DYNAMICS OF CO-INFECTIOUS CHILDHOOD RESPIRATORY DISEASES: PERTUSSIS AND PNEUMONIA

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by

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Indeed, no man is an island on his own.

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I_p	Pneumonia infected population
I_{wp}	Pertussis-Pneumonia co-infected population
M	Maternally derived immunity population
R_w	Pertussis recovered population
R_p	Pneumonia recovered population
R_{wp}	Pertussis-Pneumonia recovered population
S	Susceptible population
Λ	Maternally immunized population
Π	Per capita birth rate
$\Lambda\Pi$	Total proportion of immunized population
$(1-\Lambda)\Pi$	Non-immunized population
α	Rate of vaccine efficiency
β_w	Pertussis transmission rate
β_p	Pneumonia transmission rate
c_w	Contact rate with pertussis infected individual
c_p	Contact rate with pneumonia infected individual
δ_w	Progression rate of pertussis population
δ_p	Progression rate of pneumonia population
δ_{wp}	Progression rate of pertussis-pneumonia co-infectious population
E^e	Endemicity in the population

E^f	Absence of infectivity in the population
μ	Natural mortality rate
σ_w	Death caused by pertussis
σ_p	Death caused by pneumonia
γ	Recovery rate of co-infected
γ_w	Recovery rate of pertussis only
γ_p	Recovery rate of pneumonia only
$\gamma\eta_w$	Probability of pertussis recovery
$\gamma\eta_p(1-\eta_w)$	Probability of pneumonia recovery
$\gamma(1-\eta_w)(1-\eta_p)$	Probability of co-infected recovery
θ_1	Prevention efforts (isolation and proper hygiene
θ_2	Vaccination of susceptible against pertussis
θ_3	Vaccination of susceptible against pneumonia
θ_4	Treatment effort of pertussis
θ_5	Treatment effort of pneumonia

LIST OF ABBREVIATIONS

Ac-Hly	Adenylate cyclase-haemolysis
aPV	Acellular pertussis vaccine
CEE	Co-infection endemic equilibrium
CFE	Co-infection free equilibrium
COPD	Chronic obstructive pulmonary disease
DDE	Delay differential equation
DTaP	Diphtheria-tetanus-acellular-cell-pertussis
DTwP	Diphtheria-tetanus-whole-cell-pertussis
FHA	Filamentous haemagglutinin
Fim	Fimbrial proteins
IgG	Immunoglobulin G
LPS	lipopolysaccharide
ODE	Ordinary differential equation
PDE	Partial differential equation
PEE	Pertussis endemic equilibrium
PIFE	Pertussis infection-free equilibrium
PMP	Pontraygins Maximum Principle
PRN	Pertactin
PT	Pertussis toxin
MSEIR	Maternally derived- susceptible-exposed-infected-recovered
MSIR	Maternally derived- susceptible-infected-recovered
SIR	Susceptible-infected-recovered
TCT	Tracheal cytotoxin

DINAMIK JANGKITAN RESPIRATORI BERSAMA KANAK-KANAK: BATUK KOKOL DAN RADANG PARU PARU

ABSTRAK

Pertusis atau batuk kokol ialah penyakit pernafasan yang dapat dicegah oleh vaksin yang menyerang manusia daripada semua peringkat umur, namun terdapat kes-kes kebangkitan semula yang dilaporkan. Di peringkat global, penyakit ini sangat berjangkit dan memberi kesan buruk kepada bayi. Kesan batuk kokol bertambah buruk dengan adanya jangkitan virus seperti radang paru-paru. Oleh itu, pendekatan pemodelan matematik sangat mustahak untuk mengkaji tingkah laku penyakit ini dan seterusnya mencadangkan strategi kawalan. Dapat dilihat juga, kekurangan kajian dan literatur model matematik mengenai dinamik jangkitan pertusis dan radang paru paru telah memberi motivasi dalam kajian ini. Oleh itu, kajian ini bertujuan untuk mendapatkan persamaan model menggunakan sistem persamaan terbitan biasa tak linear untuk memahani dinamik penularan dan kawalan penyakit ini pada populasi bayi. Model ini seterusnya akan digunakan untuk menilai strategi intervensi untuk pengendalian penyakit. Model pertama yang dibangunkan adalah model umum yang menggambarkan dinamik penularan pertusis yang menggabungkan ruang imuniti berasal daripada ibu. Tingkah laku dinamik model asas dianalisis secara analitik dan berangka. Simulasi berangka akan dijalankan menggunakan perisian Mathematica, Maple, dan MATLAB. Nombor pembiakan asas bagi model yang dibangunkan seterusnya diperoleh dan tingkah lakunya juga dianalisis dengan pelbagai parameter. Keputusan berangka, ianya menunjukkan bahawa apabila parameter memalap meningkat, frekuensi apabila populasi mencapai kestabilan menjadi berbeza-beza. Walau bagaimanapun, populasi yang dijangkiti tidak pupus walaupun pada

keseimbangan. Sebagai tambahan, model ini juga ditambah baik untuk memasukkan pelbagai strategi pengendalian untuk memberikan penyelesaian bagi kebangkitan penyakit ini. Hasil dapatan kajian menunjukkan bahawa strategi yang menggabungkan pencegahan, vaksinasi, dan rawatan dalam memerangi penyebaran penyakit lebih efektif untuk memerangi penularan penyakit. Model kedua seterusnya mempertimbangkan dinamik penularan jangkitan bersama, iaitu gabungan batuk kokol dan radang paru-paru serta mengambil kira kekebalan sementara bagi bayi yang dijangkiti. Model kedua ini juga dianalisis secara kualitatif dan berangka serta ditambah baik dengan memasukkan lima strategi kawalan. Skema kawalan optimum akan diterapkan bagi penentuan keadaan yang diperlukan untuk kawalan penyakit atau pembasmian optimum. Analisis kepekaan yang dijalankan juga akan menunjukkan parameter model yang paling sensitif terhadap strategi penularan serta kawalan penyakit yang diperlukan. Hasil dapatan kajian ini menunjukkan bahawa, aspek pencegahan (pengasingan dan kebersihan), vaksinasi beserta beberapa kawalan tertentu dapat mengekang penularan penyakit batuk kokol dan radang paru-paru dalam kalangan masyarakat khususnya kalangan bayi. Hal ini penting kerana jika penyakit tidak dikawal, ia akan memberi kesan kepada penularan jangkitan lain serta memberi beban kepada perkhidmatan kesihatan sedia ada. Kajian ini seterusnya dapat memberi input untuk menambah baik polisi kesihatan sedia ada dalam memerangi penyakit ini dan menjadikan masyarakat kita bebas daripada wabak batuk kokol serta radang paru-paru.

DYNAMICS OF CO-INFECTIOUS CHILDHOOD RESPIRATORY DISEASES: PERTUSSIS AND PNEUMONIA

ABSTRACT

Pertussis is a vaccine-preventable respiratory disease that affects humans of all age groups, yet there are reported cases of resurgence. The disease is highly contagious and has posed detrimental effects on the lives of infants globally. The impact of pertussis worsened with the presence of viral infections such as pneumonia. Therefore, it is imperative to study the behavior of these diseases and suggest control strategies using a mathematical modeling approach. The study area and literature of mathematical models on pertussis and pneumonia co-infection dynamics is rather scanty. Therefore, this study is aimed at obtaining model equations using a system of nonlinear ordinary differential equations for a better understanding of the transmission dynamics and control of these diseases in the infant population. Further, the models are used to evaluate the intervention strategies for disease control. The first model is the general model describing the transmission dynamics of pertussis which incorporates a maternally derived immunity compartment. The dynamical behavior of the basic model is analyzed analytically and numerically. Numerical simulations were carried out using mathematical software. The basic reproduction number of the model is obtained and its behavior is analyzed by varying parameters. Numerically, the simulations indicate that when the waning parameter is increased, the frequency at which the population attains stability varies. However, the infected population does not go extinct even at equilibrium. In addition, the model is extended to incorporate various control strategies to proffer solutions to the resurgence of this vaccine-preventable disease. The findings revealed that the strategy which adopts using both

prevention, vaccination, and treatment in the fight against the spread of disease is more effective. The second model considers transmission dynamics of a pertussis-pneumonia co-infection, taking into account the temporary immunity of infected infants. The model is analyzed qualitatively and numerically. Subsequently, the model is extended to incorporate five control strategies. The optimal control schemes to establish the necessary conditions for the optimality of the disease eradication or control are applied. Sensitivity analysis carried out on all parameters of the model revealed the most sensitive to the disease transmission and control strategies needed. It is revealed that a successful prevention effort (isolation and hygiene) against the co-infection of the two diseases with vaccination and treatment will help control the spread of the disease.

CHAPTER 1

INTRODUCTION

1.1 Overview

There have been major advances in understanding the epidemiology of infectious diseases. However, studies have showed that an approximated 2 million children die from the disease in developing countries (Otieno *et al*., 2013). The emerging infectious diseases have become a critical burden on global economies because it constitutes most of the health issues globally. Conversely, emergence of these infectious diseases is due to socioeconomic, environmental, and ecological factors (Barreto *et al*., 2006). Globally, it is reported that there is the emergence of around 335 infectious diseases between 1940 and 2004 (Morens *et al*., 2004; Jones *et al*., 2008; Raslan *et al*., 2017), and these diseases in the regions have been a residue to untimely death. However, these diseases were estimated on the average to double the incidences (e.g., tuberculosis and HIV/AIDS) among others, maternal and perinatal conditions, as well as nutritional deficiencies (Cruz, 2007; Jones *et al*., 2008).

The World Health Organization (WHO, 2015) estimated that about one-third of the annual deaths rate worldwide are attributed to diseases spread by infections. However, an acute respiratory tract infections such as pertussis, severe acute respiratory syndrome (SARS), pneumonia, gastrointestinal infections, and malaria cause mostly the illness and mortality worldwide (Church, 2004; Raslan *et al*., 2010). In a nutshell, the low-income individuals are the most at risk for developing these respiratory diseases (Cruz, 2007).

This thesis deals with the mathematical modeling of childhood infectious disease; pertussis and pneumonia to be precise, where the dynamics of the disease

transmission is observed. The pertussis model is first studied by improving existing SIR model of pertussis to include the maternally derived immunity compartment (M), thus improved to suit the underlying purpose of the infant population. Further, the research is then extended to obtaining the optimal control of the developed mathematical model and thus choosing the appropriate control strategy to curtail or manage the spread/re-emergence of these diseases. In this chapter, an overview of respiratory disease is presented with emphasis on pertussis and pneumonia. Further, the research objectives, methodology, and structure of this thesis are outlined in this chapter.

1.2 Respiratory Diseases

In the respiratory diseases, there are advances in techniques and methods detected in sequencing microorganism in human system from the disease pattern as well as the environmental factors in the host-subject (Everard, 2016). The microbiome of humans consists of the microbiota (i.e., all organisms including bacteria, viruses, and fungi) existing in the body and the habitat they reside. These microbiomes which reside in the lungs and guts are very complex concerning the types and quantities of microbe present (Seetharam and Glass, 2019; Pichon *et al*., 2017). The sequencing technique revealed that the microbiome of the lungs is a diverse system that varies from the anterior nares to the distal airways, with different combinations of diverse species (Seetharam and Glass, 2019). Research has shown that the differences could be due to genetics, environmental factors, mucosal characteristics, immunity, and microbe-microbe interactions. Evidence suggests that the microbiome is responsible for the behavior of immunity responses, and influences the balance between health and disease (Hanada *et al*., 2018; Seetharam and Glass, 2019). In recent development,

technology is used to ameliorate the understanding of the epidemiology outbreaks for infectious disease and the evolution of an organism. These challenges include the sources of dietary components or antibiotics, and through the presence of organisms developed in humans or their habitat (Seetharam and Glass, 2019).

Respiratory disease is one of the most frequent causes of ill health for both children and adults alike worldwide (Gouveia and Fletcher, 2000). Moreso, the disease is a type that affects the lungs caused by excessive tobacco smoking or being exposed to externalities associated with air pollution such as asbestos and radon (NCI, 2018). These diseases include among many others; asthma, chronic obstructive pulmonary disease (COPD), pneumonia, pulmonary fibrosis, pertussis, and lung cancer (NCI, 2018).

In this study, the childhood respiratory disease pertussis and pneumonia are considered. These are highly infectious respiratory diseases that have been in existence for decades but remain a great concern in the health sector, both developed and developing countries (Johnston *et al.,* 1998; Pesco *et al.,* 2014; Pesco *et al.,* 2015; Tilahun *et al.,* 2017; Tilahun *et al.,* 2018; Domenech de Cellès *et al.,* 2019).

1.2.1 Pertussis

Pertussis is an acute respiratory illness that exhibits cyclical outbreaks in the last century. It is a highly contagious respiratory disease that can affect individuals of any age (Edwards, 2005)[1]. However, infants less than one-year-old bear the largest disease burden (Fabricius *et al*., 2018). The patients mostly experienced complications such as seizures, apnea, encephalopathy, pneumonia, dietary problems, or even death. On the other hand, complications in adults' patients result in chronic cough, sleep

[1] Note: in this study, it is observed that pertussis which is associated with coughing spasm and vomiting is also known as a 100-day cough.

disturbances, and restriction of activities (Kline *et al.*, 2013; Edwards, 2005). Figure 1.1 shows a diagram of the transmission of pertussis-causing bacteria. In the last two decades, there has been inflation in the incidence of the disease worldwide, with around 16 million cases occurring per year with approximately 200,000 deaths (Fabricius *et al*., 2018).

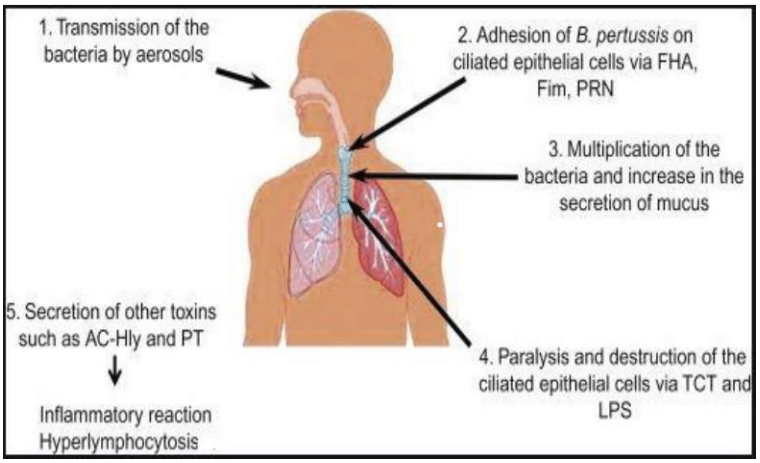

Figure 1.1 Diagram on the transmission of pertussis causing bacteria (Guiso, 2015)

The disease is carried by a Gram-negative bacterium known as the *Bordetella pertussis.* The bacteria travel via respiratory droplets infecting human hosts (Mattoo *et al*., 2005; Koenig *et al*., 2019). Pertussis is preventable through immunization. The introduction of pertussis vaccines in the 1940s and coverage of children led to a 95% decrease in the disease. Unimmunized infants or partially immunized infants and young children are at high risk of developing severe pertussis and associated complications. The resurgence of pertussis is occurring throughout the world despite high rates of vaccination coverage (Warfel *et al.*, 2012). It is observed that the complexity of this resurgence is a phenomenon that results from the number of cases and use of acellular pertussis vaccine (aPV) (Esposito *et al*., 2019). Figure 1.2 shows the overall burden of whooping cough across the world in 2015.

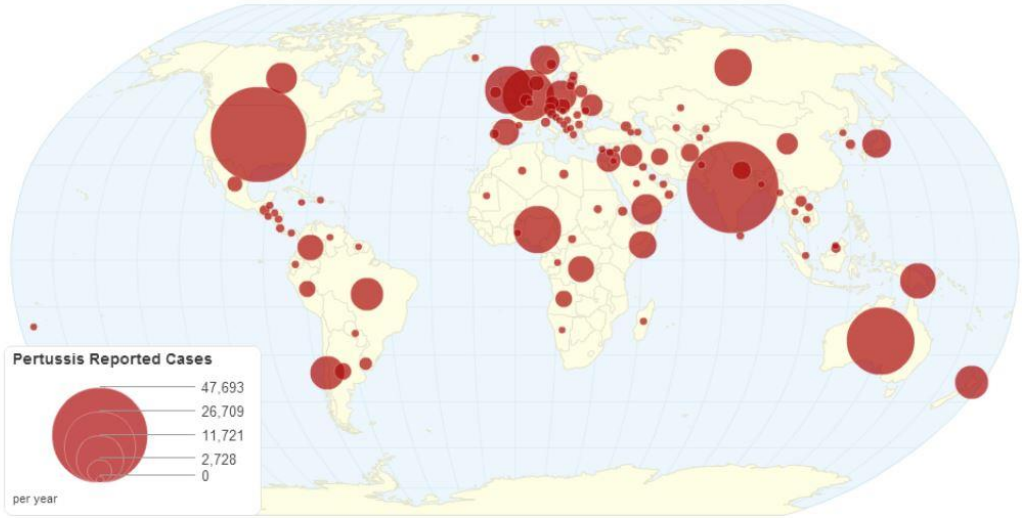

Figure 1.2 The overall burden of pertussis reported cases 2015 (Chartsbin, 2015)

1.2.2 Pertussis Challenge and Prevention

The immunity to pertussis that is acquired either from vaccination or natural infection is not permanent. Thus, the need for a more effective strategy on how to further prevent the pertussis endemic. Globally, the wide use of vaccine coverage of pertussis-containing vaccine which includes diphtheria-tetanus-whole-cell-pertussis (DTwP) and diphtheria-tetanus-acellular-pertussis (DTaP) is quite commendable in the high-income countries, however, pertussis incidence has still maintained its endemicity (Kilgore *et al*., 2016). This increasing incidence affects both young infants and also older age categories. However, there are different aPVs available, but which of them confers the most significant effect and prolonged protection is yet to be determined (Esposito *et al*., 2019).

The strategy on the use of vaccination to pregnant women with pertussis-containing vaccines has been in existence for several countries towards curtailing the effect of pertussis disease (Maertens *et al*., 2020). This strategy is to protect neonates with pertussis-specific maternal antibodies from mother to fetus before they are

vaccinated. Data on the implementation and safety of maternal immunization are reassuring (Barger-Kamate *et al*., 2016; Maertens *et al*., 2020).

1.2.3 Pneumonia

In pneumonia, an acute infection which disrupt the established microbiome may contribute to the development of bacterial pneumonia or asthma (Kim *et al*., 2018). Most viral infections account for 45-75% of childhood community-acquired pneumonia. Furthermore, the morbidity in children and mortality considering the age is greatly pronounced in children under the age of five years old and are a leading cause of paediatric hospital admissions, particularly in developing countries (Seetharam and Glass, 2019). It contributes to over 2 million deaths among children. While deaths in developed countries are rare, it, however, remains a major cause of hospital admissions for both acute and chronic morbidity (Thomas and Spencer, 2011). Pneumonia is a respiratory disease whose main characteristic is the inflammatory condition of the lungs (Thomas and Spencer, 2011; Aston, 2017). The disease is triggered by micro-organisms which include, viruses, bacteria, and fungi (Otieno *et al*., 2013), thus pneumonia is described based on how the infection is contracted. The two most common type of pneumonia which are life threatening are the bacterial pneumonia (triggered by bacteria) and viral pneumonia (triggered by viruses) (WHO, 2022). Although, differentiating between bacterial and viral pneumonia has been quite difficult, as no single test or combination of tests is sufficiently reliable for routine clinical use (Thomas and Spencer, 2011; Aston, 2017; WHO, 2022), the bacterial pneumonia is the most common cause of community acquired pneumonia. A bacterium known as *Streptococcus pneumonia* is however noticed to be the leading cause of pneumonia among the mentioned micro-organisms (Otieno *et al*., 2013; WHO, 2022). It could be contracted resulting from gasping of small droplets from

cough and sneezes that contain the pathogenic micro-organisms from an infected individual, and also when the micro-organisms which are present in the mouth, throat, or nose unwittingly enters the lungs (Lawi *et al.*, 2013; Otieno *et al*., 2013; Tilahun, 2018). The bacterial pneumonia can be treated with antibiotics unlike the viral pneumonia which can be treated using antiviral drugs (WHO, 2022).

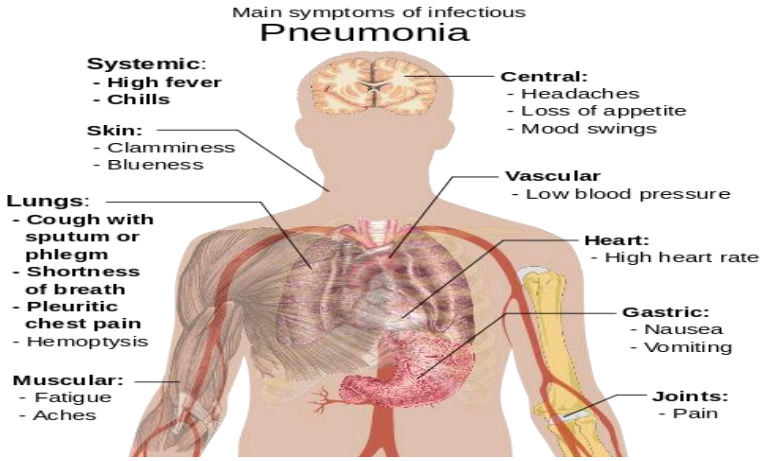

Figure 1.3 The main symptoms of infectious pneumonia (Häggström, 2014)

Some of the most observed symptoms of pneumonia include cough, respiratory distress, difficulty in breathing, chest pain, persistent fever, muscle ache, loss of appetite, and lethargy (Rasmussen *et al.*, 2005; Thomas and Spencer, 2011; Lawi *et al.*, 2013; Aston, 2017;). The symptom of pneumonia is shown in Figure 1.3, where the presenting features range from the symptoms experienced within various parts of the body, i.e.; headaches, loss of appetite are experienced in the upper part of the body; cough, chest pain, respiratory distress are experienced within the (lungs) lower part and so on (Häggström, 2014; Ticona *et al.*, 2021). Strategies for the prevention of pneumonia include; vaccination of high-risk individuals, environmental measures, and appropriate treatment of other health problems (Thomas and Spencer, 2011; Aston, 2017).

1.2.4 Co-infection Interactions in Humans

Different infectious agents may infect or colonize (Griffiths *et al*., 2011) as co-infection involves a number of pathogens and could have contingent effects on the co-infected host. There are innumerable types of pathogens that tend to infect humans. Among them are viruses, fungal parasites, bacteria, helminths and protozoa, which often co-exist in individuals. Improved comprehension of co-infection dynamics and prevalence is greatly needed particularly because co-infecting pathogens can interact either directly with one another or indirectly through the host resources or immune system (Clay *et al*., 2020; Cox, 2001; Glidden *et al*., 2021; Griffiths *et al*., 2011). In comparison to the infections by single pathogen species, the interaction in the coinfected hosts is likely to change the clinical progression as well as transmission, and the control of multiple infectious diseases (Birger *et al*., 2015; Griffiths *et al*., 2011; Pinky and Dobrovolny, 2016). However, a simultaneous infection can occur even when there is no interaction between two agents, as in the case of infection by ocular strains of chlamydia and nasopharyngeal colonization by pneumonia. The dynamics of co-infection are vital because some antimicrobials used in treating one infection may affect the treatment of the other infection (Griffiths *et al*., 2011).

1.3 Mathematical Modeling with Optimal Control and Control Strategy

In real-world phenomena, mathematical modeling is one of the powerful tools to describe the dynamical behavior of different diseases (Khan *et al*., 2017). It gives a better understanding of the transmission of the disease. Mathematical models are studied either through the deterministic or stochastic modeling approach. The deterministic modeling approach integrates physical concepts that tend to allow the exact calculation of future events without the involvement of randomness (Renard *et*

al., 2013). On the other hand, the stochastic modeling approach which possesses some inherent randomness can handle uncertainties of biological processes, especially when the population is small or early stages of an epidemic (Renard *et al*., 2013; Martins, 2019). Note that, deterministic and stochastic models should not be seen as opposing strategies, but rather as complementary approaches (Britton, 2010; Martins, 2019). In this research, the deterministic modeling approach is used, because deterministic models are straightforward. Moreover, a good number of researches conducted on epidemiological infectious diseases used the deterministic approach (Tilahun *et al*., 2018; Otieno *et al*., 2013; Khan *et al*., 2017). Mathematical models infused in epidemiological research are incredible in studying the dynamics of disease control and finding the threshold parameters (Otieno *et al*., 2013). However, theories of mathematical control provide the background which delineates the design of a control system and its analysis. The theories are used to study the disease behavior in an attempt to achieve the desired objective and determine if the disease would persist or not. Studying the mathematical model of infectious disease offers an information into the disease behavior and also adequate control measures while the epidemiological data and economic costing of controlling the infectious disease provide necessary elements in evaluating the relevance of intervention programs (Hugo *et al*., 2017). The optimal control theory will be used to model the elimination/eradication or possibly reduce the transmission of the co-infectious disease in children. The optimal control problem will be deduced and Pontryagin's Maximum Principle is applied. The control strategy is thereby defined based on the local sensitivity analysis deduced from the optimal control model and attention is focused on the appropriate control variable.

1.4 Motivation

The study is been motivated by the fact that there is a gap in the contemporary literature contingent on pertussis (whooping cough) in infants. The general approach in explaining the epidemic of whooping cough has been unsuccessful (Nguyen and Rohani, 2007; Saso *et al.*, 2021), thus the need to further investigate the dynamics of pertussis disease. Similarly, research on why the waning of vaccine immunity occurs is very scanty noting that with waning of vaccine immunity, infants are at higher risk of contracting life-threatening diseases (Hu *et* al., 2014; Thisyakorn *et al*., 2019), this has led to about 16 million cases of mortality worldwide. Furthermore, complications of pertussis if not properly managed in infants can lead to pneumonia, which increases the chances of death. Conversely, the nexus between the severity of emerging cases of pertussis have been linked to its co-infection with pneumonia or other respiratory diseases (such as influenza) which the literature had overlooked (Muloiwa, 2020), therefore an investigation on the co-infection of pertussis with pneumonia is a relatively important study.

In addition, considering the motivation highlighted above, even with the use of vaccination as a control measure, the resurgence of pertussis is yet alarming as observed by Campbell *et al*., (2015) and Esposito *et al*., (2019). Therefore, a deterministic model is developed in this thesis to study step-by-step the transmission dynamics of the disease. The novelty of this study stalks on the introduction of the maternally-derived immunity into the susceptible-infected-recovered (SIR) model as maternally-derived immunity-SIR (MSIR), and a response to the reality checks and objectives of the study.

1.5 Problem Statement

The respiratory diseases; pertussis and pneumonia, have posed a detrimental effect on the lives of infants. Thus, this study focuses on the problems associated with the negative impact of the disease which is relatively diverse as presented in the earlier sections of this chapter. The questions are then:

1. What is the effect of maternally derived immunity infants on the dynamics of the model for the infant population?
2. How does the co-dynamics of the pertussis model by dual infection with pneumonia affect the infant population?
3. What are the effects of control measures for these diseases?
4. What is the cost implication of such control?

1.6 Research Objectives

Accordingly, in relation to the problem statement, the objectives of the research are:

1. To improve on an SIR pertussis mathematical model to fit the infant population and analyze the model for a better understanding of its dynamics.
2. To develop and study a deterministic mathematical model of co-infectious disease transmission (pertussis and pneumonia).
3. To analyze the numerical simulations of both models considering the maternally-derived immunity infants.
4. To develop an optimal control in the infant population and suggest a more suitable control strategy to eliminate or further reduce the transmission of the disease.

1.7 Scope of Study

The study intended to measure the dynamics of pertussis disease and also its co-infection with pneumonia disease. The scope of this study is limited to only infants that are susceptible to pertussis contingent, and are prone to other childhood respiratory diseases such as pneumonia. Considering these infants with maternally derived immunity, we utilized the nonlinear differential equations to explore the dynamics of these diseases. However, the validation process is a very significant part of the model development process when the model development phases are completed using real data. This study does not consider validation of the model because the data used were obtained from existing literature and not specific to a particular region, thus inadequate access to real data.

1.8 Methodology

An extensive investigation of nonlinear problems requires tools that provide quantitative and theoretical information on nonlinear behavior. In this research work, the mathematical formulation of the differential equations is developed using a deterministic modeling approach. The dynamical analysis of the compartmental MSIR model is studied. The MSIR model comprises of the maternally-derived immune (M), susceptible (S), infected (I), and recovered (R) classes respectively. Qualitative properties of the models ranging from the basic properties of the models, the equilibria, condition of stability, and existence of optimal control profiles with various inferences of these properties are presented. The equilibrium state of both infection-free and endemic states of the models is obtained. Thereafter basic reproduction number which is a threshold quantity is obtained using the next generation method. The local stability analysis of the model is obtained using both Jacobian and Routh-Hurwitz methods.

Furthermore, the global stability behavior of the models for both the pertussis-only model and co-infection model is determined using a suitable Lyapunov function method. This in turn gives more explanation on the behavior of the nonlinear systems. With the help of Pontryagin's Maximum Principle, the optimal control problem of the system is deduced by calculating a piecewise continuous control and the related state variables to maximize the objective functional. Thereafter, the best control strategy is observed and applied. Numerical simulations are carried out on the system of differential equations using computer-friendly software packages which include Mathematica, Maple, and MATLAB for qualitative results.

1.9 Outline of Thesis

The thesis is structured into eight chapters with the inclusion of this preliminary chapter. Chapter 1 which is the introduction provides an extensive discussion on the research background where basic knowledge of respiratory diseases is discussed. The motivation of the research, problem statement, research objectives, and the methodology of the research are all discussed in this chapter. Chapter 2 contains the basic mathematical concepts where some of the mathematical tools used in the thesis are discussed. Chapter 3 presents the review of the mathematical dynamics of pertussis, pneumonia, and co-infectious diseases. In Chapter 4, the dynamics of the pertussis model with maternally derived immunity are studied. This is where the equilibrium state, stability analysis for local and global stability, as well as the analysis of the basic reproduction number of the nonlinear model are determined. The effect of optimal control strategy on the pertussis model is investigated in Chapter 5 to verify which control strategy is best for curtailing or eradicating the endemicity of the disease. Chapter 6 presents the dynamics of pertussis and pneumonia co-infectious

diseases. This chapter gives a detailed analysis of the interaction and behavior of the co-infectious diseases. The effect of control strategies on co-infectious diseases is studied in Chapter 7. Finally, in Chapter 8, the conclusion of the research and suggestions on possible future work are highlighted. Figure 1.4 gives a schematic representation of the flow chart of the study.

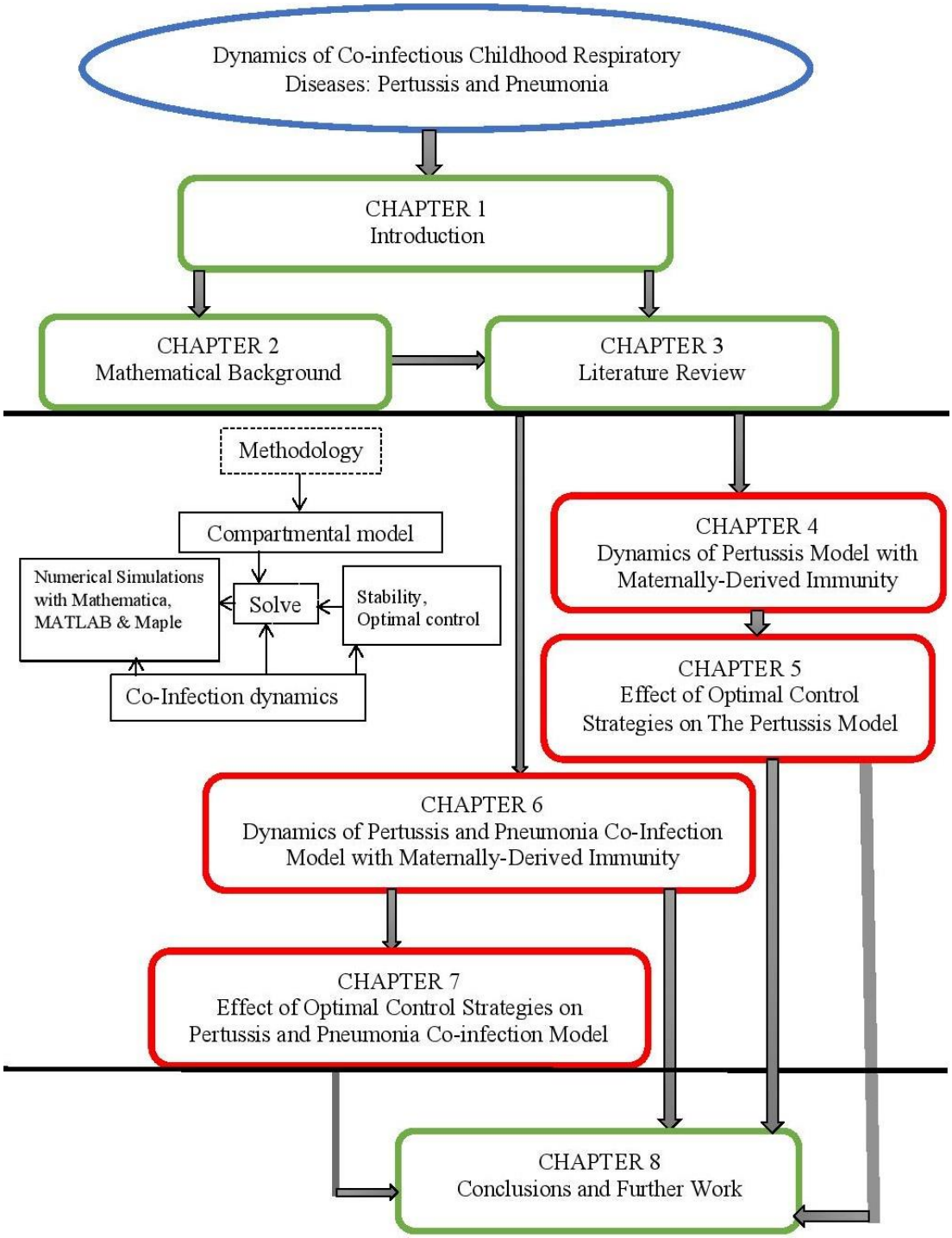

Figure 1.4 Study flow chart

CHAPTER 2

MATHEMATICAL BACKGROUND

2.1 Introduction

The mathematical background in this chapter will serve as a foundation for the main work that will be reported later. Dynamical systems developed during the mathematical model formulation are critically analyzed. These models are mostly designed using either ordinary differential equations (ODEs), partial differential equations (PDEs), delay differential equations (DDEs), or stochastic equations (Di Liddo, 2016). Especially, in this thesis, the study focuses on the system of nonlinear ODEs. Several mathematical concepts, definitions, and theories are discussed in this chapter which is required for the proper understanding of the dynamics of the models considered in this thesis. The first section begins with highlights on linear and nonlinear systems of a differential equation, and autonomous and nonautonomous differential equations. Thereafter, the general concept of a dynamical system is presented. Subsequent sections delineate various approaches (equilibrium point, stability, Jacobian, etc.) used in exploring the dynamical behavior of the system.

2.2 Basic Notation

In this section, the definition of some basic terms is given which include; linear and nonlinear systems of ODEs and then autonomous and nonautonomous differential equations.

2.2.1 Linear and Nonlinear Systems of Ordinary Differential Equations

A basic classification of differential equations is whether they are linear or nonlinear. Consider the linear system of ODEs

$$\begin{bmatrix} \frac{dx_1}{dt} \\ \vdots \\ \frac{dx_n}{dt} \end{bmatrix} = A \begin{bmatrix} x_1 \\ \vdots \\ x_n \end{bmatrix}, \qquad (2.1)$$

where, A is an $m \times n$ matrix. Then the vector

$$\begin{bmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{bmatrix} = e^{At} \begin{bmatrix} x_{0_1} \\ \vdots \\ x_{0_n} \end{bmatrix},$$

is the general solution to (2.1), with an initial condition,

$$\begin{bmatrix} x_1 \\ \vdots \\ x_n \end{bmatrix} \left(\begin{bmatrix} 0 \\ \vdots \\ 0 \end{bmatrix} \right) = \begin{bmatrix} x_{0_1} \\ \vdots \\ x_{0_n} \end{bmatrix},$$

where e^{At} is an $m \times n$ matrix defined by its Taylors series (Perko, 2001). Consider also the nonlinear system of differential equation

$$\begin{bmatrix} \frac{dx_1}{dt} \\ \vdots \\ \frac{dx_n}{dt} \end{bmatrix} = \begin{bmatrix} f_1(x_1, ..., x_n) \\ \vdots \\ f_n(x_1, ..., x_n) \end{bmatrix}, \qquad (2.2)$$

where f is a given function such that, $f : E \to \mathbb{R}^n$ and E is an open subset of $\mathbb{R}^n$. With certain conditions on f, the nonlinear system (2.2) has a unique solution through each point $x_0 \in E$ defined on a maximal interval of existence $(a, b) \subset \mathbb{R}$. However, it is not feasible to solve the nonlinear system, because so much of its qualitative information about the local behavior of the solution is needed (Perko, 2001).

In general, an *n*th-order ODE can be expressed as;

$$f\left(x, y, \frac{dy}{dx}, ..., \frac{d^n y}{dx^n}\right) = 0,$$

where, f is a linear function of the variables $x, y, dy/dx, ..., d^n y/dx^n$. An *n*th-order ODE is linear if it can be written in the form

$$a_n(x)\frac{d^n y}{dx^n} + a_{n-1}(x)\frac{d^{n-1} y}{dx^n} + ... + a_0(x)y = g(x), \qquad (2.3)$$

with $a_0(x), ..., a_n(x), g(x)$ are functions of x. Any equation that is not of the form (2.3) is a nonlinear ODE (Boyce and DiPrima, 2001; Allen, 2007; Roberts, 2010; Teschl, 2012). For illustration, an example is given for both linear and nonlinear ODEs respectively,

$$\frac{d^2 y}{dt^2} - \frac{3dy}{dt} + 2y(t) = x(t) \text{ (linear)},$$

$$\frac{d^2 y}{dt^2} + \sin(t + y) = \sin t \text{ (nonlinear)}.$$

Most physical phenomena cannot simply be represented adequately by linear equations, thus to study these phenomena, it is essential to deal with nonlinear equations. Nevertheless, the process of approximating a nonlinear equation by a linear one is called linearization and it is a valuable way to deal with nonlinear equations (Boyce and DiPrima, 2001).

2.2.2 Autonomous and Nonautonomous Differential Equations

A system of differential equations that does not explicitly depend on time t is referred to as an autonomous differential equation. That is, the independent variable does not appear explicitly. An example is seen in the form

$$\begin{aligned} \frac{dx}{dt} &= F(x, y), \\ \frac{dy}{dt} &= G(x, y), \end{aligned} \tag{2.4}$$

where it is assumed that the functions F and G are continuous and have partial derivatives in some domain D of the $xy-$plane. Observe that the functions F and G do not depend on the independent variable t, but on the dependent variables x and y. Given the system (2.1), if one or more of the elements of the coefficient matrix A is a function of the independent variable t, then the system becomes nonautonomous. For example, when (2.4) is written in the form

$$\begin{aligned} \frac{dx}{dt} &= F(t, x, y), \\ \frac{dy}{dt} &= G(t, x, y), \end{aligned}$$

then the system becomes a nonautonomous system of the differential equation (Boyce and DiPrima, 2001; Allen, 2007). These system of differential equations can be used in real life to describe important fields ranging from ecology e.g., mathematical models such as population expansion; medicine e.g., disease spread and calculate movements of items like the simple pendulum. They also exhibit useful properties: i.e., even when its exact solution cannot be found, a lot about their behavior can be predicted by looking at the equilibrium solutions and their stability to the phase plane and many more. (Boyce and DiPrima, 2001).

2.3 Dynamical Systems

A dynamical system is that aspect of mathematics, devoted to the study of systems governed by a consistent set of laws over time, such as difference and differential equations. It gives a functional description of the solution of a physical problem or a

mathematical model describing the physical system (Perko, 2001). The emphasis of the dynamical system is the understanding of geometrical properties of trajectories and long-time behavior. Dynamical systems can model a wide range of behavior such as disease spread in a population, the process that regulates electronic circuits, and heartbeats (Arizona, 2019). In general, dynamical systems are initial-value problems governed by difference and differential equations. A dynamical system is given in a compact form

$$\frac{dx}{dt} = F(x). \qquad (2.5)$$

In the subsequent subsection, equilibrium points, stability, and various techniques used to determine the stability of differential equations are discussed.

2.3.1 Equilibrium, Stability, and Linearization of Autonomous Systems

The study of equilibria plays an important role in ODEs and their application. An equilibrium point must however satisfy certain stability criteria for the system to be physically significant. Mathematical models which are also known as dynamical systems can be expressed in the form (2.5) where, $x \in \mathbb{R}^n$ is a vector of the state variable of the system, and F a nonlinear function. (Perko, 2001).

Definition 2.1: Equilibrium point

The state of equilibrium also referred to as critical point, fixed point, steady-state is the state of keeping the system still in the absence of external interference. If there is a point x^*, for any time t greater than t_0 such that

$$\frac{dx^*}{dt} = F(x^*, t) = 0, \forall t \in [t_0, \infty).$$

Then it is referred to as an equilibrium point. Thus, a model written in the form (2.5) for any point x^* such that $F(x^*)=0$ is an equilibrium point (Allen, 2007; Kong, 2014).

It is often important to know when a solution is stable, i.e., whether it persists essentially on the infinite interval $[0,\infty)$ under small changes in its initial state. An equilibrium point x^* is

- Stable if $\forall \varepsilon > 0,\ \exists \delta(\varepsilon) > 0$ such that $|x(0)-x^*| < \delta \Rightarrow |x(0)-x^*| < \varepsilon,\ \forall t > 0$, otherwise unstable
- Asymptotically stable if it is stable and δ can be chosen so that

$$|x(0)-x^*| < \delta \Rightarrow \lim_{t\to\infty} x(t) = x^*.$$

2.3.2 Local Stability Analysis of Equilibrium Points

In mathematical modeling, it is noteworthy to distinguish the behavior of a dynamical system close to an equilibrium point. Knowing whether or not future advancements of the system will remain close to the equilibrium point if initial conditions are close to the equilibrium is important. The local stability analysis is carried out to understand this behavior. Further, there are various approaches used in analyzing the stability of given system differential equations. In this thesis, for instance, the Lyapunov indirect method, Routh-Hurwitz criteria and Jacobian method are employed. These attempts establish the properties of equilibrium points by studying the behavior of the linearized system at that point.

2.3.2(a) Stability in the Sense of Lyapunov

Given an ODE

$$\frac{dx}{dt} = G(x),\ x \in \Omega, \tag{2.6}$$

where Ω is an open connected subset of $\mathbb{R}^n$ and G is a locally Lipschitz continuous map from Ω to $\mathbb{R}^n$. Let $G_t(x)$ be that solution of (2.6) satisfying $G_t(x) = x,\ \forall x \in \Omega$. An equilibrium point is a state $x^* \in \Omega$ satisfying $G(x^*) = 0$. Corresponding to all equilibrium point x^*, it has a steady-state solution $G(x^*) = x^*$ of (2.6).

Equation (2.6) is locally stable at x^*, if for all $\varepsilon > 0$, there exists a positive real number δ such that for all x with $\|x - x^*\| < \delta$, the solution $G_t(x)$ is defined for all $t > 0$ and satisfies $\|G_t(x) - x^*\| < \varepsilon$ for all $t > 0$. When the system (2.6) is not Lyapunov stable at x^* (i.e. starts and stays near x^*), then x^* is an unstable equilibrium for the system (2.6) (Iggidr, 2004; Li *et al*., 2018). Similarly, an equilibrium point x^* in (2.6) is locally asymptotically stable if it is locally stable and all the solutions established around x^* tends towards x^* as $t \to \infty$. That is $\exists\ \delta > 0$ such that

$$\|x - x^*\| < \delta \Rightarrow \lim_{t \to \infty} x(t) = x^*$$

2.3.2(b) The Routh-Hurwitz Criteria

In studying the dynamics of a nonlinear system of a differential equation, the Routh-Hurwitz criteria are used to establish the asymptotic stability of an equilibrium point (Allen, 2007). These criteria can be used conveniently to analyze the stability of low-order systems. The computational complexity grows significantly with the increase of the order (Allen, 2007). Thus, it may be preferable to use other criteria such as the Nyquist stability criterion (Sun *et al*., 2018). The Routh-Hurwitz criteria provide the necessary and sufficient conditions for all roots of the characteristic polynomial to contain negative real parts, thus, necessitating asymptotic stability.

Theorem 2.1: Routh-Hurwitz criteria (Allen, 2007; Wu and Hu, 2021)

Consider the polynomial,

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + ... + a_{n-1}\lambda + a_n, \qquad (2.7)$$

where the coefficients a_i are real constants and $i = 1, ..., n$, defining *n*-Hurwitz matrices using the coefficient a_i of the characteristic polynomial:

$$H_1 = (a_1),$$

$$H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix},$$

$$H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix},$$

$$H_4 = \begin{pmatrix} a_1 & 1 & 0 & 0 \\ a_3 & a_2 & a_1 & 0 \\ a_5 & a_4 & a_3 & a_2 \\ a_7 & a_6 & a_5 & a_4 \end{pmatrix},$$

$$H_5 = \begin{pmatrix} a_1 & 1 & 0 & 0 & 0 \\ a_3 & a_2 & a_1 & 1 & 0 \\ a_5 & a_4 & a_3 & a_2 & a_1 \\ a_7 & a_6 & a_5 & a_4 & a_3 \\ a_9 & a_8 & a_7 & a_6 & a_5 \end{pmatrix},$$

and

$$H_n = \begin{pmatrix} a_1 & 1 & 0 & 0 & ... & 0 \\ a_3 & a_2 & a_1 & 1 & ... & 0 \\ a_5 & a_4 & a_3 & a_2 & ... & 0 \\ . & . & . & . & ... & . \\ . & . & . & . & ... & . \\ . & . & . & . & ... & . \\ a_{2n-1} & a_{2n-2} & a_{2n-3} & a_{2n-4} & ... & a_n \end{pmatrix},$$

where, $a_j = 0$ 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., $\det H_j > 0,\ j = 1, 2, ..., n$.

For example, when $n = 2$, the Routh-Hurwitz criteria simplify to $\det H_1 = a_1 > 0$ and

$$\det H_2 = \det \begin{pmatrix} a_1 & 1 \\ 0 & a_2 \end{pmatrix} = a_1 a_2 > 0,$$

or $a_1 > 0$ and $a_2 > 0$. Similarly, for the polynomials of degree $n = 3,\ 4$ and 5 the Routh-Hurwitz criteria are summarized as follows:

$$n = 3 : a_1 > 0,\ a_3 > 0 \text{ and } a_1 a_2 > a_3,$$

$$n = 4 : a_1 > 0,\ a_3 > 0,\ a_4 > 0 \text{ and } a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$$

$$n = 5 : a_i > 0,\ i = 1, ..., 5,\ a_1 a_2 a_3 > a_3^2 + a_1^2 a_4, \text{ and}$$
$$(a_1 a_4 - a_5)(a_1 a_2 a_3 - a_3^2 - a_1^2 a_4) > a_5 (a_1 a_2 - a_3)^2 + a_1 a_5^2.$$

2.3.2(c) The Jacobian

In nonlinear systems, it is typical not to have an analytical solution. Thus, systems of such nature are mostly linearized around their steady state (Allen, 2007). The analytical solution of such an approximate linear system approaches the behavior of the original system closely, provided it remains around an equilibrium point. The Jacobian is a method that can be used to linearly approximate a nonlinear system around the fixed point such that the linear stability holds (Allen, 2007). Consider a general system of two differential equations in (2.4) with an equilibrium point at (x^*, y^*), satisfying $F(x^*, y^*) = 0$ and $G(x^*, y^*) = 0$. The local stability of the equilibrium for the system (2.4) is determined by the eigenvalues of the Jacobian matrix. The linearized system about the equilibrium (x^*, y^*) is given by (Allen, 2007)