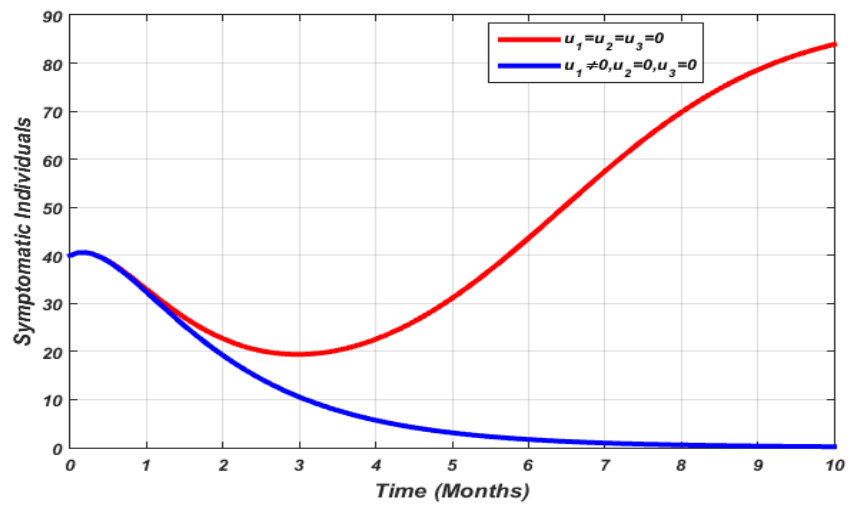


Figure 4.5: Dynamics of Symptomatic individuals

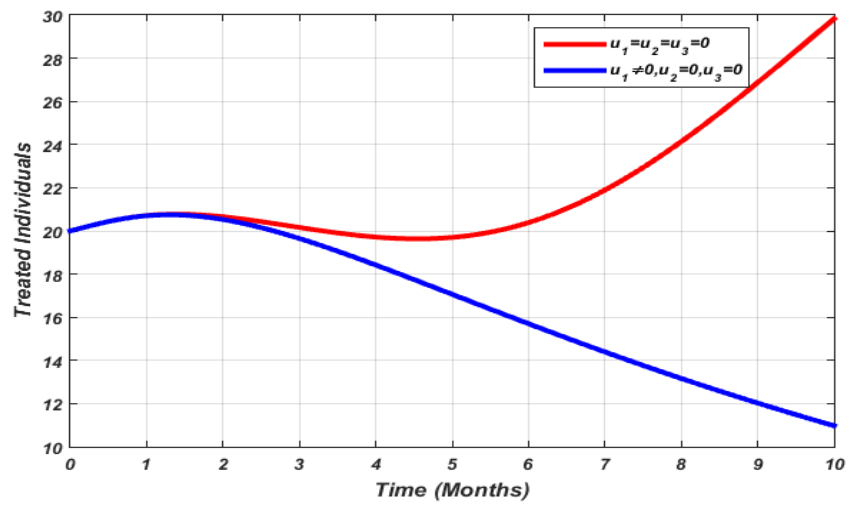


Figure 4.6: Dynamics of Treated individuals

## Scenario II: Optimal use of Prevention and Screening

We applied prevention and screening only as intervention that is screening individuals who have Gonorrhea disease infection. Figures 4.7, 4.8, 4.9 and 4.10 clearly show that all infectious individuals have gone to zero at the end of the implementation period. Therefore, we conclude that this strategy is effective in eradicating the Gonorrhea from the community in a specified period of time.

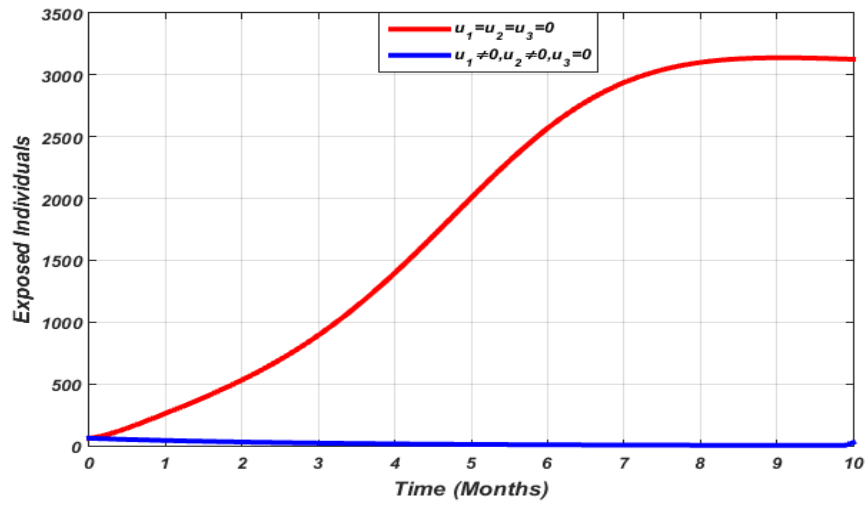


Figure 4.7: Dynamics of Gonorrhea Exposed individuals

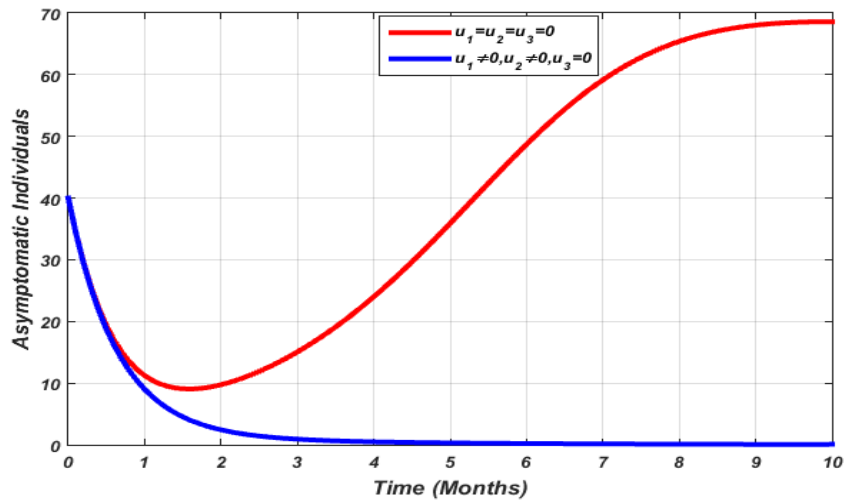


Figure 4.8: Dynamics of Asymptomatic individuals

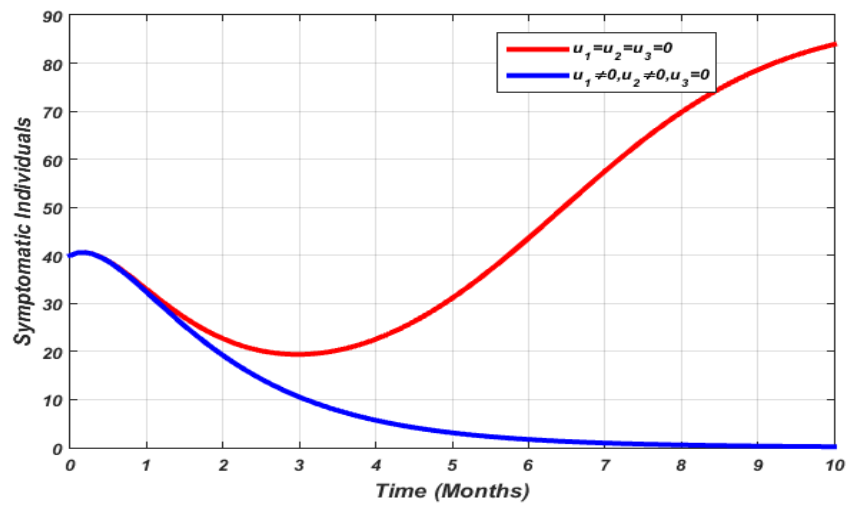


Figure 4.9: Dynamics of Symptomatic individuals

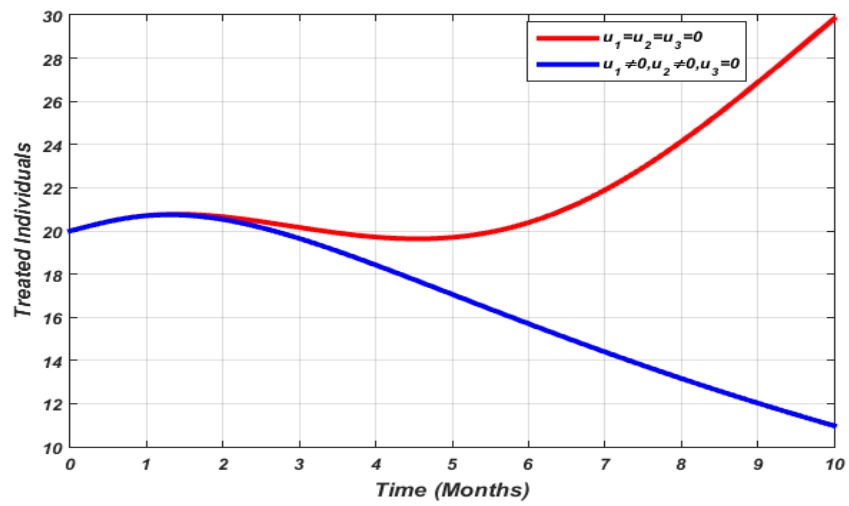


Figure 4.10: Dynamics of Treated individuals

### Scenario III: Optimal use of Prevention and Treatment

We simulate the model using a combination of prevention and treatment as intervention strategy for control of Gonorrhea in the community. Figures 4.11, 4.12, 4.13 and 4.14 shows that infectious individuals goes to zero over the period of implementation of this intervention strategy. Therefore, this strategy is effective in eradicating the Gonorrhea in the specified period of time.

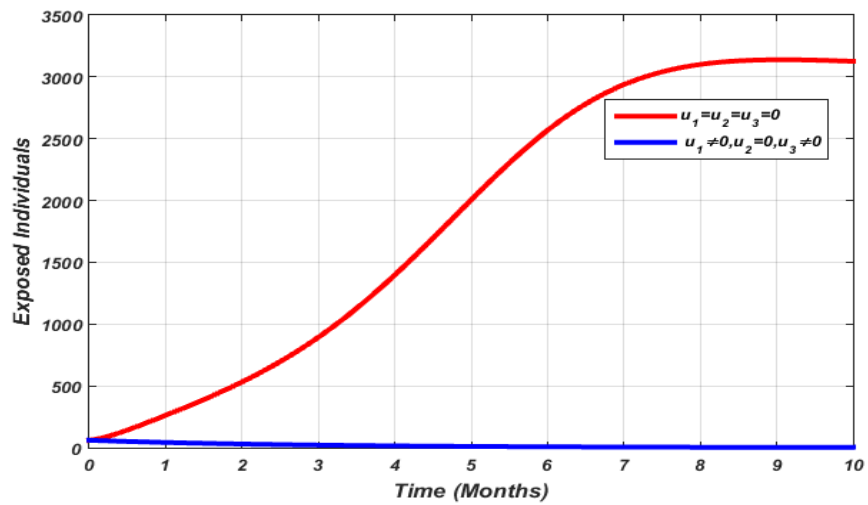


Figure 4.11: Dynamics of Gonorrhea Exposed individuals

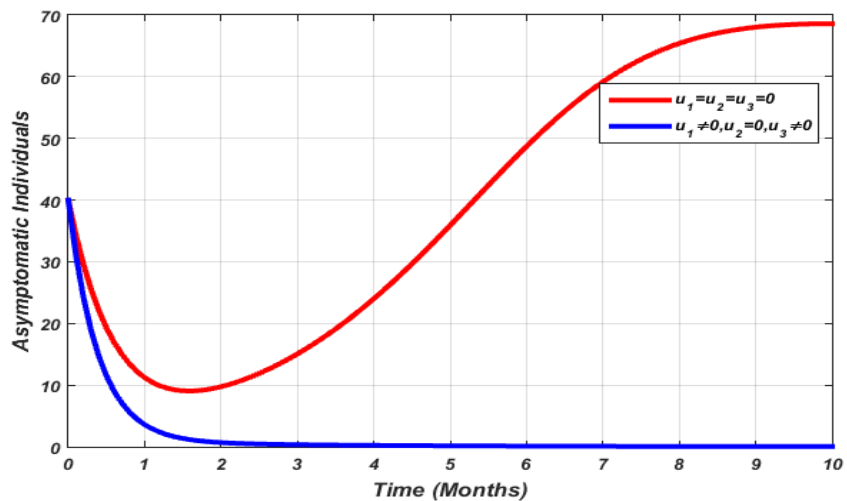


Figure 4.12: Dynamics of Asymptomatic individuals

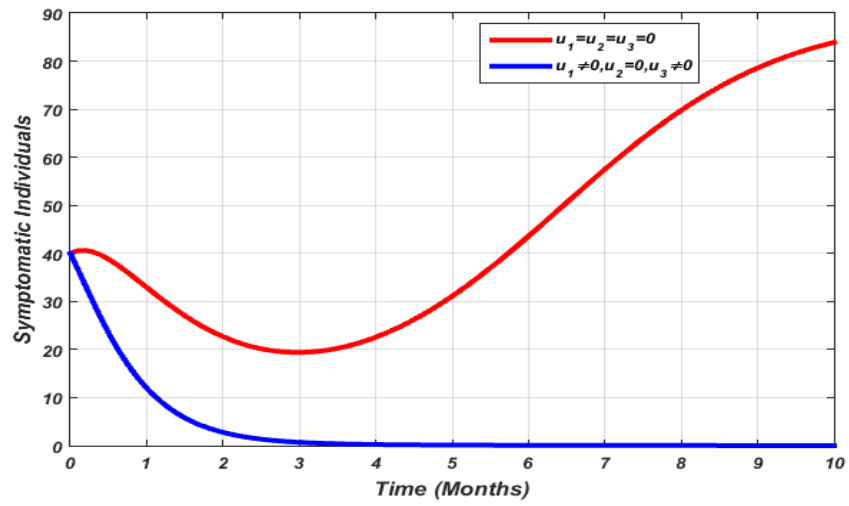


Figure 4.13: Dynamics of Symptomatic individuals

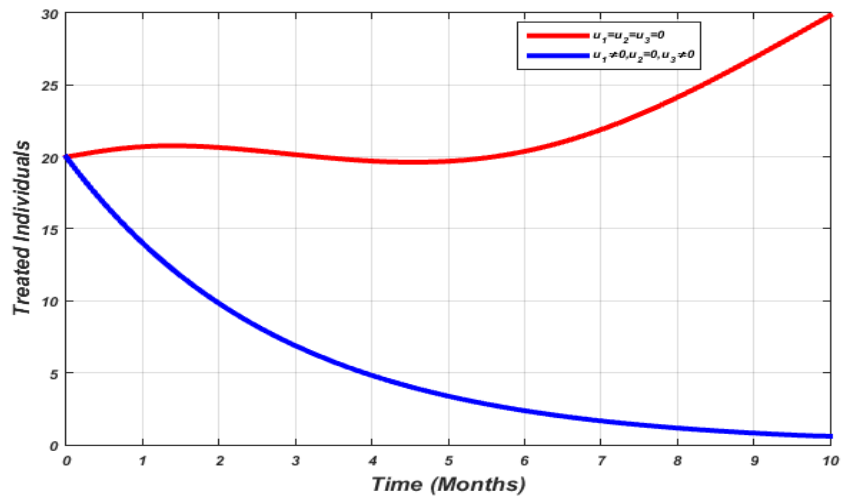


Figure 4.14: Dynamics of Treated individuals

#### Scenario IV: Optimal use of Prevention, and Treatment

We simulate the model using a combination of prevention, screening and treatment as intervention strategy for control of Gonorrhea in the community. Figures 4.15, 4.16, 4.17 and 4.18 shows that infectious individuals goes to zero over the period of implementation of this intervention strategy. Therefore, this strategy is effective in eradicating the Gonorrhea in the specified period of time.

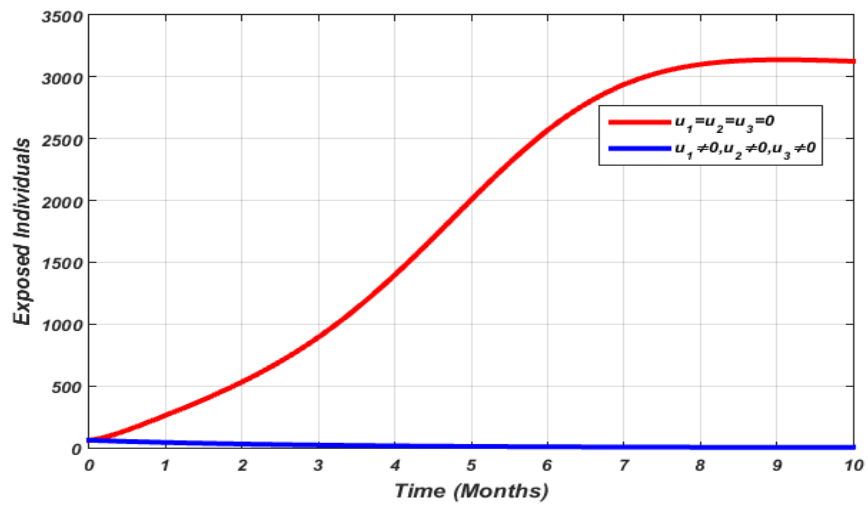


Figure 4.15: Dynamics of Gonorrhea Exposed individuals

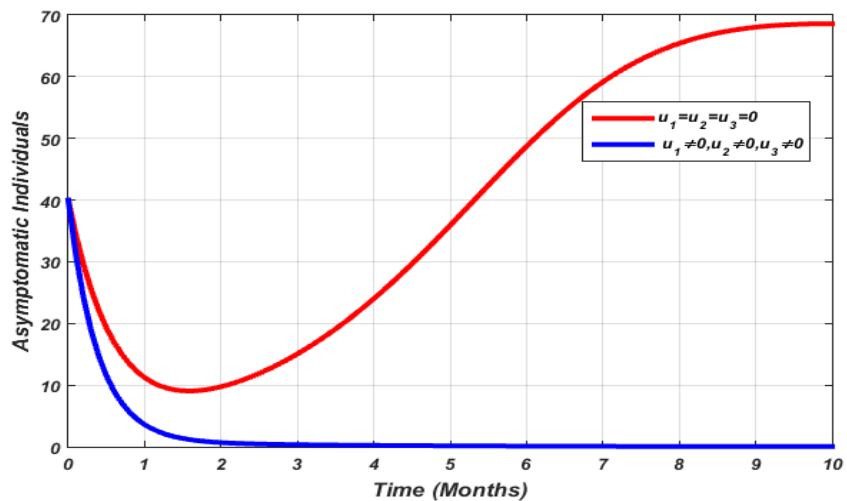


Figure 4.16: Dynamics of Asymptomatic individuals

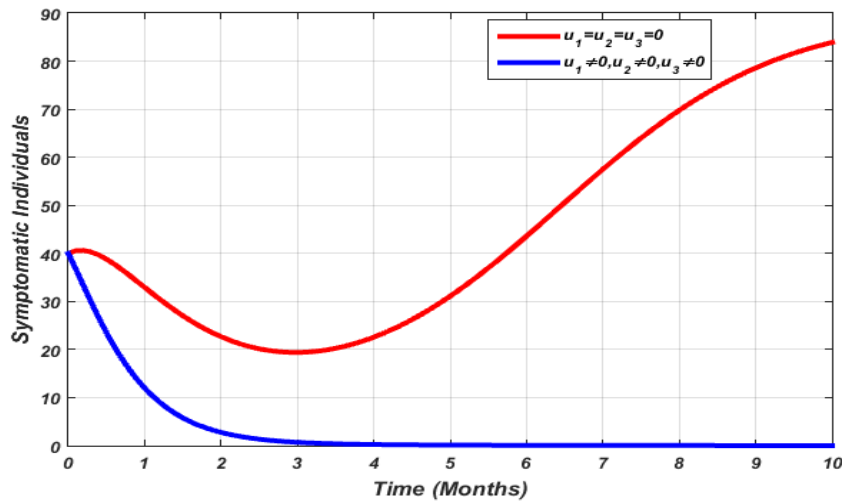


Figure 4.17: Dynamics of Symptomatic individuals

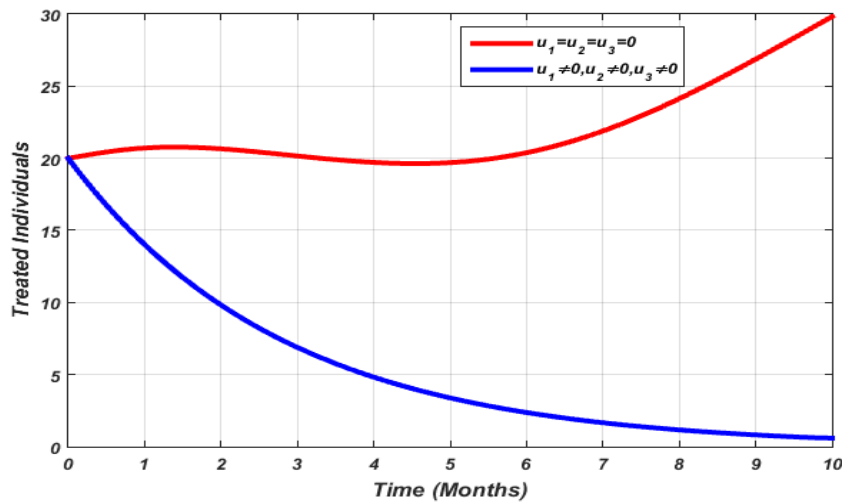


Figure 4.18: Dynamics of Treated individuals

## 4.7 Cost Effective Analysis

To determine the most cost effective strategy we used controls only prevention, only treatment and the combination of prevention and treatment. To achieve this purpose we need to compare the differences between the costs and health outcomes of these interventions. This is done by calculating the incremental cost-effectiveness ratio (ICER) which is generally described as the additional cost per additional health outcome. When comparing two or more competing intervention strategies incrementally, one intervention should be compared with



the next-less effective alternative. The ICER denominator is the differences in health outcomes. It is calculated using the following formula;

$$ICER = \frac{\text{Difference in costs between strategies}}{\text{Difference in health effects between strategies}}.$$

We rank the strategies in increasing order of effectiveness, namely scenario I, scenario II, scenario III and scenario IV based on the model simulation results. The difference between the total infectious individuals without control and the total infectious individuals with control was used to determine the "total number of infections averted" described in the Table 4.2 and 4.3 of cost-effectiveness analysis.

Table 4.4: Control scenarios in order of increasing averted

<b>Scenario</b>	<b>Total infectious averted</b>	<b>Total cost (\$)</b>
Scenario I	1817.3706	500
Scenario II	1820.87	530.25
Scenario III	1941.2884	991.2731
Scenario IV	1960.56	1020.461

Table 4.5: Total number of infection averted and total cost with their ICER

<b>Scenario</b>	<b>Total infectious averted</b>	<b>Total cost (\$)</b>	<b>ICER</b>
Scenario I	1817.3706	500	0.275
Scenario II	1820.87	530.25	8.645
Scenario III	1941.2884	991.2731	3.828
Scenario IV	1960.56	1020.461	1.5145

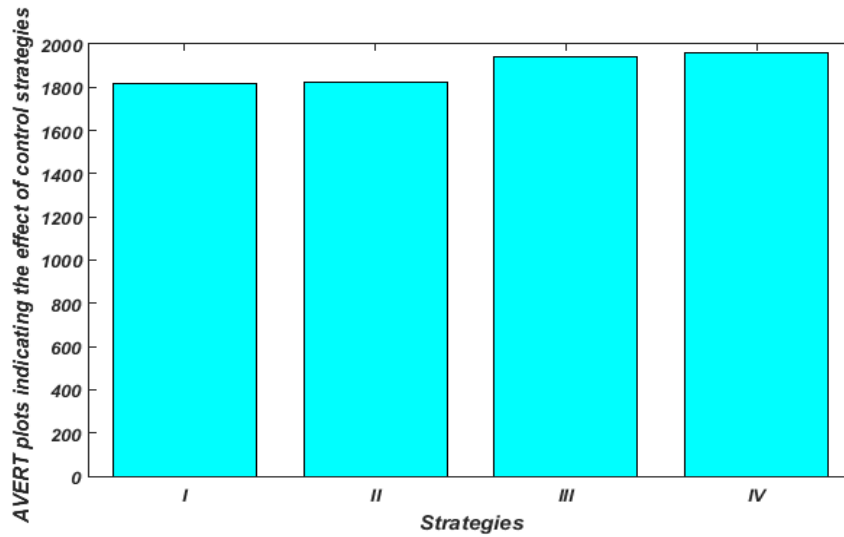


Figure 4.19: Total infectious averted plots indicating the effect of control strategies I, II, III and IV

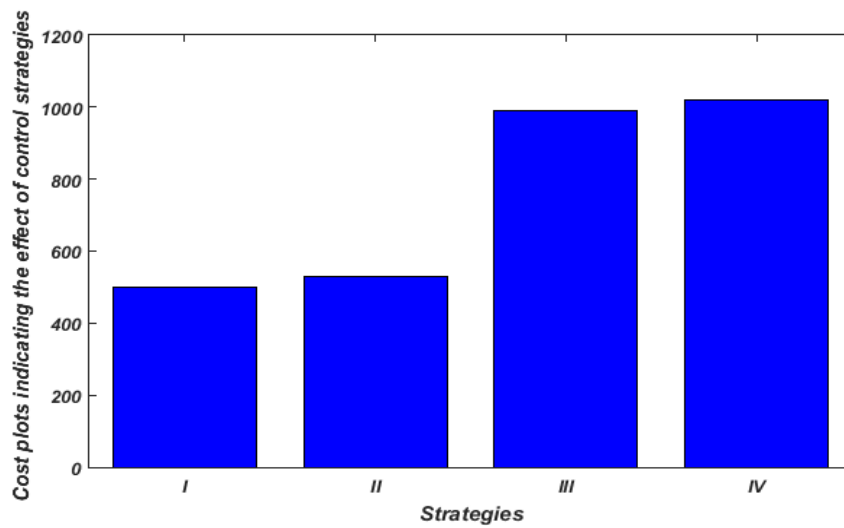


Figure 4.20: The total cost plots indicating the effect of control strategies I, II, III and IV

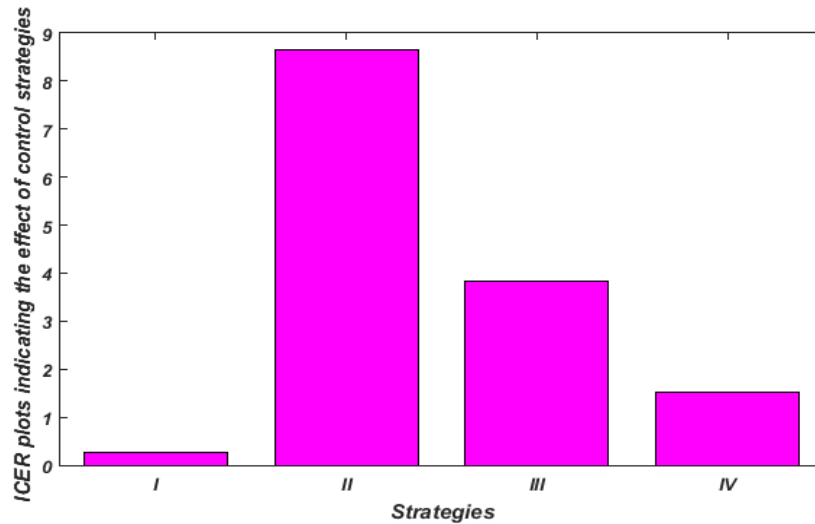


Figure 4.21: Incremental cost effective ratio (ICER) plots indicating the effect of control strategies I, II, III and IV

From the Scenario I and II with their comparison in Table 4.4, we can observe that ICER (I) is less than ICER (II). This implies that Scenario I is dominated by Scenario II. It means that Scenario II is more expensive than Scenario I. Thus, we have deleted II from the comparison Scenarios. Then again re-calculate the ICER for the remaining comparison Scenario I, III and IV as given in Table 4.5.

Table 4.6: Total number of infection averted and total cost with their ICER

Scenario	Total infectious averted	Total cost (\$)	ICER
Scenario I	1817.3706	500	0.275
Scenario III	1941.2884	991.2731	3.9645
Scenario IV	1960.56	1020.461	1.5145

From the Scenario I and III with their comparison in Table 4.5, we can observe that ICER (I) is less than ICER (III). This implies that Scenario I is dominated by Scenario III. It means that Scenario III is more expensive than Scenario I. Thus, we have deleted III from the comparison Scenarios. Then again re-calculate the ICER for the remaining comparison Scenario I, and IV as given in Table 4.6.

Table 4.7: Total number of infection averted and total cost with their ICER

Scenario	Total infectious averted	Total cost (\$)	ICER
Scenario I	1817.3706	500	0.275
Scenario IV	1960.56	1020.461	3.6347

In Table 4.6, there is a comparison between scenario I and IV. From this the ICER (I) is less than ICER (IV). This shows that scenario IV is strongly dominated by scenario I. Based upon the result, we suggest that scenario I(prevention) is the most effective and least cost to reduce Gonorrhea disease from the community. This result agrees with the results obtained in figure 4.18 for the objective functional for the various control strategies.

## CHAPTER 5

### CONCLUSION AND RECOMMENDATIONS

#### 5.1 Conclusion

The dynamics of Gonorrhea were depicted in this thesis through the use of nonlinear differential equations. When initial conditions fall within a given set, the model analysis showed that all systems solutions are positive and bounded. Using the next-generation matrix technique, and the Gonorrhea-free equilibrium's basic reproduction number was determined. The Gonorrhea-free equilibrium is asymptotically stable both locally and globally if the basic reproduction number is less than one. In contrast, the endemic equilibrium is locally and globally asymptotically stable if the basic reproduction number is greater than unity. To determine their impact on the dynamics of Gonorrhea transmission, a sensitivity analysis of the model equation was carried out on the important parameters. The model was also defined by applying optimal control theory, which combines two controls: treating infected individuals and preventing Gonorrhea. To get the prerequisites for the optimal control problem, Pontryagin's maximum principle is presented. In the end, a prevention effort presents the most effective and financially feasible strategy for reducing the prevalence of Gonorrhea from the community, according to the simulation result of the optimal control problem and the cost-effectiveness analysis.

#### 5.2 Future work

The deterministic models we have developed in this thesis have numerous future expansion possibilities. How the thesis's model of Gonorrhea progression is extended to include the susceptible stage of the disease and the onset of clinical symptoms will be interesting to observe. Gradually developing Gonorrhea will be part of the model's expansion. Moreover, we intend to investigate the formulation of a fractional differential equation model and incorporate a drug

resistance compartment into the model.

### **5.3 Recommendations**

In many developing nations, eliminating gonorrhea is a major challenge for health organizations. In order to reduce the incidence of gonorrhea, optimal strategies must be used and appropriately implemented, according to public health policy. As such, this work has the potential to provide a fundamental framework for the long-term establishment of a connection between public health organizations and mathematics. Given the limited resources in the field, our study strongly suggests that optimal control strategies be used to guide public health policymakers in managing gonorrhea.

## REFERENCES

- Adamu, I. I., Usman, S., et al. (2018). Mathematical model for the dynamics of neisseria gonorrhea disease with natural immunity and treatment effects. *J. Math. Res*, 10:151–165.
- Adedayo, O. A., Otaru, M. O., Adekunle, T. S., Ugwu, C. U., Akande, S. A., Muhammed, I., Job, O. S., Musa, I. O., et al. (2023). Mathematical model for determining the influence of treatment and vaccination on measles.
- Adediipo, A. D., Akanni, J. O., and Shangodare, O. M. (2020). Bifurcation and stability analysis of the dynamics of gonorrhea disease in the population. *World Scientific News*, (143):139–154.
- Akinboro, M. K., Mmaduabuchi, J., Beeko, P. K. A., Egwuonwu, O. F., Oluwalade, O. P., Akueme, N. T., Iyioku, B. O., Okobi, O. E., and Oghenetega, E. P. (2023). Epidemiological trends and factors associated with the morbidity rate of gonorrhea: a cdc-wonder database analysis. *Cureus*, 15(8).
- Barbaric, J., Kuchukhidze, G., Seguy, N., Vovc, E., Babovic, M. J. T., Wi, T. E., Low-Beer, D., and Bozicevic, I. (2022). Surveillance and epidemiology of syphilis, gonorrhoea and chlamydia in the non-european union countries of the world health organization european region, 2015 to 2020. *Eurosurveillance*, 27(8):2100197.
- Budkaew, J., Chumworathayi, B., Pientong, C., and Ekalaksananan, T. (2019). Prevalence and factors associated with gonorrhea infection with respect to anatomic distributions among men who have sex with men. *PLoS One*, 14(4):e0211682.
- Chen, X., Chen, S., Li, C., Shi, L., Zhu, Y., and Yao, Y. (2023). Analysis and prediction of the incidence and prevalence trends of gonorrhea in china. *Human Vaccines & Immunotherapeutics*, 19(2):2256907.
- Chidiac, O., AlMukdad, S., Harfouche, M., Harding-Esch, E., and Abu-Raddad, L. J. (2023). Epidemiology of gonorrhea in the world health organization european region, 1949-2021: Systematic review, meta-analyses, and meta-regressions. *Eurosurveillance*.
- Dunbar, M. B.-N. (2023). Transmission matrices used in epidemiologic modelling. *Infectious Disease Modelling*.
- Grad, Y. H., Goldstein, E., Lipsitch, M., and White, P. J. (2016). Improving control of antibiotic-resistant gonorrhea by integrating research agendas across disciplines: key questions arising from mathematical modeling. *The Journal of Infectious Diseases*, 213(6):883–890.
- Hethcote, H. W. (2000). The mathematics of infectious diseases. *SIAM review*, 42(4):599–653.

Kirkcaldy, R. D., Weston, E., Segurado, A. C., and Hughes, G. (2019). Epidemiology of gonorrhoea: a global perspective. *Sexual health*, 16(5):401–411.

Kwasi Adu, I., Nana-Kyere, S., Appiagyei, E., Osman, M. A., Wireko, F. A., and Asamoah, D. J. K. K. Mathematical modelling of ebola with optimal control and cost-effectiveness analysis. *Mathematical Modelling of Ebola with Optimal Control and Cost-Effectiveness Analysis*.

Mishra, N., Grant, R., Patel, M. T., Guntupalli, S., Hamilton, A., Carr, J., McKnight, E., Wise, W., Deroode, D., Jellison, J., et al. (2023). Automating case reporting of chlamydia and gonorrhea to public health authorities in illinois clinics: Implementation and evaluation of findings. *JMIR Public Health and Surveillance*, 9:e38868.

Owonaro, P., Gilbert, T., and Owonaro, A. (2023). Evaluating knowledge, preventive measures, and treatment awareness regarding gonorrhea among adolescents and adults in sagbama, bayelsa state. *J Basic Appl Pharm Sci*, 1(1):103.

Rönn, M. M., Testa, C., Tuite, A. R., Chesson, H. W., Gift, T. L., Schumacher, C., Williford, S. L., Zhu, L., Bellerose, M., Earnest, R., et al. (2020). The potential population-level impact of different gonorrhea screening strategies in baltimore and san francisco: An exploratory mathematical modeling analysis. *Sexually transmitted diseases*, 47(3):143–150.

Tuite, A. R., Rönn, M. M., Wolf, E. E., Gift, T. L., Chesson, H. W., Berruti, A., Galer, K., Menzies, N. A., Hsu, K., and Salomon, J. A. (2018). Estimated impact of screening on gonorrhea epidemiology in the united states: insights from a mathematical model. *Sexually transmitted diseases*, 45(11):713–722.



## APPENDIX

### MATHEMATICAL PRELIMINARIES

This chapter introduces some basic mathematical theories and methodologies that will be used in this dissertation.

Mathematical modeling can be defined as the use of mathematical signs, symbols and equations to represent a real-life situation in order to make it (real-life problem) easier to understand, solve, and infer a reasonable the conclusion from the solution of the problem. Mathematical models of infectious diseases have been used as a tool to study and understand the dynamics of diseases, make predictions about future outbreaks of the disease, and to suggest intervention measures that have to be implemented in order to control the disease. Mathematical models can be classified in various ways:

- Static versus dynamic models. Static models are time-independent while dynamic models are time-dependent.
- Continuous versus discrete time models. Continuous time models are models in which the independent variable is continuous, e.g,  $\frac{dx}{dt} = ax$ , while discrete time models are models used for life phenomena in which the independent variables are observed at discrete intervals, e.g,  $x_{t+1} = ax_t$ .
- Stochastic versus deterministic models. Stochastic models are models in which probabilistic concepts are used and distributions of possible behaviours are present, while deterministic models are models in which the behaviour of a population is determined completely by its history and by the rules which describe the model.
- Homogeneous versus detailed models. A detailed model involves the spatial or physiological distribution of each state variable specification while homogeneous models regard state variables as having the same spatial or

physiological distribution.

The tools used are ordinary differential equations (ODE), partial differential equations (PDE), delay differential Equation (DDE), Stochastic differential equations (SDE), integrated equations, Markov chains, game theory, etc.

## Differential Equations

Ordinary differential equations (ODEs) are equations that involve the derivatives of one or more dependent variables with respect to an independent variable. In compartmental disease models, the independent variable is time  $t$ , the rate of transfer between compartments are expressed mathematically by the derivatives of the compartments with respect to time, with an underlying assumption that the number of individuals in a compartment is a differentiable function with respect to time. The formulation of models as ordinary differential equations follows the assumption that the behaviour of a population can be determined completely by its history and the rules that govern the models.

A first order ordinary differential equation is defined as

$$\frac{dx(t)}{dt} = f(t, x(t)) \quad (5.1)$$

where  $t \in \mathbb{R}$  is an independent variable,  $x(t)$  is a dependent variable (unknown function) and  $f : \mathbb{R}^{\times} \rightarrow \mathbb{R}^{\times}$  is a vector field. Equation (5.1) is known as a nonautonomous ordinary differential equation.

When no ambiguity arises,  $\frac{dx(t)}{dt}$  is often written as  $\bar{x}$  so that (5.1) is written as

$$x' = f(t, x) \quad (5.2)$$

where the dependence of  $x(t)$  on  $t$  is also omitted unless this gives rise to ambiguities. If  $f$  does not depend explicitly on time, then (5.2) is called autonomous and takes the form

$$x' = f(x) \quad (5.3)$$

and the general solution is

$$x(t) = \int_{t_0}^t f(\tau) d\tau \quad (5.4)$$

For  $f_i : \mathbb{R}^\times \longrightarrow \mathbb{R}^\times$  and  $x_i \in \mathbb{R}^\times$ , a system of ordinary differential equations is defined when  $n > 1$ ; otherwise, for  $n = 1$  the equation is scalar.

In applications, a particular solution, which requires initial conditions is usually sought for rather than a general solution.

**Definition 1: (Initial Value Problem).** A first order ODE together with an initial condition

$$\begin{cases} x' = f(t, x) \\ x(t_0) = x_0 \end{cases} \quad (5.5)$$

is called an initial value problem. The initial condition  $x(t_0) = x_0$  represents the position of the objects at some initial time  $t_0$ . Solutions of a system of ordinary differential equations are sought for within a given interval (say, I) that contains  $t_0$ , so that the solution curves passes through the point  $(t_0, x(t_0))$ .

A solution of an initial value problem is a differentiable function  $x(t)$  such that

1.  $x' = f(t, x(t))$  for all  $t$  in an interval containing  $t_0$  where  $x(t)$  is defined, and
2.  $x(t_0) = x_0$ .

Thus, the solution can be expressed in integral form as

$$x(t) = x_0 + \int_{t_0}^t f(\tau, x(\tau)) d\tau \quad (5.6)$$

The system of ODEs to be analysed in this dissertation is autonomous and takes the form  $\bar{x} = f(x)$  with  $x \in \mathbb{R}_+^\times$  and  $f : \mathbb{R}_+^\times \longrightarrow \mathbb{R}_+^\times$ .

## Existence and Uniqueness of Solutions

In this subsection, we state some basic theorems describing general properties of solution of differential equations.

**Definition 2: (Well-posedness).** System (5.5) is well-posed if solutions exist,

are unique, and for systems describing populations, remain bounded and non-negative for all nonnegative initial conditions.

**Theorem (Cauchy- Lipschitz).** Consider the differential equation (5.5) with  $x \in \mathbb{R}^n$ , and suppose that  $f \in C'$ . Then there exists a unique solution of (5.5) such that  $x(t_0) = x_0$ , where  $t_0 \in \mathbb{R}$  and  $x_0 \in \mathbb{R}^n$  defined on the largest interval  $t_0 \in I$  on which  $f \in C'$ .

**Theorem** Let  $f$  and its partial derivatives  $(\partial f_i / \partial x_j)$  in (5.3) be continuous in  $\mathbb{R}^n$  and let  $x_0 \in \mathbb{R}^n$  and  $t_0 \in \mathbb{R}$ . Then there is an interval  $|t - t_0| < h$  in which there exists a unique solution  $x(t) = \phi(t)$  of the system that also satisfies the initial conditions.

**Definition 3: (Flow).** Consider System (5.5). The flow  $\phi(t, x_0)$  of (5.5) represents the solution of (5.5) over time given an initial condition, provided that the solutions to the differential equation exist and are unique.

**Definition 4:** An equilibrium solution of (5.3) is a solution  $\bar{x} \in \mathbb{R}^n$  such that  $f(\bar{x}) = 0$ , i.e., a solution which does not change with time. The term "equilibrium point" can be used interchangeably with the following: "fixed point", "stationary point", "singularity point", "critical point" or "steady state".

**Definition 5: (Stable and unstable equilibrium point).** Let  $\phi(t)$  be the flow of (5.3), assumed to be defined for all  $t \in \mathbb{R}$ . An equilibrium solution  $\bar{x}$  of (5.3) is said to be locally stable if for all  $\epsilon > 0$ , there exists  $\delta = \delta(\epsilon) > 0$  such that for all  $x \in N_\delta(\bar{x})$  and  $t \geq 0$ , there holds

$$\phi_t(x) \in N_\epsilon(\bar{x}).$$

The equilibrium point is unstable if it is not stable.

**Definition 6: (Asymptotically stable equilibrium point)** Let  $\phi(t)$  be the flow of (5.3) is (locally) asymptotically stable if there exists  $\delta > 0$  such that for all  $x \in N_\delta(\bar{x})$  and  $t \geq 0$ , there holds

$$\lim_{t \rightarrow \infty} \phi(t) = \bar{x}$$

## Linearization

The behaviour of system (5.3) near a hyperbolic equilibrium point  $\bar{x}$  is linked to the behaviour of the linearized system

$$x' = Df(\bar{x})(x - \bar{x}) \quad (5.7)$$

about the same equilibrium, where

$$J(\bar{x}) = Df(\bar{x}) = \begin{bmatrix} \frac{\partial f_1}{\partial x_1}(\bar{x}) & \frac{\partial f_1}{\partial x_2}(\bar{x}) & \cdots & \frac{\partial f_1}{\partial x_{n-1}}(\bar{x}) & \frac{\partial f_1}{\partial x_n}(\bar{x}) \\ \frac{\partial f_2}{\partial x_1}(\bar{x}) & \frac{\partial f_2}{\partial x_2}(\bar{x}) & \cdots & \frac{\partial f_2}{\partial x_{n-1}}(\bar{x}) & \frac{\partial f_2}{\partial x_n}(\bar{x}) \\ \vdots & & \ddots & & \\ \frac{\partial f_{n-1}}{\partial x_1}(\bar{x}) & \frac{\partial f_{n-1}}{\partial x_2}(\bar{x}) & \cdots & \frac{\partial f_{n-1}}{\partial x_{n-1}}(\bar{x}) & \frac{\partial f_{n-1}}{\partial x_n}(\bar{x}) \\ \frac{\partial f_n}{\partial x_1}(\bar{x}) & \frac{\partial f_n}{\partial x_2}(\bar{x}) & \cdots & \frac{\partial f_n}{\partial x_{n-1}}(\bar{x}) & \frac{\partial f_n}{\partial x_n}(\bar{x}) \end{bmatrix} \quad (5.8)$$

matrix  $Df(\bar{x})$  is the Jacobian matrix of (5.3) evaluated at the equilibrium point  $\bar{x}$ .

**Definition 7: (Hyperbolic fixed point)** Let  $x = \bar{x}$  be a fixed point of  $x' = f(x)$ ,  $x \in \mathbb{R}^\kappa$ . Then  $\bar{x}$  is called a hyperbolic fixed point if none of the eigenvalues of  $Df(\bar{x})$  have zero real part. A hyperbolic fixed point is called a saddle if some, but not all, of the eigenvalues have positive real parts. If all eigenvalues have negative real part, then the hyperbolic fixed point is called a stable node or sink and if all of the eigenvalues have positive real part, then the hyperbolic fixed point is called an unstable node or source.

**Definition 8:** A non hyperbolic fixed point is a fixed point having the real part of some of the eigenvalues associated to the linearized system equal to zero, that is, these eigenvalues are purely imaginary. (Such fixed point is said to be a center if the system is linear.)

**Theorem (Hartman and Grobman)** Assume that  $\bar{x} \in \mathbb{R}^\kappa$  is a hyperbolic equilibrium (all eigenvalues of the Jacobian matrix evaluated at  $\bar{x}$  have nonzero real part). Then, in a small neighbourhood of  $\bar{x}$ , the nonlinear system behaves in a

similar manner as the linearized system.

## Stability

The Hartman-Grobman theorem tells us that, in a neighbourhood of a hyperbolic equilibrium point, we can get a qualitative idea of the behaviour of solutions of the nonlinear system by studying its corresponding linear system. Thus, we can determine whether solution trajectories approach or move away from the equilibrium point over time, that is, we can determine the stability of equilibria in System (5.3) without finding explicit solutions.

**Theorem** Let  $\bar{x}$  be an equilibrium point of the autonomous system (5.3), where  $f \in C'$  in a neighborhood of  $\bar{x}$ .

1. If all the eigenvalues of  $J = Df(\bar{x})$  have negative real part, then  $\bar{x}$  is a locally asymptotically stable equilibrium point.
2. If  $J = Df(\bar{x})$  has at least one eigenvalue with positive real part, then  $\bar{x}$  is an unstable equilibrium point.

## Lyapunov functions and LaSalle's invariance Principle

Lyapunov functions and LaSalle's Invariance Principle are some of the methods often used to establish the global stability property of an equilibrium point.

**Definition 9:** A point  $x_0 \in \mathbb{R}^n$  is called an  $\omega$ -limit point of  $x_0 \in \mathbb{R}^n$  and denoted by  $\omega(x)$ , if there exists a sequence  $t_i$  such that

$$\phi(t_i, x) \rightarrow x_0 \text{ as } t_i \rightarrow \infty.$$

**Definition 10:** A point  $x_0 \in \mathbb{R}^n$  is called an  $\alpha$ -limit point of  $x_0 \in \mathbb{R}^n$  and denoted by  $\alpha(x)$ , if there exists a sequence  $t_i$  such that

$$\phi(t_i, x) \rightarrow x_0 \text{ as } t_i \rightarrow -\infty.$$

**Definition 11.** The set of all  $\omega$ -limit points of a flow is called the  $\omega$ -limit set. Similarly, the set of all  $\alpha$ -limit points of a flow is called the  $\alpha$ -limit set.

**Definition 12.** Let  $S \subseteq \mathbb{R}^n$  be a set. Then  $S$  is said to be invariant under the flow generated by (5.3) if for any  $x_0 \in S$ , we have  $x(t, x_0) \in S$  for all  $t \in \mathbb{R}$ .

If the region is restricted to positive times (*i.e.*,  $t \geq 0$ ), then  $S$  is said to be a positively-invariant set (this implies that solutions in the positive invariant set remain there for all time). The set is negatively-invariant if solutions remain there when we go backward in time.

**Definition 13:** A function  $V : \mathbb{R}^n \rightarrow \mathbb{R}$  is said to be a positive definite function if:

- $V(x) > 0$  for all  $x \neq 0$
- $V(x) = 0$  if and only if  $x = 0$

**Theorem (Lyapunov):** Consider the autonomous system defined by (5.3). Let  $\bar{x}$  be a fixed point of (5.3) and let  $V : U \rightarrow \mathbb{R}$  be a  $C^1$  function defined on some neighbourhood  $U$  of  $\bar{x}$  such that

1.  $V(\bar{x}) = 0$  and  $V(x) > 0$  if  $x \neq \bar{x}$ ,
2.  $\frac{dV(x)}{dx} \leq 0$  in  $U - \bar{x}$ .

Then  $\bar{x}$  is stable. Moreover, if

3.  $\frac{dV(x)}{dx} < 0$  in  $U - \bar{x}$ .

Then  $\bar{x}$  is asymptotically stable. Any function  $V$  that satisfies the conditions from Theorem (Lyapunov) is said to be a Lyapunov function.

**Theorem (LaSalle's Invariance Principle).** Consider system (5.3). Let

$$S = \{x \in U \mid \frac{dV(x)}{dt} = 0\} \quad (5.9)$$

and let  $M$  be the largest invariant set of (5.3) in  $S$ . If  $V$  is a Lyapunov function on  $U$  and  $\gamma^+(x_0)$  is a bounded orbit of (5.3) which lies in  $S$ , then the  $\omega$ -limit set of  $\gamma^+(x_0)$  belongs to  $M$  (that is,  $x(t, x_0) \rightarrow M$  as  $t \rightarrow \infty$ .)

- $\gamma^+(x_0)$ : part of solution trajectory where  $t \geq t_0$  (Positive orbit).

- $\gamma^-(x_0)$ : part of solution trajectory where  $t \leq t_0$  (negative orbit).

**Corollary:** If  $V(x) \rightarrow \infty$  as  $|x| \rightarrow \infty$  and  $\frac{dV}{dt} < 0$  on  $\mathbb{R}$ , then every solution of (5.3) is bounded and approaches the largest if  $M = 0$ , then the solution  $x = 0$  is globally asymptotically stable.

Subsequently  $V' = \frac{dV}{dt}$ .

## Routh-Hurwitz Criteria

**Theorem (Routh Hurwitz Stability Criteria)** Consider the  $n^{th}$  degree polynomial with real constant coefficients  $P(\lambda) = \lambda^n + a_1\lambda^{(n-1)} + \dots + a_{(n-1)}\lambda + a_n$ . Define  $n$  Hurwitz matrices using the coefficients  $a_i$  of the characteristic polynomial:

$$\begin{aligned}
 H_1 &= \begin{bmatrix} a_1 \end{bmatrix} \\
 H_2 &= \begin{bmatrix} a_1 & 1 \\ a_3 & a_2 \end{bmatrix} \\
 H_3 &= \begin{bmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{bmatrix} \\
 H_4 &= \begin{bmatrix} a_1 & 1 & 0 & 0 & \dots & 0 \\ a_3 & a_2 & a_1 & 1 & \dots & 0 \\ a_5 & a_4 & a_3 & a_2 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \dots & \vdots \\ 0 & 0 & 0 & 0 & \dots & a_n \end{bmatrix}
 \end{aligned}$$

Here  $a_j = 0$  if  $j > n$ . All roots of the polynomial  $P(\lambda)$  are negative or have negative real part if and only if the determinants of all Hurwitz matrices are positive i.e.  $\text{Det}H_j > 0, \forall j = 1, 2, \dots$ , **Theorem (Derrick and Groosman, 1976)** Let  $D$  denote the region  $|t - t_0| \leq a, \|x - x_0\| \leq 1, x = (x_1, x_2, \dots, x_n), x_0 = (x_{10}, x_{20}, \dots, x_{n0})$  and suppose that  $f(t, x)$  satisfies the Lipschitz condition  $\|f(t, x_1) - f(t, x_2)\| \leq k\|x_1 - x_2\|$ . Whenever the pairs  $(t, x_1)$  and  $(t, x_2)$  belong to  $D$  where  $k$  is positive constant then, there is a constant  $\delta \geq 0$  such that there exist a unique



n	Coefficient signs	Additional Conditions
1	$a_1 > 0, a_2 > 0$	
2	$a_1 > 0, a_2 > 0, a_3 > 0$	$a_1 a_2 > a_3$
3	$a_1 > 0, a_2 > 0, a_3 > 0, a_4 > 0$	$a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$
4	$a_1 > 0, a_2 > 0, a_3 > 0, a_4 > 0, a_5 > 0$	$a_1 a_2 a_3 > a_3^2 + a_1^2 a_4,$ $(a_1 a_4 - a_5)(a_1 a_2 a_3 - a_3^2 - a_1^2 a_4) > a_5(a_1 a_2 - a_3)^2 +$ $a_1 a_5^2.$

Table 5.1: Routh-Hurwitz Criteria

continuous vector solution of  $x(t)$  of the system in the interval  $|t - t_0| \leq \delta$ . It is important to note that the condition is satisfied by the requirement that  $\frac{(\partial f_i)}{(\partial x_i)}$ ,  $\forall i, j = 1, 2, \dots$  be continuous and bounded in D.

## Basic Reproduction Number $\mathfrak{R}_0$

The concept of the basic reproduction number is one of the central topics in mathematical Modelling of infectious diseases due to its meaning and extreme importance. Hardly can one find a publication on a mathematical model without mention of this number. It is also called the basic reproduction ratio among other variant forms. It is very important in disease Modelling because it gives an indication regarding the future state of the infection. It tells us whether or not the disease will persist or will be eradicated in due course.

**Definition 14** The basic reproduction number denoted by  $\mathfrak{R}_0$  and is defined as the expected number of people getting secondary infection among the whole susceptible population. This number determines the potential for the spread of disease within a population. When  $\mathfrak{R}_0$  each infected individual produces on average less than one new infected individual so that the disease is expected to die out. On the other hand if  $\mathfrak{R}_0$  then each individual produces more than one new infected individual so that the disease is expected to continue spreading in the population. This means that the threshold quantity for eradicating the disease is to reduce the value of  $\mathfrak{R}_0$  to less than one.

The basic reproductive number  $\mathfrak{R}_0$  can be determined using the next generation matrix. In this method,  $\mathfrak{R}_0$  is defined as the largest eigenvalue of the next

generation matrix. The formulation of this matrix involves classification of all compartments of the model into two classes: infected and non-infected. That is, the basic reproduction number cannot be determined from the structure of the mathematical model alone but depends on the definition of infected and uninfected compartments.

## Description of the Method of Driessche and Watmough

Consider a heterogeneous population whose individuals are distinguishable by age, behavior, spatial position, and/or stage of disease, but can be grouped into  $n$  homogeneous compartments. A general epidemic model for such a population is developed in this section. Let  $x = (x_1, x_2, \dots, x_n)^t$ , with each  $x_i \geq 0$ , the number of individuals in each bucket. For clarity, we order the compartments so that the first compartments of  $M$  correspond to the infected people. The distinction between infected and uninfected compartments must be determined by the epidemiological interpretation of the Model and can not be deduced from the structure alone equations, as we will discuss below. The basic reproduction number cannot be determined from the structure of the mathematical model alone, but depends on the definition of infected and uninfected compartments. We define  $X_s$  to be all states under discussion. That is  $X_s = \{x \geq 0 : x_i = 0, i = 1, \dots, m\}$ .

In order to compute  $\mathcal{R}_0$ , it is important to distinguish new infections from all other changes in population. Let  $f_i(x)$  be the rate of appearance of new infections in compartment  $i$ ,  $V_i^+(x)$  and the transfer rate of individuals into compartment  $i$  by all other means, and  $V_i^-(x)$  be the rate of transfer of individuals out of compartment  $i$ . It is assumed that each function is continuously differentiable at least twice in each variable. The disease transmission model consists of nonnegative initial conditions together with the following system of equations:

$$\dot{x} = f_i(x) - V_i(x), i = 1, \dots, n,$$

where  $V_i = V_i^- - V_i^+$  and the functions satisfy assumptions  $(A_1) - (A_5)$  described below. Since each function represents a direct transfer of individuals, they are not

negative. Thus,

A<sub>1</sub>. If  $x \geq 0$  then  $f_i, V_i^+, V_i^- \geq 0, \forall i = 1, \dots, n$ .

A<sub>2</sub>. If  $x_i = 0$  then  $V_i = 0$ . In particular if  $x \in X_s$  then  $V_i = 0 \forall i = 1, \dots, m$

A<sub>3</sub>.  $f_i = 0$  if  $i > m$ .

A<sub>4</sub>. If  $x \in X_s$  then  $f_i(x) = 0$  and  $V_i^+ = 0, \forall i = 1, \dots, m$

A<sub>5</sub>. If  $f(x)$  is set to zero, then all *dfeigenvalue*( $x_0$ ) have genuine actual parts.

Then the Jacobian matrix  $Df(x_0)$  can be partitioned as given in the following lemma.

**Lemma 1.** If  $x_0$  is a DFE of (5.3) and  $f_i(x)$  satisfies (A<sub>1</sub>) – (A<sub>5</sub>), then the derivatives  $Df(x_0)$  and  $DV(x_0)$  are partitioned as follows

$$DF(X_0) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix}, DV(X_0) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix}$$

where  $F$  and  $V$  are  $m \times m$  matrices defined by

$$F = [\frac{\partial f_i}{\partial x_i}(x_0)] \text{ and } V = [\frac{\partial V_i}{\partial x_i}(x_0)] \text{ with } i \leq m, j \leq m.$$

Further,  $F$  is non-negative,  $V$  is a non-singular M-matrix and all eigenvalues of  $J_4$  have positive real parts. The following theorem then is used to compute the threshold parameter  $\mathfrak{R}_0$ .

**Theorem .** Consider the disease transmission model given by (5.3) with  $f(x)$  satisfying conditions (A<sub>1</sub>) – (A<sub>5</sub>). If  $x_0$  is a DFE of the model, then  $x_0$  is locally asymptotically stable if  $\mathfrak{R}_0 < 1$ , where  $\mathfrak{R}_0$  is defined by

$$\mathfrak{R}_0 = \rho(FV^{-1})$$

where  $\rho(A)$  denotes the spectral radius of  $A$ .

Thus, the threshold quantity  $\mathfrak{R}_0$  plays a major role in determining the qualitative behavior of epidemic models. We note that at  $\mathfrak{R}_0 = 1$  the disease-free equilibrium and endemic equilibrium exchange stability. This phenomenon of change of stability is known as forwarding bifurcation. When forward bifurcation occurs, then  $\mathfrak{R}_0 \leq 1$  is a necessary and sufficient condition for disease elimination.

Another important concept related to the condition  $\mathfrak{R}_0 \leq 1$  is that of backward bifurcation. This occurs when a stable endemic equilibrium co-exists with a stable disease-free equilibrium. When this happens, then  $\mathfrak{R}_0 \leq 1$  only remains a necessary but not sufficient condition for disease elimination and hence disease eradication can not just be achieved by making  $\mathfrak{R}_0$

## Optimal Control Theory

The mathematical theory used to obtain optimal control strategies that vary over time are called the theory of optimal control. The simplest optimal control problem is an optimization problem that seeks to maximize/minimize an objective function subject to a dynamical system in the form of equation together with some initial or boundary conditions. Formally, the simplest optimal control problem is one of the form

$$\begin{aligned} & \text{Maximize } \int_{t_0}^{t_f} g(t, X, u) dt \\ & \text{Subject to } \frac{dx}{dt} = f(t, x, u), x(t_0) = x_0, x(t_f) \text{ free} \\ & \text{and } u(t) \in \mathcal{U}, \forall t \in [0, t_f] \end{aligned}$$

## Pontryagin Maximum Principle

Pontryagin's maximum principle, often referred to as the maximum principle, is the primary tool used to solve optimal control problems. It provides first-order necessary conditions for optimal solution of the problem. The principle provides direction as to how the control  $u$ , state variable  $x$  and a third variable known as co-state or adjoint variable  $\lambda$  should change overtime through equations of motions for  $x$  and  $\lambda$ . The Pontryagin's maximum principle is given in the following theorem.

**Theorem** Let  $u(t)$  be a time optimal control and  $X(t)$  be the corresponding response of the system. Then there exists a function  $\lambda(t) : [0, t_f] \rightarrow R^n$ , such that:

$$\begin{aligned} \dot{x} &= \frac{\partial H}{\partial x}(x, \lambda, u), x(t_0 = x_0) \text{ (State Equation)} \\ \dot{\lambda} &= -\frac{\partial H}{\partial \lambda}(x, \lambda, u) \text{ (Co-state Equation)} \end{aligned}$$

$$\lambda(t_f) = 0 \text{ (Transversality Condition)}$$

$$H(x, \lambda, u) = \max_{u \in A} H(x, \lambda, u) \left\{ \text{or } \frac{\partial H}{\partial u} = 0 \right\} \quad (5.10)$$

Where  $H = g(t, x, u) + \lambda(t)f(t, x, u)$  is called the Hamiltonian of the optimal control problem. Equation (5.10) is given in two forms because, when the Hamiltonian is differentiable with respect to  $u$ , the condition  $\frac{\partial H}{\partial u} = 0$  can often be used to replace  $H(x^*, \lambda^*, u^*) = \max_{u \in A} H(x, \lambda, u)$ .

## Sensitivity Analysis

Sensitivity analysis is commonly used to determine the robustness of model predictions parameter values a because there are usually errors in data collection and assumed parameter values. It is used to discover parameters that have a high impact on  $R_0$  and should be targeted by intervention strategies. More precisely, sensitivity indices allow measuring the relative change in a variable when the parameter changes. If the result is negative, then the relationship between the parameters and  $R_0$  is inversely proportional. In this case, we will take the sensitivity index module so that we can deduce the dimensions of the effect to change this parameter. A positive sensitivity index, on the other hand, signifies an increase in the value of a parameter.

For that, we use the normalized forward sensitivity index of a variable, with Compared to a specific parameter, which is defined as the ratio between the relative changes of the variable for the relative variation of the parameter. If this variable is differentiable with respect to the parameter, then the sensitivity index is defined by the partial derivatives, as follows:

**Definition 15** The normalized forward sensitivity index of  $R_0$ , which is differentiable with respect to a given parameter  $p$ , is defined by:

$$\Upsilon_p^{R_0} = \frac{\partial R_0}{\partial p} \cdot \frac{p}{R_0} \quad (5.11)$$