A Mathematical Model of Ebola Virus Disease

by

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Abstract

In this thesis, a modified SLIR model is formulated to describe the dynamics of Ebola virus disease. This model is peculiar in the sense that an infectious deceased compartment incorporated into the models, this is due to the fact that an infected deceased remains infectious as long as the virus remain in the blood. An isolated compartment is also added to the standard SLIR model. Mathematical analysis reveals that the disease free equilibrium is globally asymptotically stable when the basic reproduction number $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$, while the endemic equilibrium is globally asymptotically stable when $\mathcal{R}_0 > 1$ and is not biologically relevant when $\mathcal{R}_0 < 1$. From the analysis of our model, we conclude that isolation of infected individuals will help a great deal in controlling the spread of the virus alongside with proper burial for infected deceased individuals.

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Dedication Page

This thesis is dedicated to the Lord God Almighty who made it possible for me to complete my program successfully. To HIM alone be all the glory in the highest in Jesus Name.

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Chapter 1

Introduction

In this chapter, contributions from references [2, 20, 21, 22] and [35] were used.

Humanity has been plagued with infectious diseases for years. The mechanisms of transmission are known for most diseases; generally, diseases such as influenza, measles, rubella and chicken pox that are transmitted by virus confer immunity against reinfection, while diseases such as tuberculosis, meningitis and gonorrhea that are transmitted by bacteria confer no immunity against reinfection. Other diseases, such as malaria, are transmitted not directly from human to human but by vectors (usually insects), which are agents that are infected by humans and then transmit the disease to other humans. West Nile virus has mosquitoes as its vectors and birds as its hosts. For sexually transmitted diseases with heterosexual transmission, each sex acts as a vector and the disease is transmitted back and forth between the sexes.

Infectious diseases have been a major cause of death and illness throughout the world. Tens of millions of lives have been lost to them. Some of these

diseases include the Spanish influenza virus of early 20^{th} century, which swept through Africa, America, Asia and Europe with a death toll of over 30 million people, the 1348 Black Death Bubonic Plague in Europe which killed over 40 million people within five years. In recent time, measles, malaria, tuberculosis and AIDS, among others, are causing millions of deaths on a yearly basis. UNAIDS reports that an average of 1.8 million people became newly infected with HIV, 36.9 million people are living with HIV in 2016, while over 75 million people have become infected with HIV since the start of the epidemic in 1981. 1 million people died of AIDS related diseases in 2016, while over 30 million deaths have resulted from AIDS related illness since the start of the epidemic. Technological advancement have brought about remarkable fight against these diseases. Antiretroviral drug have been made available for people living with HIV. In 2010, 7.7 million were able to access antiretroviral therapy, 17.1 million in 2015 and 20.9 million as of June 2017, which reveals great appreciable progress in combating this virus and invariably reducing AIDS-related death [35].

However, while some infectious diseases have been kept under control due to technological advances, others are still ravaging lives, the reason being the diversity of the pathogens coupled with their ability to mutate and adapt to changing environments and the complexity of their transmission mechanisms. Infectious diseases impacts are usually devastating, they hamper the survival rate of children, especially in underdeveloped countries; they also impede opportunities for economic growth and development. Hence, there is a need for

a global perspective that accounts for biocomplexity, all the interrelated factors that contribute to the evolution and survival of infectious agents. In order to achieve this, individuals from various field such as biologists, ecologists, chemists, epidemiologists, mathematicians, statisticians and atmospheric scientists must work collaboratively in order to shed more light on how these diseases can be eradicated or their impact minimized.

Transmission of infectious diseases occurs through several means that can be categorized into two major routes, direct and indirect transmission. Direct transmission involves the transmission from infected people to uninfected people through close contacts. Their medium include body fluids such as blood, semen, breast milk, etc. or through shaking of hands with or touching an infected individual. Indirect transmission involves transmission by non-human infectious agents such as mosquitoes, tsetse flies, contaminated food/ water, which serve as intermediate hosts for the disease and later transmit the disease to humans.

The incidence rate of diseases describes the transmission of the disease. An infectious disease that spreads rapidly to a large number of people in a given population for a short period of time is known as an epidemic. An infectious disease that persists in the community/population is known as an endemic disease while a pandemic is an epidemic of infectious disease that has spread through human populations across a large region (several continents, or even worldwide).

Scientists have used mathematical models, which involve the use of mathe-

matical equations and formula to represent real life problems, solved and made remarkable prediction based on the solutions obtained from the problems. Epidemiologists (scientists that study infectious diseases) have played a vital role in investigating the transmission dynamics of some of these diseases and have been able come up with recommendations for different intervention strategies which have helped to control the spread of some of these diseases.

A recent outbreak of Ebola virus disease in some West African countries spread to other countries in other continents. This was triggered by the advent of modern means of transportation. Infected individuals were transported from one country to another and therefore fostered the spread of the virus. In July 2014, an infected individual was transported from Liberia to Nigeria and ended up infecting over ten individuals, who also infected several others. This happened prior to my arrival in Canada; several countries closed their borders as a result of this outbreak, several flights from Africa were canceled. African students were denied admissions into Western world countries while certain athletes were hindered from participating in competitions they were registered for. All these facts put together motivated me to base my thesis on understanding the dynamics of Ebola virus disease and to contribute to the body of existing knowledge on it.

In this thesis, a modified susceptible-exposed-infectious-recovered (SEIR) deterministic nonlinear system of equations will be used to model the dynamics of Ebola virus disease. In addition to infectious individuals, which are known to be the major carriers of infectious diseases, this model will incorporate the

effect of the transmission of the disease by deceased infectious individuals, since they also contribute to the transmission of the disease to the susceptible population. Chapter 2 will be devoted to mathematical preliminaries that are relevant to this thesis. Chapter 3 will present the epidemiological preliminaries and some infectious disease models will be analyzed. Chapter 4 will focus on a literature review of Ebola virus disease (EVD). Chapter 5 will be devoted to model formulation, steady state analysis, boundedness and positivity of the solution of the of the model. The disease free and endemic equilibrium point will be discussed, alongside with their positivity and stability. The next generation matrix will be used to compute the basic reproduction number $\mathcal{R}_0$ for the model. Chapter 6 will deal with mathematical analysis and numerical analysis of our model will be carried out in Chapter 7, while Chapter 8 will focus on a discussion and recommendations.

Chapter 2

Mathematical preliminaries

This chapter presents some basic mathematical theories and methodologies that will be used in this thesis. Material in this chapter is based on references [7] and [29].

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 to infer a reasonable 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 prediction 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 (ODEs), partial differential equations (PDE), delay differential equations (DDE), stochastic differential equations (SDE), integral equations, Markov chains, game theory, etc.

2.1 Ordinary Differential Equations

Material for this section is obtained from [3] and [40].

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

$$\frac{d}{dt}x(t) = f(t, x(t)), \tag{2.1.1}$$

where $t \in \mathbb{R}$ is an independent variable, $x(t)$ is a dependent variable (unknown function) and $f : \mathbb{R}^n \to \mathbb{R}^n$ is a vector field. Equation (2.1.1) is known as a nonautonomous ordinary differential equation.

When no ambiguity arises, $\frac{d}{dt}x(t)$ is often written as x' so that (2.1.1) is written as

$$x' = f(t, x). \tag{2.1.2}$$

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 (2.1.2) is called autonomous and takes the form

$$x' = f(x). \tag{2.1.3}$$

and the general solution is

$$x(t) = \int_{t_0}^{t} f(\tau) d\tau. \tag{2.1.4}$$

For $f_i : \mathbb{R}^n \to \mathbb{R}^n$ and $x_i \in \mathbb{R}^n$, 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 then a general solution.

Definition 2.1.1. *(Initial Value Problem). A first order ODE together with an initial condition*

$$x' = f(t, x) \tag{2.1.5a}$$

$$x(t_0) = x_0 \tag{2.1.5b}$$

*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, $\mathcal{I}$) 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. *$x'(t) = f(t, x(t))$ 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

$$x(t) = x_0 + \int_{t_0}^{t} f(\tau, x(\tau))d\tau. \tag{2.1.6}$$

The system of ODEs to be analysed in this thesis is autonomous and takes the form $x' = f(x)$ *with* $x \in \mathbb{R}^7_+$ *and* $f : \mathbb{R}^7_+ \to \mathbb{R}^7_+$.

2.1.1 Existence and uniqueness of solutions

In this section, we state some basic theorems describing general properties of solutions of differential equations. Material from this section can be found in [32, 28] and [40].

Definition 2.1.2. *(Well-posedness). System (2.1.5) is well-posed if solutions exist, are unique, and for systems describing populations, remain bounded and nonnegative for all nonnegative initial conditions.*

Theorem 2.1.1. *(Cauchy-Lipschitz). Consider the differential equation (2.1.5) with* $x \in \mathbb{R}^n$*, and suppose that* $f \in \mathrm{C}^1$*. Then there exists a unique solution of (2.1.5) 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* $f \in \mathrm{C}^1$.

Theorem 2.1.2. *Let* f *and its partial derivatives* $(\partial F_i/\partial x_j)$ *in (2.1.3) 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 2.1.3. *(Flow). Consider System (2.1.5). The flow $\phi(t, x_0)$ of (2.1.5) represents the solution of (2.1.5) over time given an initial condition, provided that the solutions to the differential equation exist and are unique.*

Definition 2.1.4. *An equilibrium solution of (2.1.3) 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 2.1.5. *(Stable and unstable equilibrium point) [29] Let $\phi(t)$ be the flow of (2.1.3), assumed to be defined for all $t \in \mathbb{R}$. An equilibrium solution $\bar{x}$ of (2.1.3) is said to be locally stable if for all $\epsilon > 0$, there exists $\delta = \delta(\epsilon) > 0$ such that for all $x \in \mathcal{N}_\delta(\bar{x})$ and $t \geq 0$, there holds*

$$\phi_t(x) \in \mathcal{N}_\epsilon(\bar{x}).$$

The equilibrium point is unstable if it is not stable.

Definition 2.1.6. *(Asymptotically stable equilibrium point) Let $\phi(t)$ be the flow of (2.1.3) is (locally) asymptotically stable if there exists $\delta > 0$ such that for all $x \in \mathcal{N}_\delta(\bar{x})$ and $t \geq 0$, there holds*

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

2.1.2 Linearization

We will be using information from [30] and [40] in this section.

The behaviour of System (2.1.3) near a hyperbolic equilibrium point $\bar{x}$ is linked to the behaviour of the linearized system

$$x' = Df(\bar{x})(x - \bar{x}) \tag{2.1.7}$$

about the same equilibrium, where

$$J(\bar{x}) = Df(\bar{x}) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1}(\bar{x}) & \frac{\partial f_1}{\partial x_2}(\bar{x}) & \cdots & \frac{\partial f_1}{\partial x_n}(\bar{x}) \\ \frac{\partial f_2}{\partial x_1}(\bar{x}) & \frac{\partial f_2}{\partial x_2}(\bar{x}) & \cdots & \frac{\partial f_2}{\partial x_n}(\bar{x}) \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1}(\bar{x}) & \frac{\partial f_n}{\partial x_2}(\bar{x}) & \cdots & \frac{\partial f_n}{\partial x_n}(\bar{x}) \end{pmatrix} \tag{2.1.8}$$

matrix $Df(\bar{x})$ is the Jacobian matrix of (2.1.3) evaluated at the equilibrium point $\bar{x}$.

Definition 2.1.7. ***(Hyperbolic fixed point)*** *Let $x = \bar{x}$ be a fixed point of $x' = f(x), x \in \mathbb{R}^n$. 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 are 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 2.1.8. *A nonhyperbolic 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.)

Definition 2.1.9. *(Homeomorphism). Let D be a space. A map $h : D \to D$ is a homeomorphism if h is a continuous bijection whose inverse is continuous.*

Definition 2.1.10. *(Topologically conjugate). Let $\phi(t, x)$ and $\psi(t, x)$ be two flows on a space D. ϕ and ψ are topologically conjugate if there exists an homeomorphism $h : D \to D$ such that*

$$h \circ \phi(t, x) = \psi(t, x) \circ h(x)$$

for all $x \in D$ and all $t \in \mathbb{R}$.

Theorem 2.1.3. *(Hartman and Grobman)[29]. Assume that $\bar{x} \in \mathbb{R}^n$ 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*

2.1.3 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 (2.1.3) without finding explicit solutions.

Theorem 2.1.4. *Let $\bar{x}$ be an equilibrium point of the autonomous system (2.1.3), where $f \in C^1$ 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.*

2.2 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 2.2.1. *A point $x_0 \in \mathbb{R}^n$ is called an ω-limit point of $x \in \mathbb{R}^n$ and denoted by $\omega(x)$, if there exists a sequence $\{t_i\}$ such that*

$$\phi(t_i, x) \to x_0 \quad as \quad t_i \to \infty.$$

Definition 2.2.2. *A point $x_0 \in \mathbb{R}^n$ is called an α-limit point of $x \in \mathbb{R}^n$ and denoted by $\alpha(x)$, if there exists a sequence $\{t_i\}$ such that*

$$\phi(t_i, x) \to x_0 \quad as \quad t_i \to -\infty.$$

Definition 2.2.3. *The set of all ω-limit points of a flow is called the ω-limit set. Similarly, the set of all α-limit points of a flow is called the α-limit set.*

Definition 2.2.4. *Let $S \subset \mathbb{R}^n$ be a set. Then S is said to be invariant under the flow generated by (2.1.3) if for any $x_0 \in S$, we have $x(0, x_0) \in S$ 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 2.2.5. *A function $V : \mathbb{R}^n \to \mathbb{R}$ 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 2.2.1. *(Lyapunov)[32]: Consider the autonomous system defined by (2.1.3). Let $\bar{x}$ be a fixed point of (2.1.3) and let $V : U \to \mathbb{R}$ be a C^1 function defined on some neighbourhood U of $\bar{x}$ such that*

i) $V(\bar{x}) = 0$ and $V(x) > 0$ if $x \neq \bar{x}$.

ii) $\frac{d}{dt}V(x) \leq 0 \quad in \quad U - \{\bar{x}\}$.

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

iii) $\frac{d}{dt}V(x) < 0 \quad in \quad U - \{\bar{x}\}$.

then $\bar{x}$ is asymptotically stable.

Any function V that satisfies the conditions from Theorem 2.2.1 is said to be a *Lyapunov function.*

Theorem 2.2.2. *(LaSalle's Invariance Principle). Consider system (2.1.3). Let*

$$S = \left\{ x \in \bar{U} : \frac{d}{dt}V(x) = 0 \right\}, \tag{2.2.1}$$

and let M be the largest invariant set of (2.1.3) in S. If V is a Lyapunov function on U and $\gamma^+(x_0)$ is a bounded orbit of (2.1.3) which lies in S, then the ω-limit set of $\gamma^+(x_0)$ belongs to M (that is, $x(t, x_0) \to M$ as $t \to \infty$.)

- $\gamma^+(x_0)$: 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 2.2.1. *If $V(x) \to \infty$ as $|x| \to \infty$ and $\frac{dV}{dt} < 0$ on $\mathbb{R}^n$, then every solution of (2.1.3) is bounded and approaches the largest invariant set M of (2.1.3) in the set where $\frac{dV}{dt} = 0$. In particular, if $M = \{0\}$, then the solution $x = 0$ is globally asymptotically stable (GAS).*

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

Example 2.2.1. *Consider the following system*

$$x' = y - x^3,$$

$$y' = -x - y^3.$$

The system has an equilibrium solution at $(x, y) = (0, 0)$. *Let* $V(x, y) = x^2 + y^2$. *Obviously,* $V(0, 0) = 0$ *and* $V(x, y) > 0$ *in any neighbourhood of* $(0, 0)$. *Furthermore,*

$$\begin{aligned} V'(x, y) &= 2xx' + 2y'y, \\ &= 2x(y - x^3) + 2y(-x - y^3), \\ &= -2(x^4 + y^4) < 0. \end{aligned}$$

Hence, $V'(x, y) < 0$ *if* $(x, y) \neq (0, 0)$. *Thus, by Corollary 2.2.1, the equilibrium point* $(x, y) = (0, 0)$ *is globally asymptotically stable.*

Chapter 3

Epidemiological and Mathematical Epidemiology Preliminaries

Some basic notation and terminology in mathematical epidemiology of infectious diseases is given in this chapter. Simple models are presented to show how infectious disease spread can be modelled.

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations and the application of this study to the control of health problems. In this chapter, we review some concepts in epidemiology.

3.1 Definition of some basic terms

The following definitions are common in the epidemiology literature. References used here are [21, 22, 23] and [24].

- *Susceptible*: Group of individuals in a given population who are not infectious by the disease under consideration but can become infected as a result of their interactions with infected individuals or by having contacts with infected objects. Their susceptibility is dependent on the disease under consideration; entering into the susceptible compartment can occur at birth, onset of sexual maturity (e.g., for sexual transmitted diseases), or loss of protective immunity.

- *Exposed (Latently infected)*: Group of individuals who have been infected with the disease, but have not started transmitting the disease due to incubation. Incubation is the time from the time of exposure to an infectious disease until on set of the disease symptoms.

- *Infectious*: Group of individuals who are infected with the disease and are capable of transmitting the infection to uninfected individuals. Transmission could be directly to other individuals or through other means such as vectors or the environment.

- *Recovered /removed*: Group of individuals who are no longer susceptible to the infection at that time. Recovered individuals are individuals who were once infected with the infection and have developed immunity

against it. The recovery can be temporary, that is, individuals can be reinfected, or permanent (no reinfection). Removed individuals do not affect the transmission dynamics of the infection. The removal could be through isolation from the rest of the population, through immunization against the infection, through recovery from the disease with full immunity against reinfection or through death caused by the disease.

- *Vertical transmission*: Process in which an infected mother transfers the infection to her child during delivery or through breast feeding.

- *Horizontal transmission*: Transmission of infection through body contact or through contact with infected equipment or materials.

- *Force of infection*: The transmission dynamics of an infection depends on the per capita incidence rate of the infection $\lambda(t)$ in relation to susceptible individuals; $\lambda(t)$ forms the basis for the transmission dynamics in the model. The force of infection accounts for the transmission process between infectious and susceptible individuals and depends on the prevalence of infectious in the population, $I(t)/N(t)$, where $I(t)$ is the number of the infectious individual at time t and $N(t)$ is the total population at time t the contact rate c' and the transmission probability per contact β. A homogeneous mixing assumption means that $\lambda(t) = \beta c' I(t)/N(t)$. Transmission between the infected and the susceptible depends on how the contact structure is expected to change with the total population. The transmission dynamic could follow

  - *Density-dependent (standard incidence) transmission*: In this case, contacts are assumed to be proportional to the total population density ($c' = cN \approx N$ and $\lambda(t) = \beta I(t)$). The number of new infected is obtained from $\lambda(t)S(t)$, which depends on the number of infectious individuals and susceptible individuals in the population, if random mixing is assumed.

  - *Frequency-dependent (mass action) transmission*: This is the case in which the number of contacts is assumed to be independent of the total population, i.e., $c' = c$.

  The type of contacts required for the transmission depends on the mode of transmission of the infection (e.g, physical contact for directly transmitted infection such as influenza, chickenpox, or physical contact for sexually transmitted infection such as gonorrhea).

- *Incidence* is the number of new cases of illness (infection) occurring in a population during a given time period.

- *Prevalence* is the number or proportion of cases of illness occurring in a given population. It is often expressed per $100,000$ people in the epidemiology literature.

- *Prevalence rate* is the proportion of persons in a population who have a particular disease at a specified point in time or over a specified period of time.

- *Latency period* is the period of inapparent pathological changes following exposure, ending with the onset of symptoms.

- *Mortality rate*: A measure of the frequency of occurrence of death in a defined population during a specified interval of time.

- *Epidemic*: the occurrence of more cases of disease, in a given area or among a specific group of people over a particular period of time, than what is expected.

- *Pandemic*: An epidemic occurring over a very wide area (several countries or continents) and usually affecting a large proportion of the population.

- *Endemic situation*: The constant presence of a disease or infectious agent within a given geographic area or population group; may also refer to the usual prevalence of a given disease within such area or group.

- *Cohort*: A well-defined group of people who have had a common experience or exposure, who are then followed up for the incidence of new diseases, as in a cohort or prospective study.

- *Immunity*: Resistance developed in response to stimulus by an antigen (infecting agent or vaccine) and usually characterized by the presence of antibody produced by the host.

- *Birth rates*: This account for the rate at which newborn are introduced into the population per unit time. It is measured as population per unit

of time

- *Natural death rate*: Rate of death of individuals from the population due to old age and causes not disease related. It has the same unit of measurement as the birth rate. In models, its value can easily be obtained by finding the inverse of the average life expectancy of healthy individuals from the population.

- *Recovery rate*: Proportional to the inverse of the average time to recovery from the disease.

- *Disease induced death rate*: As for the natural death rate, it is proportional to the inverse life expectancy, on average, of an individual affected by the disease.

3.2 Model formulation

Material from references [21, 28, 38] and [40] is used in this section.

In order to understand the dynamics of infectious diseases, models are often formulated. To achieve this, we divide the the population under study into compartments and make assumptions about the nature and rates of transfer from one compartment to another. Diseases that confer permanent immunity have a different compartmental structure from diseases without immunity. The term SIR describes a disease which confers immunity against reinfection, indicating that movement of individuals is from the susceptible compartment S

to the infectious compartment I and to the removed compartment R. The term SIS describes a disease with no immunity; movement is from the susceptible compartment S to the infectious compartment I and back to the susceptible compartment. Other possibilities include $SEIR$ and $SEIS$ models, each having exposed period between being infected and becoming infectious and $SIRS$ model describes disease with temporary immunity after recovery from the infection. Differential equations are used to describe the rates of transfer between compartments, with time being the independent variable [21].

3.2.1 Equilibria of epidemic models

Section 2.1.2 is relevant here. There are two steady states which are usually sought after in any epidemiological model; the disease free equilibrium (DFE) and the endemic equilibrium (EE).

The disease free equilibrium is the state where the population is completely free from infection; the implication is that all infected compartments are zero and the total population comprises only susceptible or immune individuals. The endemic equilibrium is the state where the infection remains in the population, so there is a positive number of infectious individuals at equilibrium.

3.3 The basic reproduction number and stability analysis

The basic reproduction number $\mathcal{R}_0$ is defined as the expected number of secondary infections caused by the introduction of an infectious individual into a totally susceptible population. This number forms the basis of any epidemiological study because it helps to predict the future occurrence of any infection under consideration.

Stability analysis of steady states of the model shall be carried out through the application of the next-generation matrix in order to determine $\mathcal{R}_0$. In determining $\mathcal{R}_0$, there must be distinction between new infections and all other changes in the population [36].

Let $x = (x_1, x_2, \ldots, x_r)^T$ be r homogeneous compartments in a heterogeneous population, with each $x_i \geq 0$ the number of individuals in each compartment. Let the first m compartments correspond to the infected individuals (disease) compartments while the rest n compartments make up the uninfected compartments, where $r = m + n$. We define X_s to be the set of all disease free states, that is,

$$\mathrm{X}_s = \{x \geq 0 \,|\, x_i = 0, i = 1, \ldots, m\}.$$

Let

$$x' = \mathrm{f}_i(x) \,=\, \mathcal{F}_i(x) \,-\, \mathcal{V}_i(x),\ \mathrm{i} = 1, ..., n, \tag{3.3.1}$$

represent the dynamics of the infected compartments, where $\mathcal{F}_i(x)$ and $\mathcal{V}_i = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)$ are continuously differentiable functions, with $\mathcal{F}_i(x)$ the appearance rate of new infections in compartment i, $\mathcal{V}_i^+(x)$ the transfer rate of individuals into compartment i by all other means and $\mathcal{V}_i^-(x)$ the transfer rate of individual out of compartment i. Each of these functions is assumed to be differentiable at least twice in each variable. The disease transmission defined in (3.3.1) is made up of nonnegative initial conditions, that is, $\mathcal{F}_i(x) \geq 0$, $\mathcal{V}_i^-(x) \geq 0$, and $\mathcal{V}_i^+(x) \geq 0$ for all i $= 1, ..., n$.

The Jacobian matrices of $\mathcal{F}_i(x)$ and $\mathcal{V}_i(x)$ are evaluated at the disease free equilibrium point $\bar{x}$, giving

$$\mathrm{F} = \left[\frac{\partial \mathcal{F}_i}{\partial x_k}(\bar{x})\right] \quad \text{and} \quad \mathrm{V} = \left[\frac{\partial \mathcal{V}_i}{\partial x_k}(\bar{x})\right], \quad 1 \leq i, k \leq m \tag{3.3.2}$$

where F and V are $m \times m$ matrices, F is a nonnegative and V is a nonsingular matrix. The basic reproduction number $\mathcal{R}_0$ is evaluated as

$$\mathcal{R}_0 = \rho(\mathrm{FV}^{-1}), \tag{3.3.3}$$

where ρ denotes the spectral radius of the matrix (FV^{-1}). The following result is proved in [37], which we closely follow.

Theorem 3.3.1. *The disease free is locally asymptotically stable if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

For the computation of the basic reproduction number using the next generation matrix, the following assumptions need to be satisfied.

The functions $\mathcal{F}_i(x)$ and $\mathcal{V}_i(x)$ involve the direct transfer of individuals, hence they are nonnegative. Thus

i) If $x \geq 0$, then $\mathcal{F}_i(x),\ \mathcal{V}_i^+(x),\ \mathcal{V}_i^-(x) \geq 0$ for i $= 1, ..., n$.

If a compartment is empty, then there can be no transfer of individuals out of the compartment by whatever means. Thus

ii) If $x_i = 0$ then $\mathcal{V}_i^-(x) = 0$, for i $= 1, ..., n$.

Consider the disease transmission model given in (3.3.1) with $\mathcal{F}_i(x)$, i $= 1, ..., n$, satisfying the two conditions above. If $X_i = 0$, then $\mathcal{F}_i(x) \geq 0$ and hence, the nonnegative cone is positively invariant. For each non negative initial condition, there is a unique, nonnegative solution.

The next condition arises from the fact that the incidence of infection for the uninfected compartment is zero:

iii) $\mathcal{F}_i = 0$ if $j > m$.

To ensure that the disease free subspace is invariant, we assume that if the population is free of disease, then the population will remain free of disease. That is, there is no immigration of infectious. This condition is stated as follows

iv) if $x \in X_s$ then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_{j(x)}^+ = 0$ for i $= 1, ..., m$.

The remaining condition is based on the derivatives of f near a DFE. For our purpose, we define a DFE of (1) to be a (locally asymptotically) stable equilibrium solution of the disease free model, i.e., (1) restricted to X_s. Note that we need not assume that the model has a unique DFE. Consider a population near the DFE $\bar{x}$. If the population remains near the DFE (i.e., if the introduction of a few infectious individuals does not result in an epidemic), then the population will return to the DFE according to the linearized system

v) $x' = Df(x_0)(x - x_0)$,

where $Df(x_0)$ is the derivative $\left[\frac{\partial f_i}{\partial x_k}\right]$ evaluated at the DFE, $\bar{x}$ (i.e., the Jacobian matrix). Here and in what follows, some derivatives are one sided, since $\bar{x}$ is on the domain boundary. We restrict our attention to systems in which the DFE is stable in the absence of new infection. That is, if $\mathcal{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts.

3.3.1 Global stability analysis

The global stability analysis will be studied using references [18, 19] and [34]. A general compartmental disease transmission model can be written as

$$i' = \mathcal{F}(i, u) - \mathcal{V}(i, u), \tag{3.3.4a}$$

$$u' = g(i, u) \tag{3.3.4b}$$

with $g = (g_1, \ldots, g_n)^T$. Here $i = (i_1, \ldots, i_m)^T \in \mathbb{R}^m$ and $u = (u_1, \ldots, u_n)^T \in \mathbb{R}^n$ represent the populations in disease compartments and non-disease compartments, respectively. $\mathcal{F}$ and $\mathcal{V}$ are as defined in (3.3.2). If the basic reproduction number $\mathcal{R}_0 \leq 1$ the disease will die out, while the disease persists at a positive level if $\mathcal{R}_0 > 1$. Global stability results for many disease models are nontrivial. Endemic equilibrium global stability results in particular, normally become challenging due to the complexity and high dimension of disease models. Cholera and other waterborne disease models among others require the incorporation of their pathogen (water) into their models. This accounts for the complexity of such models compared to other disease models that are transmitted directly by human. As was explained in Chapter 2, Lyapunov functions are commonly used to establish global stability results for infectious diseases models. The following Lyapunov function (3.3.5)

$$V = \sum_{i=1}^{n} c_i \left(x_i - x_i^* - x_i^* \ln \frac{x_i}{x_i^*} \right), \tag{3.3.5}$$

originated from the first integral of a Lotka-Volterra system, is used as a general Lyapunov function in some mathematical biology literature. Suitable values for c_i have to be determined such that V' along solutions of the model is nonpositive.

3.3.2 Global stability of the DFE: A matrix-theoretic method.

Material from [34] will be used in the analysis of the global stability analysis of the DFE. Define

$$f(i,u) := (F-V)i - \mathcal{F}(i,u) + \mathcal{V}(i,u), \tag{3.3.6a}$$

$$i' := (F-V)i - f(i,u), \tag{3.3.6b}$$

where $f(0,u) = 0$ is the DFE of (3.3.4). Equation (3.3.6a) represents the dynamics of diseased compartments of a general compartmental disease model. Let $w^T \geq 0$ be the left eigenvector of the nonnegative matrix $V^{-1}F$ corresponding to the eigenvalue $\rho(V^{-1}F) = \rho(FV^{-1}) = \mathcal{R}_0$. The following result provides a method for constructing a Lyapunov function for (3.3.4), using the Perron eigenvector.

Theorem 3.3.2. *Let F, V be defined as in (3.3.2) and $f(i,u)$ be defined as in (3.3.6a). If $f(i,u) \geq 0$ in $\Gamma \subset \mathbb{R}^{n+m}_+$, $F \geq 0$, $V^{-1} \geq 0$, and $\mathcal{R}_0 \leq 1$, then the function $Q = w^T V^{-1} i$ is a Lyapunov function for the model (3.3.4) on Γ.*

Proof. Differentiating Q along solutions of (3.3.4) gives

$$\begin{aligned} Q' = w^T V^{-1} i' &= w^T V^{-1} \left((F-V)i - f(i,u)\right) \\ &= w^T V^{-1}(F-V)i - w^T V^{-1} f(i,u) \\ &= w^T V^{-1}(\mathcal{R}_0 - 1) - w^T V^{-1} f(\mathcal{S}, \mathcal{I}) \end{aligned}$$

Since $w^T \geq 0,\ V^{-1} \geq 0$ and $f(i,u) \geq 0$ in Γ, this implies $w^T V^{-1}(\mathcal{R}_0 - 1) - w^T V^{-1} f(\mathcal{S},\mathcal{I}) \leq 0$. If $\mathcal{R}_0 \leq 1$, then $Q' \leq 0$ in Γ, and thus Q is a Lyapunov function for system (3.3.4). □

The Lyapunov function constructed in Theorem 3.3.2 can be used to prove global stability of DFE as well as uniform persistence and thus establish the existence of an EE. The result below provides a scenario in which assumptions can be conveniently checked for disease models.

Theorem 3.3.3. *Let F, V and $f(i,u)$ be defined as in (3.3.2) and (3.3.6a), respectively, and let $\Gamma \subset \mathbb{R}^{n+m}_+$ be compact such that $(0,u_0) \in \Gamma$ and Γ is positively invariant with respect to (3.3.4). Suppose that $f(i,u) \geq 0$ with $f(i,u_0) = 0$ in Γ, $F \geq 0$, $V^{-1} \geq 0$ and $V^{-1}F$ is irreducible. Assume that the disease-free system $u' = g(0,u)$ has a unique equilibrium $u = u_0 > 0$ that is GAS in $\mathbb{R}^m_+$. Then the following results hold for (3.3.4):*

1. *if $\mathcal{R}_0 < 1$, then the DFE $\mathcal{E}_0$ is GAS in Γ.*

2. *if $\mathcal{R}_0 > 1$, then $\mathcal{E}_0$ is unstable and system (3.3.4) is uniformly persistent and there exist at least one EE.*

If $f(i,u_0) = 0$ in Γ, $F \geq 0$, $V^{-1} \geq 0$ and $V^{-1}F$ is reducible then this theorem cannot be used to establish the global stability of the disease free equilibrium point.

This result was used to study global stability for some disease models in the following references [12, 33].

3.4 Susceptible-Infectious-Removed (SIR)

References [21] and [40] will be used in this section.

To illustrate the type of problems arising in mathematical epidemic models and the techniques used to solve these problems, we shall in this section consider variations on the basic SIR model.

This model was proposed by Kermack and McKendrick in 1927 [16]. It divides the total population into three compartments, the susceptible S, infectious I and removed R. This model is often used for diseases that confer natural immunity and which invariably influence the behaviour of the immune system against reinfection; such diseases include measles, chicken pox, etc. It is also used for fatal diseases.

$$S' = -\beta SI$$

$$I' = \beta SI - \gamma I$$

$$R' = \gamma I.$$

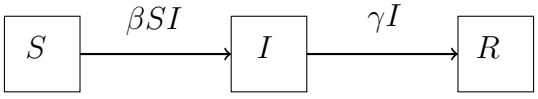


Figure 3.1: Schematic diagram for an SIR model without demography.

The model is formulated based on the following assumptions:

1. Incidence is mass action.
2. Infectious individuals leave the infectious class at rate γI per unit time, because of recovery or death.
3. There is no entry into or departure from the population.

From this model, it can be noted that the total population of the system is constant. This is deduced from the fact that

$$N' = (S + I + R)' = -\beta SI + \beta SI - \gamma I + \gamma I = 0.$$

Since this is true for all values of t, then N is constant. R can be dropped since the dynamics of (S, I) do not depend on it. The system is then

$$S' = -\beta SI \tag{3.4.1a}$$

$$I' = (\beta S - \gamma)I. \tag{3.4.1b}$$

Through a qualitative approach, much can be learned about the behaviour of solutions of (3.4.1). It is very important to note that the model makes sense as long as both $S(t)$ and $I(t)$ remain nonnegative. We observe that $S' < 0$ for all t and $I' > 0$ if and only if $S > \gamma/\beta$. Thus I increases so long as $S > \gamma/\beta$ but since S decreases for all t, I ultimately decreases and approaches zero. If $S_0 < \gamma/\beta$, I decreases to zero (there is no epidemic), while if $S_0 > \gamma/\beta$, I first

increases to a maximum attainable when $S = \gamma/\beta$ and then decreases to zero (there is an epidemic).

We want to examine if introducing a small number of infectious individuals into a totally susceptible population will result into epidemic or not.

The quantity $\beta S_0/\gamma$ is a threshold quantity, called the *basic reproduction number* and denoted by $\mathcal{R}_0$, which determines whether there is an epidemic or not. If $\mathcal{R}_0 < 1$ the infection dies out without going through a peak, while if $\mathcal{R}_0 > 1$ there is an epidemic as we will see later.

By dividing the equations from (3.4.1), we have

$$\frac{I'}{S'} = \frac{dI}{dS} = \frac{\gamma}{\beta S} - S$$

which, when integrated, gives

$$I(S) = \frac{\gamma}{\beta} \ln S - S + c,$$

where c is an arbitrary constant of integration, which is determined by the initial values S_0, I_0 of S, I, respectively, with c given as

$$c = I_0 - \left(\frac{\gamma}{\beta} \ln S_0 - S_0 \right).$$

Then

$$I(S) = \frac{\gamma}{\beta} \ln S - S + I_0 - \left(\frac{\gamma}{\beta} \ln S_0 - S_0 \right). \tag{3.4.2}$$

This gives a curve in the (S, I) plane. Consider a total population of size N, into which a small number of infectious individuals are introduced, so that $S_0 \approx N, I_0 \approx 0$ and $\mathcal{R}_0 = \beta N/\gamma$. Recall that $\lim_{t\to\infty} I(t) = 0$ and let $S_\infty = \lim_{t\to\infty} S(t)$; then

$$N - \frac{\gamma}{\beta} \ln S_0 = S_\infty - \frac{\gamma}{\beta} \ln S_\infty,$$

from which we obtain an expression for β/γ in term of the measurable quantities S_0 and S_∞, namely

$$\frac{\beta}{\gamma} = \frac{\ln S_0 - \ln S_\infty}{N - S_\infty}.$$

This may be rewritten in terms of $\mathcal{R}_0$ as the *final size relation*

$$\ln S_0 - \ln S_\infty = \mathcal{R}_0 \left[1 - \frac{S_\infty}{N}\right]. \tag{3.4.3}$$

In particular, since the right side of (3.4.3) is finite, the left side is also finite and this shows that $S_\infty > 0$.

The maximum number of infectious individuals at any time is the number of infectious individuals when the derivative of I is zero, that is, when $S = \gamma/\beta$. This maximum is given by

$$I_{\max} = S_0 + I_0 - \frac{\gamma}{\beta} \ln S_0 - \frac{\gamma}{\beta} + \frac{\gamma}{\beta} \ln \frac{\gamma}{\beta}, \tag{3.4.4}$$

which is obtained by substituting $S = \gamma/\beta, I = I_{\max}$ into (3.4.2).

3.5 Susceptible-Infectious (SI) Model

An SI model is used to describe the dynamics of a contagious and *incurable* disease. Examples of such diseases include HIV, which causes AIDS (Acquired immunodeficiency syndrome), as well as other chronic diseases. They are lifelong diseases without recovery. The model divides the population into two compartments, namely susceptible and infectious individuals. Let $S(t)$ be the number of individuals who are susceptible to the disease at time t and $I(t)$ be the number of individuals that are infectious with the disease at time t. The total population at time t is $N(t) = S(t) + I(t)$.

3.5.1 Basic SI model with standard incidence

Assume that the disease occurs on a time-scale much faster than other population processes (births and deaths) and there is no disease induced death, so the population remains constant over time. The dynamics of a basic SI model using *standard incidence* is given by:

$$S' = -\frac{\beta SI}{N} \tag{3.5.1a}$$

$$I' = \frac{\beta SI}{N}, \tag{3.5.1b}$$

with initial conditions $S(0) = S_0$ and $I(0) = I_0$. We observe that

$$\frac{dN}{dt} = \frac{d}{dt}\{S + I\} = S' + I' = 0,$$

and so the total population N remains constant over time with $N(t) = S_0 + I_0$ for all $t \geq 0$. Since N is constant, knowledge of, say, $I(t)$ implies knowledge of $S(t) = N - I(t)$. As a consequence, we now study the dynamics of $I(t)$, in which we substitute $N - I(t)$ for $S(t)$. Therefore, (3.5.1) takes the form

$$\begin{aligned} I' &= \frac{\beta SI}{N} \\ &= \beta(N - I)\frac{I}{N} \\ &= \beta\left(I - \frac{I^2}{N}\right) \\ &= \beta I\left(1 - \frac{I}{N}\right), \end{aligned} \tag{3.5.2}$$

i.e., a *logistic equation*.

3.5.2 Existence and uniqueness of solutions

Analysis of (3.5.2) requires to ascertain that solutions to the model exist and are unique. This is done by applying existence and uniqueness Theorem 2.1.2. We have

$$I' = \beta I\left(1 - \frac{I}{N}\right),$$

so

$$f(I) = \beta I\left(1 - \frac{I}{N}\right) \tag{3.5.3}$$

and thus

$$\frac{\partial f}{\partial I} = \beta\left(1 - \frac{2I}{N}\right).$$

Since both f and $\partial f/\partial I$ are continuously differentiable in the domain of f, solutions to the initial value problem in (3.5.2) exist and are unique according to the existence and uniqueness Theorem 2.1.2.

3.5.3 Positivity of solutions

Equation (3.5.3) has two equilibrium solutions which can be obtained from $I' = f(I) = \beta I\,(1 - I/N) = 0$, yielding $I(t) = 0$ and $I(t) = N$. These reveal that solutions remain nonnegative and bounded. Uniqueness of solutions implies the solution cannot cross the curve $I(t) = 0$ (nor the curve $I(t) = N$).

Equation (3.5.2) with initial condition $I(0) = I_0$ can be solved explicitly since the resulting equation is a Bernoulli equation. The explicit solution is obtained to be

$$I(t) = \frac{NI_0}{I_0 + (N - I_0)e^{-\beta t}}. \tag{3.5.4}$$

The asymptotic behavior of the solution can be evaluated by considering the following cases:

- If $I_0 = 0$, then $I(t) = 0$ for all $t \geq 0$.

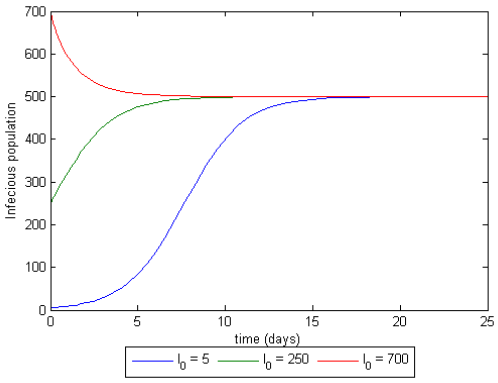


Figure 3.2: Dynamics of the SI model without demography (3.5.1). Plot of some solutions to (3.5.2), for $N = 500,$ and $\beta = 0.6$.

- If $I_0 \in (0, N)$, then $\beta I > 0$ and $1 - \frac{I}{N} > 0$, which implies that $I' > 0$. Consequently, $I(t)$ increases.

- If $I_0 = N$, then $I(t) = N$ for all $t \geq 0$.

- If $I_0 > N$, then $\beta I > 0$ and $\frac{I}{N} > 1$ so $1 - \frac{I}{N} < 0$, which implies that $I' < 0$; consequently, $I(t)$ decreases.

Hence, suppose that $I_0 > 0$, then the asymptotic behavior of the solution of (3.5.2) is such that

$$\lim_{t \to \infty} I(t) = N$$

and if $I_0 = 0$, then $I(t) = 0$ for all $t \geq 0$. This implies that in the absence of any intervention strategies, the disease invades the whole population.

Figure 3.2 reveals that regardless of the initial population of infectious

individuals that are being introduced into the total population, in the absence of intervention measure, the whole population will be infected with the disease.

3.5.4 SI model with demography using the standard incidence function.

Model (3.5.2) examined above is now modified to include demography (birth and death) and disease induced death. The study will enable us to understand the effect of birth and death on the transmission dynamics of infectious diseases. This models the situation in which the disease is fatal and a certain number of the infected individuals die as a result of the disease. The model takes the

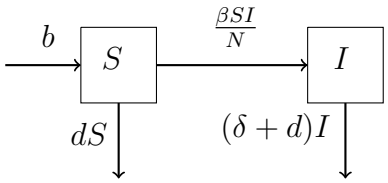


Figure 3.3: Schematic diagram for an SI model with demography and disease induced death, as given by (3.5.5).

form

$$S' = b - \frac{\beta SI}{N} - dS \tag{3.5.5a}$$

$$I' = \frac{\beta SI}{N} - dI - \delta I, \tag{3.5.5b}$$

where β is the transmission rate, b is the recruitment rate, d is the natural death rate and δ is the disease induced death rate. All parameters and initial

conditions are nonnegative. The total population satisfies

$$N' = S' + I' = b - dN - \delta I \leq b - dN. \tag{3.5.6}$$

Equation (3.5.6) can be rewritten as $N' + dN \leq b$, a first order scalar differential equation that can be solved with the technique of integrating factors. Therefore the explicit solution to (3.5.6) is

$$N(t) \leq N_0 e^{-dt} + \frac{b}{d}\left(1 - e^{-dt}\right).$$

Thus, the asymptotic behavior of the total population is such that

$$\limsup_{t\to\infty} N(t) \leq \lim_{t\to\infty}\left(N_0 e^{-dt} + \frac{b}{d}\left(1 - e^{-dt}\right)\right) = \frac{b}{d}.$$

The steady state of equation (3.5.5) can be obtained by setting $S' = I' = 0$, i.e.,

$$b - \frac{\beta SI}{N} - dS = 0 \tag{3.5.7a}$$

$$\frac{\beta SI}{N} - (\delta + d)I = 0. \tag{3.5.7b}$$

Equation (3.5.7b) can be simplified to $\left(\frac{\beta S}{N} - (\delta + d)\right) I = 0$, which can be solved further to give

$$I = 0 \qquad \text{or} \qquad S = \frac{b(\delta + d)}{\beta d}. \tag{3.5.8}$$

Substituting $I = 0$ into (3.5.7a) yields

$$S = \frac{b}{d}. \tag{3.5.9}$$

Substituting the value of S from (3.5.8) into (3.5.7a), we have

$$b - (d + \delta)I - \frac{b(d + \delta)}{\beta} = 0,$$

which after further simplification gives

$$\frac{\beta b - b(d + \delta)}{\beta(d + \delta)} = I. \tag{3.5.10}$$

Thus model (3.5.5) has two equilibrium points: the disease free equilibrium point (DFE) and the endemic equilibrium point (EE), taking the form $(\bar{S}, \bar{I}) = (b/d,\, 0)$ and $(S^*, I^*) = \left(\frac{b(\delta + d)}{\beta d},\, \frac{b(\beta - (\delta + d))}{\beta(\delta + d)}\right)$, respectively.

In order to use Theorem 3.3.1 to compute $\mathcal{R}_0$ for system (3.5.5), we must ensure that conditions $i)$ to $v)$ are satisfied. This means the following must be true. The incidence function is $\mathcal{F}(I, S) = \beta SI/N$ and transition function is $\mathcal{V}(I, S) = (\delta + d)I$. Furthermore,

- $\mathcal{F}(0, S) = \frac{\beta S0}{N} = 0$, and $\mathcal{V}(0, S) = (\delta + d)0 = 0$ for $S \geq 0$.
- $\mathcal{F}(I, S) = \frac{\beta SI}{N} \geq 0$ for $S > 0$ and $I > 0$.

- $\mathcal{V}(I,S) = (\delta + d)I \leq 0$ when $I = 0$.
- $\mathcal{V}(I,S) = (\delta + d)I \geq 0$ for all $S > 0$ and $I > 0$.
- $S' = b - \dfrac{\beta SI}{N} - dS$ has a unique disease free equilibrium $\left(0, \frac{b}{d}\right)$ that is locally asymptotically stable.

Based on the definition of F and V in (3.3.2), we have

$$F = \frac{\partial \mathcal{F}}{\partial I} = \frac{\beta S}{N},\ V = \frac{\partial \mathcal{V}}{\partial I} = (\delta + d),$$

At the DFE, $S = N$; then $\mathcal{R}_0 = \rho(FV^{-1})$ is computed to be

$$\mathcal{R}_0 = \frac{\beta}{\delta + d}$$

and hence the endemic equilibrium point can be expressed as a function of $\mathcal{R}_0$,

$$(S^*, I^*) = \left(\frac{b}{d\mathcal{R}_0}, \frac{b}{\beta}(\mathcal{R}_0 - 1)\right).$$

Based on Theorem 3.3.1, the disease free equilibrium point is then locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.

3.5.5 Stability analysis of the endemic equilibrium point for the SI model with demography

The local stability of the endemic equilibrium point can be evaluated by substituting the endemic equilibrium state into the Jacobian matrix obtained

after the model equations have been linearized as defined in (2.1.8) and then evaluating the eigenvalues. We have, at an arbitrary (S, I),

$$J(S,I) = \begin{pmatrix} -\frac{\beta I}{N} - d & -\frac{\beta S}{N} \\ \\ \frac{\beta I}{N} & \frac{\beta S}{N} - (\delta + d) \end{pmatrix}. \tag{3.5.11}$$

Therefore,

$$J(S^*, I^*) = \begin{pmatrix} -\frac{\beta d}{\delta+d} & -(\delta+d) \\ \\ \frac{d(\beta-(\delta+d))}{\delta+d} & 0 \end{pmatrix} = \begin{pmatrix} -d\mathcal{R}_0 & -(\delta+d) \\ \\ d(\mathcal{R}_0 - 1) & 0 \end{pmatrix}. \tag{3.5.12}$$

The characteristic polynomial resulting from the Jacobian matrix evaluated at the endemic equilibrium point is given by

$$P(\lambda) = \lambda^2 + d\mathcal{R}_0\lambda + d(\delta+d)(\mathcal{R}_0 - 1).$$

The two eigenvalues of the characteristic polynomial can be obtained from the quadratic formula

$$\lambda_{1,2} = \left\{ -\frac{d\mathcal{R}_0}{2} \pm \frac{1}{2}\sqrt{\triangle} \right\},$$

where $\triangle = d^2\mathcal{R}_0^2 - 4d(\delta+d)(\mathcal{R}_0 - 1)$. Therefore,

- if $\mathcal{R}_0 > 1$, then $\sqrt{\triangle} < d\mathcal{R}_0$, hence the two eigenvalues have negative real parts, which implies the endemic equilibrium point is locally asymptotically stable stable.

- if $\mathcal{R}_0 < 1$, then $\sqrt{\triangle} > d\mathcal{R}_0$, hence the eigenvalues have one positive and one negative real parts, which implies the endemic equilibrium point is unstable.

By Theorem 2.1.4, the endemic equilibrium point is locally asymptotically stable if $\mathcal{R}_0 > 1$ and unstable if $\mathcal{R}_0 < 1$.

3.6 Other examples of epidemic models

References [21, 23] and [24] were used in this section.

- **Susceptible-Infectious-Susceptible (SIS)**: This type of model has to do with infections which are transient in nature; the infected individuals recover without immunity. Such diseases include gonorrhea. A typical

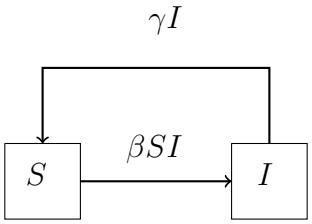


Figure 3.4: Schematic diagram for an SIS model with no demography.

SIS model takes the form:

$$S' = \gamma I - \beta SI$$

$$I' = \beta SI - \gamma I.$$

- **Susceptible infectious removed susceptible (SIRS)**: This type of model is used for a disease that is curable; the recovered individuals have temporary immunity which wanes after a while, so they become susceptible to the disease again.

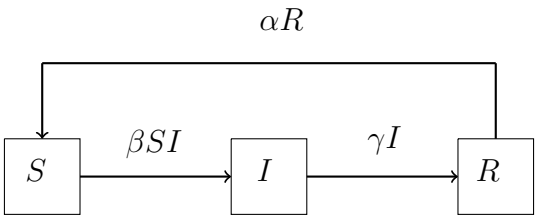


Figure 3.5: Schematic diagram for an SIRS model with no demography.

An SIRS model without demography takes the form

$$S' = \alpha R - \beta SI$$

$$I' = \beta SI - \gamma I$$

$$R' = \gamma I - \alpha R.$$

- **Susceptible-Latent-Infectious-Recovered (SLIR)**: This type of model is used for a disease in which infected individuals undergo an incubation period before becoming infectious. Infected individuals are latently infected before becoming infectious and the length of their latent period depends on the disease. Such individuals do not transmit the disease until the onset of symptoms.

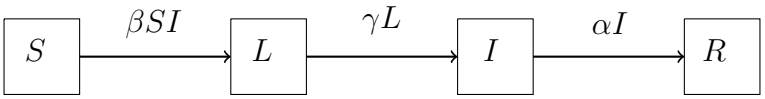


Figure 3.6: Schematic diagram for an SLIR model without demography and no loss of immunity.

A typical SLIR model without demography takes the form

$$S' = -\beta SI$$

$$L' = \beta SI - \gamma L$$

$$I' = \gamma L - \alpha I$$

$$R' = \alpha I.$$

Here, $\frac{1}{\gamma}$ is the average duration of the incubation period.

3.7 SI model with mass action incidence

The model is similar to the SI model with vital dynamic (3.5.5) analyzed earlier, except for the fact that it uses a mass action incidence function, while the previously analyzed model used standard incidence. This is to illustrate how to analyze a model with mass action incidence as the force of infection in the Ebola model that will be analyzed in this thesis uses mass action incidence. The model takes the form

$$S' = b - \beta SI - dS \tag{3.7.1a}$$

$$I' = \beta SI - (\delta + d)I. \tag{3.7.1b}$$

Equilibrium points for this model satisfy

$$b - \beta SI - dS = 0 \tag{3.7.2a}$$

$$\beta SI - (\delta + d)I = 0. \tag{3.7.2b}$$

Solving (3.7.2b) for S or I,

$$(\beta S - (\delta + d))I = 0 \;\Leftrightarrow\; I = 0 \text{ or } \beta S - (\delta + d) = 0$$

$$\Leftrightarrow I = 0 \text{ or } S = \frac{\delta + d}{\beta}. \tag{3.7.2c}$$

In the absence of the disease, substituting $I = 0$ into (3.7.2a) gives

$$b - dS = 0 \;\Leftrightarrow\; S = \frac{b}{d}.$$

This gives the disease free equilibrium point $(\bar{S}, \bar{I}) = \left(\frac{b}{d},\ 0\right)$. In the case when $I \neq 0$, substituting $S = \frac{\delta+d}{\beta}$ into (3.7.2a) gives

$$b - (\delta + d)I - \frac{d(\delta + d)}{\beta} = 0 \;\Leftrightarrow\; I = \frac{\beta b - d(\delta + d)}{\beta(\delta + d)}.$$

This gives the endemic equilibrium point $(S^*,\ I^*) = \left(\frac{(\delta+d)}{\beta},\ \frac{\beta b - d(\delta+d)}{\beta(\delta+d)}\right)$.

The basic reproduction number for this model, computed using the next generation matrix, is given by $\mathcal{R}_0 = \dfrac{\beta b}{d(\delta + d)}$, so the endemic equilibrium point can be written in term $\mathcal{R}_0$ as $(S^*,\ I^*) = \left(\frac{b}{d\mathcal{R}_0},\ \frac{d}{\beta}(\mathcal{R}_0 - 1)\right)$. Also the local stability of the DFE follows from using Theorem 3.3.1.

Local stability of the endemic equilibrium point can be evaluated by substituting the endemic equilibrium state into the Jacobian matrix for (3.7.1),

$$J(S,I) = \begin{pmatrix} -\beta I - d & -\beta S \\ \beta I & \beta S - (\delta + d) \end{pmatrix} \tag{3.7.3}$$

and then evaluating the eigenvalues. Note that this is similar to the result found in Section 3.5.5. We obtain

$$J(S^*,I^*) = \begin{pmatrix} -\frac{\beta d}{(\delta+d)} & -(\delta+d) \\ \frac{(\beta b - d(\delta+d))}{(\delta+d)} & 0 \end{pmatrix} = \begin{pmatrix} -d\mathcal{R}_0 & -(\delta+d) \\ d(\mathcal{R}_0 - 1) & 0 \end{pmatrix}. \tag{3.7.4}$$

The characteristic polynomial is $P(\lambda) = \lambda^2 + d\mathcal{R}_0\lambda + d(\delta+d)(\mathcal{R}_0 - 1)$. The two roots of the characteristic polynomial take the form

$$\lambda_{1,2} = \left\{ -\frac{d\mathcal{R}_0}{2} \pm \frac{1}{2}\sqrt{\triangle} \right\},$$

where $\triangle = d^2\mathcal{R}_0^2 - 4d(\delta+d)(\mathcal{R}_0 - 1)$.

- if $\mathcal{R}_0 > 1$ then $\sqrt{\triangle} < d\mathcal{R}_0$, hence the two eigenvalues have negative real part, which implies the endemic equilibrium point is locally asymptotically stable.

- if $\mathcal{R}_0 < 1$ then $\sqrt{\triangle} > d\mathcal{R}_0$, hence the eigenvalues have one positive and one negative real part, which implies the endemic equilibrium point is unstable.

By Theorem 2.1.4, the endemic equilibrium point is locally asymptotically stable if $\mathcal{R}_0 > 1$ and unstable if $\mathcal{R}_0 < 1$.

Chapter 4

Background on Ebola Virus Disease

Material in this chapter can be found in references [1, 2, 6, 8, 10, 13, 20, 26, 27, 31, 35] and [39]. Ebola virus disease (EVD), also known as Ebola hemorrhagic fever (EHF), is a viral hemorrhagic fever of humans and other primates, caused by Ebola viruses. Ebola first emerged in Sudan and Zaire in 1976. It was named after the Ebola River in Zaire. The first outbreak of Ebola (Ebola-Sudan) killed 53% of the 284 infected people. Months later, a second outbreak emerged in Yambuku, Zaire (Ebola-Zarie, EBOZ). EBOZ led to higher mortality than Ebola-Sudan: 318 people were infected with EBOZ and over 80% of the infected people died as a result of the disease. The third strain of the virus, known as Ebola-Reston (EBOR), was first identified in 1989 when infected monkeys were imported into Reston, Virginia, from Mindanao in the Philippine. The people who were infected with EBOR never developed Ebola hemorrhagic fever (EHF).

The last strain was discovered in Cote d'Ivoire in 1994 (Ebola Cote d'Ivoire).

4.1 West Africa 2014 Ebola Outbreak

Ebola virus outbreaks have occurred, most notably in parts of Central Africa. However, the largest and most devastating outbreak of EVD is the 2014 epidemic in three West African countries (Guinea, Liberia and Sierra Leone). The first outbreak in West Africa occurred in Guinea in March, 2014. The outbreak was widely spread in Liberia (its capital city Monrovia and other metropolitan cities) and Sierra Leone. The disease also spread to Nigeria by an airline passenger who arrived from Liberia. It spread to Senegal by a student from Guinea who arrived by land transportation. This spread was not limited to Africa alone; it affected a Western European country (Madrid, Spain) and the United States of America (Dallas, Texas; New York City). However, outside the 3 West African countries, there was little to no local transmission, with the only local transmission happening in Nigeria which was quickly contained.

4.2 Transmission mechanisms

Several attempts have been made to identify the natural reservoir of Ebola virus. The fruit bats of the *Pteropodidae* family are believed to be the natural host for Ebola virus. The virus is introduced into the human population through close contact with blood secretions, organs and other bodily fluids of infected

animals such as chimpanzees, gorillas, fruit bats, monkeys, forest antelope and porcupines found ill or dead in the rainforest. Transmission is possible through direct contact with bodily fluids such as blood of infected individuals, breast milk or through recently contaminated surfaces and materials such as beddings and clothings. EVD is also transmitted during burial rites of infected individuals, where the mourners have direct contact with the corpses. This occurs because infected individuals remain infectious as long as the virus remains in their blood.

An infected individual does not start to show symptoms immediately, neither do they start to transmit the virus. This is because the virus undergoes incubation, the period between the infection and the onset of symptoms, which usually ranges from $2 - 21$ days in the case of EVD. During incubation, the virus infects cells, replicates and bursts out of the infected cells, producing EVD glycoproteins that become prevalent in blood vessels, thus rendering blood vessels more permeable. The increased permeability causes blood vessels to ooze blood. The natural defense system of the infected individual is also tampered with by EVD, thereby infecting the immune cells, which are channels through which the virus can be transported to other body parts and organs such as the liver, spleen, kidney and brain. This eventually causes the organs to fail, leading to the death of the individual.

After the incubation period, an infected individual begins to show acute symptoms, which include fever, sore throat, muscular pain, headaches, loss of appetite and abdominal pain. After these symptoms comes vomiting, diarrhea

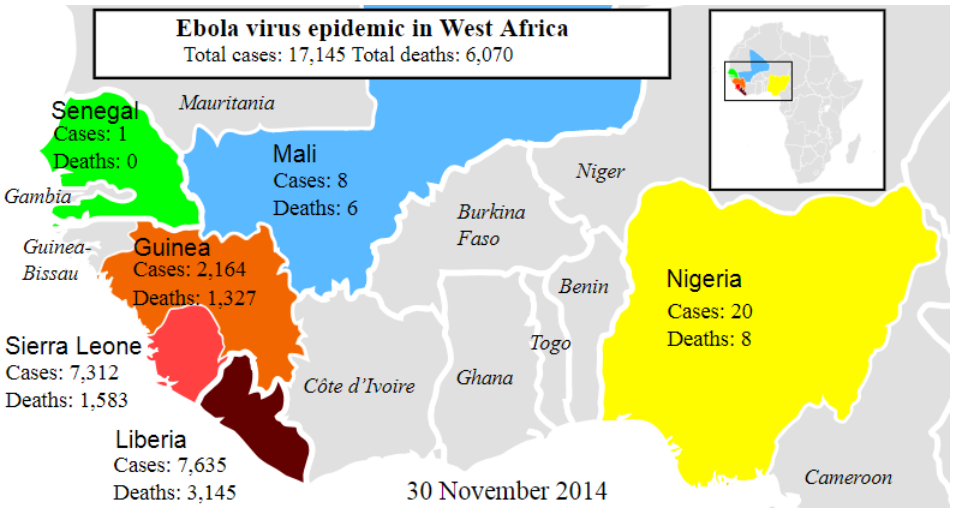


Figure 4.1: 2014 Ebola outbreak in West Africa [41].

and a rash. Infected individuals also experience liver and kidney dysfunction, bleed both internally and externally. They become infectious at the onset of symptoms. The virus has an average case fatality of 50%. During this outbreak, death usually takes place within $6 - 16$ days after the onset of the symptoms.

4.3 Literature Review

The recent outbreak of Ebola Virus Disease has led researchers to develop mathematical models to help understand the dynamic of the virus and the appropriate intervention techniques which have to be put in place in order to be able to combat the disease effectively. A stochastic SEIR model was proposed in [9]. The Ebola outbreak data of Congo in 1995 and Uganda in 2000 were fitted with this model. The basic reproduction number in the absence of

intervention for Congo was estimated to be $\mathcal{R}_0 = 1.83$ while that in Uganda was $\mathcal{R}_0 = 1.34$. A similar model was formulated in [25], which used the same data for the epidemic outbreak in Congo and yielded a lower estimate for the basic reproduction number $\mathcal{R}_0 \approx 1.4$. An extension was made to the stochastic model SEIR model formulated in [9]. This extension, which can be seen in [17], incorporated two other compartments, namely the hospitalized and the unburied deceased. The basic reproduction number estimated for this new model yields $\mathcal{R}_0 \approx 2.7$ with $(95\%\text{C.I} : 1.19 - 2.8)$ for EVD Congo outbreak in 1995 and $\mathcal{R}_0 \approx 2.7$ with $(95\%\text{C.I} : 2.5 - 4.1)$ for the 2000 Uganda epidemic.

Due to a peculiarity of EVD, which is the fact that an infected individual remains infectious after death, an SEIR model for the 2014 outbreak was also formulated in [5] that keeps track of the infections that occurred in the community, in the hospital and during funerals. It was discovered from the model that the rate of transmission of the virus during traditional burial was much higher than the rate at which it is being transmitted at all other places under consideration. The conclusion from this model was that the time of burial and the funeral rite play a major role in the reduction of the basic reproduction number $\mathcal{R}_0$.

A relentless dissemination among several countries, dramatic number of cases including health care workers and the inability to control the outbreak which grew exponentially [4] are the main features of the 2014 EVD outbreak.

Statistics reveal that in October 2014, the new cases count for 2014 EVD

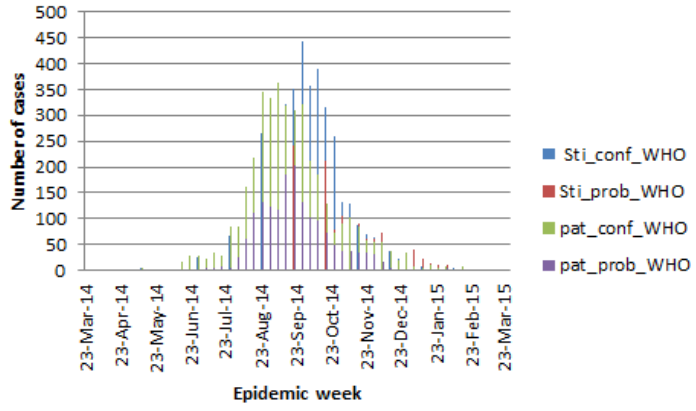
Legend terms	Meaning
Sti-conf-WHO	Situation report of confirmed cases
Sti-prob-WHO	Situation report of probable cases
pat-conf-WHO	Patient database of confirmed cases
pat-prob-WHO	Patient database of probable cases
cumsc-WHO	Cumulative number of confirmed cases of the situation report
cumsp-WHO	Cumulative number of probable cases of the situation report
cumpc-WHO	Cumulative number of confirmed cases of the patient database
cumpp-WHO	Cumulative number of probable cases of the patient database
HW-deaths-WHO	Cumulative number of death by health care workers
HW-cases-WHO	Cumulative number of cases by health care workers

Table 4.1: Terms used in the legends of Figure 4.2.

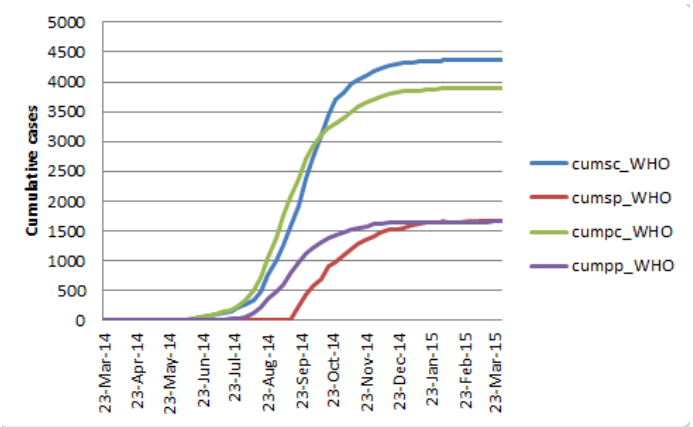
was $8,997$ with fatalities of $4,493$. These numbers increased to $15,035$ and $5,689$ respectively by 23^{rd} of November 2014 [1]. The latest statistical update from March 2015 reveals that $28,646$ were infected and $11,323$ died from the disease [27].

Figure 4.2(a) was generated with the situation report and patient database data obtained from the World Health Organization website. It shows the confirmed and probable cases of Ebola virus in Liberia. Figure 4.2(b) reveals the cumulative number of confirmed and probable cases from the situation report and patient databases of the WHO report. Figure 4.2(c) reveals that health care workers are not exempt from infection. It shows the cumulative number of health care workers that were infected and that died as a result of the infection in Liberia within a one year period.

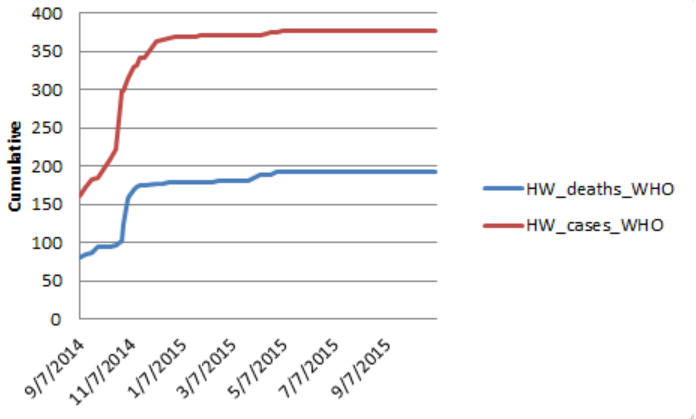
All these figures reveal that proper attention is needed in order to understand the transmission dynamics of this virus, in order to successfully combat the



(a)



(b)



(c)

Figure 4.2: (a) Cases of Ebola virus in Liberia; (b) cumulative number of confirmed and probable cases of Ebola virus in Liberia; and (c) cumulative number of Liberia health care workers cases. Legends meaning can be found in Table 4.1.

infection and prevent future outbreaks.

A metapopulation stochastic epidemic model for 2014 EVD outbreak was formulated by Gomes et al [11]. This model was used to assess international spreading risk associated with the outbreak. Their model was formulated as a global epidemic and mobility model. The mobility model used integrates daily airline passenger traffic between over 200 countries. It was used to generate stochastic, individual based simulation of the epidemic spread worldwide. The compartmental disease model was used to illustrate transmission dynamics within a community, hospital and during funeral ceremonies. The results found an estimate of $1.5 - 2.0$ for the basic reproduction number for the short-time growth rate of the diseased in affected West African countries. They also found that surveillance and containment notwithstanding, the major component of the overall transmissibility of the disease is from the hospital and during funeral rites.

Chapter 5

A mathematical model for Ebola virus disease

This chapter is dedicated to the formulation of a mathematical model for Ebola virus disease.

Assumptions about the model

The following assumptions will be used in the formulation of the model.

- Individuals can be categorized into different compartments based on their epidemiological state.
- There is no vertical transmission of the infection: there is no infection from mother to unborn baby.
- There is no reinfection: after having recovered from the disease, individuals do not become infected again.

- There is no asymptomatic infection: to infect others, individuals must be in the infectious compartment.
- There is homogeneous mixing; all susceptible individuals have equal likelihood of becoming infected by infectious individuals.
- Incidence follows a mass action law.
- There is no other intervention procedure than isolation and treatment of infectious individuals.
- Isolated individuals are under close surveillance, do not contribute to the transmission of the infection, dead resulting from this compartment are properly buried.
- Death resulting from the disease only takes place in the infectious and isolated compartments. Natural death rate for each compartment is the same.

5.1 Model formulation

A system of nonlinear ordinary differential equations will be used to model the transmission of Ebola virus disease.

The total population at time t, denoted by $N(t)$, is subdivided into six compartments of susceptible ($S(t)$), latent (those who have been infected but are not yet infectious) ($L(t)$), infected individuals ($I(t)$), isolated individuals

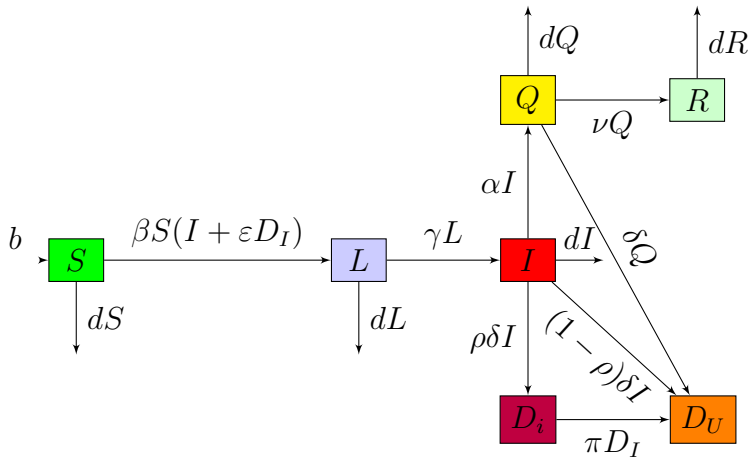


Figure 5.1: Schematic diagram for Ebola Virus Disease transmission with demography.

$(Q(t))$, removed individual $(R(t))$ and the deceased. The latter compartment is further categorized into two compartments, the infectious (improperly buried) deceased $(D_I(t))$ and the properly buried deceased $(D_U(t))$. So the total population at time t is

$$N(t) = S(t) + L(t) + I(t) + Q(t) + R(t) + D_I(t) + D_U(t),$$

Since the model consists of both living infectious individuals and infectious deceased, the total population for the living is given by

$$N_L(t) = S(t) + L(t) + I(t) + Q(t) + R(t).$$

The susceptible population is increased by the recruitment of individuals into the susceptible population, at a rate b. Susceptible individuals may acquire infection, following effective contact with infected individuals and infectious

deceased at a rate $\lambda(t)$, where $\lambda(t) = \beta(I(t)+\varepsilon D_I(t))$, β is the effective contact rate (contact capable of leading to infection), while the parameter $0 < \varepsilon < 1$ is the reduction in infectiousness due to being deceased. This population is further decreased by natural mortality at the per capita rate d. Thus, the rate of change of the susceptible population is given by

$$S(t)' = b - \beta S(t)(I(t) + \varepsilon D_I(t)) - dS(t).$$

The latent population is generated by the infection of susceptible individuals at the rate $\lambda(t)$. This population is decreased by development of disease symptoms at the rate γ and natural mortality rate d, so that

$$L(t)' = \beta S(t)(I(t) + \varepsilon D_I(t)) - (\gamma + d)L(t).$$

The average duration of the incubation period is $1/\gamma$ time units, so infectious individuals are generated from the latent compartment at the rate γL. The infectious population decreases as infectious individuals are isolated (hospitalized) at the rate α, die due to the disease at the rate δ or die naturally at the rate d. This gives

$$I(t)' = \gamma L(t) - (\alpha + \delta + d)I(t).$$

The isolated population is generated at the rate α, decreases as individuals recover at the rate ν, die due to infection at the rate δ and also die naturally at the rate d, so that

$$Q(t)' = \alpha I(t) - (\nu + \delta + d)Q(t).$$

The recovered population is generated at the rate ν and decreases due to natural mortality, at the rate d. This gives

$$R(t)' = \nu Q(t) - dR(t).$$

Infectious deceased (improperly buried dead infectious individuals) are generated at the rate $\rho\delta$, where ρ accounts for the fraction of the dead that are improperly buried. This population decreases as individuals are reburied properly at the rate π. Hence, the rate of change of this compartment is given by

$$D_I(t)' = \rho\delta I - \pi D_I.$$

Finally, the properly buried population (D_U) is generated at the rate $(1-\rho)\delta$ from the infectious population, δ from the isolated population and π from the improperly buried population, so that

$$D_U(t)' = (1 - \rho)\delta I + \delta Q + \pi D_I.$$

Thus, the model for the transmission dynamics of Ebola virus disease with infectious deceased population is given by the following nonlinear system of

differential equations:

$$S' = b - \beta S(I + \varepsilon D_I) - dS, \tag{5.1.1a}$$

$$L' = \beta S(I + \varepsilon D_I) - (\gamma + d)L, \tag{5.1.1b}$$

$$I' = \gamma L - (\alpha + \delta + d)I, \tag{5.1.1c}$$

$$Q' = \alpha I - (\nu + \delta + d)Q, \tag{5.1.1d}$$

$$R' = \nu Q - dR, \tag{5.1.1e}$$

$$D_I' = \rho\delta I - \pi D_I, \tag{5.1.1f}$$

$$D_U' = (1 - \rho)\delta I + \delta Q + \pi D_I. \tag{5.1.1g}$$

The associated initial conditions to equations of model (5.1.1) are

$$S_0 > 0,\ L_0 \geq 0,\ I_0 > 0,\ Q_0 \geq 0,\ R_0 \geq 0, \tag{5.1.2}$$

$$D_{I0} \geq 0 \text{ and } D_{U0} \geq 0.$$

The analysis of this model is presented in the next chapter and parameters are defined in Table 7.1.

Chapter 6

Mathematical analysis of the EVD model

This chapter deals with the basic mathematical analysis of the model formulated in Chapter 5. It presents existence and uniqueness of solutions, nonnegativity, boundedness, existence of equilibria, reproduction number and stability analysis of equilibria.

6.1 Basic Properties

6.1.1 Existence and uniqueness

Proposition 6.1.1. *(Existence and uniqueness of solutions). Consider System* (5.1.1) *with nonnegative initial conditions* (5.1.2). *Solutions to* (5.1.1) *considered with* (5.1.2) *exist and are unique for all* $t \geq 0$.

Proof. Let $x(t) = (S(t), L(t), I(t), Q(t), R(t), D_I(t), D_U(t))^T \in \mathbb{R}^7$. System (5.1.1) is written in the form (2.1.2), that is, $x' = f(x)$. The components of the vector field f are denoted by f_i for $i = \{1, 2, 3, 4, 5, 6, 7\}$;

$$f_1 = b - \beta S(I + \varepsilon D_I) - dS$$

$$f_2 = \beta S(I + \varepsilon D_I) - (\gamma + d)L,$$

$$f_3 = \gamma L - (\alpha + \delta + d)I,$$

$$f_4 = \alpha I - (\nu + \delta + d)Q,$$

$$f_5 = \nu Q - dR,$$

$$f_6 = \rho\delta I - \pi D_I,$$

$$f_7 = (1 - \rho)\delta I + \delta Q + \pi D_I.$$

The vector field f consists of sums of linear and bilinear terms written in terms of S, L, I, Q, R, D_I and D_U. Thus, the f_i are continuous autonomous functions (no time dependence) on $\mathbb{R}^7$ and partial derivatives $\partial f_i/\partial S$, $\partial f_i/\partial L$, $\partial f_i/\partial I$, $\partial f_i/\partial Q$, $\partial f_i/\partial R$, $\partial f_i/\partial D_I$ and $\partial f_i/\partial D_U$ exist and are continuous, hence, by Theorem (2.1.2), a unique solution exists to the initial value problem $x' = f(x)$ for any initial condition $x(0) \in \mathbb{R}^7$. □

6.1.2 Nonnegativity of solutions

Given nonnegative initial condition (5.1.2) for System (5.1.1), we require the solutions of the equation to remain nonnegative. Thus the solutions should

remain in

$$\Gamma = \left\{(S, L, I, Q, R, D_I, D_U) \in \mathbb{R}^7_+ : 0 \leq S, L, I, Q, R, D_I, D_U\right\}, \quad (6.1.1)$$

i.e Γ should be positively invariant. We show this is the case.

Proof. To prove that Γ is invariant, we examine the behaviour of the state variables at the boundaries of Γ.

- At the boundary $S = 0$, then $S' = b > 0$. Thus, the solution cannot exit Γ by crossing this boundary.

- At the boundary $L = 0$, L' then become $L' = \beta S(I + \varepsilon D_I) \geq 0$. If $L(t) = 0, S(t) > 0, I(t) > 0$ and $D_I(t) > 0$ then $\beta S(I + \varepsilon D_I) > 0$ and the solution cannot exit Γ by crossing the boundary $L = 0$ in this case. If $L = 0, S(t) > 0, I(t) > 0$ and $D_I(t) = 0$, then $L' = \beta SI > 0$, If $L = 0, S(t) > 0, I(t) = 0$ and $D_I(t) = 0$, then $L' = 0$. If $L = 0, S(t) = 0, I(t) > 0$ and $D_I(t) > 0$ we have $L' = 0$. In each of these cases $L' \geq 0$, so the solution cannot cross $L = 0$.

- At the boundary $I = 0$, we have $I' = \gamma L$. If $I(t) = 0$ and $L(t) > 0$ then $I' = \gamma L > 0$ and thus the solution cannot exit Γ through the $I = 0$ boundary in this case. The case $I(t) = 0$ and $L(t) = 0$ has already been considered above. Thus the solution cannot exit Γ via the boundary $I = 0$.

In a similar manner, we can show that the solution cannot exit Γ via the boundary of any of the states variables. This completes the proof of nonnegativity of solutions. □

6.1.3 Boundedness

Lemma 6.1.1. *The closed set*

$$\Gamma_L = \left\{ (S, L, I, Q, R) \in \mathbb{R}^5_+ : 0 \leq S, L, I, Q, R \leq N_L \leq \frac{b}{d} \right\} \tag{6.1.2}$$

is positively-invariant and attracting for (5.1.1).

Proof. To obtain the rate of change of the total living population N_L with time, note that

$$N_L{}' = (S + L + I + Q + R)' = S' + L' + I' + Q' + R'.$$

$$N_L{}' = b - dN_L - \delta(I + Q). \tag{6.1.3}$$

It follows from (6.1.3) that

$$N_L{}' + dN_L = b - \delta(I + Q) \leq b,$$

so that

$$N_L{}' + dN_L \leq b.$$

By solving the resulting first order differential equation explicitly using the integrating factor technique, we obtain

$$\begin{aligned}\frac{d}{dt}\left(\mathrm{e}^{dt}N_L\right) \leq b\mathrm{e}^{dt} &\Longleftrightarrow \int_0^t \frac{d}{dt}\left(\mathrm{e}^{dt}N_L\right)dt \leq \int_0^t b\mathrm{e}^{dt}dt \\ &\Longleftrightarrow N_L(t)\mathrm{e}^{dt} - N_L(0) \leq \frac{b}{d}(\mathrm{e}^{dt} - 1) \\ &\Longleftrightarrow N_L(t) \leq N_L(0)\mathrm{e}^{-dt} + \frac{b}{d}\left(1 - \mathrm{e}^{-dt}\right). \qquad (6.1.4)\end{aligned}$$

Thus, the asymptotic behaviour of the total living population is such that

$$\limsup_{t\to\infty} N_L(t) \leq \lim_{t\to\infty}\left(N_L(0)e^{-dt} + \frac{b}{d}\left(1 - e^{-dt}\right)\right) = \frac{b}{d}.$$

Hence, the total living population is bounded above by b/d. Since solutions to (5.1.1) considered with initial conditions (5.1.2) exist and are unique, remain nonnegative and are bounded, System (5.1.1) is well posed. □

6.2 Steady state analysis

In this section, we investigate the existence of steady states for the system of nonlinear ordinary differential equations (5.1.1) describing the transmission dynamics of Ebola virus disease. These steady states can be obtained by

equating the right hand sides of (5.1.1) to zero, giving

$$b - \beta S(I + \varepsilon D_I) - dS = 0 \tag{6.2.1a}$$

$$\beta S(I + \varepsilon D_I) - (\gamma + d)L = 0 \tag{6.2.1b}$$

$$\gamma L - (\alpha + \delta + d)I = 0 \tag{6.2.1c}$$

$$\alpha I - (\nu + \delta + d)Q = 0 \tag{6.2.1d}$$

$$\nu Q - dR = 0 \tag{6.2.1e}$$

$$\rho\delta I - \pi D_I = 0 \tag{6.2.1f}$$

$$(1 - \rho)\delta I + \delta Q + \pi D_I = 0. \tag{6.2.1g}$$

Solving for D_I from (6.2.1f), we obtain

$$D_I = \frac{\rho\delta}{\pi} I.$$

From (6.2.1b), using the latter expression, we obtain

$$L = \frac{\beta S I(\pi + \varepsilon\rho\delta)}{\pi(\gamma + d)},$$

while from (6.2.1c), we obtain

$$L = \frac{(\alpha + \delta + d)I}{\gamma}.$$

Equating the two equations together,

$$\frac{\beta SI(\pi + \varepsilon\rho\delta)}{\pi(\gamma + d)} = \frac{(\alpha + \delta + d)I}{\gamma} \tag{6.2.2}$$

$$\iff S\{\beta(\pi + \varepsilon\rho\delta)\} = \frac{\pi(\gamma + d)(\alpha + \delta + d)}{\gamma}.$$

Equation (6.2.2) yields two solutions

$$I = 0 \qquad \text{and} \qquad S = \frac{\pi(\gamma + d)(\alpha + \delta + d)}{\beta\gamma(\pi + \varepsilon\rho\delta)}. \tag{6.2.3}$$

6.3 Disease Free Equilibrium (DFE)

Substituting $I = 0$ into (6.2.1), we obtain what is called the disease free equilibrium point. Equation (6.2.1) is at the DFE if $L = I = Q = R = D_i = 0$. Thus equation (6.2.1a) gives $S = b/d$ where $d > 0$ for b/d to be defined. Hence, let $\mathcal{E}_0 = (\bar{S}, \bar{L}, \bar{I}, \bar{Q}, \bar{R}, \bar{D_I}, \bar{D_U})$ denote the DFE of (5.1.1):

$$\mathcal{E}_0 = \left(\frac{b}{d}, 0, 0, 0, 0, 0, 0\right). \tag{6.3.1}$$

6.3.1 $\mathcal{R}_0$ and stability of the disease free equilibrium

As discussed in Chapter 2, the local asymptotic stability of the disease free equilibrium point $\mathcal{E}_0$ can be established by using the next generation matrix method on System (5.1.1).

The disease (infected) compartments of (5.1.1) are L, I, D_I and the non disease (non infected) compartments are S, Q, R. Although compartment Q contains infected individuals, since they do not partake in the transmission of the infection and do not later progress to D_I, only to D_U, it is grouped together with non disease compartments. D_U is dropped since the dynamics of all other compartments do not depend on it and it is not involved in the transmission of the disease. The model equations (5.1.1) can be written as

$$\frac{d}{dt}\underbrace{\begin{bmatrix} L \\ I \\ D_I \\ S \\ Q \\ R \end{bmatrix}}_{X} = f(X) = \underbrace{\begin{bmatrix} \beta S(I + \varepsilon D_I) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}}_{\mathcal{F}} - \left(\underbrace{\begin{bmatrix} (\gamma + d)L \\ (\alpha + \delta + d)I \\ \pi D_I \\ dS \\ (\nu + \delta + d)Q \\ dR \end{bmatrix}}_{\mathcal{V}^-} - \underbrace{\begin{bmatrix} 0 \\ \gamma L \\ \rho\delta I \\ b \\ \alpha I \\ \nu Q \end{bmatrix}}_{\mathcal{V}^+} \right)$$

The function f satisfies the five conditions given under next generation matrix method of computing $\mathcal{R}_0$:

i) If $S, L, I, Q, R, D_I \geq 0$, then $\mathcal{F} \geq 0, \mathcal{V}^- \geq 0$, and $\mathcal{V}^+ \geq 0$.

ii) If $S = L = I = Q = R = D_I = 0$, then $\mathcal{V}^- = 0$.

iii) If DFE $\mathcal{E}_0 = \left(\frac{b}{d}, 0, 0, 0, 0, 0\right)$, then $\mathcal{F}_{i(\mathcal{E}_0)} = 0, \mathcal{V}_{i(\mathcal{E}_0)} = 0,\ i \in \{2, 3, 4, 5, 6\}$, since new entry into the population is only into the susceptible compartments, in the absence of the disease, all other compartment do not exist.

iv) If $\mathcal{F} = 0$, we have the resulting model for (5.1.1) as

$$\frac{d}{dt}\left[S\right] = \left[b - dS\right],$$

with Jacobian matrix

$$J = \left[-d\right].$$

Then $\lambda = -d < 0$. Hence, DFE $\mathcal{E}_0 = \left(\frac{b}{d}, 0, 0, 0, 0, 0\right)$ is locally asymptotically stable.

Computation of the basic reproduction number $\mathcal{R}_0$ requires the application of the next generation matrix, which was explained in Section 3.3. The subsystem that constitutes the infected compartments of system (5.1.1) are the latent L, infectious I and infectious dead D_I compartments, with dynamics given by

$$L' = \beta S(I + \varepsilon D_I) - (\gamma + d)L,$$

$$I' = \gamma L - (\alpha + \delta + d)I,$$

$$D_I' = \rho(\delta + d)I - \pi D_I.$$

This can be grouped as follows

$$\underbrace{\frac{d}{dt}\begin{bmatrix} L \\ I \\ D_I \end{bmatrix}}_{X} = \underbrace{\begin{bmatrix} \beta S(I + \varepsilon D_I) \\ 0 \\ 0 \end{bmatrix}}_{\mathcal{F}} - \underbrace{\begin{bmatrix} (\gamma + d)L \\ -\gamma L + (\alpha + \delta + d)I \\ -\rho\delta I + \pi D_I \end{bmatrix}}_{\mathcal{V}}$$

New infections only occur in the L compartment, while transition from one compartment to the other are common to all the three compartments L, I and D_I. Hence, using the notation of (3.3.2), the nonnegative matrix F representing new cases and the M-matrix V representing transitions associated with model (5.1.1) evaluated at the disease free equilibrium point $\mathcal{E}_0$ are given respectively as:

$$F = \begin{pmatrix} 0 & \beta\frac{b}{d} & \beta\varepsilon\frac{b}{d} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} \gamma + d & 0 & 0 \\ -\gamma & \alpha+\delta+d & 0 \\ 0 & -\rho\delta & \pi \end{pmatrix}. \tag{6.3.2}$$

Since V is a triangular matrix, it has all its eigenvalues having positive real parts, $\lambda_1 = \gamma + d > 0$, $\lambda_2 = \alpha + \delta + d > 0$ and $\lambda_3 = \pi > 0$. Hence V^{-1} exists and is computed as

$$V^{-1} = \begin{pmatrix} \frac{1}{\gamma+d} & 0 & 0 \\ \frac{\gamma}{(\gamma+d)(\alpha+\delta+d)} & \frac{1}{(\alpha+\delta+d)} & 0 \\ \frac{\gamma\rho\delta}{\pi(\gamma+d)(\alpha+\delta+d)} & \frac{\rho\delta}{\pi(\alpha+\delta+d)} & \frac{1}{\pi} \end{pmatrix}. \tag{6.3.3}$$

Hence, we have

$$FV^{-1} = \begin{pmatrix} \frac{b\beta\gamma(\pi+\epsilon\rho\delta)}{d\pi(\alpha+\delta+d)(\gamma+d)} & \frac{b\beta(\pi+\epsilon\rho\delta)}{d\pi(\alpha+\delta+d)} & \frac{\beta b\varepsilon}{d\pi} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \tag{6.3.4}$$

so the basic reproduction number $\mathcal{R}_0$ is given by

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{b\beta\gamma(\pi + \epsilon\rho\delta)}{d\pi(\alpha + \delta + d)(\gamma + d)}, \tag{6.3.5}$$

where ρ represents the spectral radius. Hence, using Theorem 3.3.1, the following result is established.

Lemma 6.3.1. *The disease free equilibrium point $\mathcal{E}_0$ of model (5.1.1) is locally asymptotically stable whenever $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.*

Lemma 6.3.1 implies that Ebola virus disease can be effectively controlled in the population (when $\mathcal{R}_0 < 1$) if the initial sizes of the subpopulations of model (5.1.1) are in the basin of attraction of the disease free equilibrium point (DFE) $\mathcal{E}_0$.

6.3.2 Global stability of DFE

Global analysis of disease free equilibrium is carried out here to establish the asymptotic behaviour of model (5.1.1).

Theorem 6.3.1. *The DFE $\mathcal{E}_0$ of model (5.1.1) is globally asymptotically stable (GAS) in (6.1.2) whenever $\mathcal{R}_0 \leq 1$.*

Proof. The disease compartment for the model are the latent L, infectious I and improperly buried dead D_I. Let G be a Lyapunov function for model (5.1.1).

The matrix of new infections F, and transition matrix V are as defined in (6.3.2), so

$$V^{-1}F = \begin{pmatrix} 0 & \frac{\beta S}{\gamma+d} & \frac{\beta\varepsilon S}{\gamma+d} \\ 0 & \frac{\beta\gamma S}{(\gamma+d)(\alpha+\delta+d)} & \frac{\beta\gamma\varepsilon S}{(\gamma+d)(\alpha+\delta+d)} \\ 0 & \frac{\beta\gamma\rho\delta S}{\pi(\gamma+d)(\alpha+\delta+d)} & \frac{\beta\gamma\rho\delta\varepsilon S}{\pi(\gamma+d)(\alpha+\delta+d)} \end{pmatrix}, \tag{6.3.6}$$

$$(F-V)i = \begin{pmatrix} -(\gamma+d) & S_0\beta & S_0\beta\varepsilon \\ \gamma & -(\alpha+\delta+d) & 0 \\ 0 & \rho\delta & -\pi \end{pmatrix} \begin{pmatrix} L \\ I \\ D_I \end{pmatrix}$$

$$\begin{aligned} f(i,u) &= (F-V)i - \mathcal{F}(i,u) + \mathcal{V}(i,u) \\ &= \beta(I+\varepsilon D_I)(S_0 - S) \end{aligned} \tag{6.3.7}$$

where $i = (L, I, D_I)^T$ is the infected compartments and $f(i,u)$ is the dynamics of the model. Since matrix $V^{-1}F$ in (6.3.6) is reducible (the first column is a zero column), Theorem 3.3.3 fails. Instead, Theorem 3.3.2 will be used to construct a Lyapunov function for the global stability analysis of the disease free equilibrium point of the model. Let the infected compartments be $i = (L, I, D_I)^T$, then $i' = (F-V)i - f(i,u)$, with $f(i,u) = \beta(I+\varepsilon D_I)(S_0 - S) \geq 0$ in Γ. By Theorem 3.3.2, $G = w^T V^{-1} i$ is a Lyapunov function, where $w^T = (0,1,1)$ is the left eigenvector of nonnegative matrix $V^{-1}F$ corresponding to the eigenvalue

$\rho(V^{-1}F) = \mathcal{R}_0$. Then

$$
\begin{aligned}
G &= w^T V^{-1} i \\
&= (0,1,1) \begin{pmatrix} \frac{1}{(\gamma+d)} & 0 & 0 \\ \frac{\gamma}{(\gamma+d)(\alpha+\delta+d)} & \frac{1}{(\alpha+\delta+d)} & 0 \\ \frac{\gamma\rho\delta}{\pi(\gamma+d)(\alpha+\delta+d)} & \frac{\rho\delta}{\pi(\alpha+\delta+d)} & \frac{1}{\pi} \end{pmatrix} \begin{pmatrix} L \\ I \\ D_I \end{pmatrix}, \\
&= \left(\frac{\gamma(\pi+\rho\delta)}{\pi(\gamma\ +\ d)(\alpha+\delta\ +\ d)} \right) L + \left(\frac{\pi+\rho\delta}{\pi(\alpha+\delta\ +\ d)} \right) I + \frac{1}{\pi} D_I, \\
&= \frac{\mathcal{R}_0}{\beta S_0} \left[L + \frac{\gamma+d}{\gamma} I + \frac{(\gamma\ +\ d)(\alpha+\delta\ +\ d)}{(\pi+\rho\delta)} D_I \right].
\end{aligned}
$$

We have

$$
\begin{aligned}
G' &= w^T V^{-1} i' \\
&= w^T V^{-1} \left((F-V)i - f(i,u) \right) \\
&= w^T V^{-1} (F-V) i - w^T V^{-1} f(i,u) \\
&= (\mathcal{R}_0 - 1)(I + D_I) - \frac{\mathcal{R}_0}{S_0} (I + D_I)(S_0 - S) \leq 0,
\end{aligned}
$$

provided $\mathcal{R}_0 \leq 1$. Furthermore, $G' = 0$ implies that $(I + D_I) = 0$ or $S = S_0$, since having $I < 0$ is not biologically feasible. Therefore, $I = D_I = 0$. Then $\mathcal{E}_0$ is the only invariant set containing $S = S_0$, $I = 0$ and $D_I = 0$. Therefore, by LaSalle's invariance principle (Theorem 2.2.2), $\mathcal{E}_0$ is globally asymptotically stable in Γ. □

6.4 Endemic equilibrium point (EE)

In this section, the endemic equilibrium for model (5.1.1) will be evaluated and conditions for its local and global asymptotic stability will be given.

From (6.2.1a),

$$b - \beta S(I + \varepsilon D_I) - dS = 0 \Longleftrightarrow b - \frac{\beta SI(\pi + \varepsilon\rho\delta)}{\pi} - dS = 0$$

$$\Longleftrightarrow \frac{\beta SI(\pi + \varepsilon\rho\delta)}{\pi} = b - dS.$$

Replacing S with the right hand side of (6.2.3), we obtain

$$\frac{b\beta\gamma(\pi + \varepsilon\rho\delta) - d\pi(\gamma + d)(\alpha + \delta + d)}{\beta\gamma(\pi + \varepsilon\rho\delta)} = \frac{(\gamma + d)(\alpha + \delta + d)}{\gamma} I.$$

By further simplification, we obtain the unique endemic equilibrium value for I,

$$I = \frac{1}{(\gamma + d)(\alpha + \delta + d)} \left[\frac{b\beta\gamma(\pi + \varepsilon\rho\delta) - d\pi(\gamma + d)(\alpha + \delta + d)}{\beta\gamma(\pi + \varepsilon\rho\delta)} \right]. \tag{6.4.1}$$

Let $k_1 = (\gamma + d)$, $k_2 = (\alpha + \delta + d)$, $k_3 = (\pi + \varepsilon\rho\delta)$ and $k_4 = (\nu + \delta + d)$. Then the endemic equilibrium of (5.1.1) takes the form

$$S^* = \frac{\pi k_1 k_2}{\beta\gamma k_3} \text{ [the other solution of (6.2.3)]} \tag{6.4.2a}$$

$$L^* = \frac{b\gamma k_3 - d\pi k_1 k_2}{\beta\gamma k_1 k_3} \tag{6.4.2b}$$

$$I^* = \frac{b\beta\gamma k_3 - d\pi k_1 k_2}{\beta k_1 k_2 k_3} \tag{6.4.2c}$$

$$Q^* = \frac{\alpha}{\pi k_1 k_2 k_4}\left[\frac{b\beta\gamma k_3 - d\pi k_1 k_2}{\beta\gamma k_3}\right] \tag{6.4.2d}$$

$$R^* = \frac{\alpha\nu}{\pi k_1 k_2 k_4 d}\left[\frac{b\beta\gamma k_3 - d\pi k_1 k_2}{\beta\gamma k_3}\right] \tag{6.4.2e}$$

$${D_I}^* = \frac{\rho\delta}{\pi k_1 k_2}\left[\frac{b\beta\gamma k_3 - d\pi k_1 k_2}{\beta\gamma k_3}\right] \tag{6.4.2f}$$

$${D_U}^* = (1-\rho)\delta I^* + \delta Q^* + \pi {D_I}^*. \tag{6.4.2g}$$

6.4.1 Existence and uniqueness of the endemic equilibrium

For the purpose of establishing the existence and uniqueness of the endemic equilibrium (EE), we want to express the equilibrium point in a different form, for simplicity.

Let $\mathcal{E}_1 = (S^*, L^*, I^*, Q^*, R^*, D_I^*, D_u^*)$ represent any arbitrary equilibrium of model (5.1.1). Further, let

$$\lambda^* = \beta(I^* + \varepsilon D_I^*) \tag{6.4.3}$$

be the associated force of infection of model (5.1.1) at this equilibrium point. The model equations (5.1.1) are solved in terms of the aforementioned force of infection at λ^*. Setting the right-hand side of (5.1.1) to zero gives

$$\begin{aligned} S^* &= \frac{b}{\lambda^* + d}, \; L^* = \frac{\lambda^* S^*}{\gamma + d}, \; I^* = \frac{\gamma L^*}{(\alpha + \delta + d)}, \\ Q^* &= \frac{\alpha I^*}{(\nu + \delta + d)}, \; R^* = \frac{\nu Q^*}{d}, \; {D_I}^* = \frac{\rho \delta I^*}{\pi}. \end{aligned} \tag{6.4.4}$$

Substituting equation (6.4.4) into the expression for λ^* in equation (6.4.3) gives

$$\begin{aligned} \lambda^* &= \beta \left(\frac{\pi + \varepsilon \rho \delta}{\pi} \right) I^* \\ &= \beta \left(\frac{\pi + \varepsilon \rho \delta}{\pi} \right) \left(\frac{\gamma}{(\alpha + \delta + d)} \right) \left(\frac{\lambda^* b}{(\lambda^* + d)(\gamma + d)} \right), \end{aligned}$$

so that

$$\lambda^* = \frac{b\beta\gamma\lambda^*(\pi + \varepsilon\rho\delta)}{\pi(\lambda^* + d)(\gamma + d)(\alpha + \delta + d)}. \tag{6.4.5}$$

From (6.3.5),

$$d\mathcal{R}_0 = \frac{b\beta\gamma(\pi + \varepsilon\rho\delta)}{\pi(\gamma + d)(\alpha + \delta + d)}. \tag{6.4.6}$$

Substituting (6.4.6) into (6.4.5) gives

$$\lambda^* = \frac{d\mathcal{R}_0\lambda^*}{\lambda^* + d}, \tag{6.4.7}$$

so the nonzero endemic equilibrium of model (5.1.1) satisfies

$$\lambda^* - d(\mathcal{R}_0 - 1) = 0, \tag{6.4.8}$$

which has the unique solution

$$\lambda^* = d(\mathcal{R}_0 - 1). \tag{6.4.9}$$

It is clear that the unique solution of λ^* from (6.4.9) is positive if $\mathcal{R}_0 > 1$, since all model parameters are positive. The components of the endemic equilibrium $\mathcal{E}_1$ are then determined by substituting (6.4.9) into the equations in (6.4.4). It follows from (6.4.9) that for $\mathcal{R}_0 < 1$, $\lambda^* < 0$ (which is biologically not meaningful). Hence model (5.1.1) has no positive endemic equilibrium point when $\mathcal{R}_0 < 1$. Moveover, if $\mathcal{R}_0 = 1$, then $\lambda^* = 0$, corresponding to the disease free equilibrium point. These results are summarized below .

Theorem 6.4.1. *Model* (5.1.1) *has unique endemic equilibrium* $\mathcal{E}_1$ *if* $\mathcal{R}_0 > 1$ *and none otherwise.*

6.4.2 Global stability of endemic equilibrium for special case

The global asymptotic stability of the endemic equilibrium of model (5.1.1) is given for a special case when deceased individuals do not transmit infection ($\varepsilon = 0$). Model (5.1.1) with $\varepsilon = 0$ reduces to:

$$
\begin{aligned}
S' &= b - (\beta I - d)S, \\
L' &= (\beta I - d)S - (\gamma + d)L, \\
I' &= \gamma L - (\alpha + \delta + d)I, \\
Q' &= \alpha I - (\nu + \delta + d)Q, \\
R' &= \nu Q - dR, \\
D_I' &= \rho\delta I - \pi D_I, \\
D_U' &= (1 - \rho)\delta I + \delta Q + \pi D_I.
\end{aligned} \tag{6.4.10}
$$

The reproduction number associated to model (6.4.10) is given by

$$
\mathcal{R}_{0r} = \mathcal{R}_0|_{\varepsilon=0} = \frac{b\beta\gamma}{d(\gamma + d)(\alpha + \delta + d)}. \tag{6.4.11}
$$

We claim the following result.

Theorem 6.4.2. *The endemic equilibrium of the reduced model, given by (6.4.10), is GAS in Γ_L given by (6.1.2) if $\mathcal{R}_{0r} > 1$.*

Proof 6.4.1. *Consider the reduced model given by (6.4.10) Let $\mathcal{R}_{0r} > 1$, so that the associated endemic equilibrium exists. Further, consider the following*

nonlinear Lyapunov function:

$$\mathcal{V} = S - S^* - S^* \ln\left(\frac{S}{S^*}\right) + L - L^* - L^* \ln\left(\frac{L}{L^*}\right) \tag{6.4.12}$$
$$+ \frac{(\gamma + d)}{\gamma}\left[I - I^* - I^* \ln\left(\frac{I}{I^*}\right)\right]$$

with derivative with respect to time

$$\begin{aligned}
\mathcal{V}' &= S' - \left(\frac{S^*}{S}\right) S' + L' - \left(\frac{L^*}{L}\right) L' + \left(\frac{\gamma + d}{\gamma}\right)\left[I' - \left(\frac{I^*}{I}\right) I'\right] \\
&= b - \beta SI - dS - \left(\frac{S^*}{S}\right)(b - \beta SI - dS) \\
&+ \beta SI - (\gamma + d)L - \left(\frac{L^*}{L}\right)(\beta SI - (\gamma + d)L) \\
&+ \left(\frac{\gamma + d}{\gamma}\right)\left[\gamma L - (\alpha + \delta + d)I - \left(\frac{I^*}{I}\right)(\gamma L - (\alpha + \delta + d)I)\right] \qquad (6.4.13) \\
&= b\left(1 - \frac{S^*}{S}\right) - dS\left(1 - \frac{S^*}{S}\right) + \beta S^* I^* - \left(\frac{(\gamma + d)(\alpha + \delta + d)}{\gamma}\right) I \\
&+ (\gamma + d)L^* - \left(\frac{\beta SI}{E}\right) L^* - \left(\frac{(\gamma + d)L}{I}\right) I^* + \left(\frac{(\gamma + d)(\alpha + \delta + d)}{\gamma}\right) I^*.
\end{aligned}$$

From (6.4.10), at the endemic equilibrium point,

$$\begin{aligned}
b &= (\beta I^* + d)S^*, \\
(\gamma + d) &= \frac{\beta I^* S^*}{L^*}, \qquad (6.4.14) \\
(\alpha + \delta + d) &= \frac{\gamma L^*}{I^*}.
\end{aligned}$$

Substituting (6.4.14) *into* (6.4.13) *gives*

$$\mathcal{V}' = -dS^* \left(\frac{S^*}{S} + \frac{S}{S^*} - 2 \right) - \beta S^* I^* \left(\frac{S^*}{S} + \frac{I^* L}{L^* I} + \frac{I}{I^*} + \frac{S I L^*}{S^* I^* L} - 4 \right). \tag{6.4.15}$$

We have

$$\left(\frac{S^*}{S} + \frac{S}{S^*} - 2 \right) \geq 0$$

and

$$\left(\frac{S^*}{S} + \frac{I^* L}{L^* I} + \frac{I}{I^*} + \frac{S I L^*}{S^* I^* L} - 4 \right) \geq 0.$$

Further, since all model parameters are nonnegative, it follows that $\mathcal{V}' \leq 0$ *for* $\mathcal{R}_{0r} > 1$ *with* $\mathcal{V}' = 0$ *if and only if* $S = S^*$, $L = L^*$, $I = I^*$. *Hence,* $\mathcal{V}$ *is a Lyapunov function for the reduced model. Hence, the endemic equilibrium for model* (6.4.10) *is globally asymptotically stable when* $\mathcal{R}_{0r} > 1$.

Chapter 7

Numerical simulation

Numerical simulations of System (5.1.1) are performed in this chapter in order to further investigate the transmission dynamics of Ebola virus and to complement the mathematical analysis carried out in the Chapter 6.

7.1 Numerical solution

Parameters used for our analysis are estimated based on related literature and data from the World Health Organization website. The parameter values can be found in Table 7.1. Numerical simulation of model (5.1.1) was carried out with MATLAB software.

Figure 7.1(a) depicts the behaviour of the susceptible population for the model using the defined parameters values. This figure reveals a decline in the susceptible population, as the members of the population are becoming infected and therefore moving to other compartments. Figure 7.1(b) reveals

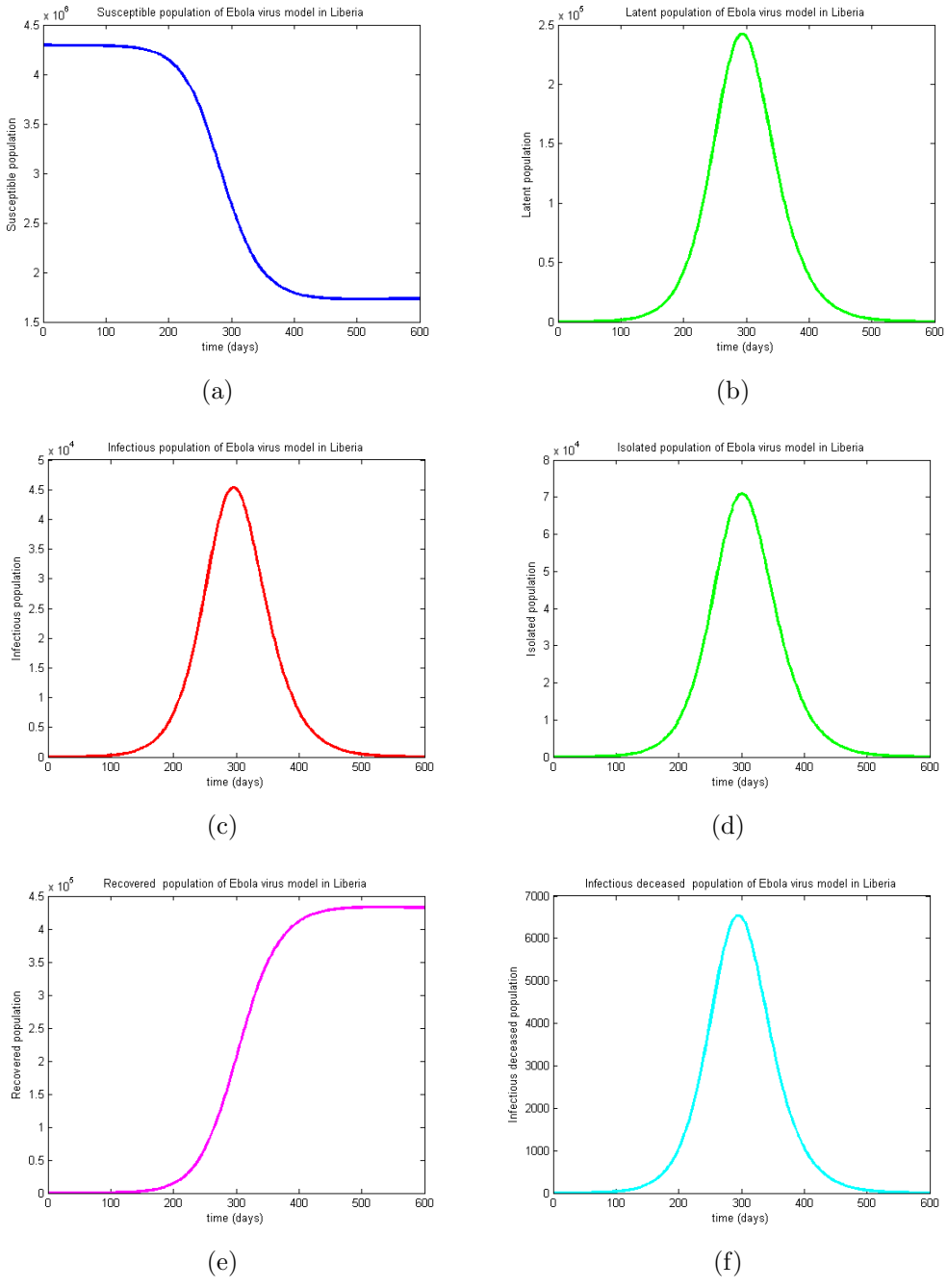


Figure 7.1: Numerical simulation of the Ebola virus disease on population of the (a) susceptible; (b) latent; (c) infectious; (d) isolated; (e) recovered; and (f) infectious deceased.

Parameter	Base value	Source
b: Recruitment rate	183	World Bank
β: Transmission rate	$1.4173e^{-7}$	Estimated
ε: Deceased transmission rate	0.489	[15]
d: Natural death rate	$1/(63 \times 365)$	[42]
γ: Progression rate	0.0869	[42]
α: Isolation rate	0.25	[42]
ρ: Improperly buried fraction	0.6	Estimated
δ: Disease induced death rate	0.0901	[15]
ν: Recovery rate	0.1	Assumed
π: Burial rate	$0 < \pi \leq 1$	Assumed

Table 7.1: Parameters values for the numerical simulation. The units are days, base values are therefore per day. The estimate are obtained from some computation related the them. E.g, the recruitment rate was obtained from the total population and the life expectancy of Liberians.

increase in the latent population which reaches its peak at about 300 day and afterwards declines. Similarly Figure 7.1(c) reveals an increase in the infection population which also reaches its peak at almost the same time as the latent population. The infectious population also decreases but never to zero (what is seen in the picture is due to the scale of the figure). Figure 7.1(d) represents the isolated population; it also witnesses its own peak and reduction as there was decrease in the infectious population, but later stabilizes to a positive value (not zero as appears in the figure). The recovered population is presented in Figure 7.1(e). Infectious deceased population is presented in Figure 7.1(f). As usual, we have an increase in the population before a decrease. All these are what accounts for the decrease in the susceptible population. After the population of the latent, infectious, Isolated, recovered and infectious deceased

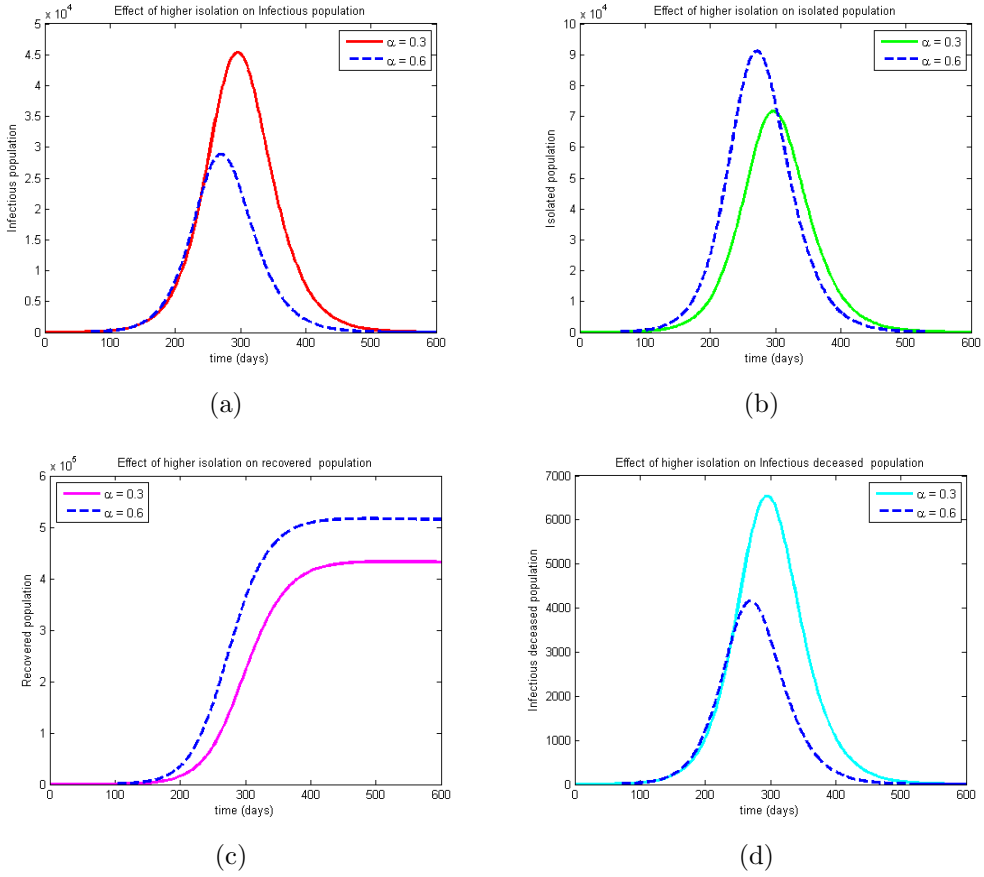


Figure 7.2: Numerical simulation for effect of higher isolation rate on (a) infectious; (b) isolated; (c) recovered; and (d) infectious deceased populations.

reaches equilibrium, the susceptible population stabilizes.

The effect of increase of the isolation rate was then investigated in our simulation. It shows that early isolation of infected individuals can help reduce the spread of the disease. Figures 7.2(a), 7.2(b), 7.2(c) and 7.2(d) are the numerical simulation plots for higher isolation rates for the infectious, isolated, recovered and infectious deceased populations, respectively. As can be seen in

each of these figures, there is reduction in the infectious population and the infectious deceased population, which in return will affect the number of new cases. While there is increase in the isolated and the recovered population, they are not contributing to the transmission of the disease. The implication is that we have less people transmitting the disease when infectious individuals are isolated early or their rate of isolation is increased. This is in accordance with the sensitivity analysis of the basic reproduction number, which showed that increase in isolation rates will reduce the reproduction number, implying a decrease in the number of new cases.

Effect of isolation alongside with increase in burial rate of infectious deceased was also simulated and is shown in Figures 7.3(a), 7.3(b), 7.3(c) and 7.3(d). Increase in burial rate has more impact in the infectious deceased population as opposed to only when when increase isolation was made, as increase in burial rate affect this population directly and has little effect on the infectious, isolated and the recovered. This is because these individuals are dead, so they do not increase the isolated or the recovered population but only help to reduce the number of infectious deceased individuals transmitting the disease. The sensitivity analysis also reveals that an increase burial rate has less impact on the reproduction number reduction than an increase in isolation rate.

Figures 7.4(a) and 7.4(b) show the bifurcation diagram of the latent and infectious population, respectively, as a function the basic reproduction number $\mathcal{R}_0$. The interpretation of the figures is that the higher the basic reproduction number $\mathcal{R}_0$, the larger the number of individuals in latent and infectious

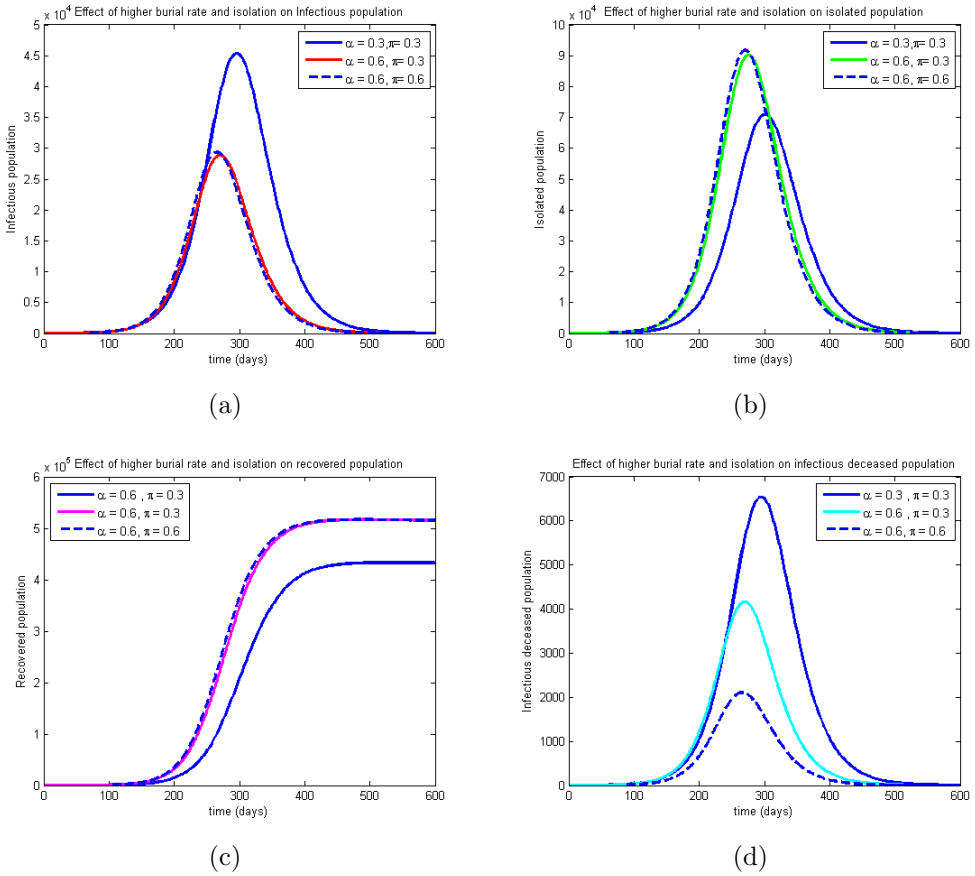
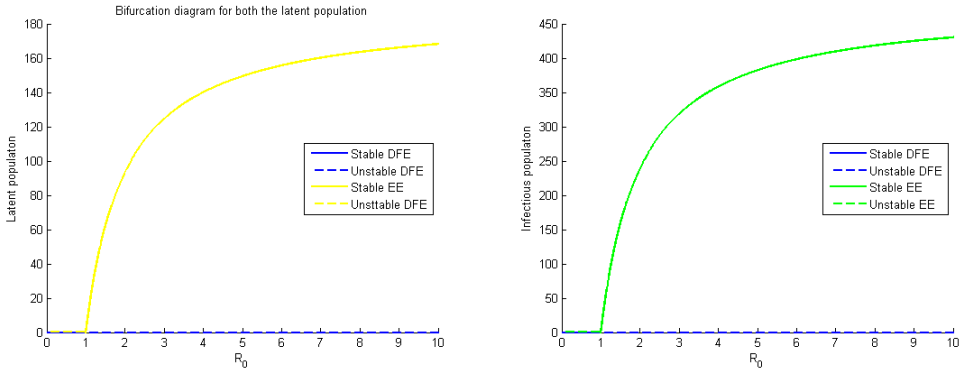


Figure 7.3: Numerical simulation for effect of proper burial and higher isolation rate on (a) infectious; (b) isolated; (c) recovered; and (d) infectious deceased populations.



(a) (b)

Figure 7.4: Bifurcation diagram for (a) latent; (b) infectious populations.

compartments.

7.2 Sensitivity and uncertainty analyses

Material from [1] and [14] is used in this section.

A deterministic model has been formulated, which implies that the output of the model is completely determined by the input parameters, the initial conditions [to explain: here, we don't have multistability. But a deterministic a deterministic model can have it, in general, in which case initial conditions matter] and the structure of the model. Therefore, the uncertainty of the output is dependent on the input variation. Hence the need for uncertainty and sensitivity analyses.

Parameter values and initial conditions used as the input factor for most mathematical model parameters are not known with a sufficient degree of certainty because of natural variation, lack of current techniques to measure them or error in measurement. Uncertainty analysis is a technique for assessing the variability in an outcome variable that arises due to uncertainty in estimating input values.

Sensitivity analysis is concerned with identifying the key input parameters that contribute to imprecision in the estimation of the output variables. That is, uncertainty analysis focuses on accessing the impact of uncertainties in parameters values of the model being studied (model simulation), sensitivity analysis focuses on identifying the key parameters of the model that most influence the outcome (response function).

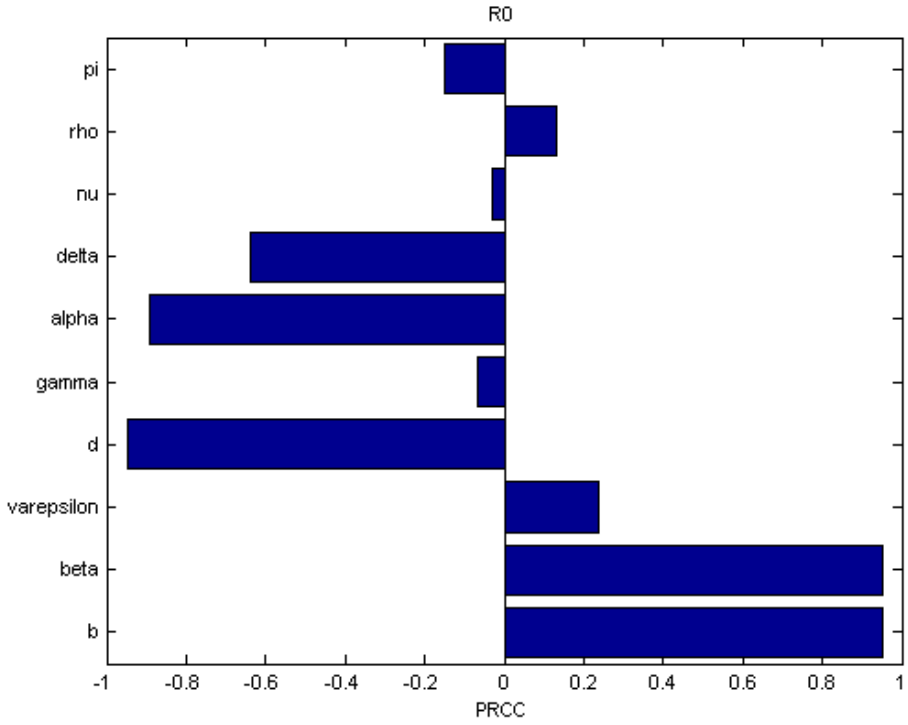


Figure 7.5: Sensitivity analysis plot of the basic reproduction $\mathcal{R}_0$ number as a function of the parameters of the basic model (5.1.1), using the baseline parameter values defined in Table 7.1.

Sensitivity analysis is a method used to quantify the uncertainty of the model parameters. It identifies critical inputs (parameters and initial conditions) of the model and quantifies how input uncertainties impact model outcomes. Sensitivity analysis is carried out by finding the partial derivative of the output function (the basic reproduction number $\mathcal{R}_0$ in our case) with respect to the input factors.

The partial rank correlation coefficient (PRCC) plot in Figure 7.5 was

generated with the baseline of parameter values and range in Table 7.1 as the input parameter, while $\mathcal{R}_0$ is the input function. Figure 7.5 shows partial rank correlation coefficient (PRCC) plot of sensitivity analysis of the basic reproduction number. This figure was generated by using the parameters values defined in Table 7.1 and simulating with respect to the basic reproduction number computed for the model. It reveals the parameters that have relative high impact on the transmission dynamics of Ebola virus in Liberia. We see that the parameters having the strongest impact are the transmission rate β, natural death rate d, fraction of the infectious deceased ε, the isolation rate α, diseased induced death rate δ and the recruitment rate of susceptible.

It follows from Figure 7.5 that an increase (decrease) in the baseline values of the aforementioned parameters that have positive impact on $\mathcal{R}_0$ lead to a corresponding increase (decrease) in the value of $\mathcal{R}_0$ which increases (decrease) the number of new cases of Ebola virus disease, while increase (decrease) in the baseline values of aforementioned parameters with negative impact on $\mathcal{R}_0$ leads to a corresponding decrease (increase) in the value $\mathcal{R}_0$. The identification of these parameters is vital to the formulation of the most effective and efficient prevention measure for combating the spread the disease.

Figure 7.6 is the Latin Hypercube Sampling (LHS) box plot for the basic model (5.1.1); it depicts the uncertainty in the parameter values for the model. This plot was generated by defining the baseline value of each of the parameters for the basic model (5.1.1) as having continuous uniform distributions, with

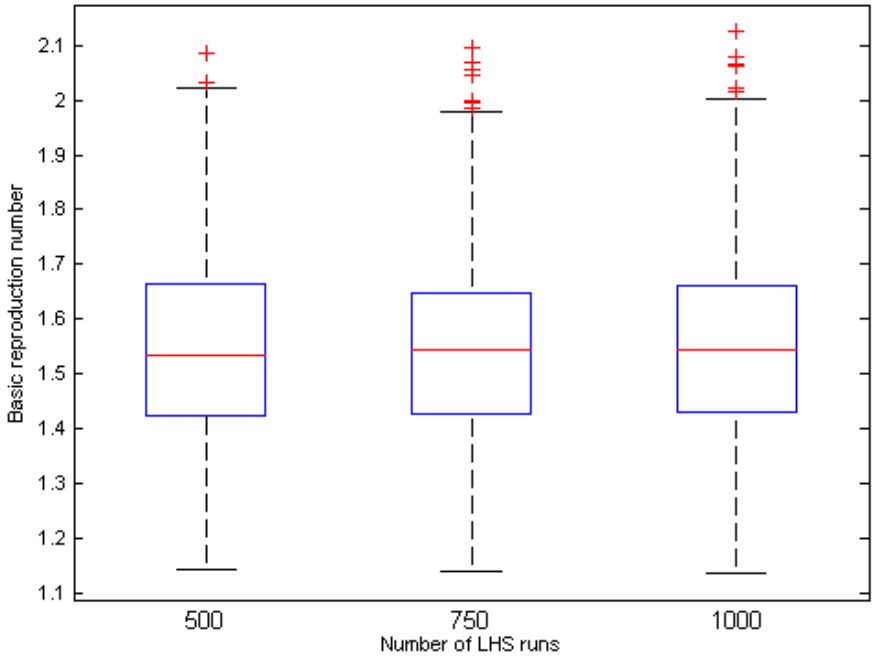


Figure 7.6: Box plot of the basic reproduction number $\mathcal{R}_0$ as a function of number of runs for basic model (5.1.1), using the baseline parameter values defined in Table 7.1

the basic reproduction number being the output function. For each number of runs, each box displays the lower and the upper quartile ranges of $\mathcal{R}_0$ (lower and upper horizontal lines on a box, respectively). The horizontal line within a box denotes the median value of $\mathcal{R}_0$. The extreme values of $\mathcal{R}_0$ are presented by the lower and the upper whiskers. From Figure 7.6, it can be seen that the distribution of $\mathcal{R}_0$ lies in the range $\mathcal{R}_0 \in [1.15, 2.03]$, with median $\mathcal{R}_0 = 1.54$. The essence of Figure 7.6 is to shown that the basic reproduction number $\mathcal{R}_0$ obtained for the model is greater than one. Since $\mathcal{R}_0$ exceeds unity, it follows from Theorem 3.3.1 that the Ebola virus disease will persist in the population which is also confirmed in our simulation as the infectious population remain positive. Thus, this reveals the need for intervention strategies that can help to reduce (and maintain) $\mathcal{R}_0$ to a value less than unity.

Chapter 8

Discussion and conclusion

In this manuscript, a modified SLIR mathematical model was used to study the transmission dynamics of Ebola virus disease. The model also incorporated the infectiousness of the deceased individuals bearers of the disease, where the virus is transmitted during funeral rites carried out by family members and mourners. The analysis revealed that it is possible to have a state where the disease is completely absent from the population (as we have presently) and a state where the disease is established in the population. Data from WHO on Ebola situation report, World Bank and from other sources were used to carry out the numerical simulations of the model.

The numerical simulation reveals that the spread of the disease could be minimized in the population if the infected individuals are isolated as soon as their infection has been confirmed (due to medical test), or are suspected to be infected (individuals that have a feverish feeling who do not respond to treatment for usual causes of fever in that area, and showing one of the symp-

toms for Ebola virus) or the probable (suspected cases with an epidemiological link to a confirmed case), and the dead are properly handled by professionals trained for this purpose, then the disease can be suppressed to a barest minimal level even without therapeutic method.

Our analysis is not exempt of limitations. Mobility of individuals was not incorporated into the model. Also, the number of cases may be under-ascertained as reported cases may represent only a portion of the total number of cases. Another limitation in our model is the assumption that the disease-induced death rate for infectious and isolated are equal. If some of the assumptions are modified, this could lead to a different result entirely. On the long run, we may have the same outcome, but it will definitely change the dynamics of the diseases and how fatal it will be.

For instance, suppose the assumption that isolated individuals do not transmit the infection is removed; this implies that infectious individuals, isolated individuals and infectious deceased are responsible for the transmission of the virus to susceptible individuals, meaning that we have more individuals leaving the susceptible compartment for the exposed compartments. This will also affect the analytic solution and the numerical simulation of the model.

Having stated this, it is important for us to know what we aim at obtaining at the end of our analysis, as there is no model that is able to answer all the questions about a particular disease. With this model, we have been able to study the dynamics of Ebola virus disease in one of the countries affected by the

2014 outbreak and to see from the sensitivity analysis some of the parameters that affect the transmission of the virus and the precautionary measures that need to be taken in case of future outbreaks of the disease. Although the analysis reveals that the disease could be eliminated completely from the population, we still need to be vigilant due to the fact that we know that viruses are capable of transforming their genetic makeup to a different strain of that virus. This is the reason we must not fold our hands as if everything that can be done has been done. Recent outbreaks (August 2018) in the Democratic Republic on Congo (DRC) emphasize that hands must be kept on deck.

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