Mathematical Analysis of The Role of Quarantine and Isolation in Epidemiology

by

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Abstract

The quarantine of people suspected of being exposed to a disease, and the isolation of those with clinical symptoms of the disease, constitute what is probably the oldest infection control mechanism since the beginning of recorded human history. The thesis is based on using mathematical modelling and analysis to gain qualitative insight into the transmission dynamics of a disease that is controllable using quarantine and isolation. A basic model, which takes the form of an autonomous deterministic system of non-linear differential equations with standard incidence, is formulated first of all. Rigorous analysis of the basic model shows that its disease-free equilibrium is globally-asymptotically stable whenever a certain epidemiological threshold (denoted by $\mathcal{R}_c$) is less than unity. The epidemiological implication of this result is that the disease will be eliminated from the community if the use of quarantine and isolation could result in making $\mathcal{R}_c < 1$. The model has a unique endemic equilibrium whenever $\mathcal{R}_c > 1$. Using a Lyapunov function of Goh-Volterra type, it is shown that the unique endemic equilibrium is globally-asymptotically stable for a special case. The basic model is extended to incorporate various epidemiological and biological aspects relating to the transmission dynamics and control of a communicable disease, such as the use of time delay to model the latency period, effect of periodicity (seasonality), the use of an imperfect vaccine and the use of multiple latent and infectious stages (coupled with gamma-distributed average waiting times in these stages). One of the main mathematical findings of this thesis is that adding time delay, periodicity and multiple latent and infectious stages to the basic quarantine/isolation model does not alter the essential qualitative features of the basic model (pertaining to the persistence or elimination of the disease). On the other hand, the use of an imperfect vaccine induces the phenomenon of backward bifurcation (a dynamical feature not present in the basic model), the consequence of which is that disease elimination becomes more difficult using quarantine and isolation (since, in this case, the epidemiological requirement $\mathcal{R}_c < 1$ is, although necessary, no longer sufficient for disease elimination). Numerous numerical simulations are carried out, using parameter values relevant to the 2003 SARS outbreaks in the Greater Toronto Area of Canada, to illustrate some of the theoretical findings as well as to evaluate the population-level impact of quarantine/isolation and an imperfect vaccine. In particular, threshold conditions for which the aforementioned control measures could have a positive or negative population-level impact are determined.

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Dedication

To my lovely mother and wife

Glossary

Abbreviation	Meaning
DDE	Delay differential equation
DFE	Disease-free equilibrium
EEP	Endemic equilibrium point
GAS	Globally-asymptotically stable
LAS	Locally-asymptotically stable
ODE	Ordinary differential equation

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Chapter 1

Introduction

Epidemics, described as sudden outbreaks of diseases which infect a substantial fraction of the population in a region before disappearing (while leaving many members of the population susceptible)[2], have been occurring since the beginning of recorded human history. For example, the Black Death (bubonic plague) spread from Asia throughout Europe during the 14th century (beginning in 1346) resulting in the death of about one third of the population of Europe between 1346 and 1350 [8]. The disease recurred in various parts of Europe for more than 300 years (notably, the Great Plague of London (1656-1666)) and then gradually disappeared from Europe. Smallpox killed over 300 million people in the 19th century alone [78]. The 1918 influenza pandemic (also known as Spanish Flu) affected about one third of the human population (500 million people) and killed between 20 to 100 million people [78]. More recently, since its inception in the 1980s, the human immuno-deficiency virus (HIV) has killed about 25 million people globally (and about 33 million people are currently living with HIV/AIDS)[72]. Malaria infects about 300 million people, and causes about 2 million deaths annually [28]. Diseases such as plague, cholera, hemorrhagic fevers continue to erupt occasionally [44], while others (such as malaria, HIV/AIDS, *mycobacterium* tuberculosis, typhus, cholera, schistosomiasis etc.) are endemic (i.e., always present) in some regions of the

world.

Unfortunately, despite the major advances in the medical sciences, infectious diseases continue to cause significant morbidity and mortality in human populations worldwide, with disproportionate impact in developing countries (in general). A recent survey estimated that infectious diseases are responsible for more than half of human deaths in sub-Saharan Africa (and such diseases continue to impose heavy public health and socio-economic burdens on the affected populations) [30]. Furthermore, the adverse impact of infectious diseases extend beyond human populations, inflicting tolls on domestic animal, wildlife and plant populations. The combination of complex ecology, rapid evolution in response to changing circumstances, and the on-going emergence of novel pathogens, ensures that infectious diseases will continue to pose serious challenges for the foreseeable future [81].

When confronted with a possible epidemic, public health officials often ask questions such as [8]:

(i) How many people will be infected and require hospitalization (i.e., how severe will the epidemic be)?

(ii) What is the maximum number of people needing care at any given time?

(iii) How long will the epidemic last?

(iv) What will be the potential efficacy of some intervention strategies (such as quarantine, use of vaccine etc. in curtailing the severity of the epidemic)?

Mathematical modelling plays a major role in epidemiology, by way of providing deeper insight into the underlying mechanisms for the spread of infectious diseases and suggesting effective control strategies. Infectious diseases can exhibit complex nonlinear dynamics and mathematical models enable clear and rigorous analysis of the

associated underlying mechanisms. Some of the main roles of mathematical modelling of infectious diseases include the following:

(a) Building and testing theories; assessing quantitative conjectures; determining sensitivities to changes in parameter values; estimating key parameters from data;

(b) Assessing and comparing the impact of various preventive and therapeutic measures;

(c) Identifying trends and making general forecasts;

(d) Providing early estimates of epidemiological thresholds (such as the basic reproduction number) and expected disease burden (attack rate, morbidity, hospitalization, mortality).

1.1 Modelling of Infectious Diseases

The use of compartmental mathematical models in epidemiology dates back to the pioneering works of Sir Ronald Ross, Kermack and McKendrick [2, 3, 44, 53, 54]. The models, typically of the forms of deterministic or stochastic systems of non-linear differential equations, are used to evaluate various control strategies, such as vaccination, the use of antibiotics or antivirals, quarantine and isolation.

The basic differential equation model proposed by Kermack and McKendrick in 1927 (to describe the Great Plague of London of 1665-1666), which splits the total population at time t, denoted by $N(t)$, into three mutually-exclusive compartments of those who are susceptible ($S(t)$), infected ($I(t)$) and recovered or removed ($R(t)$) (so that, $N(t) = S(t) + I(t) + R(t)$), is given by the following system of equations [54]:

$$\begin{aligned} \frac{dS}{dt} &= -\beta\frac{SI}{N}, \\ \frac{dI}{dt} &= \beta\frac{SI}{N} - \alpha I, \\ \frac{dR}{dt} &= \alpha I, \end{aligned} \tag{1.1}$$

where β is the transmission coefficient (effective contact rate) and α is the *per capita* rate of recovery (or removal) for infected individuals. Susceptible individuals become infected upon successful transmission of the disease when two individuals from the susceptible (S) and infected (I) compartments interact. Infectious individuals are removed from the infectious state at the given recovery rate. The model (1.1) is *deterministic*. That is, the behaviour of the model is completely determined by its history and by the rules which govern the development of the model. For small compartment sizes, the behaviour of the compartment size may be strongly influenced by random perturbations, and other types of models (*stochastic*) are more appropriate (see, for instance, [1] for a general introduction of stochastic models).

Numerous extensions of the Kermack-McKendrick SIR model above, incorporating important epidemiological and biological concepts such as vaccination, quarantine, isolation, antiviral treatment and periodicity (or seasonality), have been designed and used in the mathematical epidemiology literature over the decades. Some of these models include a class of exposed individuals (denoted by E). In summary, most of the compartmental models used in the literature (which typically take the forms of SIR, SIS, SIRS, SEIR, SEIRS compartmental models) are built based on the modelling framework of Kermack and McKendrick [53, 54].

1.2 Disease Incidence Functions

Disease incidence in a community is defined in terms of the number of new infections generated *per* unit time in that community. Incidence, in disease models, is generally characterized by an incidence function (which describes the rate at which new infections are generated). Various types of incidence functions have been used in disease modelling (see, for example, [46] for general discussion), and the choice of such function can play an important role in the dynamics of the disease. A general approach for constructing disease incidence function (required for modelling), as described in [46], is given below.

Let $S(t)$, $I(t)$ and $N(t)$ denote the number of susceptible individuals, infected individuals and the total population size at time t, respectively. Suppose $\beta(N)$ is the effective contact rate (i.e., the average number of contacts sufficient to transmit infection) *per* person *per* unit time. Then, $\beta(N)I/N$ is the average number of contacts with infectious individuals a susceptible individual makes *per* unit time. Thus, the number of new cases coming from all susceptible individuals (S) is λS, where $\lambda = \beta(N)I/N$ is the *force of infection*. If $\beta(N) = \beta$, a constant, then λS is referred to as a *standard incidence function*. When $\beta(N) = \beta N$ (that is, the contact rate depends on the total population), then λS is called *mass action incidence* [44]. It is worth stating that standard incidence models with constant total population (i.e., $N(t)$ is constant), such as the model in [56], are essentially mass action models.

The aforementioned two incidence functions (standard and mass action incidence) appear to be the most widely used in the mathematical biology literature. Although some studies have suggested that the standard incidence formulation is more realistic for human diseases [2, 3], the choice of one incidence over the other, generally depends on the disease being modeled (and, in some cases, the need for analytical tractability).

1.3 Reproduction Number and Bifurcations

As stated earlier, compartmental models have been widely used to gain insight into the spread and control of emerging and re-emerging human diseases, dating back to the pioneering work of the likes of Ross, Kermack and McKendrick and others (see, for instance, [2, 3, 44] and the references therein). The qualitative dynamics of these models tend (generally) to be completely determined by a threshold quantity, known as the *basic reproduction number* (denoted by $\mathcal{R}_0$), which measures the average number of new cases generated by a typical infected individual in a completely susceptible population [2, 22, 44].

Typically, when $\mathcal{R}_0$ is less than unity, a small influx of infected individuals will not generate large outbreaks, and the disease dies out in time (in this case, the corresponding disease-free equilibrium (DFE) is asymptotically-stable). On the other hand, the disease will persist in the population if $\mathcal{R}_0$ exceeds unity, where, typically, anasymptotically-stable endemic equilibrium point (EEP) exists. This phenomenon, where the DFE and an EEP exchange their stability at $\mathcal{R}_0 = 1$, is known as *forward bifurcation* (or *transcritical bifurcation*). Bifurcation represents a change in the qualitative behavior of the model as a related parameter or quantity (typically $\mathcal{R}_0$) varies. A schematic description of forward bifurcation is given in Figure 1.1.

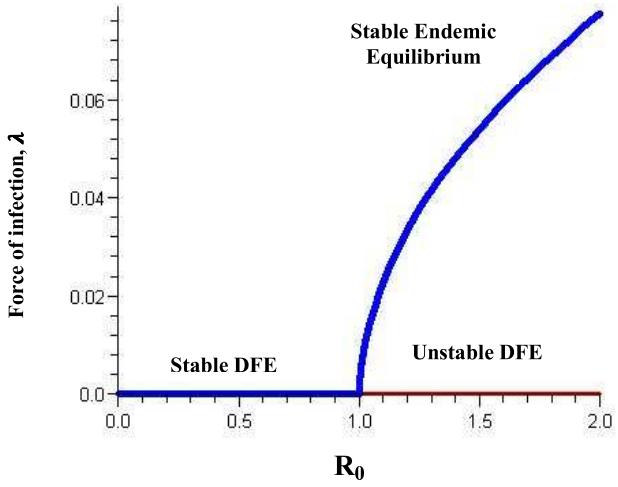


Figure 1.1: Forward bifurcation diagram.

Forward bifurcation, first noted by Kermack and McKendrick [54], has been observed in many disease transmission models (see, for instance, [12, 13, 44, 47] and some of the references therein). In general, for models that exhibit forward bifurcation, the requirement $\mathcal{R}_0 < 1$ is necessary and sufficient for effective disease control or elimination

However, some modelling studies have shown that although $\mathcal{R}_0 < 1$ is necessary for disease elimination, this requirement may not be sufficient. This is due to the phenomenon of *backward bifurcation*, where (typically) a stable endemic equilibrium co-exists with a stable disease-free equilibrium when $\mathcal{R}_0 < 1$. Backward bifurcation has been observed in numerous disease transmission models, such as those for behavioral responses to perceived risks [40], multiple groups [12], vaccination [27, 56], vector-borne diseases [35] and the transmission dynamics of *mycobacterium* tuberculosis with exogenous re-infection [31, 79]. The public health implication of backward bifurcation is that the classical requirement of having the associated reproduction number of the model being less than unity is insufficient (in general) for disease elimination (in a

backward bifurcation situation, effective disease control when $\mathcal{R}_0 < 1$ is dependent on the initial sizes of the sub-populations of the model). A schematic description of the backward bifurcation phenomenon is given in Figure 1.2 (it should be emphasized that, in a backward bifurcation situation, the global asymptotic stability property of the DFE is only feasible outside the region of the co-existence of the two stable attractors, such as the region $0 < \mathcal{R}_0 \leq 0.59$ in Figure 1.2).

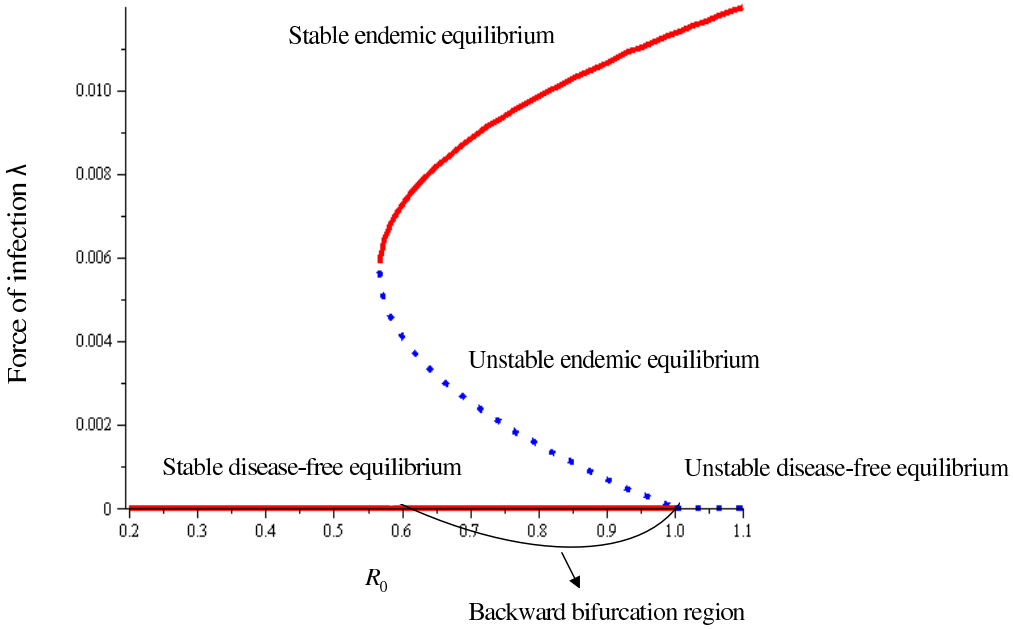


Figure 1.2: Backward bifurcation diagram showing the co-existence of a stable DFE and two branches of endemic equilibria (a stable and an unstable branch).

1.4 Quarantine and Isolation

Quarantine of individuals suspected of being exposed to a disease, and the isolation of those with disease symptoms, constitute what is probably the first infection control measure since the beginning of recorded human history [44]. Over the decades, quar-

antine and isolation have been used to reduce the transmission of numerous emerging and re-emerging human diseases, such as leprosy, plague, cholera, typhus, yellow fever, smallpox, diphtheria, tuberculosis, measles, ebola, pandemic influenza and, more recently, severe acute respiratory syndrome (SARS) [16, 48, 61, 64, 67, 73, 90, 93, 99]. Furthermore, these basic public health control measures are also applied to combat the spread of animal diseases, such as bovine tuberculosis, rinderpest, foot-and-mouth, psittacosis, Newcastle disease and rabies [48, 52].

The term quarantine is used to characterize the deliberate separation of individuals exposed (i.e., suspected of being infected) to a contagious (communicable) disease (by coming in contact with an infected individual), irrespective of their infectivity or symptomatic status, from a population of susceptible individuals [68]. Quarantined individuals are monitored, typically over the duration of the incubation period (the time from infection to the onset of symptoms) of the disease (see Table 1.1 for a list of some communicable diseases and their respective incubation periods). Individuals who show disease symptoms (during the quarantine period) are isolated (typically in hospitals). Isolation refers to the strict separation of individuals with disease symptoms from all of the members of the population at risk. On the other hand, those who do not show symptoms at the end of the quarantine period remain susceptible to the disease [68].

Although, as stated above, some quarantined individuals may remain susceptible at the end of the quarantine period [32, 61], in this thesis, the quarantine class involves only newly-infected individuals detected either *via* contact tracing of symptomatic cases, random testing (if a suitable diagnostic test exists) or the quarantine of suspected cases. As noted by Feng [32], it is plausible to assume that, for large total population sizes (N), the quarantine of susceptible individuals is unlikely to have a significant impact on the disease dynamics (and, hence, it is ignored in this thesis). In other words, the term quarantine in this thesis refers only to the detection and removal

of new (asymptomatic) infections. It should be mentioned that the mass quarantine adopted in the Greater Toronto Area of Canada during the 2003 SARS outbreaks only resulted in the detection of very few confirmed SARS cases (see, for instance, [20]).

Table 1.1: Incubation period for some of communicable diseases [3, 95]

Disease	**Incubation period**
Chicken pox	14-16 days
Ebola	2-21 days
Influenza	1-3 days
Measles	9-12 days
SARS	up to 10 days
Smallpox	7-17 days

1.5 Motivation and Outline of the Thesis

The main objective of this thesis is to provide a rigorous qualitative study of various deterministic models for the spread of a (general) contagious disease in a population in the presence of quarantine and isolation, to gain deeper insight into the population-level impact of these measures on the transmission dynamics and control of the disease. In other words, the thesis focuses on designing new, robust, and realistic models for the spread of a communicable disease in the presence of quarantine and isolation, and then providing detailed qualitative analyses of the resulting models with emphasis on determining the existence and stability of the associated solutions (equilibrium or periodic), as well as to characterize the kind of bifurcation the resulting models will undergo. The knowledge of these dynamical properties is not only crucial for determining important

epidemiological thresholds that govern the persistence or elimination of the disease, but also allows for the realistic assessment of the impact of these measurers (quarantine and isolation) in effectively controlling the spread of a given communicable disease in a population.

A basic quarantine/isolation model is designed and qualitatively analysed first of all. The basic model monitors the temporal dynamics of susceptible (S), latent or exposed (E), quarantined (Q), infectious (I), isolated (H) and recovered (R) individuals. It also allows for the loss of infection-acquired immunity (so that individuals who recovered from infection can become susceptible again). The resulting $SEIQHRS$ model (with standard incidence) is then extended to include various related epidemiological and biological concepts (such as time delay, effect of periodicity, effect of an imperfect vaccine and the effect of using multiple latent and infectious stages).

Some of the main mathematical and epidemiological questions the thesis seeks to address are:

(a) What kind of dynamics does the basic quarantine/isolation model with standard incidence exhibit? In other words, how many equilibria does the system have? Under what conditions do they exist (and/or are stable)? What kind of bifurcation does the system undergo?

(b) Does the dynamical behavior of the basic model change if the associated incubation period is modelled using time delay? In such a setting, will the choice of incidence function have any effect on the theoretical result obtained?

(c) What is the role of periodicity in the transmission dynamics of a disease that is controllable using quarantine and isolation?

(d) What is the (mathematical and public health) impact of an imperfect vaccine on the dynamics of a disease that is controllable using quarantine and isolation?

(e) What is the impact of using multiple latent and infectious stages on the transmission dynamics of a disease in the presence of quarantine and isolation? A related question of interest is: what is the role of modelling the associated waiting times in the respective latent and infectious compartments using gamma distribution assumptions?

The thesis is organized as follows. In Chapter 2, some basic mathematical preliminaries, relevant to the thesis, are described. A basic quarantine/isolation model, with standard incidence, is developed in Chapter 3. A detailed discussion on the existence and stability of the associated equilibria of the resulting $SEIQHRS$ model is given. In Chapter 4, the quarantine/isolation model studied in Chapter 3 is extended to incorporate the effect of time delay (to model the incubation period of the disease) and two different disease incidence functions (namely, the Holling Type II incidence and standard incidence).

To qualitatively assess the impact of seasonality (periodicity) on the transmission dynamics of the communicable disease (being considered) in the presence of quarantine and isolation, the model developed in Chapter 3 is studied, in Chapter 5, for the case where some of the associated epidemiological and biological parameters are periodic. Furthermore, the effect of an imperfect vaccine on the transmission dynamics of the disease, in the presence of quarantine and isolation, is investigated in Chapter 6. The basic model is further extended in Chapter 7, by considering multiple infection stages for individuals in the exposed, infectious, quarantined and hospitalized classes. A major feature of the model considered in Chapter 7 is that the average waiting times in the exposed and infectious compartments is modelled using gamma distribution assumptions. The main contributions of the thesis, together with some discussions on future work, are summarized in Chapter 8. It should be mentioned that the terms "exposed" and "latent" are used interchangeably in this thesis (although some have argued that the two terms are not exactly the same biologically). For the purpose of

this thesis, "exposed/latent" means newly-infected individuals who have not yet shown clinical symptoms of the disease.

Chapter 2

Mathematical Preliminaries

This chapter introduces some of the key mathematical theories and methodologies relevant to the thesis (the material presented in this chapter are mostly standard definitions and results obtained from the literature).

2.1 Equilibria of Linear and Non-linear Systems

Consider the system of ordinary differential equation (ODEs) below (where a dot represents differentiation with respect to time ($\frac{d}{dt}$)):

$$\dot{x} = f(x, t; \mu), \;\; x \in U \subset \mathbb{R}^n, \;\; t \in \mathbb{R}^1, \;\; \text{and} \;\; \mu \in V \subset \mathbb{R}^p, \tag{2.1}$$

where, U and V are open sets in $\mathbb{R}^n$ and $\mathbb{R}^p$, respectively, and μ is a parameter. The right-hand side function, $f(x, t; \mu)$, of equation (2.1) is called a *vector field*. ODEs which explicitly depend on time are called *non-autonomous*, while those that are independent of time are called *autonomous*.

Consider the following general autonomous system:

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n. \tag{2.2}$$

Definition 2.1. *An equilibrium solution of the system* (2.2) *is given by* $x = \bar{x} \in \mathbb{R}^n$, *where* $f(\bar{x}) = 0$. *The vector or point* $\bar{x}$ *is called an equilibrium point.*

Theorem 2.1. (Fundamental Existence-Uniqueness Theorem [71]). *Let* E *be an open subset of* $\mathbb{R}^n$ *containing* x_0 *and assume that* $f \in C^1(E)$. *Then, there exists an* $a > 0$ *such that the initial value problem (IVP):*

$$\dot{x} = f(x), \;\; x(0) = x_0,$$

has a unique solution $x(t)$ *on the interval* $[-a, a]$.

Lemma 2.1. ([71]). *Let* E *be an open subset of* $\mathbb{R}^n$ *and let* $f : E \to \mathbb{R}^n$. *Then, if* $f \in C^1(E)$, f *is locally Lipschitz on* E.

Definition 2.2. *The Jacobian matrix of* f *at the equilibrium point* $\bar{x}$, *denoted by* $Df(\bar{x})$, *is the matrix of partial derivatives of* f *evaluated at* $\bar{x}$. *It is given by:*

$$J(\bar{x}) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1}(\bar{x}) & \cdots & \frac{\partial f_1}{\partial x_n}(\bar{x}) \\ \vdots & \vdots & \vdots \\ \frac{\partial f_n}{\partial x_1}(\bar{x}) & \cdots & \frac{\partial f_n}{\partial x_n}(\bar{x}) \end{pmatrix},$$

Definition 2.3. *Let* $x = \bar{x}$ *be an equilibrium solution of* (2.2). *Then* $\bar{x}$ *is called hyperbolic if none of the eigenvalues of* $Df(\bar{x})$ *has zero real part. An equilibrium point that is not hyperbolic is called non-hyperbolic.*

Consider the system:

$$\begin{aligned} \dot{x} &= f(x), \quad x \in \mathbb{R}^n, \\ \dot{y} &= g(y), \quad y \in \mathbb{R}^n, \end{aligned} \tag{2.3}$$

where f and g are two C^r $(r \geq 1)$ functions defined on $\mathbb{R}^n$.

Definition 2.4. ([94]). *The dynamics generated by the vector fields f and g of* (2.3) *are said to be locally C^k conjugate ($k \leq r$) if there exist a C^k diffeomorphism h which takes the orbits of the flow generated by f, $\phi(t,x)$, to the orbits of the flow generated by g, $\psi(t,y)$, preserving orientation and parametrization by time.*

Theorem 2.2. (Hartman and Grobman [94]). *Consider a $C^r(r \geq 1)$ vector field f and the system*

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n, \tag{2.4}$$

with domain of f an open subset of $\mathbb{R}^n$. Suppose also that (2.4) *has equilibrium solutions which are hyperbolic. Consider the associated linear ODE system*

$$\dot{\xi} = Df(\bar{x})\xi, \quad \xi \in \mathbb{R}^n. \tag{2.5}$$

Then the flow generated by (2.4) *is C^0 conjugate to the flow generated by the linearized system* (2.5) *in a neighbourhood of the equilibrium point.*

A direct implication of the Hartman-Grobman Theorem is that an orbit structure near a hyperbolic equilibrium solution is (topologically) qualitatively-equivalent to the orbit structure given by the associated linearized (around the equilibrium) dynamical system.

2.2 Stability of Solutions and Bifurcations

The following are standard definitions and theorems used to analyze the stability of a solution of an autonomous system. Let $\bar{x}(t)$ be any solution of the general autonomous system (2.2). Then, $\bar{x}(t)$ is *stable* if solutions starting "close" to $\bar{x}(t)$ at a given time remain close to $\bar{x}(t)$ for all later times. It is *asymptotically-stable* if nearby solutions

converge to $\bar{x}(t)$ as $t \to \infty$. These concepts are formally defined below:

Definition 2.5. ([94]). *The solution $\bar{x}(t)$ is said to be stable if given $\epsilon > 0$, there exists a $\delta = \delta(\epsilon) > 0$ such that, for any solution $y(t)$ of (2.2) satisfying $|\bar{x}(t_0) - y(t_0)| < \delta$, $|\bar{x}(t) - y(t)| < \epsilon$ for $t > t_0$, $t_0 \in \mathbb{R}$.*

Definition 2.6. ([94]). *The solution $\bar{x}(t)$ is said to be asymptotically-stable if (i) it is stable and (ii) there exists a constant $c > 0$ such that, for any solution $y(t)$ of (2.2) satisfying $|\bar{x}(t_0) - y(t_0)| < c$, $\lim_{t\to\infty} |\bar{x}(t) - y(t)| = 0$.*

Definition 2.7. *A solution which is not stable is said to be unstable.*

Theorem 2.3. ([94]). *Suppose all the eigenvalues of $Df(\bar{x})$ have negative real parts. Then the equilibrium solution $x = \bar{x}$ of the system (2.2) is locally-asymptotically stable. The equilibrium $\bar{x}$ is unstable if at least one of the eigenvalues has positive real part.*

Bifurcations

In general, systems of physical interest typically have parameters which appear in the defining (governing) system of equations. As these parameters are varied, changes may occur in the qualitative structures of the solutions for certain parameter values. These changes are called *bifurcations.* The parameter values where bifurcations occur are called *bifurcation values* (or *bifurcation points*). A standard definition of bifurcation at a point is given below.

Definition 2.8. *Let*

$$\dot{x} = f(x, \mu), \quad x \in \mathbb{R}, \ \ \mu \in \mathbb{R}, \tag{2.6}$$

be a one-parameter family of one-dimensional ODEs. An equilibrium solution of (2.6) given by $(x, \mu) = (0, 0)$ is said to undergo bifurcation at $\mu = 0$ if the flow for μ near

zero and x near zero is not qualitatively the same as the flow near $x = 0$ at $\mu = 0$.

There are various types of bifurcations in dynamical systems, including saddle-node, transcritical, pitchfork, backward, Bogdanov-Takens and Hopf bifurcations [94]. Two of these, forward and backward bifurcations, are relevant to this thesis (and were briefly described in Chapter 1). In particular, the following theorem is used to establish the presence of the backward bifurcation phenomenon for the vaccination model considered in Chapter 6.

Theorem 2.4. (**Castillo-Chavez and Song** [13]). *Consider the following general system of ordinary differential equations with a parameter ϕ*

$$\frac{dx}{dt} = f(x, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n, \text{ and } f \in C^2(\mathbb{R}^n \times \mathbb{R}). \tag{2.7}$$

Without loss of generality, it is assumed that 0 is an equilibrium for system (2.7) for all values of the parameter ϕ, (that is $f(0, \phi) \equiv 0$ for all ϕ). Assume

A1: $A = D_x f(0, 0) = \left(\frac{\partial f_i}{\partial x_j}, 0, 0\right)$ is the linearized matrix of system (2.7) around the equilibrium point 0 with ϕ evaluated at 0, zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts;

A2: Matrix A has a nonnegative right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.

Let f_k be the kth component of f and

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0),$$

$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0, 0).$$

Then the local dynamics of system (2.7) around 0 are totally determined by a and b.

i. $a > 0$, $b > 0$. *When* $\phi < 0$ *with* $|\phi| \ll 1$, *0 is locally asymptotically stable and there exists a positive unstable equilibrium; when* $0 < \phi \ll 1$, *0 is unstable and there exists a negative and locally asymptotically stable equilibrium.*

ii. $a < 0$, $b < 0$. *When* $\phi < 0$ *with* $|\phi| \ll 1$, *0 is unstable; when* $0 < \phi \ll 1$, *0 is locally asymptotically stable, and there exists a positive unstable equilibrium;*

iii. $a > 0$, $b < 0$. *When* $\phi < 0$ *with* $|\phi| \ll 1$, *0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when* $0 < \phi \ll 1$, *0 is stable, and a positive unstable equilibrium appears;*

iv. $a < 0$, $b > 0$. *When* ϕ *changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

Particularly, if $a > 0$ *and* $b > 0$, *then a backward bifurcation occurs at* $\phi = 0$.

2.3 Irreducible Cooperative Systems

Consider the autonomous system (2.2), where f is continuously differentiable on an open subset $\mathcal{D} \subset \mathbb{R}^n$. Let $\phi_t(x)$ denote the solution of the system (2.2) with initial value x.

Definition 2.9. ([82]). *f is said to be of Type K in $\mathcal{D}$ if for each i, $f_i(a) \leq f_i(b)$ for any two points in $\mathcal{D}$ satisfying $a \leq b$ and $a_i = b_i$.*

The Type K Condition can easily be identified from the sign structure of the Jacobian matrix of the system (2.2). The following definition describes this structure.

Definition 2.10. ([82]). *$\mathcal{D}$ is p-convex if $tx + (1-t)y \in \mathcal{D}$ for all $t \in [0,1]$ whenever $x, y \in \mathcal{D}$ and $x \leq y$.*

It is clear that if $\mathcal{D}$ is a convex set, then it is also p-convex. Furthermore, if $\mathcal{D}$ is a p-convex subset of $\mathbb{R}^n$ and

$$\frac{\partial f_i}{\partial x_j} \geq 0, \quad i \neq j, \quad x \in \mathcal{D}, \tag{2.8}$$

then f is of Type K in $\mathcal{D}$.

Definition 2.11. ([82]). *The system* (2.2) *is said to be a cooperative system if* (2.8) *holds on the p-convex domain* $\mathcal{D}$. *It is called a competitive system on* $\mathcal{D}$ *if* $\mathcal{D}$ *is p-convex and the inequalities* (2.8) *are reversed:*

$$\frac{\partial f_i}{\partial x_j} \leq 0, \quad i \neq j, \quad x \in \mathcal{D}.$$

Definition 2.12. ([82]). *An* $n \times n$ *matrix* $A = (a_{ij})$ *is irreducible if for every nonempty, proper subset* $\mathcal{I}$ *of the set* $\mathcal{N} = \{1, 2, \cdots, n\}$, *there is an* $i \in \mathcal{I}$ *and* $j \in \mathcal{N} \setminus \mathcal{I}$ *such that* $a_{ij} \neq 0$.

Definition 2.13. ([82]). *The system* (2.2) *is called irreducible in* $\mathcal{D}$ *if the Jacobian matrix of the system* (2.2) *is an irreducible matrix for every* $x \in \mathcal{D}$.

Theorem 2.5. ([82]). *Suppose the system* (2.2) *is irreducible and cooperative in* $\mathcal{D}$. *Then*

$$\frac{\partial \phi_t}{\partial x} \gg 0, \quad t > 0.$$

Furthermore, if $x_0, y_0 \in D$ *satisfy* $x_0 < y_0, t > 0$ *and if* $\phi_t(x_0), \phi_t(y_0)$ *are defined, then*

$$\phi_t(x_0) \ll \phi_t(y_0), \quad t > 0.$$

The theory of irreducible cooperative systems will be used in establishing some of the properties of the periodic solution discussed in Chapter 5.

2.4 Lyapunov Functions and LaSalle's Invariance Principle

Definition 2.14. *A point $x_0 \in \mathbb{R}^n$ is called an $\omega-$limit point of $x \in \mathbb{R}^n$, 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 2.15. *A point $x_0 \in \mathbb{R}^n$ is called an $\alpha-$limit point of $x \in \mathbb{R}^n$, 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 2.16. ([94]). *The set of all $\omega-$limit points of a flow is called the $\omega-$limit set. Similarly, the set of all $\alpha-$limit points of a flow is called the $\alpha-$limit set.*

Definition 2.17. ([94]). *Let $S \subset \mathbb{R}^n$ be a set. Then, S is said to be invariant under the flow generated by $\dot{x} = f(x)$ if for any $x_0 \in S$ we have $x(t, 0, x_0) \in S$ for all $t \in \mathbb{R}$.*

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

Definition 2.18. *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 $x = 0$.*

Definition 2.19. *Consider the following system*

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n. \tag{2.9}$$

Let, $\bar{x}$ be an equilibrium solution of (2.9) and let $V : U \to \mathbb{R}$ be a C^1 function defined on some neighbourhood U of $\bar{x}$ such that

i) *V is positive-definite,*

ii) *$\dot{V}(x) \leq 0$ in $U \backslash \{\bar{x}\}$.*

Any function, V, that satisfies the Conditions (i) and (ii) above is called a *Lyapunov Function* [50, 94]. The general Lyapunov Function Theorem is given below.

Theorem 2.6. (LaSalle's Invariance Principle [41]). *Consider the system (2.9). Let,*

$$S = \{x \in \bar{U} : \ \dot{V}(x) = 0\}, \tag{2.10}$$

and let M be the largest invariant set of (2.9) in S. If V is a Lyapunov function on U and $\gamma^+(x_0)$ is a bounded orbit of (2.9) which lies in S, then the $\omega-$limit set of $\gamma^+(x_0)$ belongs to M (that is, $x(t, x_0) \to M$ as $t \to \infty$.)

Corolary 2.1. *If $V(x) \to \infty$ as $|x| \to \infty$ and $\dot{V} \leq 0$ on $\mathbb{R}^n$, then every solution of (2.9) is bounded and approaches the largest invariant set M of (2.9) in the set where $\dot{V} = 0$. In particular, if $M = \{0\}$, then the solution $x = 0$ is is globally-asymptotically stable (GAS).*

Theorem 2.7. ([41, 58]). *Suppose there is a continuously differentiable, positive definite, and radially unbounded function $V : \mathbb{R}^n \to \mathbb{R}$, such that*

$$\frac{\partial V}{\partial x}(x - \bar{x}).f(x) = \nabla V(x - \bar{x}).f(x) \leq W(x) \leq 0, \ \ \forall\, x \in \mathbb{R}^n,$$

where $W(x)$ is any continuous function on U. Then, $\bar{x}$ is a globally-stable equilibrium. The solution $x(t)$ converges to the largest invariant set S contained in $E = \{x \in \mathbb{R}^n : W(x) = 0\}$.

Example 2.1. *Consider the following system,*

$$\begin{aligned} \dot{x} &= y - x^3, \\ \dot{y} &= -x - y^3. \end{aligned}$$

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

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

Hence, $\dot{V} < 0$ if $(x, y) \neq (0, 0)$. Thus, by Corollary 2.1, the equilibrium $(0, 0)$ is GAS.

Comparison Theorem

Another approach for establishing the global asymptotic stability of equilibria is by using the comparison theorem. The main idea is to compare the solutions of the system of differential equations

$$\dot{x} = f(t, x), \tag{2.11}$$

with the solutions of the differential inequality system

$$\dot{z} \leq f(t, z), \tag{2.12}$$

or,

$$\dot{y} \geq f(t, y), \tag{2.13}$$

on an interval. This method requires that the solution of the system (2.11) is unique.

Theorem 2.8 (Comparison Theorem [83])**.** *Let f be continuous on $\mathbb{R} \times D$ and of type K. Let $x(t)$ be a solution of (2.11) defined on $[a, b]$. If $z(t)$ is a continuous function on $[a, b]$ satisfying (2.12) on (a, b) with $z(a) \leq x(a)$, then $z(t) \leq x(t)$ for all t in $[a, b]$. If $y(t)$ is continuous on $[a, b]$ satisfying (2.13) on (a, b) with $y(a) \geq x(a)$, then $y(t) \geq x(t)$ for all t in $[a, b]$.*

2.5 Stability of Non-autonomous Systems

In this section, the results presented in Section 2.4 (for autonomous systems) are extended to non-autonomous systems.

Definition 2.20. ([41]). *Consider the non-autonomous system:*

$$\dot{x} = f(t, x). \tag{2.14}$$

Let $V(t, x) : \mathbb{R}^+ \times \mathbb{R}^n \to \mathbb{R}$ be continuous, U be any set in $\mathbb{R}^n$ and $\bar{U}$ be the closure of U. Then V is called a Lyapunov function of (2.14) on U if

- *given x in $\bar{U}$ there is a neighborhood N of x such that $V(t, x)$ is bounded from below for all $t \geq 0$ and all $x \in U \cap N$.*
- *$\dot{V}(t, x) \leq W(x) \leq 0$ for $(t, x) \in \mathbb{R}^+ \times U$ and W is continuous on $\bar{U}$.*

Theorem 2.9. ([41]). *Define, $E = \{x \in \bar{U} : \quad W(x) = 0\}$. Let V be a Lyapunov function for (2.14) and let $x(t)$ be a solution of (2.14) which is bounded and remains in U for $t \geq t_0 \geq 0$.*

(a) If for each $p \in \bar{U}$, there is a neighborhood N of p such that $|f(t,x)|$ is bounded for all $t \geq 0$ and all $x \in N \cap U$, then $x(t) \to E$ as $t \to \infty$.

(b) If W has continuous first derivative on $\bar{U}$ and $\dot{W}$ is bounded from above (or from below) along the solution $x(t)$, then $x(t) \to E$ as $t \to \infty$.

Example 2.2. Consider the following system [41],

$$\begin{aligned} \dot{x} &= y, \\ \dot{y} &= -x - p(t)y, \end{aligned} \tag{2.15}$$

where $p(t) \geq \delta > 0$. Let $V(x,y) = (x^2 + y^2)/2$, then $\dot{V} = -p(t)y^2 \leq -\delta y^2$, and V is a Lyapunov function on $\mathbb{R}^2$ with $W(x,y) = \delta y^2$. Furthermore, $\dot{W} = -2\delta(xy + p(t)y^2) \leq -2\delta xy$. Since every solution of (2.15) is bounded, it follows that the Condition (b) in Theorem 2.9 is satisfied. The set E, for system (2.15), is the $x-$ axis. Hence, it follows from Theorem 2.9 that each solution $(x(t), y(t))$ of (2.15) satisfies $y(t) \to 0$ as $t \to \infty$.

2.6 Next Generation Operator Method

The next generation operator method [21, 87] is popularly used to compute the reproduction number of disease transmission models (and, subsequently, establish the local asymptotic stability of the associated disease-free equilibrium). The formulation given in [87], for autonomous systems, is briefly described below.

Suppose the given disease transmission model, with non-negative initial conditions, can be written in terms of the following autonomous system:

$$\dot{x}_i = f(x_i) = \mathrm{F}_i(x) - \mathrm{V}_i(x), \quad i = 1, \cdots, n, \tag{2.16}$$

where $\mathrm{V}_i = \mathrm{V}_i^- - \mathrm{V}_i^+$ and the functions satisfy the following axioms below. First of all,

$X_s = \{x \geq 0 | x_i = 0,\ i = 1, \cdots, m\}$ is defined as the disease-free states (non-infected state variables) of the model, where $x = (x_1, \cdots, x_n)^t, x_i \geq 0$ represents the number of individuals in each compartment of the model.

(A1) if $x \geq 0$, then $\mathrm{F}_i, \mathrm{V}_i^+, \mathrm{V}_i^- \geq 0$ for $i = 1, \cdots, m$.

(A2) if $x_i = 0$, then $\mathrm{V}_i^- = 0$. In particular, if $x \in X_s$ then $\mathrm{V}_i^- = 0$ for $i = 1, \cdots, m$.

(A3) $\mathrm{F}_i = 0$ if $i > m$.

(A4) if $x \in X_s$, then $\mathrm{F}_i(x) = 0$ and $\mathrm{V}_i^+(x) = 0$ for $i = 1, \cdots, m$.

(A5) If $\mathrm{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real part.

In the above, $\mathrm{F}_i(x)$ represents the rate of appearance of new infections in compartment i, $\mathrm{V}_i^+(x)$ represents the rate of transfer of individuals into compartment i by all other means, and $\mathrm{V}_i^-(x)$ represents the rate of transfer of individuals out of compartment i. It is assumed that these functions are at least twice continuously-differentiable in each variable [87].

Definition 2.21. ($M-$Matrix). *An $n \times n$ matrix A is an $M-$matrix if and only if every off-diagonal entry of A is non-positive and the diagonal entries are all positive.*

Lemma 2.2. (van den Driessche and Watmough [87]). *If $\bar{x}$ is a DFE of* (2.16) *and $f_i(x)$ satisfy $(A1) - (A5)$, then the derivatives $D\mathrm{F}(\bar{x})$ and $D\mathrm{V}(\bar{x})$ are partitioned as*

$$D\mathrm{F}(\bar{x}) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \ D\mathrm{V}(\bar{x}) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

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

$$F = \left[\frac{\partial \mathrm{F}_i}{\partial x_j}(\bar{x})\right] \text{ and } V = \left[\frac{\partial \mathrm{V}_i}{\partial x_j}(\bar{x})\right] \text{ with } 1 \leq i, j \leq m.$$

Furthermore, F is non-negative, V is a non-singular $M-$matrix and J_3, J_4 are matrices associated with the transition terms of the model, and all eigenvalues of J_4 have positive real parts.

Theorem 2.10. (van den Driessche and Watmough [87]). *Consider the disease transmission model given by* (2.16) *with $f(x)$ satisfying axioms $(A1)-(A5)$. If $\bar{x}$ is a DFE of the model, then $\bar{x}$ is LAS if $\mathcal{R}_0 = \rho(FV^{-1}) < 1$ (where ρ is the spectral radius), but unstable if $\mathcal{R}_0 > 1$.*

The formulation above has been extended by Wang and Zhao [91] to compute the reproduction ratio for disease transmission models in a periodic environment (see Appendix A).

2.7 The Poincaré Map

Definition 2.22. (Periodic Solution). *A solution $x(t)$ is said to be periodic if $x(t+T) = x(t)$ for all t, for some $T > 0$.*

Consider the system defined by

$$\dot{x} = f(x), \tag{2.17}$$

with $f \in \mathcal{C}^1(E)$, where E is a open set of $\mathbb{R}^n$. Assume that $\phi(t, x_0)$ represents the flow of the system (2.17). Then, $\phi(., x_0)$ defines a closed solution of (2.17) if and only if for all $t \in \mathbb{R}$, $\phi(t+T, x_0) = \phi(t, x_0)$ for some $T > 0$. The minimal time where this equality holds is called the period of the periodic orbit $\phi(t, x_0)$.

Consider the system (2.17) through the point x_0, with hyperplane S perpendicular to γ at x_0. Then, for any point $x \in S$ sufficiently close to x_0, the solution of (2.17) through x at $t = 0$, given by $\phi(t, x)$, will cross S again at a point $P(x)$ near x_0 (as depicted in Figure 2.1).

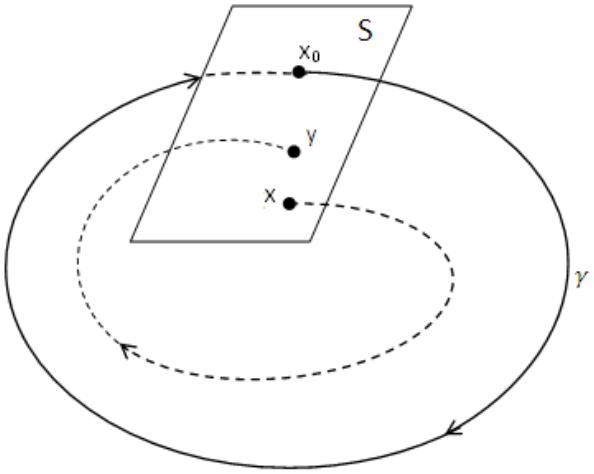


Figure 2.1: Geometry of Poincaré map with $x_0 \in \gamma$, a closed orbit, where $x \in S$, $y = P(t, x)$ [71].

Definition 2.23. *A Poincaré Map of the local section S is the map $P : S \to S$ defined by $P(x) = \phi(\tau, x)$ for x in some open subset of S and $\tau(x)$ is the first return of the flow to S.*

Theorem 2.11. ([71].) *Suppose γ is a closed orbit that is linearly asymptotically-stable. Then, γ is asymptotically-stable.*

Properties of Poincaré Map

- $P^0 := I$, where I is the identity operator;
- $P^{n+1} := P \circ P^n$;
- $P^{-n-1} := P^{-1} \circ P^{-n}$.

Theorem 2.12. ([71]). *Let γ be a stable closed orbit of* (2.17). *Then, no eigenvalue of $DP(x_0)$ has magnitude larger than one, where x_0 is any point on γ.*

2.8 Uniform Persistence Theory

Suppose X is a metric space with a metric d. Let $P : X \to X$ be a continuous map and $X_0 \subset X$ is an open set. Define $\partial X_0 = X \setminus X_0$, and $M_\partial = \{x \in \partial X_0 : P^m(x) \in \partial X_0, \forall m \geq 0\}$, which may be empty.

Definition 2.24. ([104]). *A bounded set A is said to attract a bounded set B in X if*

$$\limsup_{m\to\infty, x\in B} d(P^m(x), A) = 0.$$

- *A subset $A \subset X$ is said to be an attractor for f if A is nonempty, compact and invariant ($P(A) = A$), and A attracts some open neighborhood of itself.*
- *A global attractor for $P : X \to X$ is an attractor that attracts every point in X.*
- *For a nonempty invariant set M, the set $W^s(M) := \{x \in X : \lim_{m\to\infty} d(P^m(x), M) = 0\}$ is called the stable set of M.*

It should be recalled that a continuous mapping $P : X \to X$ is said to be point-dissipative if there is a bounded set B_0 in X such that B_0 attracts each point in X.

Definition 2.25. ([104]). *P is said to be uniformly-persistent with respect to $(X_0, \partial X_0)$ if there exists an $\vartheta > 0$ such that $\liminf_{m\to\infty} d(P^m(x), \partial X_0) \geq \vartheta$ for all $x \in X_0$.*

Definition 2.26. ([104]). *P is said to be weakly uniformly-persistent with respect to $(X_0, \partial X_0)$ if there exists an $\vartheta > 0$ such that $\limsup_{m\to\infty} d(P^m(x), \partial X_0) \geq \vartheta$ for all $x \in X_0$.*

The following theorems are used in Chapter 5.

Theorem 2.13. ([104]). *Assume that*

(C1) $P(X_0) \subset X_0$ and P has a global attractor A;

(C2) The maximal compact invariant set $A_\partial = A \cap M_\partial$ of P in ∂X, admits a Morse Decomposition $\{M_1, \cdots, M_k\}$ with the following properties

(a) M_i *is isolated in* X;

(b) $W^s(M_i) \cap X_0 = \phi$ *for each* $1 \leq i \leq k$.

Then there exists δ *such that for any compact internally chain transitive set* L *with* $L \not\subseteq M_i$ *for all* $1 \leq i \leq k$, *we have* $\inf_{x \in L} d(x, \partial X_0) > \delta$.

Theorem 2.14. ([104]). *Let* $P : X \to X$ *be a continuous map with* $P(X_0) \subset X_0$. *Assume* P *has a global attractor* A. *Then weak uniform-persistence implies uniform-persistence.*

Theorem 2.15. ([104]). *Let* $T(t)$ *be an* ω*-periodic semiflow on* X *with* $T(t)X_0 \subset X_0$, *for all* $t \geq 0$. *Assume that* $S = T(\omega)$ *satisfies the following:*

(1) $S : X \to X$ *is dissipative;*

(2) S *is compact.*

Then, uniform-persistence of S *with respect to* $(X_0, \partial X_0)$ *implies that of* $T(t)$.

Theorem 2.16. ([104]). *Let* $S : X \to X$ *be a continuous map with* $S(X_0) \subset X_0$. *Assume*

(1) $S : X \to X$ *is dissipative;*

(2) S *is compact;*

(3) S *is uniformly-persistent with respect to* $(X_0, \partial X_0)$.

Then there exists a global attractor A_0 *for* S *in* X_0, *and* S *has a coexistence state* $x_0 \in A_0$.

2.9 Delay Differential Equations (DDEs)

Time delays are used to model several mechanisms in the dynamics of epidemics, such as incubation periods, latent periods and age structure. A brief introduction (and basic properties) of DDEs is given below.

2.9.1 Existence and uniqueness of solutions

Suppose $\tau \geq 0$ is a given real number, $\mathbb{R}^n$ is an n-dimensional linear vector space over the real numbers with norm $|.|$, $C = C([-\tau, 0], \mathbb{R}^n)$ is the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^n$ with the topology of uniform convergence.

If $\phi \in C$, then the norm $\|\phi\| = \sup_{\theta \in [-\tau,0]} |\phi(\theta)|$. If

$$\sigma \in \mathbb{R}, \quad A \geq 0 \quad \text{and} \quad x \in C([\sigma - \tau, \sigma + A], \mathbb{R}^n),$$

then for any $t \in [\sigma, \sigma + A]$, let x_t be defined by

$$x_t(\theta) = x(t + \theta), \qquad -\tau \leq \theta \leq 0.$$

If D is a subset of $\mathbb{R} \times C$, $f : D \to \mathbb{R}^n$, then the DDE on D is given by

$$\dot{x}(t) = f(t, x_t). \tag{2.18}$$

The existence and uniqueness of solutions of the DDE (2.18) are stated below.

Theorem 2.17. ([42]). *Suppose Ω is an open subset of $\mathbb{R} \times C$ and $f^0 \in C(\Omega, \mathbb{R}^n)$. If $(\sigma, \phi) \in \Omega$, then there is a solution of the delay differential equation* (2.18) *passing through (σ, ϕ).*

More generally, if $W \subseteq \Omega$ is compact and $f^0 \in C(\Omega, \mathbb{R}^n)$ is given, then there is

a neighborhood $V \subseteq \Omega$ of W such that $f^0 \in C^0(V, \mathbb{R}^n)$, there is a neighborhood $U \subseteq C^0(V, \mathbb{R}^n)$ of f^0 and an $\alpha > 0$ and $r > 0$ such that, for any $(\sigma, \phi) \in W$, $f \in U$, there is a solution $x(\sigma, \phi, f)$ of the equation (2.18) through (σ, ϕ) which exists on $[\sigma - r, \sigma + \alpha]$.

Theorem 2.18. ([42]). *Suppose Ω is an open set in $\mathbb{R} \times C$, $f : \Omega \to \mathbb{R}^n$ is continuous, and $f(t, \phi)$ is Lipschitzian in ϕ on each compact set in Ω. If $(\sigma, \phi) \in \Omega$, then there is a unique solution of equation (2.18) through (σ, ϕ).*

The DDE (2.18) can contain distributed or discrete delay. A distributed DDE has the form

$$\dot{x} = f\bigg(t, x(t), \int_{-\infty}^{0} x(t+\tau) d\mu(\tau)\bigg),$$

where f depends on x computed on a continuum (possibly unbounded set of past values). On the other hand, a discrete DDE has the form

$$\dot{x} = f(t, x(t), x(t-\tau_1), \cdots, x(t-\tau_n)) \quad \text{for} \quad \tau_1, \cdots, \tau_n \geq 0,$$

where only a finite number of past values of the state variables x are involved.

2.9.2 Global stability of equilibria

The following results can be used to establish the global stability property of the equilibria of some DDE systems.

Lemma 2.3. ([97]). *Consider the following delay differential equation*

$$\dot{u} = \frac{au(t-\tau)}{1+\omega u(t-\tau)} - bu(t), \quad u(\theta) = \phi(\theta) \geq 0, \quad \theta \in [-\tau, 0), \phi(0) > 0 \tag{2.19}$$

where a,b and ω are positive constants and $\tau \geq 0$. Then,

(i) Equation (2.19) *has a trivial equilibrium* $u = 0$ *and it is globally asymptotically stable if* $a < b$.

(ii) If $a > b$ *equation* (2.19) *has a unique positive equilibrium* $u^* = \frac{a-b}{\omega b}$ *which is globally asymptotically stable.*

Lemma 2.4. ([57]). *Given a measurable sequence of non-negative uniformly bounded functions* f_n,

$$\int \liminf f_n \leq \liminf \int f_n \leq \limsup \int f_n \leq \int \limsup f_n.$$

2.10 Gamma Distribution

A gamma distribution is a two-parameter family of continuous probability distributions [49]. It has a scale parameter θ and a shape parameter k. If κ is an integer, then the distribution represents the sum of k independent exponentially distributed random variables, each of which has a mean of θ. The probability density function of the gamma distribution can be expressed in terms of the gamma function parameterized in terms of a shape parameter k and scale parameter θ. Both k and θ will be positive values. The equation defining the probability density function of a gamma-distributed random variable x is given by

$$f(x; k, \theta) = x^{k-1} \frac{\theta^k e^{-x\theta}}{\Gamma(k)} \text{ for } x > 0 \text{ and } k, \theta > 0.$$

A random variable X that is gamma-distributed, with scale θ and shape k, is denoted by

$$X \sim \Gamma(k, \theta) \text{ or } X \sim \text{Gamma}(k, \theta).$$

Properties of Gamma Gistribution

Gamma distribution has the following properties [49]:

(i) **Summation:**

if X_i has a $\Gamma(k_i, \theta)$ distribution for $i = 1, 2, ..., N$, then $\sum_{i=1}^{N} X_i \sim \Gamma\left(\sum_{i=1}^{N} k_i, \theta\right)$ provided all X_i $(i = 1, 2, \cdots, N)$ are independent;

(ii) **Scaling:**

If $X \sim \Gamma(k, \theta)$ then for any $\alpha > 0$, $\alpha X \sim \Gamma(k, \frac{\theta}{\alpha})$.

Example 2.3. *If* $E_i \sim \Gamma(1, a_i\alpha)$ *for* $i = 1, 2, \cdots, m$, *it follows, from (ii), that* $a_i E_i \sim \Gamma(1, \alpha)$. *Similarly,* $\frac{a_i E_i}{m} \sim \Gamma(1, m\alpha)$. *Finally, it follows from Item (i) above that* $\sum_{i=1}^{m} \frac{a_i E_i}{m} \sim \Gamma(m, m\alpha)$.

It should be mentioned that the numerical simulations in this thesis are carried out using two Matlab routines, namely ODE45 (for the models in Chapters 3, 5, 6 and 7) and DDE23 (for the DDE model in Chapter 4).

Chapter 3

Basic Quarantine/Isolation Model

3.1 Introduction

As stated in Chapter 1, the quarantine (of individuals suspected of been infected) and isolation (of those with disease symptoms) have, historically (over many decades or even centuries), been applied to control the spread of of numerous emerging and re-emerging human diseases, such as leprosy, plague, cholera, typhus, yellow fever, smallpox, diphtheria, tuberculosis, measles, ebola, pandemic influenza and, more recently, SARS [16, 48, 61, 64, 67, 73, 90, 93, 99].

Numerous mathematical modelling work have been carried out to assess the impact of quarantine and isolation in controlling the spread of communicable diseases in human and animal populations. Hethcote *et al.* [48] presented six endemic models of SIQR-type (susceptible-infectious-quarantined-recovered) using three different incidence functions (mass action, standard incidence and quarantine-adjusted incidence). The study shows that the use of quarantine-adjusted incidence could lead to the presence of periodic solutions *via* a Hopf bifurcation. Nuno *et al.* [70] also established the

presence of oscillatory solutions using an SIQR model for multiple strains of influenza, which employs a quarantine-adjusted incidence function. Furthermore, the emergence of SARS in 2003 led to the formulation of numerous quarantine and isolation models for curtailing its spread (see, for instance, [16, 20, 38, 61, 64, 67, 73, 90, 93]). These models typically take the form of the SIR or SEIR Kermack-McKendrick formulation, with additional compartments for the quarantined and isolated classes. Most of the disease modelling studies, published in the literature, that use quarantine and isolation are numerical in nature (see, for instance, the models in [16, 20, 38, 61, 64, 67, 73, 90, 93]). That is, they provided quantitative evaluation of the control measures (quarantine and isolation) by simulating the models with available epidemiological and demographic data.

The purpose of this chapter is to provide a rigorous qualitative analysis of a deterministic model for quarantine and isolation, aimed at providing deeper insight into the impact of these control measures on the spread of an arbitrary disease that is controllable using quarantine and isolation. The model to be designed extends some of the quarantine/isolation models, published in literature, notably by assuming that infection does not confer permanent immunity against re-infection.

3.2 Model Formulation and Basic Properties

The total population at time t, denoted by $N(t)$, is sub-divided into six compartments of susceptible ($S(t)$), exposed (those who have been infected but do not show clinical symptoms of the disease yet) ($E(t)$), quarantined ($Q(t)$), infectious ($I(t)$), hospitalized ($H(t)$) and recovered ($R(t)$) individuals, so that

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

The susceptible population is increased by the recruitment of individuals into the popu-

lation (assumed susceptible), at a rate Π. Susceptible individuals may acquire infection, following effective contact with infectious individuals (in the I or H class) at a rate λ, where

$$\lambda = \frac{\beta(I + \eta H)}{N}. \tag{3.1}$$

In other words, unlike in [38], it is assumed that the exposed and quarantined individuals (in the E and Q classes, respectively) do not transmit infection (i.e., only infected individuals with clinical symptoms of the disease are assumed capable of transmitting the disease to susceptible individuals). Furthermore, in (3.1), the parameter β is the effective contact rate (that is, contact capable of leading to infection), while the modification parameter, $0 \leq \eta < 1$, accounts for the assumed reduction in disease transmission by hospitalized individuals in comparison to non-hospitalized infectious individuals in the I class. Thus, η measures the efficacy of isolation or treatment given to hospitalized individuals (isolation is perfect if $\eta = 0$, leaky if $0 < \eta < 1$ and completely ineffective if $\eta = 1$). The population of susceptible individuals is further decreased by natural death (at a rate μ), and increased when recovered individuals lose their infection-acquired immunity (at a rate ψ). Thus, the rate of change of the susceptible population is given by

$$\frac{dS}{dt} = \Pi + \psi R - \frac{\beta S(I + \eta H)}{N} - \mu S.$$

The population of exposed individuals is generated by the infection of susceptible individuals (at the rate λ). This population is decreased by development of disease symptoms (at a rate κ), quarantine (at a rate σ) and natural death (at the rate μ), so that

$$\frac{dE}{dt} = \frac{\beta S(I + \eta H)}{N} - (\kappa + \sigma + \mu)E.$$

The population of infectious individuals is generated at the rate κ. It is decreased by natural recovery (at a rate γ_1), hospitalization (at a rate ϕ), natural death (at the rate μ) and disease-induced death (at a rate δ_1). This gives

$$\frac{dI}{dt} = \kappa E - (\gamma_1 + \phi + \mu + \delta_1)I.$$

Exposed individuals are quarantined at the rate σ. The population of quarantined individuals is decreased by hospitalization (at a rate α) and natural death (at the rate μ). Thus,

$$\frac{dQ}{dt} = \sigma E - (\alpha + \mu)Q.$$

The population of hospitalized individuals is generated by the hospitalization of quarantined individuals (at the rate α) and symptomatic individuals (at the rate ϕ). This population is decreased by recovery (at a rate γ_2), natural death (at the rate μ) and disease-induced death (at a rate $\delta_2 < \delta_1$). It is assumed that hospitalized individuals have reduced disease-induced mortality rate in comparison to non-hospitalized infectious individuals because of the hospital care (treatment etc.) given to hospitalized infectious individuals. Hence, the rate of change of the population of hospitalized individuals is given by

$$\frac{dH}{dt} = \alpha Q + \phi I - (\gamma_2 + \mu + \delta_2)H.$$

Finally, the population of recovered individuals is generated by the recovery of non-hospitalized and hospitalized infectious individuals (at the rates γ_1 and γ_2, respectively). It is decreased by the loss of natural immunity (at the rate ψ) and natural death (at the rate μ), so that

$$\frac{dR}{dt} = \gamma_1 I + \gamma_2 H - (\psi + \mu)R.$$

Thus, the model for the transmission dynamics of an infectious disease in the presence of quarantine (of exposed individuals) and isolation (of infectious individuals) is given by the following non-linear system of differential equations (a flow diagram is given in Figure 3.1; and the associated variables and parameters are described and estimated in Tables 3.1 and 3.2) [77]:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi + \psi R - \lambda S - \mu S, \\
\frac{dE}{dt} &= \lambda S - (\kappa + \sigma + \mu)E, \\
\frac{dI}{dt} &= \kappa E - (\gamma_1 + \phi + \mu + \delta_1)I, \\
\frac{dQ}{dt} &= \sigma E - (\alpha + \mu)Q, \\
\frac{dH}{dt} &= \alpha Q + \phi I - (\gamma_2 + \mu + \delta_2)H, \\
\frac{dR}{dt} &= \gamma_1 I + \gamma_2 H - (\psi + \mu)R.
\end{aligned} \tag{3.2}$$

Table 3.1: Description of variables and parameters of the model (3.2).

Variable	Description
$S(t)$	Population of susceptible individuals
$E(t)$	Population of exposed individuals
$I(t)$	Population of infectious (symptomatic) individuals
$Q(t)$	Population of quarantined individuals
$H(t)$	Population of hospitalized individuals
$R(t)$	Population of recovered individuals

Parameter	Description
Π	Recruitment rate
μ	Natural death rate
β	Effective contact rate
η	Modification parameter for reduction in infectiousness of hospitalized individuals
κ	Progression rate from exposed to infectious class
σ	Quarantine rate for exposed individuals
α	Hospitalization rate for quarantined individuals
ϕ	Hospitalization rate for infectious individuals
ψ	Rate of loss of infection-acquired immunity
γ_1	Recovery rate for infectious individuals
γ_2	Recovery rate for hospitalized individuals
δ_1	Disease-induced death rate for infectious individuals
δ_2	Disease-induced death rate for hospitalized individuals

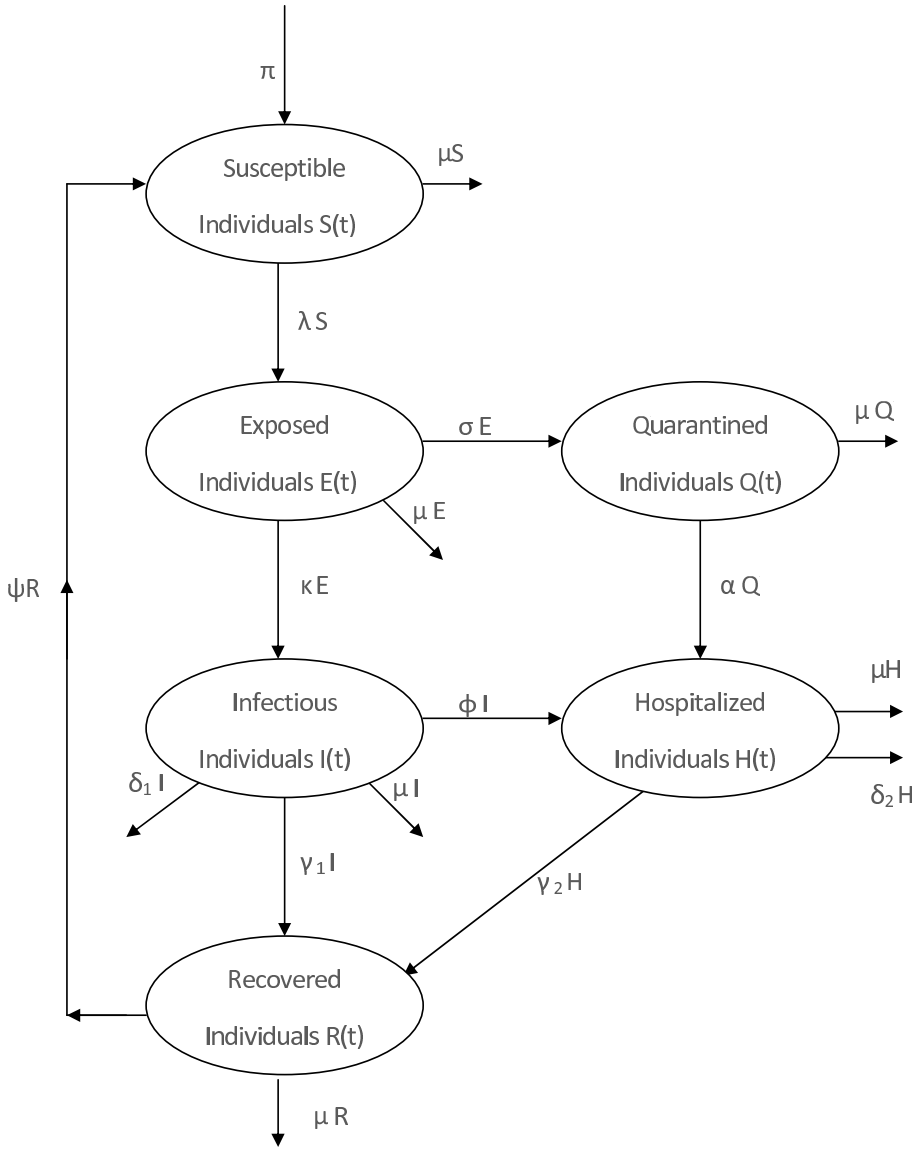


Figure 3.1: Flow diagram of the model (3.2).

The model (3.2) is a slight extension of the $SEIQHR$ model for SARS given in [38], by including a term for the loss of infection-acquired immunity (at the rate ψ). The main objective of this chapter is to carry out a detailed rigorous mathematical analyses of the model (3.2) (no such analyses was provided in [38]). Such analyses will provide insight into the transmission dynamics of the disease (*vis-a-vis* the persistence or elimination of the disease) as well as the role of the control measures (quarantine and isolation) in effectively combatting the spread of the disease in a population.

Since the model (3.2) monitors human populations, all its associated parameters are non-negative. Further, the following non-negativity result holds.

Theorem 3.1. *The variables of the model* (3.2) *are non-negative for all time* $t > 0$. *In other words, solutions of the model system* (3.2) *with positive initial data will remain positive for all* $t > 0$.

Proof. Let $t_1 = \sup\{t > 0 : S > 0, E > 0, I > 0, Q > 0, H > 0\}$. Thus, $t_1 > 0$. It follows from the first equation of the system (3.2) that

$$\frac{dS}{dt} = \Pi + \psi R(t) - \lambda(t)S(t) - \mu S(t) \geq \Pi - (\lambda + \mu)S(t),$$

which can be re-written as,

$$\frac{d}{dt}\left\{S(t)\exp\left[\mu t + \int_0^t \lambda(\tau)d\tau\right]\right\} \geq \Pi \exp\left[\mu t + \int_0^t \lambda(\tau)d\tau\right].$$

Hence,

$$S(t_1)\exp\left[\mu t_1 + \int_0^{t_1} \lambda(\tau)d\tau\right] - S(0) \geq \int_0^{t_1} \Pi \exp\left[\mu y + \int_0^y \lambda(\tau)d\tau\right] dy,$$

so that,

$$\begin{aligned} S(t_1) \geq\ & S(0)\exp\left[-\mu t_1 - \int_0^{t_1} \lambda(\tau)d\tau\right] \\ & + \left\{\exp\left[-\mu t_1 - \int_0^{t_1} \lambda(\tau)d\tau\right]\right\} \int_0^{t_1} \Pi \exp\left[\mu y + \int_0^y \lambda(\tau)d\tau\right] dy > 0. \end{aligned}$$

Similarly, it can be shown that $E > 0, I > 0, Q > 0, H > 0$ and $R > 0$ for all $t > 0$.

□

Theorem 3.1 can also be proven by using the method in Appendix A of [86].

Lemma 3.1. *The closed set*

$$\mathcal{D} = \left\{(S, E, I, Q, H, R) \in \mathbb{R}^6_+ : S + E + I + Q + H + R \leq \frac{\Pi}{\mu}\right\}$$

is positively-invariant for the model (3.2).

Proof. Adding all the equations of the model (3.2) gives,

$$\frac{dN}{dt} = \Pi - \mu N - (\delta_1 I + \delta_2 H). \tag{3.3}$$

Since $dN/dt \leq \Pi - \mu N$, it follows that $dN/dt \leq 0$ if $N \geq \Pi/\mu$. Thus, a standard comparison theorem (Theorem 2.8) can be used to show that $N \leq N(0)e^{-\mu t} + \dfrac{\Pi}{\mu}(1 - e^{-\mu t})$. In particular, $N(t) \leq \Pi/\mu$ if $N(0) \leq \Pi/\mu$. Thus, the region $\mathcal{D}$ is positively-invariant. Further, if $N(0) > \Pi/\mu$, then either the solution enters $\mathcal{D}$ in finite time, or $N(t)$ approaches Π/μ asymptotically. Hence, the region $\mathcal{D}$ attracts all solutions in $\mathbb{R}^6_+$. □

Since the region $\mathcal{D}$ is positively-invariant, it is sufficient to consider the dynamics of the flow generated by the model (3.2) in $\mathcal{D}$, where the usual existence, uniqueness, continuation results hold for the system [46].

3.3 Stability of Disease-free Equilibrium (DFE)

3.3.1 Local stability

The model (3.2) has a DFE, obtained by setting the right-hand sides of the equations in (3.2) to zero, given by

$$\mathcal{E}_0 = (S^*,\ E^*,\ I^*,\ Q^*,\ H^*,\ R^*) = (\Pi/\mu,\ 0,\ 0,\ 0,\ 0,\ 0). \tag{3.4}$$

The local stability property of $\mathcal{E}_0$ will be explored using the next generation operator method [21, 87]. Using the notation in [87], the non-negative matrix, F, of the new infection terms, and the M-matrix, V, of the transition terms associated with the model (3.2), are given, respectively, by

$$F = \begin{pmatrix} 0 & \beta & 0 & \eta\beta \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

and,

$$V = \begin{pmatrix} \mu+\kappa+\sigma & 0 & 0 & 0 \\ -\kappa & \mu+\delta_1+\gamma_1+\phi & 0 & 0 \\ -\sigma & 0 & \mu+\alpha & 0 \\ 0 & -\phi & -\alpha & \mu+\gamma_2+\delta_2 \end{pmatrix}.$$

It follows that the *control reproduction number* [2, 44], denoted by $\mathcal{R}_c = \rho(FV^{-1})$, where ρ is the spectral radius, is given by

$$\mathcal{R}_c = \frac{\beta[\kappa(\mu+\alpha)(\mu+\gamma_2+\delta_2)+\eta\phi\kappa(\mu+\alpha)+\alpha\eta\sigma(\mu+\delta_1+\gamma_1+\phi)]}{(\mu+\kappa+\sigma)(\mu+\delta_1+\gamma_1+\phi)(\mu+\alpha)(\mu+\gamma_2+\delta_2)}.$$

Using Theorem 2.10, the following result is established.

Lemma 3.2. *The DFE of the model* (3.2)*, given by* (3.4)*, is locally-asymptotically stable (LAS) if* $\mathcal{R}_c < 1$*, and unstable if* $\mathcal{R}_c > 1$*.*

The threshold quantity, $\mathcal{R}_c$, measures the average number of new infections generated by a single infectious individual in a population.

Interpretation of $\mathcal{R}_c$

In order to interpret the reproduction threshold, the expression for $\mathcal{R}_c$ above is re-written as

$$\mathcal{R}_c = \frac{\beta\kappa}{(\mu+\kappa+\sigma)(\mu+\delta_1+\gamma_1+\phi)} + \frac{\beta\eta\phi\kappa}{(\mu+\kappa+\sigma)(\mu+\delta_1+\gamma_1+\phi)(\mu+\gamma_2+\delta_2)} + \frac{\beta\alpha\sigma}{(\mu+\kappa+\sigma)(\mu+\alpha)(\mu+\gamma_2+\delta_2)}. \tag{3.5}$$

The first term of (3.5) represents the number of new infections generated by non-hospitalized infectious individuals (in the I class). It consists of the product of the infection rate in the I class (i.e., rate at which a single infected individual in class I produces new infections in a wholly susceptible population) (β), the fraction of exposed individuals that survived the exposed class and move to the symptomatic class $\left(\frac{\kappa}{\kappa+\sigma+\mu}\right)$ and the average duration in the I class $\left(\frac{1}{\gamma_1+\phi+\mu+\delta_1}\right)$.

Similarly, the last two terms in (3.5) represent the number of infections generated by hospitalized individuals (in the H class). In particular, the second term represents contributions into the hospitalized class by infectious individuals (in class I). It is a product of the infection rate of hospitalized individuals ($\beta\eta$), the fraction that survived the exposed class and move to the infectious class $\left(\frac{\kappa}{\kappa+\sigma+\mu}\right)$, the fraction of individuals that survived the I class and move to the hospitalized class $\left(\frac{\phi}{\gamma_1+\phi+\mu+\delta_1}\right)$ and the average duration in the hospitalized class $\left(\frac{1}{\gamma_2+\mu+\delta_2}\right)$. Finally, the last term of (3.5) represents the contributions of quarantined individuals into the hospitalized class. It is a product of the infection rate of hospitalized individuals ($\beta\eta$), the fraction of quarantined individuals that survived the quarantine class and move to the hospitalized class $\left(\frac{\alpha}{\alpha+\mu}\right)$ and the duration in the hospitalized class $\left(\frac{1}{\gamma_2+\mu+\delta_2}\right)$.

Lemma 3.2 implies that the disease can be eliminated from the community (when $\mathcal{R}_c < 1$) if the initial sizes of the sub-populations of the model are in the basin of

attraction of the DFE ($\mathcal{E}_0$). To ensure that disease elimination is independent of the initial sizes of sub-populations, it is necessary to show that the DFE is globally-asymptotically stable (GAS) if $\mathcal{R}_c < 1$. This is explored below.

3.3.2 Global stability

It is convenient to express $\mathcal{R}_c$ as

$$\mathcal{R}_c = \frac{\beta[\kappa k_3 k_4 + \eta(\phi\kappa k_3 + \alpha\sigma k_2)]}{k_1 k_2 k_3 k_4},$$

where,

$$k_1 = \mu + \kappa + \sigma, \quad k_2 = \mu + \delta_1 + \gamma_1 + \phi, \quad k_3 = \mu + \alpha \quad \text{and} \quad k_4 = \mu + \gamma_2 + \delta_2.$$

Theorem 3.2. *The DFE of the model* (3.2)*, given by* (3.4)*, is GAS in* $\mathcal{D}$ *whenever* $\mathcal{R}_c \leq 1$.

Proof. Consider the following Lyapunov function:

$$\mathcal{F} = \left(\frac{k_4\mathcal{R}_c}{\eta\beta}\right) E + \left(\frac{k_4 + \eta\phi}{k_2\eta}\right) I + \left(\frac{\alpha}{k_3}\right) Q + H,$$

with Lyapunov derivative given by

$$\dot{\mathcal{F}} = \left(\frac{k_4\mathcal{R}_c}{\eta\beta}\right)\dot{E} + \left(\frac{k_4+\eta\phi}{k_2\eta}\right)\dot{I} + \left(\frac{\alpha}{k_3}\right)\dot{Q} + \dot{H},$$

$$= \frac{k_4\mathcal{R}_c}{\eta\beta}\left[\frac{\beta S(I+\eta H)}{N} - k_1E\right] + \left(\frac{k_4+\eta\phi}{k_2\eta}\right)(\kappa E - k_2 I) + \left(\frac{\alpha}{k_3}\right)(\sigma E - k_3 Q)$$
$$+ \alpha Q + \phi I - k_4 H,$$

$$\leq \frac{k_4\mathcal{R}_c}{\eta}(I+\eta H) - \frac{k_1k_4\mathcal{R}_c}{\eta\beta}E + \frac{\kappa(k_4+\eta\phi)}{k_2\eta}E - \frac{(k_4+\eta\phi)}{\eta}I + \frac{\alpha\sigma}{k_3}E$$
$$+ \phi I - k_4 H, \qquad \text{since } S \leq N \text{ in } \mathcal{D}$$

$$= \left[\frac{-k_1k_4\mathcal{R}_c}{\eta\beta} + \frac{\kappa(k_4+\eta\phi)}{k_2\eta} + \frac{\alpha\sigma}{k_3}\right]E + \left(\phi + \frac{k_4\mathcal{R}_c}{\eta} - \frac{k_4+\eta\phi}{\eta}\right)I + k_4(\mathcal{R}_c - 1)H,$$

$$= \frac{k_4}{\eta}(\mathcal{R}_c - 1)(I+\eta H) \leq 0 \quad \text{for } \mathcal{R}_c \leq 1.$$

Since all parameters of the model (3.2) and variables are non-negative, it follows that $\dot{\mathcal{F}} \leq 0$ for $\mathcal{R}_c \leq 1$ with $\dot{\mathcal{F}} = 0$ if and only if $E = I = Q = H = 0$. Hence, $\mathcal{F}$ is a Lyapunov function on $\mathcal{D}$.

Thus, it follows, by the LaSalle's Invariance Principle (Theorem 2.6), that

$$(E, I, Q, H) \to (0, 0, 0, 0) \text{ as } t \to \infty. \tag{3.6}$$

Furthermore, it follows from (3.6) that $\limsup_{t\to\infty} I = \liminf_{t\to\infty} I = 0$ and $\limsup_{t\to\infty} H = \liminf_{t\to\infty} H = 0$. Since $\limsup_{t\to\infty} I = 0$ and $\limsup_{t\to\infty} H = 0$, it follows that, for sufficiently small $\varpi^* > 0$, there exist constants $M_1, M_2 > 0$ such that $\limsup_{t\to\infty} I \leq \varpi^*$ for all $t > M_1$ and $\limsup_{t\to\infty} H \leq \varpi^*$ for all $t > M_2$.

Hence, it follows from the last equation of the model (3.2) that, for $t > \max\{M_1, M_2\}$,

$$\dot{R} \leq \gamma_1 \varpi^* + \gamma_2 \varpi^* - \mu R.$$

Thus, by the comparison theorem (Theorem 2.8),

$$R^\infty = \limsup_{t \to \infty} R \leq \frac{\gamma_1 \varpi^* + \gamma_2 \varpi^*}{\mu},$$

so that, by letting $\varpi^* \to 0$,

$$R^\infty = \limsup_{t \to \infty} R \leq 0. \tag{3.7}$$

Similarly (by using $\liminf_{t \to \infty} I = 0$ and $\liminf_{t \to \infty} H = 0$), it can be shown that

$$R_\infty = \liminf_{t \to \infty} R \geq 0. \tag{3.8}$$

Thus, it follows from (3.7) and (3.8) that

$$R_\infty \geq 0 \geq R^\infty.$$

Hence,

$$\lim_{t \to \infty} R = 0. \tag{3.9}$$

Similarly, it can be shown that

$$\lim_{t \to \infty} S(t) = \Pi/\mu. \tag{3.10}$$

Thus, it follows from (3.6), (3.9) and (3.10), that every solution of the equations in the model (3.2), with initial conditions in $\mathcal{D}$, approaches $\mathcal{E}_0$ as $t \to \infty$ when $\mathcal{R}_c < 1$. □

The epidemiological implication of the above result is that, the combined use of

quarantine and isolation can lead to disease elimination if they can bring (and keep) the threshold quantity, $\mathcal{R}_c$, to a value less than unity (that is, the condition $\mathcal{R}_c < 1$ is necessary and sufficient for disease elimination). Figure 3.2 depicts the numerical results obtained by simulating the model (3.2) using various initial conditions for the case when $\mathcal{R}_c < 1$. It is evident from this figure that all initial solutions converged to the DFE, $\mathcal{E}_0$ (in line with Theorem 3.2).

3.4 Existence and Stability of Endemic Equilibria

In this section, the possible existence and stability of endemic (positive) equilibria of the model (3.2) (i.e., equilibria where at least one of the infected components of the model is non-zero) will be explored.

3.4.1 Existence

Let, $\mathcal{E}_1 = (S^{**}, E^{**}, I^{**}, Q^{**}, H^{**}, R^{**})$ represent any arbitrary endemic equilibrium of the model (3.2), so that $N^{**} = S^{**} + E^{**} + I^{**} + Q^{**} + H^{**} + R^{**}$.

Solving the equations of the model (3.2) at steady-state gives

$$\begin{aligned} S^{**} &= \frac{\Pi + \psi R^{**}}{\lambda^{**} + \mu}, \qquad E^{**} = \frac{\lambda^{**} S^{**}}{k_1}, \qquad I^{**} = \frac{\kappa E^{**}}{k_2}, \\ Q^{**} &= \frac{\sigma E^{**}}{k_3}, \qquad H^{**} = \frac{\alpha Q^{**} + \phi I^{**}}{k_4}. \end{aligned} \tag{3.11}$$

It should be noted that the force of infection, λ, defined in (3.1), can be expressed, at endemic steady-state, as

$$\lambda^{**} = \frac{\beta(I^{**} + \eta H^{**})}{N^{**}}. \tag{3.12}$$

For computational convenience, the expressions in (3.11) are re-written in terms of

$\lambda^{**}S^{**}$ as below:

$$E^{**} = \frac{\lambda^{**}S^{**}}{k_1}, \qquad I^{**} = \frac{\kappa\lambda^{**}S^{**}}{k_2k_1},$$
$$Q^{**} = \frac{\sigma\lambda^{**}S^{**}}{k_3k_1}, \qquad H^{**} = \frac{\alpha\sigma\lambda^{**}S^{**}}{k_1k_3k_4} + \frac{\phi\kappa\lambda^{**}S^{**}}{k_1k_2k_4} = P_1\lambda^{**}S^{**}, \quad (3.13)$$

$$R^{**} = \frac{\gamma_1\kappa\lambda^{**}S^{**}}{k_1k_2(\mu+\psi)} + \frac{\gamma_2\alpha\sigma\lambda^{**}S^{**}}{k_1k_3k_4(\mu+\psi)} + \frac{\lambda^{**}S^{**}}{k_1k_2k_4(\mu+\psi)} = P_2\lambda^{**}S^{**},$$

where,

$$P_1 = \frac{\alpha\sigma}{k_1k_3k_4} + \frac{\phi\kappa}{k_1k_2k_4} \text{ and } P_2 = \frac{\gamma_1\kappa}{k_1k_2(\mu+\psi)} + \frac{\gamma_2\alpha\sigma}{k_1k_3k_4(\mu+\psi)} + \frac{\gamma_2\phi\kappa}{k_1k_2k_4(\mu+\psi)}.$$

Substituting the expressions in (3.13) into (3.12) gives,

$$\lambda^{**}S^{**} + \frac{\lambda^{**}S^{**}}{k_1}\lambda^{**} + \frac{\kappa\lambda^{**}S^{**}}{k_2k_1}\lambda^{**} + P_1\lambda^{**}S^{**} + \psi P_2\lambda^{**}S^{**} = \beta\lambda^{**}S^{**}\left(\frac{\kappa}{k_1k_2} + \eta P_1\right). \quad (3.14)$$

Dividing each term in (3.14) by $\lambda^{**}S^{**}$(and noting that, at the endemic steady-state, $\lambda^{**}S^{**} \neq 0$) gives

$$1 + P_3\lambda^{**} = \frac{\beta\kappa}{k_1k_2} + \beta\eta P_1, \text{ where } P_3 = \frac{1}{k_1} + \frac{\kappa}{k_2k_1} + P_1 + \psi P_2 \geq 0.$$

It should be noted that

$$
\begin{aligned}
1 + P_3\lambda^{**} &= \frac{\beta\kappa}{k_1k_2} + \beta\eta P_1, \\
&= \beta\frac{\kappa}{k_1k_2} + \beta\eta\left(\frac{\alpha\sigma}{k_1k_3k_4} + \frac{\phi\kappa}{k_1k_2k_4}\right), \\
&= \beta\left(\frac{\kappa k_3k_4 + \eta\phi k_3\kappa + \alpha\eta\sigma k_2}{k_1k_2k_3k_4}\right), \\
&= \mathcal{R}_c.
\end{aligned}
\tag{3.15}
$$

Hence,

$$
\lambda^{**} = \frac{\mathcal{R}_c - 1}{P_3} > 0, \text{ whenever } \mathcal{R}_c > 1. \tag{3.16}
$$

The components of $\mathcal{E}_1$ can then be obtained by substituting the unique value of λ^{**}, given by (3.16), into the expressions in (3.13). Thus, the following result is established.

Lemma 3.3. *The model* (3.2) *has a unique endemic (positive) equilibrium, given by* $\mathcal{E}_1$*, whenever* $\mathcal{R}_c > 1$.

3.4.2 Local stability

The local stability of the unique endemic equilibrium of the model is now considered for a special case (where the total population is at the disease-free steady-state).

Theorem 3.3. *The unique endemic equilibrium of the model* (3.2)*, with* $N = N^*$*, is LAS if* $\mathcal{R}_c > 1$.

Proof. It should be stated that, for the case when $N = N^*$, it can be shown that the model (3.2) has a unique endemic equilibrium point, denoted by $\tilde{\mathcal{E}}_1 = \mathcal{E}_1|_{N=N^*}$, whenever $\mathcal{R}_c > 1$. The proof of Theorem 3.3 is based on using a Krasnoselskii sub-linearity trick (see [46, 85], and also [28, 29]).

Let $\mathcal{R}_c > 1$ and $N = N^*$ (so that the associated endemic equilibrium exists). Furthermore, the substitution $S = N^* - E - Q - I - H - R$ is used to re-write the model (3.2) as:

$$\begin{aligned}
\frac{dE}{dt} &= \frac{\beta(I+\eta H)(N^* - E - Q - I - H - R)}{N^*} - (\kappa+\sigma+\mu)E,\\
\frac{dI}{dt} &= \kappa E - (\gamma_1+\phi+\mu+\delta_1)I,\\
\frac{dQ}{dt} &= \sigma E - (\alpha+\mu)Q,\\
\frac{dH}{dt} &= \alpha Q + \phi I - (\gamma_2+\mu+\delta_2)H,\\
\frac{dR}{dt} &= \gamma_1 I + \gamma_2 H - (\psi+\mu)R.
\end{aligned} \tag{3.17}$$

Linearizing the system (3.17) around the endemic equilibrium, $\tilde{\mathcal{E}}_1$, gives

$$\begin{aligned}
\frac{dE}{dt} &= [-a_1 - (\mu+\kappa+\sigma)]E + (a_2 - a_1)I - a_1 Q + (\eta a_2 - a_1)H - a_1 R,\\
\frac{dI}{dt} &= \kappa E - (\gamma_1+\phi+\mu+\delta_1)I,\\
\frac{dQ}{dt} &= \sigma E - (\alpha+\mu)Q,\\
\frac{dH}{dt} &= \alpha Q + \phi I - (\gamma_2+\mu+\delta_2)H,\\
\frac{dR}{dt} &= \gamma_1 I + \gamma_2 H - (\psi+\mu)R,
\end{aligned} \tag{3.18}$$

where, $a_1 = \beta(I^{**} + \eta H^{**})/N^*$ and $a_2 = \beta S^{**}/N^*$.

It follows that the Jacobian of the system (3.18), evaluated at $\tilde{\mathcal{E}}_1$, is given by

$$J(\tilde{\mathcal{E}}_1) = \begin{pmatrix} -a_1 - k_1 & a_2 - a_1 & -a_1 & \eta a_2 - a_1 & -a_1 \\ \kappa & -k_2 & 0 & 0 & 0 \\ \sigma & 0 & -k_3 & 0 & 0 \\ 0 & \phi & \alpha & -k_4 & 0 \\ 0 & \gamma_1 & 0 & \gamma_2 & -(\mu + \psi) \end{pmatrix}.$$

Assume that the system (3.18) has solution of the form

$$\mathbf{Z}(t) = \mathbf{Z}_0 e^{\omega t}, \tag{3.19}$$

with $\mathbf{Z}_0 = (Z_1, Z_2, Z_3, Z_4, Z_5), \omega, Z_i \in \mathbb{C} \quad (i = 1, 2, \ldots, 5)$. Substituting a solution of the form (3.19) into the system (3.18) gives

$$\begin{aligned} \omega Z_1 &= [-a_1 - (\mu + \kappa + \sigma)]Z_1 + (a_2 - a_1)Z_2 - a_1 Z_3 + (\eta a_2 - a_1)Z_4 - a_1 Z_5, \\ \omega Z_2 &= \kappa Z_1 - (\gamma_1 + \phi + \mu + \delta_1)Z_2, \\ \omega Z_3 &= \sigma Z_1 - (\mu + \alpha)Z_3, \\ \omega Z_4 &= \phi Z_2 + \alpha Z_3 - (\gamma_2 + \mu + \delta_2)Z_4, \\ \omega Z_5 &= \gamma_1 Z_2 + \gamma_2 Z_4 - (\mu + \psi)Z_5. \end{aligned} \tag{3.20}$$

System (3.20) is simplified as follows. Firstly, all the negative terms in the last four equations of (3.20) are moved to the respective left-hand sides. Secondly, the (resulting) last four equations are then re-written in terms of Z_1 and substituted into the first equation of (3.20), and all its negative terms are moved to the right-hand side. Doing all these lead to the following system:

$$
\begin{aligned}
[1 + F_1(\omega)]\, Z_1 &= (MZ)_1, \\
[1 + F_2(\omega)]\, Z_2 &= (MZ)_2, \\
[1 + F_3(\omega)]\, Z_3 &= (MZ)_3, \\
[1 + F_4(\omega)]\, Z_4 &= (MZ)_4, \\
[1 + F_5(\omega)]\, Z_5 &= (MZ)_5,
\end{aligned}
\tag{3.21}
$$

where,

$$
\begin{aligned}
F_1(\omega) = {} & \frac{\omega}{\mu+\kappa+\sigma} + \frac{a_1}{\mu+\kappa+\sigma}\left[1 + \frac{\kappa}{\omega+\mu+\gamma_1+\phi+\delta_1} + \frac{\sigma}{\omega+\mu+\alpha}\right] \\
& + \frac{a_1}{\mu+\kappa+\sigma}\left[\frac{\kappa\phi}{(\omega+\gamma_1+\phi+\mu+\delta_1)(\omega+\gamma_2+\mu+\delta_2)} + \frac{\alpha\sigma}{(\omega+\mu+\alpha)(\omega+\gamma_2+\mu+\delta_2)}\right] \\
& + \frac{a_1}{\mu+\kappa+\sigma}\left[\frac{\kappa\gamma_1}{(\omega+\mu+\psi)(\omega+\mu+\alpha)} + \frac{\alpha\sigma\gamma_2}{(\omega+\gamma_2+\mu+\delta_2)(\omega+\mu+\psi)(\omega+\mu+\alpha)}\right] \\
& + \frac{a_1}{\mu+\kappa+\sigma}\left[\frac{\kappa\gamma_2\phi}{(\omega+\gamma_1+\phi+\mu+\delta_1)(\omega+\gamma_2+\mu+\delta_2)(\omega+\mu+\psi)}\right],
\end{aligned}
$$

$$
F_2(\omega) = \frac{\omega}{\mu+\gamma_1+\phi+\delta_1},\ \ F_3(\omega) = \frac{\omega}{\mu+\alpha},\ \ F_4(\omega) = \frac{\omega}{\gamma_2+\mu+\delta_2}\ \text{ and }\ F_5(\omega) = \frac{\omega}{\mu+\psi},
$$

with,

$$M = \begin{pmatrix} 0 & \dfrac{\beta S^{**}}{N^*(\mu+\kappa+\sigma)} & 0 & \dfrac{\eta\beta S^{**}}{N^*(\mu+\kappa+\sigma)} & 0 \\ \dfrac{\kappa}{\mu+\gamma_1+\phi+\delta_1} & 0 & 0 & 0 & 0 \\ \dfrac{\sigma}{\mu+\alpha} & 0 & 0 & 0 & 0 \\ 0 & \dfrac{\phi}{\gamma_2+\mu+\delta_2} & \dfrac{\alpha}{\gamma_2+\mu+\delta_2} & 0 & 0 \\ 0 & \dfrac{\gamma_1}{\mu+\psi} & 0 & \dfrac{\gamma_2}{\mu+\psi} & 0 \end{pmatrix}.$$

The equilibrium $\tilde{\mathcal{E}}_1 = (E^{**}, I^{**}, Q^{**}, H^{**}, R^{**})$ satisfies $\tilde{\mathcal{E}}_1 = M\tilde{\mathcal{E}}_1$. Furthermore, the notation $(M\mathbf{Z})_i$ $(i = 1, \ldots, 5)$ denotes the ith coordinate of the vector $M\mathbf{Z}$, and the matrix M has non-negative entries.

If $\mathbf{Z}$ is a solution of (3.21), then it is possible to find a minimal positive real number, r, such that [28, 29]

$$\|\mathbf{Z}\| \leq r\tilde{\mathcal{E}}_1, \tag{3.22}$$

where, $\|\mathbf{Z}\| = (\|Z_1\|, \|Z_2\|, \|Z_3\|, \|Z_4\|, \|Z_5\|)$ with lexicographic order, and $\|.\|$ is a norm in $\mathbb{C}$. The main goal is to show that $\mathrm{Re}(\omega) < 0$. Assume, now, that $\mathrm{Re}(\omega) \geq 0$, and consider the following two cases.

Case 1: $\omega = 0$.

In this case, (3.20) is a homogeneous linear system in the variables Z_i $(i = 1, \ldots, 5)$. The determinant of this system is given by

$$\Delta = -A_1 + \left(\frac{S^{**}\mathcal{R}_c}{N^*} - 1\right) A_2, \tag{3.23}$$

where,

$$
\begin{aligned}
A_1 = {} & (\gamma_1+\phi+\mu+\delta_1)(\mu+\alpha)(\gamma_2+\mu+\delta_2)(\mu+\psi)a_1 + \kappa(\mu+\alpha)(\gamma_2+\mu+\delta_2)(\mu+\psi)a_1 \\
& + \kappa\phi(\mu+\alpha)(\mu+\psi)a_1 + \kappa\gamma_1(\mu+\alpha)(\gamma_2+\mu+\delta_2)a_1 \\
& + \sigma(\gamma_1+\phi+\mu+\delta_1)(\gamma_2+\mu+\delta_2)(\mu+\psi)a_1 \\
& + \alpha\sigma\gamma_2(\mu+\gamma_1+\phi+\delta_1)a_1 + \alpha\sigma(\gamma_1+\phi+\mu+\delta_1)(\mu+\psi)a_1 \\
& + \kappa\phi\gamma_2(\mu+\alpha)a_1 > 0,
\end{aligned}
$$

$$
A_2 = (\mu+\kappa+\sigma)(\gamma_1+\phi+\mu+\delta_1)(\mu+\alpha)(\gamma_2+\mu+\delta_2)(\mu+\psi).
$$

To finally determine the sign of Δ, the sign of $\frac{S^{**}\mathcal{R}_c}{N^*} - 1$ in (3.23) must be obtained. This is investigated below. Solving (3.17) at the endemic steady-state ($\tilde{\mathcal{E}}_1$) gives

$$
\frac{\beta S^{**}}{N^*} = \frac{(\mu+\kappa+\sigma)E^{**}}{I^{**}+\eta H^{**}}, \tag{3.24}
$$

$$
I^{**} = \frac{\kappa E^{**}}{\mu+\gamma_1+\phi+\delta_1}, \tag{3.25}
$$

$$
Q^{**} = \frac{\sigma E^{**}}{\mu+\alpha}, \tag{3.26}
$$

$$
H^{**} = \frac{\alpha Q^{**}+\phi I^{**}}{\gamma_2+\mu+\delta_2}. \tag{3.27}
$$

Substituting equations (3.25) and (3.26) into (3.27) gives

$$H^{**} = \left[\frac{\alpha\sigma}{(\mu+\alpha)(\gamma_2+\mu+\delta_2)} + \frac{\kappa\phi}{(\mu+\delta_1+\gamma_1+\phi)(\gamma_2+\mu+\delta_2)}\right] E^{**}. \tag{3.28}$$

Furthermore, using equations (3.25) and (3.28) in (3.24) gives

$$\begin{aligned}\frac{S^{**}}{N^*} &= \frac{(\mu+\kappa+\sigma)(\gamma_1+\phi+\mu+\delta_1)(\mu+\alpha)(\gamma_2+\mu+\delta_2)}{\beta[\kappa(\mu+\alpha)(\gamma_2+\mu+\delta_2)+\eta\alpha\sigma(\gamma_1+\phi+\mu+\delta_1)+\eta\phi\kappa(\mu+\alpha)]} \\ &= \frac{1}{\mathcal{R}_c},\end{aligned} \tag{3.29}$$

so that,

$$\frac{S^{**}}{N^*} - \frac{1}{\mathcal{R}_c} = 0.$$

Thus, equation (3.23) becomes

$$\Delta = -A_1 < 0.$$

Since the determinant Δ is negative, it follows that the system (3.20) has a unique solution, given by $\mathbf{Z} = \mathbf{0}$ (which corresponds to the DFE ($\mathcal{E}_0$) of the model (3.2)).

Case 2: $\omega \neq 0$.

Since $\text{Re}(\omega) > 0$ (by assumption), then $|1 + F_i(\omega)| > 1$ for all $i = 1, \ldots, 5$. Define $F(\omega) = \min_i |1 + F_i|$. Then, $F(\omega) > 1$, and $\dfrac{r}{F(\omega)} < r$. Furthermore, since r is a minimal positive real number such that $\|\mathbf{Z}\| \leq r\tilde{\mathcal{E}}_1$, it follows then that

$$\|\mathbf{Z}\| > \frac{r}{F(\omega)}\tilde{\mathcal{E}}_1. \tag{3.30}$$

On the other hand, by taking the norm of both sides of the second equation in (3.21), and noting that M is a non-negative matrix, it follows that:

$$F(\omega)\|Z_2\| \leq |1 + F_2(\omega)| \ \|Z_2\| = \|(MZ)_2\| \leq M\|Z_2\| \leq rM(\tilde{\mathcal{E}}_1)_2 = r(\tilde{\mathcal{E}}_1)_2 = rI^{**}. \tag{3.31}$$

Furthermore, it follows from (3.31) that $\|Z_2\| \leq \dfrac{r}{F(\omega)} I^{**}$, which contradicts (3.30). Hence, $\mathrm{Re}(\omega) < 0$. Thus, all eigenvalues of the characteristic equation associated with the linearized system (3.18) will have negative real part, so that the unique endemic equilibrium, $\tilde{\mathcal{E}}_1$, is LAS whenever $\mathcal{R}_c > 1$. □

It should be noted that the condition $N = N^*$ in Theorem 3.3 represents the case where the disease-related mortality is assumed to be negligible (in this case, it follows from (3.3) with $\delta_1 = \delta_2 = 0$ that $\frac{dN}{dt} = \Pi - \mu N$, so that $N \to N^*$ as $t \to \infty$) or the case where mass action incidence is used in (3.2), as against standard incidence (i.e., the rate β in (3.1) is replaced by $\frac{\mu\beta N}{\Pi}$). The epidemiological implication of Theorem 3.3 is that the disease will persist in the population if $\mathcal{R}_c > 1$ (and the initial sizes of the sub populations of the model are in the basin of attraction of the endemic equilibrium $\tilde{\mathcal{E}}_1$). Numerical simulation results, depicted in Figure 3.3, using numerous initial conditions, show convergence of the solutions to $\tilde{\mathcal{E}}_1$ for the case $\mathcal{R}_c > 1$ (in line with Theorem 3.3).

3.4.3 Global stability for special case

Here, the global asymptotic stability property of the endemic equilibrium of the model (3.2) is given for the special case when recovered individuals do not lose their infection-acquired immunity ($\psi = 0$), hospitalized individuals do not transmit infection ($\eta = 0$) and the associated disease-induced mortality is negligible ($\delta_1 = \delta_2 = 0$). The model (3.2), with $\psi = \eta = \delta_1 = \delta_2 = 0$, then reduces to:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \lambda S - \mu S, \\
\frac{dE}{dt} &= \lambda S - (\kappa + \sigma + \mu)E, \\
\frac{dI}{dt} &= \kappa E - (\gamma_1 + \phi + \mu)I, \\
\frac{dQ}{dt} &= \sigma E - (\alpha + \mu)Q, \\
\frac{dH}{dt} &= \alpha Q + \phi I - (\gamma_2 + \mu)H, \\
\frac{dR}{dt} &= \gamma_1 I + \gamma_2 H - \mu R,
\end{aligned} \tag{3.32}$$

where, now,

$$\lambda = \frac{\beta I}{N}. \tag{3.33}$$

Adding the equations of the reduced model (3.32) gives $dN/dt = \Pi - \mu N$, so that $N \to \Pi/\mu$ as $t \to \infty$. Thus, Π/μ is an upper bound of $N(t)$ provided that $N(0) \leq \Pi/\mu$. Further, if $N(0) > \Pi/\mu$, then $N(t)$ will decrease to this level. Using $N = \Pi/\mu$ in (3.33) gives a limiting (mass action) system given by (3.32) with

$$\lambda = \beta_1 I, \text{where } \beta_1 = \frac{\beta\mu}{\Pi}. \tag{3.34}$$

It can be shown that the associated reproduction number of the reduced model (3.32) with (3.34) is given by

$$\mathcal{R}_{cr} = \frac{\beta\kappa}{(\mu + \kappa + \sigma)(\mu + \gamma_1 + \phi)} = \frac{\beta\kappa}{b_1 b_2},$$

with $b_1 = \mu + \kappa + \sigma$ and $b_2 = \mu + \gamma_1 + \phi$. Furthermore, it is easy to show, using the technique in Section 3.4.1, that the reduced model, given by (3.32) with (3.34), has a unique EEP whenever $\mathcal{R}_{cr} > 1$.

Lemma 3.4. *The reduced model, given by* (3.32) *with* (3.34)*, has a unique positive endemic equilibrium whenever* $\mathcal{R}_{cr} > 1$.

Define, $\mathcal{D}_0 = \left\{(S, E, I, Q, H, R) \in \mathcal{D} : E = I = Q = H = R = 0\right\}$.

Theorem 3.4. *The unique endemic equilibrium of the reduced model, given by* (3.32) *with* (3.34)*, is GAS in* $\mathcal{D} \setminus \mathcal{D}_0$ *if* $\mathcal{R}_{cr} > 1$.

Proof. Consider the reduced model, given by (3.32) with (3.34). Let $\mathcal{R}_{cr} > 1$, so that the associated unique endemic equilibrium (of the model (3.32) with (3.34)) exists (Lemma 3.3). Further, consider the following non-linear Lyapunov function (non-linear functions of this type have been used in the ecology and epidemiology literature, such as in [33, 37, 39]) for the sub-system of the model (3.32) consisting of the first three equations of the model (3.32), given by:

$$\mathcal{F} = S - S^{**} - S^{**} \ln\left(\frac{S}{S^{**}}\right) + E - E^{**} - E^{**} \ln\left(\frac{E}{E^{**}}\right) + \frac{b_1}{\kappa}\left[I - I^{**} - I^{**} \ln\left(\frac{I}{I^{**}}\right)\right],$$

with Lyapunov derivative,

$$\dot{\mathcal{F}} = \dot{S} - \frac{S^{**}}{S}\dot{S} + \dot{E} - \frac{E^{**}}{E}\dot{E} + \frac{b_1}{\kappa}\left(\dot{I} - \frac{I^{**}}{I}\dot{I}\right),$$

$$\begin{aligned} &= \Pi - \beta_1 SI - \mu S - \frac{S^{**}}{S}\left(\Pi - \beta_1 SI - \mu S\right) + \beta_1 SI - b_1 E \\ &\quad - \frac{E^{**}}{E}\left(\beta_1 SI - b_1 E\right) + \frac{b_1}{\kappa}\left[\kappa E - b_2 I - \frac{I^{**}}{I}\left(\kappa E - b_2 I\right)\right], \end{aligned} \tag{3.35}$$

$$\begin{aligned} &= \Pi\left(1 - \frac{S^{**}}{S}\right) - \mu S\left(1 - \frac{S^{**}}{S}\right) + \left(\beta_1 S^{**} - \frac{b_1 b_2}{\kappa}\right) I - \frac{E^{**}\beta_1 SI}{E} \\ &\quad + b_1 E^{**} - \frac{b_1 I^{**} E}{I} + \frac{b_1 b_2 I^{**}}{\kappa}. \end{aligned}$$

It can be shown from (3.32) that, at the endemic steady-state,

$$\beta_1 S^{**} = \frac{(\mu + \kappa + \sigma)(\mu + \gamma_1 + \phi)}{\kappa} = \frac{b_1 b_2}{\kappa}. \tag{3.36}$$

Using the relation (3.36) in equation (3.35) gives

$$= \Pi\left(1-\frac{S^{**}}{S}\right) - \mu S\left(1-\frac{S^{**}}{S}\right) - \frac{E^{**}\beta_1 SI}{E} + E^{**}b_1 - \frac{b_1 I^{**}E}{I}$$
$$+ \beta_1 S^{**}I^{**},$$

$$= (\beta_1 S^{**}I^{**} + \mu S^{**})\left(1-\frac{S^{**}}{S}\right) - \mu S\left(1-\frac{S^{**}}{S}\right) - \frac{E^{**}\beta_1 SI}{E} + E^{**}b_1$$
$$- \frac{b_1 I^{**}E}{I} + \beta_1 S^{**}I^{**},$$

$$= \mu S^{**}\left(2-\frac{S^{**}}{S}-\frac{S}{S^{**}}\right) + \beta_1 S^{**}I^{**} - \frac{\beta_1 S^{**2}}{S} - \frac{\beta_1 SIE^{**}}{E} + b_1 E^{**}$$
$$- \frac{b_1 I^{**}E}{I} + \beta_1 S^{**}I^{**},$$

$$= \mu S^{**}\left(2-\frac{S^{**}}{S}-\frac{S}{S^{**}}\right) + \beta_1 S^{**}I^{**}\left(3-\frac{S^{**}}{S}-\frac{SIE^{**}}{S^{**}I^{**}E}-\frac{EI^{**}}{IE^{**}}\right).$$

In the above calculation, the relation $b_1 E^{**} = \beta_1 S^{**}I^{**}$ (obtained from (3.32) at endemic steady-state) has been used. The first term in the last equation of $\dot{\mathcal{F}}$ can be simplified as follows.

$$\left(2-\frac{S^{**}}{S}-\frac{S}{S^{**}}\right) = \frac{2SS^{**} - S^{**2} - S^2}{SS^{**}} = -\frac{(S-S^{**})^2}{SS^{**}} \leq 0.$$

Finally, since the arithmetic mean exceeds the geometric mean, it follows that

$$\left(3-\frac{S^{**}}{S}-\frac{SIE^{**}}{S^{**}I^{**}E}-\frac{EI^{**}}{IE^{**}}\right) \leq 0.$$

Further, since all the model parameters are non-negative, it follows that $\dot{\mathcal{F}} \leq 0$ for

$\mathcal{R}_{cr} > 1$. Hence, $\mathcal{F}$ is a Lyapunov function of the sub-system of the model (3.32) consisting of the first three equations, on $\mathcal{D} \setminus \mathcal{D}_0$. Therefore, it follows, by the LaSalle's Invariance Principle (Theorem 2.6), that

$$(S, E, I) \to (S^{**}, E^{**}, I^{**}) \text{ as } t \to \infty. \tag{3.37}$$

It is clear from (3.37) that $\limsup_{t\to\infty} E = E^{**}$. Thus, for sufficiently small $\epsilon > 0$, there exists a $T_1 > 0$ such that $E \leq E^{**} + \epsilon$ for all $t > T_1$. Furthermore, it follows from the fourth equation of (3.32) that, for $t > T_1$,

$$\dot{Q} \leq \sigma(E^{**} + \epsilon) - (\alpha + \mu)Q.$$

Thus, by comparison theorem (Theorem 2.8),

$$Q^{\infty} = \limsup_{t\to\infty} Q \leq \frac{\sigma(E^{**} + \epsilon)}{\alpha + \mu}.$$

Hence, by letting $\epsilon \to 0$,

$$Q^{\infty} = \limsup_{t\to\infty} Q \leq \frac{\sigma E^{**}}{\alpha + \mu}. \tag{3.38}$$

Similarly, by using $\liminf_{t\to\infty} E = E^{**}$, it can be shown that

$$Q_{\infty} = \liminf_{t\to\infty} Q \geq \frac{\sigma E^{**}}{\alpha + \mu}. \tag{3.39}$$

Thus, it follows from (3.38) and (3.39) that

$$Q_{\infty} \geq \frac{\sigma E^{**}}{\alpha + \mu} \geq Q^{\infty}.$$

Hence, $\lim_{t\to\infty} Q = \dfrac{\sigma E^{**}}{\alpha + \mu} = Q^{**}$. In a similar way, it can be shown that $\lim_{t\to\infty} H = H^{**}$ and $\lim_{t\to\infty} R = R^{**}$. Thus,

$$(Q, H, R) \to (Q^{**}, H^{**}, R^{**}) \text{ as } t \to \infty. \tag{3.40}$$

Hence, it follows from (3.37) and (3.40) that every solution to the equations of the reduced model, with initial conditions in $\mathcal{D} \setminus \mathcal{D}_0$, approaches the unique endemic equilibrium of the reduced system (3.32) with (3.34) as $t \to \infty$ for $\mathcal{R}_{cr} > 1$.

□

Although no global asymptotic stability result is given for the endemic equilibrium ($\mathcal{E}_1$), further extensive numerical simulations of the model (3.2) suggest that the unique endemic equilibrium of the model (3.2), $\mathcal{E}_1$, is GAS in $\mathcal{D} \setminus \mathcal{D}_0$, whenever $\mathcal{R}_c > 1$. This suggests the following conjecture.

Conjecture. *The unique endemic equilibrium of the model* (3.2)*, given by* $\mathcal{E}_1$*, is GAS in* $\mathcal{D} \setminus \mathcal{D}_0$ *if* $\mathcal{R}_c > 1$.

3.5 Threshold Analysis

In order to qualitatively measure the effect of quarantine and isolation on the transmission dynamics, a threshold analysis on the parameters associated with the quarantine of exposed individuals (σ) and the isolation of individuals with disease symptoms (ϕ) is carried out by computing the partial derivative of $\mathcal{R}_c$ with respect to these parameters.

For the case of the quarantine of exposed individuals, it is easy to see that

$$\frac{\partial \mathcal{R}_c}{\partial \sigma} = \frac{\beta \left\{ \left[\mu^2 + (\kappa + \phi + \gamma_1 + \delta_1)\, \mu + \kappa(\gamma_1 + \delta_1) \right] \alpha\, \eta - \eta\, \kappa \phi \mu \right\}}{(\mu + \kappa + \sigma)^2 \, (\mu + \gamma_1 + \delta_1 + \phi)\, (\mu + \alpha)\, (\mu + \gamma_2 + \delta_2)}$$

$$- \frac{\beta \kappa \left[\mu^2 + \mu\, (\delta_2 + \alpha + \gamma_2) + \alpha(\gamma_2 + \delta_2) \right]}{(\mu + \kappa + \sigma)^2 \, (\mu + \gamma_1 + \delta_1 + \phi)\, (\mu + \alpha)\, (\mu + \gamma_2 + \delta_2)},$$

so that,

$$\frac{\partial \mathcal{R}_c}{\partial \sigma} < 0\,(>0) \text{ iff } \eta < \eta_\sigma\,(\eta > \eta_\sigma),$$

where,

$$0 < \eta_\sigma = \frac{\kappa\left[\mu^2 + (\delta_2 + \alpha + \gamma_2)\,\mu + \alpha(\gamma_2 + \delta_2)\right]}{\left[\mu^2 + (\kappa + \phi + \gamma_1 + \delta_1)\,\mu + \kappa(\gamma_1 + \delta_1)\right]\alpha - \phi\,\kappa\,\mu}.$$

Thus, the quarantine of exposed individuals will reduce the reproduction number ($\mathcal{R}_c$) and, therefore, reduce disease burden (new infections, hospitalization, mortality etc.) if the relative infectiousness of hospitalized individuals (η) does not exceed the threshold η_σ.

On the other hand, if $\eta > \eta_\sigma$, then the use of quarantine (of exposed individuals) will increase the reproduction number ($\mathcal{R}_c$), and, consequently, increase disease burden (hence, the use of quarantine is detrimental to the community in this case). This result is summarized below.

Lemma 3.5. *The use of quarantine of the exposed individuals will have positive (negative) population-level impact if* $\eta < (>)\,\eta_\sigma$.

Similarly, the impact of the isolation of infectious individuals is monitored by computing the partial derivative of $\mathcal{R}_c$ with respect to the isolation parameter ϕ. This gives

$$\frac{\partial \mathcal{R}_c}{\partial \phi} = \frac{\beta\kappa\left[(\mu + \gamma_1 + \delta_1)\,\eta - (\gamma_2 + \delta_2 + \mu)\right]}{(\mu + \gamma_2 + \delta_2)\,(\mu + \gamma_1 + \delta_1 + \phi)^2\,(\mu + \kappa + \sigma)}.$$

Thus,

$$\frac{\partial \mathcal{R}_c}{\partial \phi} < 0\,(>0) \text{ iff } \eta < \eta_\phi\,(\eta > \eta_\phi),$$

where,

$$0 < \eta_\phi = \frac{\gamma_2 + \delta_2 + \mu}{\gamma_1 + \delta_1 + \mu}.$$

Hence, the use of isolation (of individuals with disease symptoms) will be beneficial to the community if the relative infectiousness of hospitalized individuals (represented by the parameter η) does not exceed the threshold η_ϕ. This result is summarized below.

Lemma 3.6. *The use of isolation of infectious individuals will have positive (negative) population-level impact if* $\eta < (>)\, \eta_\phi$.

In summary, the qualitative analyses carried out in this section show that the combined use of quarantine (of exposed individuals) and isolation (of individuals with symptoms) will have positive population-level impact if and only if

$$\eta < \min\{\eta_\sigma, \eta_\phi\}. \tag{3.41}$$

Condition (3.41) makes $\mathcal{R}_c$ a decreasing function of the quarantine and isolation parameters σ and ϕ. These strategies (quarantine and isolation) will fail (i.e., have no population-level impact) if

$$\eta \geq \max\{\eta_\sigma, \eta_\phi\}. \tag{3.42}$$

Figure 3.4 shows that whenever condition (3.41) holds, the use of quarantine and isolation would have positive impact, since the cumulative number of new cases of infection in the presence of quarantine and isolation is less than that for the case when quarantine and isolation are not implemented. However, for the case when Condition (3.42) holds, the use of quarantine and isolation induce detrimental population-level impact since, in this case, the cumulative number of new cases exceeds that for the case when quarantine and isolation are not used (Figure 3.5).

3.6 Summary

A deterministic model for assessing the combined impact of quarantine of asymptomatic cases and the isolation of symptomatic cases on curtailing the spread of a communicable disease is presented and rigorously analyzed. The model, which consists of six mutually-exclusive epidemiological compartments, uses standard incidence formulation (for the infection rate) and assumes the loss of infection-acquired immunity among recovered individuals. Simulation results, using a reasonable set of parameters values (consistent with the SARS outbreaks of 2003), are reported. The main findings of this chapter are summarized below:

(i) The model (3.2) has a globally-asymptotically stable disease-free equilibrium whenever the associated reproduction number of the model is less than unity (Theorem 3.2);

(ii) The model has a unique endemic equilibrium whenever the reproduction number exceeds unity (Lemma 3.3);

(iii) The unique endemic equilibrium is shown to be locally-asymptotically stable and globally-asymptotically stable for special cases (Theorems 3.3 and 3.4);

(iv) The effectiveness of quarantine (of asymptomatic cases) and isolation (of symptomatic cases) is dependent on the size of the modification parameter for the reduction in infectiousness of hospitalized individuals (η). The combined use of quarantine and isolation will have positive population-level impact if $\eta < \max\{\eta_\sigma, \eta_\phi\}$ and will have no, or result in detrimental, population-level impact if $\eta \geq \max\{\eta_\sigma, \eta_\phi\}$ (Lemmas 3.5 and 3.6).

Table 3.2: Estimated values for the parameters of the model (3.2)

Parameters	Values (*per day*)	Sources
β	[0.1, 0.2]	[38]
μ	0.0000351	[38]
γ_1	0.03521	[15]
γ_2	0.042553	[15]
δ_1	0.04227	[59]
δ_2	0.027855	[15]
κ	0.156986	[23]
α	0.156986	[23]
ϕ	0.20619	[15]
Π	136	[38]
σ	0.1	[38]
ψ	0.005	Assumed
η	(0,1]	Variable

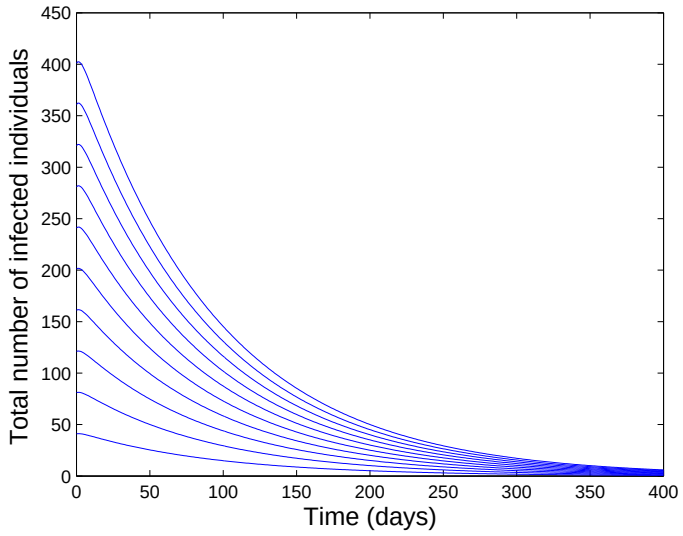


Figure 3.2: Simulation of the model (3.2) showing the total number of infected individuals as a function of time for $\mathcal{R}_c < 1$. Parameter values used are as given in Table 3.2, with $\beta = 0.1$ and $\eta = 0.5$ (so that, $\mathcal{R}_c = 0.8065$.)

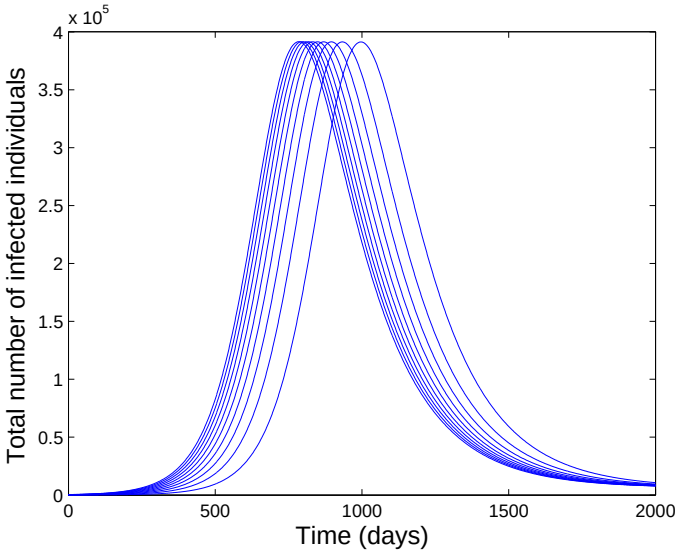


Figure 3.3: Simulation of the model (3.2) showing the total number of infected individuals as a function of time for $\mathcal{R}_c > 1$. Parameter values used are as given in Table 3.2, with $\beta = 0.15$ and $\eta = 0.5$ (so that, $\mathcal{R}_c = 1.2097$).

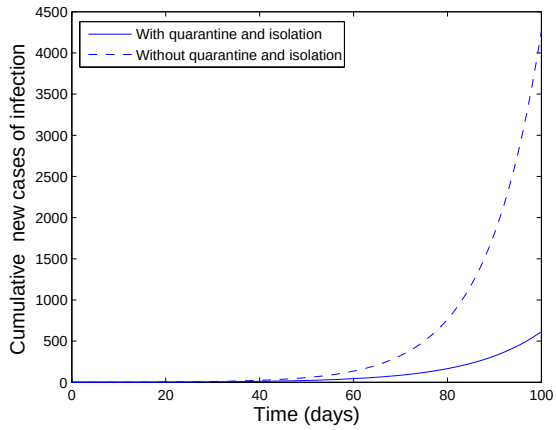


Figure 3.4: Simulation of the model (3.2) giving the cumulative number of new cases of infection as a function of time. Parameter values used are as given in Table 3.2, with $\beta = 0.2$ and $\eta = 0.65$ (so that, $\eta_\sigma = 0.9088$, $\eta_\phi = 0.9088$ and $\eta < \min\{\eta_\sigma, \eta_\phi\}$).

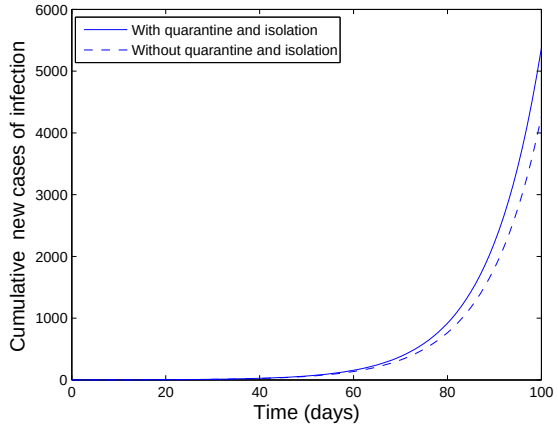


Figure 3.5: Simulation of the model (3.2) giving the cumulative number of new cases of infection as a function of time. Parameter values used are given as in Table 3.2, with $\beta = 0.2$ and $\eta = 0.95$ (so that, $\eta_\sigma = 0.9088$, $\eta_\phi = 0.9088$ and $\eta > \max\{\eta_\sigma, \eta_\phi\}$).

Chapter 4

Quarantine/Isolation Model With Time Delay

4.1 Introduction

The aim of this chapter is to assess the roles of time delay and the choice of incidence function on the transmission dynamics of a communicable disease in the presence of quarantine and isolation. To achieve the objective of this chapter, the autonomous quarantine/isolation model considered in Chapter 3, given by (3.2), will be extended to incorporate time delay and two different incidence functions. The functional form of the incidence functions to be considered are derived based on the framework described below (this derivation follows the general description given in Section 1.2).

Let $S(t), I(t)$ and $N(t)$ denote the number of susceptible individuals, infectious individuals and the total size of the population at time t, respectively. Further, let $\beta(N)$ be the average number of contacts that is sufficient to transmit infection (effective contact rate). Then, *the force of infection*, given by $\beta(N)I/N$, represents the average number of contacts a susceptible individual makes with infectious individuals *per* unit time. If $\beta(N) = \beta N$ (i.e., the contact rate depends on the total population, N), then

the incidence function $g_1(I) = \beta I$ is called *mass action incidence*. If $\beta(N) = \beta$ (a constant), then the incidence function, $g_2(I) = \beta I/N$, is called *standard incidence* [44, 80]. These two functions are widely used in the modeling of the transmission dynamics of human diseases [2, 3].

Another type of incidence function used in mathematical epidemiology is the Holling type II incidence function, given by $g_3(I) = \frac{\beta I}{1+\omega I}$, with $\omega > 0$, [10, 51, 63, 74]. The non-linear incidence function of type $g_3(I)$ was first introduced by Capasso and Serio [10], in their study of cholera epidemic in Bari, Italy. The main justification for using such a functional form of the incidence function stems from the fact that the number of effective contacts between infective individuals and susceptible individuals may saturate at high infective levels due to crowding of infective individuals, or due to the preventive measures (and behavioral changes) taken by the susceptible individuals in response to the severity of the disease [51, 63, 74].

4.2 Model with Standard Incidence

The model to be considered in this chapter is that for the transmission dynamics of an infectious disease, in the presence of quarantine of exposed individuals and isolation of infected individuals with disease symptoms, and is given by the following system of delay integro-differential equations [75]:

$$
\begin{aligned}
\frac{dS}{dt} &= \Pi - \frac{\beta S(t)I(t)}{N(t)} - \mu S(t),\\
E &= \int_{t-\tau}^{t} \frac{\beta S(x)I(x)e^{-(\mu+\sigma)(t-x)}}{N(x)}dx,\\
\frac{dI}{dt} &= \frac{e^{-\tau(\mu+\sigma)}\beta S(t-\tau)I(t-\tau)}{N(t-\tau)} - (\gamma_1+\phi+\mu+\delta_1)I(t),\\
\frac{dQ}{dt} &= \sigma E(t) - (\alpha+\mu)Q(t),\\
\frac{dH}{dt} &= \alpha Q(t) + \phi I(t) - (\gamma_2+\mu+\delta_2)H(t),\\
\frac{dR}{dt} &= \gamma_1 I(t) + \gamma_2 H(t) - \mu R(t),
\end{aligned}
\tag{4.1}
$$

where, S, E, I, Q, H, R denote the populations of susceptible, exposed, infectious, quarantined, hospitalized and recovered individuals at time t, respectively.

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

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

The initial data for the model (4.1) is given by

$$
\begin{aligned}
&S(\theta) = \phi_1(\theta),\ E(\theta) = \phi_2(\theta),\ I(\theta) = \phi_3(\theta),\\
&Q(\theta) = \phi_4(\theta),\ H(\theta) = \phi_5(\theta),\ R(\theta) = \phi_6(\theta), \theta \in [-\tau, 0],
\end{aligned}
\tag{4.2}
$$

where, $\phi = [\phi_1, \phi_2, \phi_3, \phi_4, \phi_5, \phi_6] \in \mathcal{C}$ such that $\phi_i(\theta) = \phi_i(0) \geq 0$ for $(\theta \in [-\tau, 0],\ i = 1, 3, 4, 5, 6),\ \phi_2(\theta) \geq 0\ (\theta \in [-\tau, 0])$, and $\mathcal{C}$ denotes the Banach space $\mathcal{C}([-\tau, 0], \mathbb{R}^6)$ of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^6$, equipped with the uniform norm defined by $\|\phi\| = \sup_{\theta\in[-\tau,0]} |\phi(\theta)|$. Furthermore, it is assumed that $\phi_i(0) > 0$ (for $i = 1, \cdots, 6$).

In (4.1), the parameter Π represents the recruitment rate into the population, β is the effective contact rate. The delay parameter $\tau > 0$ represents the associated incu-

bation period [18]. Exposed individuals are quarantined at a rate α. Quarantined and infectious individuals are hospitalized at the rates α and ϕ, respectively. The parameters γ_1 and γ_2 represent the recovery rates of infectious and hospitalized individuals, respectively, while μ is the natural death rate. Finally, δ_1 and δ_2 are the disease-induced death rates for infectious and hospitalized individuals, respectively. A flow diagram of the model (4.1) is given in Figure 4.1, and the associated variables and parameters are described and estimated in Tables 4.1 and 4.2.

Table 4.1: Description of variables and parameters of the model (4.3).

Variable	Description
$S(t)$	Population of susceptible individuals
$E(t)$	Population of exposed individuals
$I(t)$	Population of infectious individuals
$Q(t)$	Population of quarantined individuals
$H(t)$	Population of hospitalized individuals
$R(t)$	Population of recovered individuals
Parameter	**Description**
Π	Recruitment rate into the community
μ	Natural death rate
β	Effective contact rate
τ	Incubation period
ω	Parameter for measuring psychological or inhibitory effect
σ	Quarantine rate of exposed individuals
α	Hospitalization rate for quarantined individuals
ϕ	Hospitalization rate for infectious individuals
ψ	Rate of loss of infection-acquired immunity
γ_1	Recovery rate for infectious individuals
γ_2	Recovery rate for hospitalized individuals
δ_1	Disease-induced death rate for infectious individuals
δ_2	Disease-induced death rate for hospitalized individuals

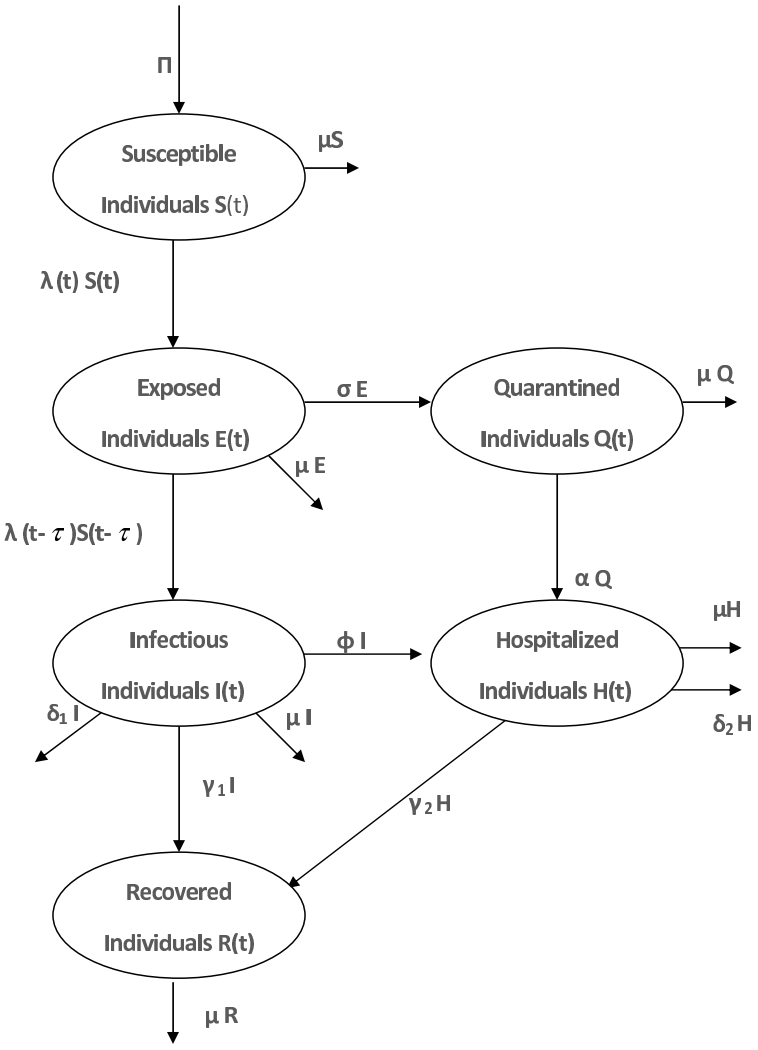


Figure 4.1: Flow diagram of the delayed model (4.3).

The DDE model (4.1) is an extension of the autonomous quarantine/isolation model (3.2) by incorporating time delay ($\tau > 0$), but with the assumption of loss of infection-acquired immunity relaxed (so that recovered individuals do not become susceptible again) and hospitalized individuals do not transmit infection (i.e., we set $\psi = \eta = 0$ in (3.2)). One of the main aims of this chapter is to determine whether or not incorporating time delay alters the qualitative dynamics of the autonomous quarantine/isolation model (3.2). Another major objective is to determine whether replacing the standard incidence function in the model (4.1) with Holling type II incidence function ($g_3(I) = \frac{I}{1+\omega I}$) will introduce new (or different) dynamical features for the model (4.1).

4.2.1 Basic properties

Using the generalized Leibnitz rule of differentiation, the model (4.1) can be re-written as:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \frac{\beta S(t)I(t)}{N(t)} - \mu S(t),\\
\frac{dE}{dt} &= \frac{\beta S(t)I(t)}{N(t)} - \frac{e^{-\tau(\mu+\sigma)}\beta S(t-\tau)I(t-\tau)}{N(t-\tau)} - (\sigma+\mu)E,\\
\frac{dI}{dt} &= \frac{e^{-\tau(\mu+\sigma)}\beta S(t-\tau)I(t-\tau)}{N(t-\tau)} - (\gamma_1+\phi+\mu+\delta_1)I(t),\\
\frac{dQ}{dt} &= \sigma E(t) - (\alpha+\mu)Q(t),\\
\frac{dH}{dt} &= \alpha Q(t) + \phi I(t) - (\gamma_2+\mu+\delta_2)H(t),\\
\frac{dR}{dt} &= \gamma_1 I(t) + \gamma_2 H(t) - \mu R(t).
\end{aligned} \tag{4.3}$$

The basic properties of the model (4.3) will now be investigated.

Lemma 4.1. *The solution* $(S(t), E(t), I(t), Q(t), H(t), R(t))$ *of the system* (4.3)*, with the initial data* (4.2)*, exists for all* $t \geq 0$ *and is unique. Furthermore,* $S(t) > 0,\ E(t) > 0,\ I(t) > 0,\ Q(t) > 0,\ H(t) > 0,$ *and* $R(t) > 0$ *for all* $t \geq 0$.

Proof. The DDE system (4.3) can be written as

$$\dot{X} = f(t, X_\tau),$$

where, $X = (S(t), E(t), I(t), Q(t), H(t), R(t)) \in \mathcal{C}$. Since $f(t, X)$ is continuous and Lipschitz in X, it follows then, by the Fundamental Theory of Functional Differential Equations [42], that the system (4.3) has a unique solution $(S(t), E(t), I(t), Q(t), H(t), R(t))$ satisfying the initial data (4.2).

It is clear from the first equation of the model (4.3) that

$$\frac{dS}{dt} \geq -\left[\frac{\beta I(t)}{N(t)} + \mu\right] S(t),$$

so that,

$$S(t) \geq S(0) \exp\left\{ - \int_0^t \left[\frac{\beta I(u)}{N(u)} + \mu \right] du \right\} > 0, \text{ for all } t > 0.$$

Similarly, it follows, from the third equation of the system (4.3), that $I(t) > 0$ for all $t > 0$. Since the second equation of (4.3) is equivalent to the second equation of (4.1), it follows (by using the fact that $S(t) > 0$ and $I(t) > 0$ for all $t > 0$, together with the fact that all the parameters of the model are positive) that:

$$E(t) = \int_{t-\tau}^{t} \frac{\beta S(x) I(x) e^{-(\mu+\sigma)(t-x)}}{N(x)} dx > 0.$$

Furthermore, using the same approach as that for $S(t)$, it can be shown that $Q(t) > 0$, $H(t) > 0$ and $R(t) > 0$ for all $t > 0$. □

Lemma 4.2. *The closed set*

$$\mathcal{D} = \left\{ (S, E, I, Q, H, R) \in \mathbb{R}_+^6 : S + E + I + Q + H + R \leq \frac{\Pi}{\mu} \right\}$$

is positively-invariant for the DDE model (4.1).

Proof. Adding all the equations of the model (4.3) gives,

$$\frac{dN}{dt} = \Pi - \mu N - (\delta_1 I + \delta_2 H). \tag{4.4}$$

Since $dN/dt \leq \Pi - \mu N$, it follows that $dN/dt \leq 0$ if $N \geq \Pi/\mu$. Thus, a standard comparison theorem (Theorem 2.8) can be used to show that

$$N(t) \leq N(0) e^{-\mu t} + \frac{\Pi}{\mu} \left(1 - e^{-\mu t}\right).$$

In particular, $N(t) \leq \Pi/\mu$ if $N(0) \leq \Pi/\mu$. Thus, the region $\mathcal{D}$ is positively-invariant.

Further, if $N(0) > \Pi/\mu$, then either the solution enters $\mathcal{D}$ in finite time, or $N(t)$ approaches Π/μ asymptotically. Hence, the region $\mathcal{D}$ attracts all solutions in $\mathbb{R}^6_+$. $\square$

4.2.2 Global stability of DFE

The DFE of the system (4.3), obtained by setting the derivatives in the model (4.3) to zero, is given by

$$\mathcal{E}_0 = \left(\frac{\Pi}{\mu}, 0, 0, 0, 0, 0\right). \tag{4.5}$$

The global asymptotic stability property of $\mathcal{E}_0$ will be explored using the methodology given in [56, 69]. It is convenient to define:

$$\mathcal{R}_0^S = \frac{\beta e^{-\tau(\mu+\sigma)}}{\gamma_1 + \phi + \mu + \delta_1}.$$

The quantity, $\mathcal{R}_0^S$, is the *basic reproduction number* of the DDE model (4.3).

Theorem 4.1. *The DFE of the model* (4.3)*, given by* (4.5)*, is GAS in* $\mathcal{D}$ *whenever* $\mathcal{R}_0^S < 1$.

Proof. Let $\mathcal{R}_0^S < 1$. Furthermore, let $(S(t), E(t), I(t), Q(t), H(t), R(t))$ be any positive solution of the system (4.3) with the initial data (4.2). The third equation of the system (4.3) can be re-written as

$$\begin{aligned} I(t) &= \int_{-\infty}^{t} \frac{\beta e^{-\tau(\sigma+\mu)} S(x-\tau) I(x-\tau)}{N(x-\tau)} e^{-(\gamma_1+\phi+\mu+\delta_1)(t-x)} dx \\ &\leq \int_{-\infty}^{t} \beta e^{-\tau(\sigma+\mu)} I(x-\tau) e^{-(\gamma_1+\phi+\mu+\delta_1)(t-x)} dx, \ \text{ since } \ S(t) \leq N(t) \text{ in } \mathcal{D}. \end{aligned} \tag{4.6}$$

It follows, by using the substitution $s = t - x$ in (4.6), that

$$I(t) \leq \int_0^{\infty} \beta e^{-\tau(\sigma+\mu)} I(t-s-\tau) e^{-(\gamma_1+\phi+\mu+\delta_1)(s)} ds. \tag{4.7}$$

Taking the lim sup of both sides of (4.7), and noting that $\limsup \int f \leq \int \limsup f$

(Lemma 2.4), gives

$$\begin{aligned}\limsup_{t\to\infty} I(t) &\leq \int_0^\infty \beta e^{-\tau(\sigma+\mu)} e^{-(\gamma_1+\phi+\mu+\delta_1)(s)} ds \limsup_{t\to\infty} I(t), \\ &= \frac{\beta e^{-\tau(\mu+\sigma)}}{\gamma_1+\phi+\mu+\delta_1} \limsup_{t\to\infty} I(t) = \mathcal{R}_0^S \limsup_{t\to\infty} I(t).\end{aligned} \tag{4.8}$$

Since $\mathcal{R}_0^S < 1$, it follows that $\limsup_{t\to\infty} I(t) < \limsup_{t\to\infty} I(t)$. This is a contradiction, unless $\limsup_{t\to\infty} I(t) = 0$. Thus, for any $\epsilon > 0$ sufficiently small, there exists a $T > 0$ such that if $t > T$, then $I(t) < \epsilon$.

Using $S(t)/N(t) \leq 1$ and $I(t) < \epsilon$, for $t > T$, in the second equation of (4.3), gives

$$\dot{E} \leq \beta\epsilon - (\sigma+\mu)E.$$

Furthermore, by the comparison theorem,

$$\limsup_{t\to+\infty} E(t) \leq \frac{\beta\epsilon}{\sigma+\mu}.$$

Since ϵ is arbitrary, it follows (by setting $\epsilon \to 0$) that

$$\limsup_{t\to+\infty} E(t) = 0.$$

Hence, for $\epsilon_1 > 0$ small, there exists a $T_1 > T$ such that if $t > T_1$, then $E(t) < \epsilon_1$. Using $E(t) < \epsilon_1$, for $t > T_1$, in the fourth equation of (4.3), gives

$$\dot{Q} \leq \epsilon_1\sigma - (\alpha+\mu)E,$$

so that, by the comparison theorem,

$$\limsup_{t\to+\infty} Q(t) \leq \frac{\epsilon_1\sigma}{\alpha+\mu}.$$

Hence,

$$\limsup_{t\to+\infty} Q(t) = 0.$$

In a similar way, it can be shown that

$$\limsup_{t\to+\infty} H(t) = 0 \text{ and } \limsup_{t\to+\infty} R(t) = 0.$$

Finally, it follows from the first equation of (4.3), for $t > T$, that

$$\dot{S} \geq \Pi - \epsilon - \mu S,$$

so that, using the comparison theorem,

$$\liminf_{t\to+\infty} S(t) \geq \frac{\Pi - \epsilon}{\mu}.$$

Hence, by letting $\epsilon \to 0$,

$$\liminf_{t\to+\infty} S(t) \geq \frac{\Pi}{\mu}.$$

Additionally, since $\limsup_{t\to+\infty} S(t) \leq \frac{\Pi}{\mu}$, it follows that

$$\lim_{t\to+\infty} S(t) = \frac{\Pi}{\mu}.$$

Thus,

$$\lim_{t\to+\infty} (S(t), E(t), I(t), Q(t), H(t), R(t)) = \left(\frac{\Pi}{\mu}, 0, 0, 0, 0, 0\right) = \mathcal{E}_0.$$

□

This result (Theorem 4.1) is consistent with that given for the model without delay (3.2) for the case where recovered individuals do not lose their infection-acquired immunity and hospitalized individuals do not transmit infection (i.e., system (3.2) with

$\eta = \psi = 0$) in regards to the DFE of the model (3.2). That is, adding time delay to the quarantine/isolation model without time delay (3.2), for the case where $\psi = \eta = 0$, does not alter the global asymptomatic stability property of the DFE ($\mathcal{E}_0$) of the model (3.2). The epidemiological implication of Theorem 4.1 is that the combined use of quarantine and isolation can lead to disease elimination if the two interventions can bring (and keep) the threshold quantity, $\mathcal{R}_0^S$, to a value less than unity (i.e., for the DDE model (4.3), the condition $\mathcal{R}_0^S < 1$ is necessary and sufficient for disease elimination).

By solving for the delay parameter (τ) from the equation $\mathcal{R}_0^S = 1$ (and noting Theorem 4.1), the following result can be obtained.

Lemma 4.3. The DFE of the model (4.3), given by (4.5), is GAS in $\mathcal{D}$ whenever

$$\tau > \ln\left(\frac{\beta}{\mu + \phi + \gamma_1 + \delta_1}\right)^{\left(\frac{1}{\sigma+\mu}\right)} = \tau_c^S.$$

In other words, Lemma 4.3 shows that the disease will be eliminated from the community if and only if $\tau > \tau_c^S$. Furthermore, it follows from Lemma 4.3 that the longer infected individuals remain in the exposed class (E), the higher the likelihood of disease elimination from the community. Figure 4.2 depicts the numerical results obtained by simulating the model (4.3) using the parameter values in Table 4.2, and various initial conditions, for the case $\tau > \tau_c^S$ ($\mathcal{R}_0^S < 1$). It is evident from this figure that all solutions converged to the DFE, $\mathcal{E}_0$ (in line with Theorem 4.1 and Lemma 4.3). It should be stated that the parameter values in Table 4.2 are relevant to the transmission dynamics of SARS [16, 23, 38, 59].

Table 4.2: Estimated values of the parameters of the model (4.3).

Parameter	Value (per day)	Source
Π	136	[38]
β	(0,0.5)	[38]
μ	0.0000351	[38]
γ_1	0.03521	[15]
γ_2	0.042553	[15]
δ_1	0.04227	[59]
δ_2	0.027855	[15]
κ	0.156986	[23]
α	0.156986	[23]
ϕ	0.20619	[15]
σ	0.1	[38]
ω	0.1	Assumed

4.2.3 Existence of EEP

In this section, the possible existence and stability of endemic equilibria of the model (4.3) will be explored.

Let $\mathcal{E}_1^S = (S^{**}, E^{**}, I^{**}, Q^{**}, H^{**}, R^{**})$ represent any arbitrary endemic equilibrium point of the model (4.3), so that $N^{**} = S^{**} + E^{**} + I^{**} + Q^{**} + H^{**} + R^{**}$. Solving the equations of the model (4.3) at steady-state gives

$$\begin{aligned} S^{**} &= \frac{\Pi}{\lambda^{**} + \mu}, \quad E^{**} = \frac{\lambda^{**} S^{**}(1 - e^{-\tau(\sigma+\mu)})}{\sigma + \mu}, \quad I^{**} = \frac{e^{-\tau(\sigma+\mu)} \lambda^{**} S^{**}}{\gamma_1 + \phi + \mu + \delta_1}, \\ Q^{**} &= \frac{\sigma E^{**}}{\alpha + \mu}, \qquad H^{**} = \frac{\alpha Q^{**} + \phi I^{**}}{\gamma_2 + \mu + \delta_2}, \qquad R^{**} = \frac{\gamma_1 I^{**} + \gamma_2 H^{**}}{\mu}, \end{aligned} \tag{4.9}$$

where,

$$\lambda^{**} = \frac{\beta I^{**}}{N^{**}}. \tag{4.10}$$

For computational convenience, the expressions in (4.9) are re-written in terms of

$\lambda^{**}S^{**}$ as below:

$$E^{**} = \frac{\lambda^{**}S^{**}(1-e^{-\tau(\sigma+\mu)})}{\sigma+\mu}, \qquad I^{**} = \frac{e^{-\tau(\sigma+\mu)}\lambda^{**}S^{**}}{\gamma_1+\phi+\mu+\delta_1},$$
$$Q^{**} = P_1\lambda^{**}S^{**}, \qquad H^{**} = P_2\lambda^{**}S^{**}, \qquad R^{**} = P_3\lambda^{**}S^{**}, \tag{4.11}$$

where,

$$P_1 = \frac{\sigma(1-e^{-\tau(\sigma+\mu)})}{(\sigma+\mu)(\alpha+\mu)}, \qquad P_2 = \frac{\alpha P_1}{\gamma_2+\mu+\delta_2} + \frac{\phi e^{-\tau(\sigma+\mu)}}{(\gamma_2+\mu+\delta_2)(\gamma_1+\phi+\mu+\delta_1)},$$
$$P_3 = \frac{\gamma_1 e^{-\tau(\sigma+\mu)}}{\mu(\gamma_1+\phi+\mu+\delta_1)} + \frac{\gamma_2 P_2}{\mu}.$$

Substituting the expressions in (4.11) into (4.10) gives

$$\begin{aligned}&\lambda^{**}S^{**} + \frac{\lambda^{**}S^{**}(1-e^{-\tau(\sigma+\mu)})\lambda^{**}}{\sigma+\mu} + \frac{\lambda^{**}e^{-\tau(\sigma+\mu)}\lambda^{**}S^{**}}{\gamma_1+\phi+\mu+\delta_1} \\ &+ \lambda^{**}P_1\lambda^{**}S^{**} + \lambda^{**}P_2\lambda^{**}S^{**} + \lambda^{**}P_3\lambda^{**}S^{**} = \frac{\beta e^{-\tau(\sigma+\mu)}\lambda^{**}S^{**}}{\gamma_1+\phi+\mu+\delta_1}.\end{aligned} \tag{4.12}$$

Dividing each term in (4.12) by $\lambda^{**}S^{**}$(and noting that, at the endemic steady-state, $\lambda^{**}S^{**} \neq 0$) gives

$$1 + P_4\lambda^{**} = \frac{\beta e^{-\tau(\sigma+\mu)}}{\gamma_1+\phi+\mu+\delta_1} = \mathcal{R}_0^S. \tag{4.13}$$

Since,

$$P_4 = \frac{1-e^{-\tau(\sigma+\mu)}}{\sigma+\mu} + \frac{e^{-\tau(\sigma+\mu)}}{\gamma_1+\phi+\mu+\delta_1} + P_1 + P_2 + P_3 \geq 0,$$

it follows from (4.13) that,

$$\lambda^{**} = \frac{\mathcal{R}_0^S - 1}{P_4} > 0, \quad \text{whenever } \mathcal{R}_0^S > 1. \tag{4.14}$$

The components of the endemic equilibrium, $\mathcal{E}_1^S$, can then be obtained by substituting the unique value of λ^{**}, given in (4.14), into the expressions in (4.9). Thus, the following result is established.

Lemma 4.4. *The model* (4.3) *has a unique endemic equilibrium, given by* $\mathcal{E}_1^S$*, whenever* $\mathcal{R}_0^S > 1$.

Although not proven here, numerical simulations of the model (4.3) suggest that the EEP ($\mathcal{E}_1^S$) of the model (4.3) is asymptotically-stable for $\mathcal{R}_0^S > 1$ (Figure 4.3). It should be mentioned, however, that the solutions depicted in Figure 4.3 did not converge to zero, as they appear to (see Figure 4.4 for a blow up of the tail end of Figure 4.3). In other words, Figures 4.3 and 4.4 show convergence of the solutions to the unique EEP, $\mathcal{E}_1^S$, of the model (4.3) for the case $\mathcal{R}_0^S > 1$. The following conjecture is suggested:

Conjecture 4.1. *The unique EEP,* $\mathcal{E}_1^S$*, of the model* (4.3) *is LAS whenever* $\mathcal{R}_0^S > 1$.

In summary, the model (4.3) has a globally-asymptotic stable disease-free equilibrium whenever $\mathcal{R}_0^S < 1$, and it has a unique endemic equilibrium whenever $\mathcal{R}_0^S > 1$. These results are consistent with those reported for the corresponding autonomous model (3.2) with $\eta = \psi = 0$. In other words, adding time delay to the model (3.2) with $\eta = \psi = 0$ does not alter its qualitative (equilibrium) dynamics. The next task is to determine whether or not the dynamics of the quarantine/isolation model (3.2) is affected by the combined use of time delay and the substitution of the standard incidence function with the Holling type II incidence function. This is considered below.

4.3 Model with Holling Type II Incidence

In this section, the DDE model (4.3) will be analyzed subject to the use of the Holling type II incidence function, given by $g_3(I) = \frac{I}{1+\omega I}$ (with $\omega > 0$), in place of the standard incidence function. The DDE model (4.3), with the standard incidence function replaced by $g_3(I)$, is given by

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \frac{\beta S(t)I(t)}{1+\omega I(t)} - \mu S(t),\\
\frac{dE}{dt} &= \frac{\beta S(t)I(t)}{1+\omega I(t)} - \frac{e^{-\tau(\mu+\sigma)}\beta S(t-\tau)I(t-\tau)}{1+\omega I(t-\tau)} - (\sigma+\mu)E,\\
\frac{dI}{dt} &= \frac{\beta e^{-\tau(\mu+\sigma)}S(t-\tau)I(t-\tau)}{1+\omega I(t-\tau)} - (\gamma_1+\phi+\mu+\delta_1)I(t),\\
\frac{dQ}{dt} &= \sigma E(t) - (\alpha+\mu)Q(t),\\
\frac{dH}{dt} &= \alpha Q(t) + \phi I(t) - (\gamma_2+\mu+\delta_2)H(t),\\
\frac{dR}{dt} &= \gamma_1 I(t) + \gamma_2 H(t) - \mu R.
\end{aligned} \tag{4.15}$$

4.3.1 Global stability of DFE

The DDE system (4.15) has the same DFE, $\mathcal{E}_0$, as the system (4.3). Further, the invariant region, $\mathcal{D}$, holds for system (4.15) as well. The GAS property of the DFE of the system (4.15) will be explored using the methodology given in [97] (which uses Lemma 2.3). Define,

$$\mathcal{R}_0^H = \frac{\beta\Pi e^{-\tau(\mu+\sigma)}}{\mu(\gamma_1+\phi+\mu+\delta_1)}.$$

Theorem 4.2. *The DFE of the model* (4.15)*, given by* (4.5)*, is GAS in* $\mathcal{D}$ *whenever* $\mathcal{R}_0^H < 1$.

Proof. Let $\mathcal{R}_0^H < 1$. Furthermore, let $(S(t), E(t), I(t), Q(t), H(t), R(t))$ be any positive

solution of the system (4.15) with the initial data (4.2). Since $\mathcal{R}_0^H < 1$, it is clear that

$$\beta e^{-\tau(\mu+\sigma)}\Pi/\mu < \gamma_1 + \phi + \mu + \delta_1. \tag{4.16}$$

Since $S(t) \leq \Pi/\mu$ in $\mathcal{D}$ for all $t > 0$, it follows from the second equation of (4.15) that

$$\dot{I} \leq \frac{\beta\Pi e^{-\tau(\mu+\sigma)} I(t-\tau)}{\mu[1+\omega I(t-\tau)]} - (\gamma_1 + \phi + \mu + \delta_1) I(t). \tag{4.17}$$

Consider, next, the auxiliary (with equality) equation associated with the inequality (4.17) (where u is a dummy variable)

$$\dot{u} = \frac{\beta\Pi e^{-\tau(\mu+\sigma)} u(t-\tau)}{\mu[1+\omega u(t-\tau)]} - (\gamma_1 + \phi + \mu + \delta_1) u(t). \tag{4.18}$$

Using Item (i) of Lemma 2.3, together with equation (4.16), in (4.18) gives

$$\lim_{t\to+\infty} u(t) = 0.$$

Thus, it follows from (4.17), using comparison theorem (Theorem 2.8), that

$$\limsup_{t\to+\infty} I(t) = 0.$$

Thus, for any $\epsilon > 0$ sufficiently small, there exists a $T > 0$ such that if $t > T$, then $I(t) < \epsilon$. Using $S \leq \Pi/\mu$ in $\mathcal{D}$ and $I < \epsilon$, for $t > T$, in the second equation of (4.15) (note that $g(I)$ is monotone increasing) gives,

$$\dot{E} \leq \frac{\beta\Pi\epsilon}{\mu(1+\omega\epsilon)} - (\sigma + \mu) E.$$

Furthermore, by the comparison theorem,

$$\limsup_{t\to+\infty} E(t) \leq \frac{\beta\Pi\epsilon}{\mu(\sigma+\mu)(1+\omega\epsilon)}.$$

Since ϵ is arbitrary, it follows (by setting $\epsilon \to 0$) that

$$\limsup_{t\to+\infty} E(t) = 0.$$

Hence, for $\epsilon_1 > 0$ small, there exists a $T_1 > T$ such that if $t > T_1$, then $E(t) < \epsilon_1$. Using $E(t) < \epsilon_1$, for $t > T_1$, in the fourth equation of (4.15) gives

$$\dot{Q} \leq \epsilon_1\sigma - (\alpha + \mu)E,$$

so that, by the comparison theorem,

$$\limsup_{t\to+\infty} Q(t) \leq \frac{\epsilon_1\sigma}{\alpha + \mu}.$$

Hence,

$$\limsup_{t\to+\infty} Q(t) = 0.$$

In a similar way, it can be shown that

$$\limsup_{t\to+\infty} H(t) = 0 \text{ and } \limsup_{t\to+\infty} R(t) = 0.$$

Finally, it follows from the first equation of (4.15), for $t > T$, that

$$\dot{S} \geq \Pi - \frac{\beta S\epsilon}{1 + \omega\epsilon} - \mu S,$$

so that, using the comparison theorem,

$$\liminf_{t\to+\infty} S(t) \geq \frac{\Pi(1 + \omega\epsilon)}{\mu + \epsilon(\beta + \omega\mu)}.$$

Hence (by letting $\epsilon \to 0$)

$$\liminf_{t\to+\infty} S(t) \geq \frac{\Pi}{\mu}.$$

Additionally, since $\limsup_{t\to+\infty} S(t) \leq \frac{\Pi}{\mu}$ in $\mathcal{D}$ it follows that

$$\lim_{t\to+\infty} S(t) = \frac{\Pi}{\mu}.$$

Thus,

$$\lim_{t\to+\infty} (S(t), E(t), I(t), Q(t), H(t), R(t)) = \left(\frac{\Pi}{\mu}, 0, 0, 0, 0, 0\right) = \mathcal{E}_0.$$

□

The epidemiological implication of the above result (Theorem 4.2) is that the combined use of quarantine and isolation can lead to disease elimination if they can bring (and keep) the threshold quantity, $\mathcal{R}_0^H$, to a value less than unity (i.e., for the DDE model (4.15), the condition $\mathcal{R}_0^H < 1$ is necessary and sufficient for disease elimination).

By solving for τ from the equation $\mathcal{R}_0^H = 1$ (and noting Theorem 4.2), the following result can be obtained.

Lemma 4.5. *The DFE of the model* (4.15)*, given by* (4.5)*, is GAS in* $\mathcal{D}$ *whenever* $\tau > \ln\left[\frac{\beta\Pi}{\mu(\mu+\phi+\gamma_1+\delta_1)}\right]^{\left(\frac{1}{\sigma+\mu}\right)} = \tau_c^H$.

In other words, like in the case of system (4.3), the disease will be eliminated from the community if and only if $\tau > \tau_c^H$. Figure 4.5 depicts the numerical results obtained by simulating the model (4.15) using the parameter values in Table 4.2 and various initial conditions for the case $\tau > \tau_c^H$ ($\mathcal{R}_0^H < 1$). It is evident from this figure that all solutions converged to the DFE, $\mathcal{E}_0$ (in line with Theorem 4.2 and Lemma 4.5).

4.3.2 Existence of EEP and disease permanence

In this section, the possible existence of endemic equilibria of the model (4.15), and the permanence of the disease, will be explored.

Existence of EEP

Let $\mathcal{E}_1^H = (S^{**}; E^{**}; I^{**}; Q^{**}; H^{**}; R^{**})$ represent any arbitrary endemic equilibrium of the model (4.15). Solving the equations of the model (4.15) at steady-state gives

$$\begin{aligned} S^{**} &= \frac{\Pi(1+\omega I^{**})}{\mu(1+\omega I^{**})+\beta I^{**}}, \quad E^{**} = \frac{\beta(1-e^{-(\sigma+\mu)\tau})S^{**}I^{**}}{\sigma+\mu}, \\ S^{**} &= \frac{(1+\omega I^{**})(\gamma_1+\phi+\mu+\delta_1)}{\beta e^{-(\sigma+\mu)\tau}}, \quad Q^{**} = \frac{\sigma E^{**}}{\alpha+\mu}, \\ H^{**} &= \frac{\phi I^{**}+\alpha Q^{**}}{\gamma_2+\mu+\delta_2}, \quad R^{**} = \frac{\gamma_1 I^{**}+\gamma^{**}H^{**}}{\mu}. \end{aligned} \tag{4.19}$$

Equating the first and third equations of (4.19), and solving for I^{**} in terms of $\mathcal{R}_0^H$, gives

$$I^{**} = \frac{\mathcal{R}_0^H - 1}{\mu(\beta+\omega\mu)(\gamma_1+\phi+\mu+\delta_1)^2} > 0, \quad \text{whenever } \mathcal{R}_0^H > 1. \tag{4.20}$$

Substituting for I^{**} from (4.20) into the first equation of (4.19) gives

$$S^{**} = \frac{\omega\Pi e^{-(\sigma+\mu)\tau} + (\gamma_1+\phi+\mu+\delta_1)}{e^{-(\sigma+\mu)\tau}(\beta+\omega\mu)}. \tag{4.21}$$

It follows from (4.19) (noting from (4.20) and (4.21) that both I^{**} and S^{**} are positive if $\mathcal{R}_0^H > 1$) that $\mathcal{E}_1^H \in \mathbb{R}_+^6$ whenever $\mathcal{R}_0^H > 1$. Thus, the following result is established.

Lemma 4.6. *The model* (4.15) *has a unique endemic equilibrium, given by* $\mathcal{E}_1^H$*, whenever* $\mathcal{R}_0^H > 1$.

Permanence of the disease

The permanence of the disease will now be explored in the context of the model (4.15). That is, the objective is to determine whether or not the number of infectious cases in the population will persist above a certain positive number for a long time period (for the case when $\mathcal{R}_0^H > 1$).

Theorem 4.3. *If $\mathcal{R}_0^H > 1$, then for any solution of (4.15) with the initial data (4.2), there exists a positive number $\nu = e^{-\tau(\gamma_1+\phi+\mu+\delta_1)}I^{**}$, such that $\liminf_{t\to\infty} I(t) \geq \nu$.*

Proof. The proof of Theorem 4.3 is based on using the approach given in [34, 66, 89, 103]. It should be noted, first of all, that the second equation of (4.15) can be re-written as

$$\dot{I} = \frac{\beta e^{-\tau(\sigma+\mu)}S(t)I(t)}{1+\omega I(t)} - (\gamma_1+\phi+\mu+\delta_1)I(t) - \frac{d}{dt}\int_{t-\tau}^{t}\frac{\beta e^{-\tau(\sigma+\mu)}S(x)I(x)}{1+\omega I(x)}dx. \quad (4.22)$$

Consider the following function:

$$V(t) = I(t) + \int_{t-\tau}^{t}\frac{\beta e^{-\tau(\sigma+\mu)}S(x)I(x)}{1+\omega I(x)}dx.$$

Clearly, $V(t)$ is bounded (since $I(t)$ and $S(t)$ are bounded). Furthermore, it follows, using (4.22), that

$$\dot{V} = \frac{\beta e^{-\tau(\sigma+\mu)}S(t)I(t)}{1+\omega I(t)} - (\gamma_1+\phi+\mu+\delta_1)I(t). \quad (4.23)$$

Since, at endemic steady-state, $S(t)$ is given by $S^{**} = \dfrac{\Pi}{\mu+\frac{\beta I^{**}}{1+\omega I^{**}}} > 0$ whenever $\mathcal{R}_0^H > 1$, it is clear that for any $0 < q < 1$, $S^{**} < K$, where $K = \dfrac{\Pi}{\mu+\frac{\beta q I^{**}}{1+\omega q I^{**}}}$. Hence, there exists a number $m \geq 1$ such that $S^{**} < K(1-e^{-m\Pi\tau/K})$.

The next task is to show that $I(t) \geq qI^{**}$ for all $t \geq (m+1)\tau$. Suppose, by contradiction, that $I(t) < qI^{**}$ for all $t \geq (m+1)\tau$. It then follows, from the first

equation of (4.15), for $t \geq (m+1)\tau$, that

$$\dot{S}(t) > \Pi - \left(\mu + \frac{\beta q I^{**}}{1+\omega q I^{**}}\right) S(t) = \Pi - \frac{\Pi}{K} S(t).$$

Hence,

$$S(t) > K - e^{-\Pi/K[t-(m+1)\tau]} \left\{K - S[(m+1)\tau]\right\},$$

$$> K\left\{1 - e^{-\Pi/K[t-(m+1)\tau]}\right\},$$

so that, for $t \geq (2m+1)\tau$,

$$S(t) > K(1 - e^{-m\Pi\tau/K}) = \hat{S} > S^{**}. \tag{4.24}$$

Since $I(t) < qI^{**} < I^{**}$, it follows from (4.23), for $t \geq (2m+1)\tau$, that

$$\dot{V} > \frac{\beta e^{-\tau(\mu+\sigma)} S(t) I(t)}{1+\omega I^{**}} - (\gamma_1 + \phi + \mu + \delta_1) I(t),$$

$$> \frac{\beta e^{-\tau(\mu+\sigma)} \hat{S} I(t)}{1+\omega I^{**}} - (\gamma_1 + \phi + \mu + \delta_1) I(t), \tag{4.25}$$

$$= \left[\frac{\beta e^{-\tau(\mu+\sigma)} \hat{S}}{1+\omega I^{**}} - (\gamma_1 + \phi + \mu + \delta_1)\right] I(t).$$

Let $\hat{I} = \min_{\theta \in [-\tau, 0]} I(\theta + 2\tau(m+1))$. It can be claimed that $I(t) \geq \hat{I}$ for all $t \geq (2m+1)\tau$. Suppose the claim does not hold. Then there exists a constant $d_1 > 0$ such that $I(t) \geq \hat{I}$ for $t \in ([2m+1]\tau, 2[m+1]\tau + d_1 = t_*)$, with $I(t_*) = \hat{I}$ and $\dot{I}(t_*) \leq 0$.

However, it follows from the third equation of (4.15), when $t = t_*$, that

$$\dot{I}(t_*) = \frac{e^{-\tau(\sigma+\mu)}\beta S(t_*-\tau)I(t_*-\tau)}{1+\omega I(t_*-\tau)} - (\phi+\gamma_1+\mu+\delta_1)I(t_*),$$

$$= \frac{e^{-\tau(\sigma+\mu)}\beta S(t_*-\tau)I(t_*-\tau)}{1+\omega I(t_*-\tau)} - (\phi+\gamma_1+\mu+\delta_1)\hat{I}, \text{ since } I(t_*)=\hat{I},$$

$$\geq \frac{e^{-\tau(\sigma+\mu)}\beta S(t_*-\tau)\hat{I}}{1+\omega I(t_*-\tau)} - (\phi+\gamma_1+\mu+\delta_1)\hat{I}, \text{ since } I(t)\geq\hat{I} \text{ for } t\in([2m+1]\tau,t_*),$$

$$> \left[\frac{e^{-\tau(\sigma+\mu)}\beta S(t_*-\tau)}{1+\omega I^{**}} - (\phi+\gamma_1+\mu+\delta_1)\right]\hat{I}, \text{ since } I(t)<I^{**} \text{ for } t\geq(2m+1)\tau,$$

$$> \left[\frac{e^{-\tau(\sigma+\mu)}\beta S^{**}}{1+\omega I^{**}} - (\phi+\gamma_1+\mu+\delta_1)\right]\hat{I} = 0.$$

This contradicts the fact that $\dot{I}(t_*)\leq 0$. Hence, $I(t)\geq\hat{I}$ for $t\geq(2m+1)\tau$. Thus, it follows from (4.25) that $\dot{V} > \left[\frac{\beta e^{-\tau(\mu+\sigma)}\hat{S}}{1+\omega I^{**}} - (\gamma_1+\phi+\mu+\delta_1)\right]\hat{I}$ for all $t\geq 2(m+1)\tau$. Hence, $\lim_{t\to\infty} V(t)=\infty$, which contradicts the fact that $V(t)$ is bounded. Finally, to complete the proof, we need to show that $I(t)\geq\nu$ for sufficiently large t.

Let t_1 be sufficiently large and $I(t_1)=qI^{**}$. Consider the following interval $[t_1,t_2]$. It follows, from the second equation of (4.15), that

$$\dot{I}\geq -(\phi+\gamma_1+\mu+\delta_1)I.$$

Hence,

$$I(t) > I(t_1)e^{-(\phi+\gamma_1+\mu+\delta_1)(t-t_1)} = qI^{**}e^{-(\phi+\gamma_1+\mu+\delta_1)(t-t_1)}, \text{ for } t\in[t_1,t_2]. \tag{4.26}$$

It is clear from (4.26) that if $t_2-t_1\leq\tau$, then $I(t)\geq qI^{**}e^{-\tau(\phi+\gamma_1+\mu+\delta_1)} = q\nu$.

For the other case (where $t_2 - t_1 > \tau$), it is easy to see that the inequality $I(t) \geq qI^{**}e^{-\tau(\phi+\gamma_1+\mu+\delta_1)} = q\nu$ also holds for $t \in [t_1, t_1 + \tau]$. We claim that (4.26) also holds for $t \in (t_1 + \tau, t_2]$. If not, then there exists a constant $d > 0$ such that $I(t) \geq q\nu$ for $t \in (t_1 + \tau, t_1 + \tau + d = t_0)$, with $I(t_0) = q\nu$ and $\dot{I}(t_0) \leq 0$.

However, it follows from the third equation of (4.15), when $t = t_0$, that

$$\dot{I}(t_0) = \frac{e^{-\tau(\sigma+\mu)}\beta S(t_0-\tau)I(t_0-\tau)}{1+\omega I(t_0-\tau)} - (\phi+\gamma_1+\mu+\delta_1)I(t_0),$$

$$= \frac{e^{-\tau(\sigma+\mu)}\beta S(t_0-\tau)I(t_0-\tau)}{1+\omega I(t_0-\tau)} - (\phi+\gamma_1+\mu+\delta_1)q\nu, \text{ since } I(t_0) = q\nu,$$

$$\geq \frac{e^{-\tau(\sigma+\mu)}\beta S(t_0-\tau)q\nu}{1+\omega q\nu} - (\phi+\gamma_1+\mu+\delta_1)q\nu, \text{ since } I(t) \geq q\nu,$$

$$\geq \left[\frac{e^{-\tau(\sigma+\mu)}\beta S(t_0-\tau)}{1+\omega I^{**}} - (\phi+\gamma_1+\mu+\delta_1)\right] q\nu, \text{ since } q\nu \leq I^{**},$$

$$> \left[\frac{e^{-\tau(\sigma+\mu)}\beta S^{**}}{1+\omega I^{**}} - (\phi+\gamma_1+\mu+\delta_1)\right] q\nu = 0.$$

This contradicts the fact that $\dot{I}(t_0) \leq 0$. Hence, $I(t) \geq q\nu$ for $t \in [t_1, t_1]$. Since this interval and $q \in (0, 1)$ are chosen arbitrarily, it is concluded that $I(t) \geq \nu$. Thus, $\liminf_{t\to\infty} I(t) \geq \nu$. □

The epidemiological implication of Theorem 4.3 is that the number of infectious cases will persist in the population (as $t \to \infty$) above a certain positive number (ν) whenever $\mathcal{R}_0^H > 1$.

4.3.3 Global stability of EEP

Here, the global stability of the EEP, $\mathcal{E}_1^H$, of the model (4.15) will be explored. It is convenient to define.

$$\mathcal{D}_0 = \left\{(S, E, I, Q, H, R) \in \mathcal{D} : E = I = Q = H = R = 0\right\}.$$

Theorem 4.4. *The unique endemic equilibrium of the model* (4.15)*, given by* (4.19)*, is GAS in* $\mathcal{D} \setminus \mathcal{D}_0$ *if* $\mathcal{R}_0^H > 1$ *and* $\omega\Pi e^{-\tau(\sigma+\mu)} > \phi + \gamma_1 + \mu + \delta_1$.

Proof. The proof of Theorem 4.4 is based on using a comparison argument and the iteration technique given in [97, 98].

Let $(S(t), E(t), I(t), Q(t), H(t), R(t))$ be any solution of (4.15) with initial conditions given by (4.2). Further, let

$$S_\infty = \liminf_{t\to\infty} S(t), \quad S^\infty = \limsup_{t\to\infty} S(t), \quad E_\infty = \liminf_{t\to\infty} E(t), \quad E^\infty = \limsup_{t\to\infty} E(t),$$
$$I_\infty = \liminf_{t\to\infty} I(t), \quad I^\infty = \limsup_{t\to\infty} I(t), \quad Q_\infty = \liminf_{t\to\infty} Q(t), \quad Q^\infty = \limsup_{t\to\infty} Q(t),$$
$$H_\infty = \liminf_{t\to\infty} H(t), \quad H^\infty = \limsup_{t\to\infty} H(t), \quad R_\infty = \liminf_{t\to\infty} R(t), \quad R^\infty = \limsup_{t\to\infty} R(t).$$

The goal is to show that $S_\infty = S^\infty = S^{**}$, $E_\infty = E^\infty = E^{**}$, $I_\infty = I^\infty = I^{**}, Q_\infty = Q^\infty = Q^{**}$, $H_\infty = H^\infty = H^{**}$ and $R_\infty = R^\infty = R^{**}$. It follows from the first equation of (4.15) that

$$\dot{S}(t) \leq \Pi - \mu S,$$

so that, by the comparison theorem,

$$\limsup_{t\to\infty} S(t) \leq \Pi/\mu.$$

Let $U_1^S = \Pi/\mu$. Thus, for sufficiently small $\epsilon > 0$, there exists a $T_1 > 0$ such that

$S(t) \leq U_1^S + \epsilon$ for $t > T_1$. It follows from the third equation of (4.15) that, for $t > T_1 + \tau$,

$$\dot{I}(t) \leq \frac{\beta e^{-\tau(\sigma+\mu)}(U_1^S + \epsilon)I(t-\tau)}{1 + \omega I(t-\tau)} - (\phi + \gamma_1 + \mu + \delta_1)I(t). \tag{4.27}$$

Consider the auxiliary equation of (4.27):

$$\dot{u}(t) = \frac{\beta e^{-\tau(\sigma+\mu)}(U_1^S + \epsilon)u(t-\tau)}{1 + \omega u(t-\tau)} - (\phi + \gamma_1 + \mu + \delta_1)u(t). \tag{4.28}$$

Since $\mathcal{R}_0^H > 1$, it follows that, for sufficiently small $\epsilon > 0$, $\beta e^{-\tau(\sigma+\mu)}(U_1^S + \epsilon) > (\phi + \gamma_1 + \mu + \delta_1)$. Hence, by Item (ii) of Lemma 2.3 and (4.28),

$$\lim_{t\to\infty} u(t) = \frac{\beta e^{-\tau(\sigma+\mu)}(U_1^S + \epsilon) - (\phi + \gamma_1 + \mu + \delta_1)}{\omega(\phi + \gamma_1 + \mu + \delta_1)}.$$

Thus, by the comparison theorem,

$$I^\infty = \limsup_{t\to\infty} I(t) \leq \frac{\beta e^{-\tau(\sigma+\mu)}(U_1^S + \epsilon) - (\phi + \gamma_1 + \mu + \delta_1)}{\omega(\phi + \gamma_1 + \mu + \delta_1)},$$

so that, $I^\infty \leq \dfrac{\beta e^{-\tau(\sigma+\mu)}U_1^S - (\phi + \gamma_1 + \mu + \delta_1)}{\omega(\phi + \gamma_1 + \mu + \delta_1)}$.

Similarly, let $U_1^I = \dfrac{\beta e^{-\tau(\sigma+\mu)}U_1^S - (\phi + \gamma_1 + \mu + \delta_1)}{\omega(\phi + \gamma_1 + \mu + \delta_1)}$. Then, for sufficiently small $\epsilon > 0$, there exists a $T_2 > T_1 + \tau$ such that $I(t) \leq U_1^I + \epsilon$ for $t > T_2$. It follows from the first equation of (4.15), for $t > T_2$, that

$$\dot{S}(t) \geq \Pi - \mu S - \frac{\beta(U_1^I + \epsilon)}{1 + \omega(U_1^I + \epsilon)},$$

so that, by the comparison theorem,

$$S_\infty = \liminf_{t\to\infty} S(t) \geq \frac{\Pi[1 + \omega(U_1^I + \epsilon)]}{\mu + (\beta + \mu\omega)(U_1^I + \epsilon)}.$$

Hence, $S_\infty \geq L_1^S$, where $L_1^S = \dfrac{\Pi[1 + \omega U_1^I]}{\mu + (\beta + \mu\omega)U_1^I}$. In other words, for sufficiently small

$\epsilon > 0$, there exists a $T_3 > T_2 + \tau$ such that $S(t) \geq L_1^S - \epsilon$ for $t > T_3$. It follows from the third equation of (4.15), for $t > T_3 + \tau$, that

$$\dot{I}(t) \geq \frac{\beta e^{-\tau(\sigma+\mu)}(L_1^S - \epsilon)I(t-\tau)}{1 + \omega I(t-\tau)} - (\phi + \gamma_1 + \mu + \delta_1)I(t),$$

so that (by considering the auxiliary equation)

$$\dot{u}(t) = \frac{\beta e^{-\tau(\sigma+\mu)}(L_1^S - \epsilon)u(t-\tau)}{1 + \omega u(t-\tau)} - (\phi + \gamma_1 + \mu + \delta_1)u(t).$$

Hence, it follows from Item (ii) of Lemma 2.3 (since $\mathcal{R}_0^H > 1$) that

$$\lim_{t\to\infty} u(t) = \frac{\beta e^{-\tau(\sigma+\mu)}(L_1^S - \epsilon) - (\phi + \gamma_1 + \mu + \delta_1)}{\omega(\phi + \gamma_1 + \mu + \delta_1)},$$

and comparison theorem gives

$$I_\infty = \liminf_{t\to\infty} I(t) \geq \frac{\beta e^{-\tau(\sigma+\mu)}(L_1^S - \epsilon) - (\phi + \gamma_1 + \mu + \delta_1)}{\omega(\phi + \gamma_1 + \mu + \delta_1)}.$$

Hence, for sufficiently small $\epsilon > 0$, there exists a $T_4 > T_3 + \tau$ such that $I(t) \geq L_1^I - \epsilon$ for $t > T_4$, where

$$L_1^I = \frac{\beta e^{-\tau(\sigma+\mu)}L_1^S - (\phi + \gamma_1 + \mu + \delta_1)}{\omega(\phi + \gamma_1 + \mu + \delta_1)}.$$

Using $S(t) \leq U_1^S + \epsilon$, $I(t) \leq U_1^I + \epsilon$, $S(t) \geq L_1^S - \epsilon$ and $I(t) \geq L_1^I - \epsilon$ in the second equation of (4.15), for $t > T_4 + \tau$, gives

$$\dot{E} \leq \frac{\beta(U_1^S + \epsilon)(U_1^I + \epsilon)}{1 + \omega(U_1^I + \epsilon)} - \frac{\beta e^{-\tau(\sigma+\mu)}(L_1^S - \epsilon)(L_1^I - \epsilon)}{1 + \omega(L_1^I - \epsilon)} - (\sigma + \mu)E.$$

Hence, by comparison theorem,

$$E^{\infty} = \limsup_{t\to\infty} E(t) \leq \frac{\beta(U_1^S+\epsilon)(U_1^I+\epsilon)}{[1+\omega(U_1^I+\epsilon)](\sigma+\mu)} - \frac{\beta e^{-\tau(\sigma+\mu)}(L_1^S-\epsilon)(L_1^I-\epsilon)}{[1+\omega(L_1^I-\epsilon)](\sigma+\mu)}.$$

Therefore, for sufficiently small $\epsilon > 0$, there exists a $T_5 > T_4+\tau$ such that $E(t) \leq U_1^E+\epsilon$ for $t > T_5$, where

$$U_1^E = \frac{\beta U_1^S U_1^I}{(1+\omega U_1^I)(\sigma+\mu)} - \frac{\beta e^{-\tau(\sigma+\mu)} L_1^S L_1^I}{(1+\omega L_1^I)(\sigma+\mu)}.$$

Similarly, by using $S(t) \leq U_1^S+\epsilon$, $I(t) \leq U_1^I+\epsilon$, $S(t) \geq L_1^S-\epsilon$ and $I(t) \geq L_1^I-\epsilon$ in the second equation of (4.15), for $t > T_4+\tau$, we have

$$\dot{E} \leq \frac{\beta(L_1^S-\epsilon)(L_1^I-\epsilon)}{1+\omega(L_1^I-\epsilon)} - \frac{\beta e^{-\tau(\sigma+\mu)}(U_1^S+\epsilon)(U_1^I+\epsilon)}{1+\omega(U_1^I+\epsilon)} - (\sigma+\mu)E,$$

so that,

$$E_{\infty} = \liminf_{t\to\infty} E(t) \geq \frac{\beta(L_1^S-\epsilon)(L_1^I-\epsilon)}{[1+\omega(L_1^I-\epsilon)](\sigma+\mu)} - \frac{\beta e^{-\tau(\sigma+\mu)}(U_1^S+\epsilon)(U_1^I+\epsilon)}{[1+\omega(U_1^I+\epsilon)](\sigma+\mu)}.$$

Hence, for sufficiently small $\epsilon > 0$, there exists a $T_6 > T_5+\tau$ such that $E(t) \geq L_1^E-\epsilon$ for $t > T_6$, where

$$L_1^E = \frac{\beta L_1^S L_1^I}{(1+\omega L_1^I)(\sigma+\mu)} - \frac{\beta e^{-\tau(\sigma+\mu)} U_1^S U_1^I}{(1+\omega U_1^I)(\sigma+\mu)}.$$

Using $E(t) \leq U_1^E+\epsilon$ in the fourth equation of (4.15), for $t > T_5$, gives

$$\dot{Q}(t) \leq \sigma(U_1^E+\epsilon) - (\alpha+\mu)Q,$$

so that,

$$Q^{\infty} = \limsup_{t\to\infty} Q(t) \leq \frac{\sigma(U_1^E + \epsilon)}{\alpha + \mu}.$$

Thus, for sufficiently small $\epsilon > 0$, there exists a $T_7 > T_6 + \tau$ such that $Q(t) \leq U_1^Q + \epsilon$ for $t > T_7$, where $U_1^Q = \dfrac{\sigma U_1^E}{\alpha + \mu}$.

Similarly, by using $E(t) \geq L_1^E - \epsilon$ in the fourth equation of (4.15), for $t > T_6$, we have:

$$\dot{Q}(t) \geq \sigma(L_1^E - \epsilon) - (\alpha + \mu)Q,$$

and,

$$Q_{\infty} = \liminf_{t\to\infty} Q(t) \geq \frac{\sigma(L_1^E - \epsilon)}{\alpha + \mu}.$$

Thus, for sufficiently small $\epsilon > 0$, there exists a $T_8 > T_7 + \tau$ such that $Q(t) \geq L_1^Q - \epsilon$ for $t > T_8$, where $L_1^Q = \dfrac{\sigma L_1^E}{\alpha + \mu}$. Using $I(t) \leq U_1^I + \epsilon$ and $Q(t) \leq U_1^Q + \epsilon$ in the fifth equation of (4.15), for $t > T_7$, gives

$$\dot{H}(t) \leq \alpha(U_1^Q + \epsilon) + \phi(U_1^I + \epsilon) - (\gamma_2 + \mu + \delta_2)H,$$

and,

$$H^{\infty} = \limsup_{t\to\infty} H \leq \frac{\alpha(U_1^Q + \epsilon) + \phi(U_1^I + \epsilon)}{\gamma_2 + \mu + \delta_2}.$$

Thus, for sufficiently small $\epsilon > 0$, there exists a $T_9 > T_8 + \tau$ such that $H(t) \leq U_1^H + \epsilon$, for $t > T_9$, where $U_1^H = \dfrac{\alpha U_1^Q + \phi U_1^I}{(\gamma_2 + \mu + \delta_2)}$. Similarly, it follows by using $I(t) \geq L_1^I - \epsilon$ and $Q(t) \geq L_1^Q - \epsilon$ in the fifth equation of (4.15), for $t > T_8$, that

$$\dot{H}(t) \geq \alpha(L_1^Q - \epsilon) + \phi(L_1^I - \epsilon) - (\gamma_2 + \mu + \delta_2)H,$$

so that,

$$H_\infty = \liminf_{t\to\infty} H \leq \frac{\alpha(L_1^Q - \epsilon) + \phi(L_1^I - \epsilon)}{\gamma_2 + \mu + \delta_2}.$$

Hence, for sufficiently small $\epsilon > 0$, there exists a $T_{10} > T_9 + \tau$ such that $H(t) \geq L_1^H - \epsilon$ for $t > T_{10}$, where $L_1^H = \dfrac{\alpha L_1^Q + \phi L_1^I}{\gamma_2 + \mu + \delta_2}$.

Using $I(t) \leq U_1^I + \epsilon$ and $H(t) \leq U_1^H + \epsilon$ in the last equation of (4.15), for $t > T_9$, gives

$$\dot{R} \leq \gamma_1(U_1^I + \epsilon) + \gamma_2(U_1^H + \epsilon) - \mu R.$$

Hence,

$$R^\infty = \limsup_{t\to\infty} R(t) \leq \frac{\gamma_1(U_1^I + \epsilon) + \gamma_2(U_1^H + \epsilon)}{\mu}.$$

Thus, $R^\infty \leq U_1^R$, where $U_1^R = \dfrac{\gamma_1 U_1^I + \gamma_2 U_1^H}{\mu}$. Using $I(t) \geq L_1^I - \epsilon$ and $H(t) \geq L_1^H - \epsilon$ in the last equation of (4.15), for $t > T_{10}$, gives

$$\dot{R} \geq \gamma_1(L_1^I - \epsilon) + \gamma_2(L_1^H - \epsilon) - \mu R,$$

so that (by comparison theorem)

$$R_\infty = \liminf_{t\to\infty} R(t) \geq \frac{\gamma_1(L_1^I - \epsilon) + \gamma_2(L_1^H - \epsilon)}{\mu}.$$

Hence, $R_\infty \geq L_1^R$, where $L_1^R = \dfrac{\gamma_1 L_1^I + \gamma_2 L_1^H}{\mu}$.

Continuing in this manner leads to the following sequences:

$$
\begin{aligned}
U_n^S &= \frac{\Pi[1+\omega L_{n-1}^I]}{\mu+(\beta+\mu\omega)L_{n-1}^I}, \quad L_n^S = \frac{\Pi[1+\omega U_n^I]}{\mu+(\beta+\mu\omega)U_n^I}, \\
U_n^I &= \frac{\beta e^{-\tau(\sigma+\mu)}U_n^S-(\phi+\gamma_1+\mu+\delta_1)}{\omega(\phi+\gamma_1+\mu+\delta_1)}, \quad L_n^I = \frac{\beta e^{-\tau(\sigma+\mu)}L_n^S-(\phi+\gamma_1+\mu+\delta_1)}{\omega(\phi+\gamma_1+\mu+\delta_1)}, \\
U_n^E &= \frac{\beta U_n^I U_n^S}{(1+\omega U_n^I)(\sigma+\mu)} - \frac{\beta e^{-\tau(\sigma+\mu)}L_n^I L_n^S}{(1+\omega L_n^I)(\sigma+\mu)}, \\
L_n^E &= \frac{\beta L_n^I L_n^S}{(1+\omega L_n^I)(\sigma+\mu)} - \frac{\beta e^{-\tau(\sigma+\mu)}U_n^I U_n^S}{(1+\omega U_n^I)(\sigma+\mu)}, \\
U_n^Q &= \frac{\sigma U_n^E}{(\alpha+\mu)}, \quad L_n^Q = \frac{\sigma L_n^E}{(\alpha+\mu)}, \\
U_n^H &= \frac{\alpha U_n^Q+\phi U_n^I}{(\gamma_2+\mu+\delta_2)}, \quad L_n^H = \frac{\alpha L_n^Q+\phi L_n^I}{(\gamma_2+\mu+\delta_2)}, \\
U_n^R &= \frac{\gamma_1 U_n^I+\gamma_2 U_n^H}{\mu}, \quad L_n^R = \frac{\gamma_1 L_n^I+\gamma_2 L_n^H}{\mu}.
\end{aligned}
\tag{4.29}
$$

Finally, since $L_n^S \leq S_\infty \leq S^\infty \leq U_n^S$, $L_n^E \leq E_\infty \leq E^\infty \leq U_n^E$, $L_n^I \leq I_\infty \leq I^\infty \leq U_n^I$, $L_n^Q \leq Q_\infty \leq Q^\infty \leq U_n^Q$, $L_n^H \leq H_\infty \leq H^\infty \leq U_n^H$ and $L_n^R \leq R_\infty \leq R^\infty \leq U_n^R$, the proof is concluded by showing that

$$
\begin{aligned}
&\lim_{n\to\infty} U_n^S = S^{**} = \lim_{n\to\infty} L_n^S, \quad \lim_{n\to\infty} U_n^I = I^{**} = \lim_{n\to\infty} L_n^I, \\
&\lim_{n\to\infty} U_n^E = E^{**} = \lim_{n\to\infty} L_n^E, \quad \lim_{n\to\infty} U_n^Q = Q^{**} = \lim_{n\to\infty} L_n^Q, \\
&\lim_{n\to\infty} U_n^H = H^{**} = \lim_{n\to\infty} L_n^H, \quad \lim_{n\to\infty} U_n^R = R^{**} = \lim_{n\to\infty} L_n^R.
\end{aligned}
$$

Using the first four sequences of (4.29), it is easy to see that the sequence U_{n+1}^S can be written in terms of U_n^S as:

$$
U_{n+1}^S = \frac{\omega^2\Pi^2 e^{-2\tau(\sigma+\mu)}U_n^S}{k^2+e^{-\tau(\sigma+\mu)}(\beta+\omega\mu)[\omega\Pi e^{-\tau(\sigma+\mu)}-k]U_n^S}, \tag{4.30}
$$

where, $k=\phi+\gamma_1+\mu+\delta_1$. Furthermore, it can be shown that whenever $\omega\Pi e^{-\tau(\sigma+\mu)} > k$, the sequence U_n^S is monotone as follows:

$$U_{n+1}^S - U_n^S = \frac{[\omega\Pi e^{-\tau(\sigma+\mu)} - k][\omega\Pi e^{-\tau(\sigma+\mu)} + k - (\beta+\omega\mu)e^{-\tau(\sigma+\mu)}U_n^S]U_n^S}{k^2 + e^{-\tau(\sigma+\mu)}(\beta+\omega\mu)[\omega\Pi e^{-\tau(\sigma+\mu)} - k]U_n^S}.$$

Since $S^{**} \leq U_n^S$, it follows that

$$\begin{aligned} U_{n+1}^S - U_n^S &\leq \frac{[\omega\Pi e^{-\tau(\sigma+\mu)} - k][\omega\Pi e^{-\tau(\sigma+\mu)} + k - (\beta+\omega\mu)e^{-\tau(\sigma+\mu)}S^{**}]U_n^S}{k^2 + e^{-\tau(\sigma+\mu)}(\beta+\omega\mu)[\omega\Pi e^{-\tau(\sigma+\mu)} - k]U_n^S}, \\ &= 0 \quad \left(\text{since } S^{**} = \frac{\omega\Pi e^{-\tau(\sigma+\mu)} + k}{e^{-\tau(\sigma+\mu)}(\beta+\omega\mu)}\right). \end{aligned}$$

Thus, $\lim_{n\to\infty} U_n^S$ exists.

Let $M = \lim_{n\to\infty} U_n^S$. Then, it follows from (4.30) that

$$M = \frac{\omega^2\Pi^2 e^{-2\tau(\sigma+\mu)}M}{k^2 + e^{-\tau(\sigma+\mu)}(\beta+\omega\mu)[\omega\Pi e^{-\tau(\sigma+\mu)} - k]M},$$

so that,

$$M = \lim_{t\to\infty} U_n^S = \frac{\omega\Pi e^{-\tau(\sigma+\mu)} + k}{e^{-\tau(\sigma+\mu)}(\beta+\omega\mu)} = S^{**}.$$

Taking the limit as $n \to \infty$ of both sides of the third sequence of (4.29), gives

$$\lim_{n\to\infty} U_n^I = \frac{\beta e^{-\tau(\sigma+\mu)}S^{**} - (\phi+\gamma_1+\mu+\delta_1)}{\omega(\phi+\gamma_1+\mu+\delta_1)} = I^{**}.$$

Similarly by taking the limits of both sides of the remaining sequences in (4.29), and using the previous results, gives

$$\lim_{n\to\infty} L_n^S = S^{**}, \quad \lim_{n\to\infty} L_n^I = I^{**}, \quad \lim_{n\to\infty} U_n^E = \lim_{n\to\infty} L_n^E = E^{**}$$
$$\lim_{n\to\infty} U_n^Q = \lim_{n\to\infty} L_n^Q = Q^{**}, \quad \lim_{n\to\infty} U_n^H = \lim_{n\to\infty} L_n^H = H^{**},$$
$$\lim_{n\to\infty} U_n^R = \lim_{n\to\infty} L_n^R = R^{**}.$$

Hence, $\lim_{t\to\infty} (S(t), E(t), I(t), Q(t), H(t), R(t)) = \mathcal{E}_1^H$. □

Theorem 4.4 shows that the disease will persist in the population whenever $\mathcal{R}_0^H > 1$. Here, too, by solving for τ from $\mathcal{R}_0^H > 1$, the following result can be shown.

Lemma 4.7. *The unique endemic equilibrium of the model* (4.15)*, given by* (4.19)*, is GAS in* $\mathcal{D} \setminus \mathcal{D}_0$ *if* $\tau < \ln\left[\frac{\beta\Pi}{\mu(\mu+\phi+\gamma_1+\delta_1)}\right]^{\left(\frac{1}{\sigma+\mu}\right)} = \tau_c$ *and* $\omega\Pi e^{-\tau(\sigma+\mu)} > \phi + \gamma_1 + \mu + \delta_1$.

Theorem 4.4 shows that the disease will persist in the population provided that $\mathcal{R}_0^H > 1$ ($\tau < \tau_c$) and $\omega\Pi e^{-\tau(\sigma+\mu)} > \phi + \gamma_1 + \mu + \delta_1$. Thus, Lemma 4.5 and Lemma 4.7 suggest that $\tau = \tau_c$ is a sharp epidemiological threshold that governs the persistence ($\tau < \tau_c$) and elimination ($\tau > \tau_c$) of the disease in the population. Figure 4.6 shows a time series plot of the total number of infected individuals for various of initial conditions. This figure clearly shows convergence of the solutions to the EEP for the case $\tau < \tau_c$ ($\mathcal{R}_0^H > 1$) (in line with Theorem 4.4 and Lemma 4.7). Figure 4.7 depicts the total number of cases as a function of time for various values of τ. This figure shows a decreasing number of cases with increasing values of the delay parameter τ. That is, the longer individuals stay in the exposed class, the lower the disease burden.

4.4 Summary

A deterministic quarantine/isolation model with time delay is considered, subject to two incidence functions (namely, the standard incidence function and the Holling type II incidence function). The main findings of this chapter are summarized below:

(i) The model with standard incidence function, given by (4.3), has a globally-asymptotically stable disease-free solution whenever a certain epidemiological threshold quantity ($\mathcal{R}_0^S$) is less than unity (Theorem 4.1). Furthermore, this model has a unique positive endemic equilibrium whenever the threshold quantity ($\mathcal{R}_0^S$) exceeds unity (Lemma 4.4).

(ii) The model with Holling type II incidence function, given by (4.15), has a globally-asymptotically stable disease-free solution whenever its associated epidemiological threshold quantity ($\mathcal{R}_0^H$) is less than unity (Theorem 4.2). This model has a unique positive endemic equilibrium whenever the threshold quantity ($\mathcal{R}_0^H$) exceeds unity (Lemma 4.6). Furthermore, the model system is permanent whenever $\mathcal{R}_0^H > 1$ (Theorem 4.3). The unique endemic equilibrium of the model (4.15) is globally-asymptomatic stable under certain conditions (Theorem 4.4).

In summary, the analyses in this chapter show that adding time delay and/or replacing the standard incidence function by a Holling type II incidence function in the autonomous (without delay) quarantine/isolation model (3.2) with $\eta = \psi = 0$ does not alter the qualitative dynamics (with regards to the elimination or persistence of the disease) of the model (3.2). In other words, the theoretical results in this chapter show that the quarantine/isolation model with time delay ($\tau > 0$) and standard or non-linear incidence function of Holling type II has essentially the same qualitative (equilibrium) dynamics as the corresponding autonomous quarantine/isolation model ($\tau = 0$) with standard incidence function and $\psi = \eta = 0$ considered in Chapter 3. Furthermore, numerical simulations of the model with time delay and standard incidence function shows that the associated disease burden decreases with increasing time delay (τ).

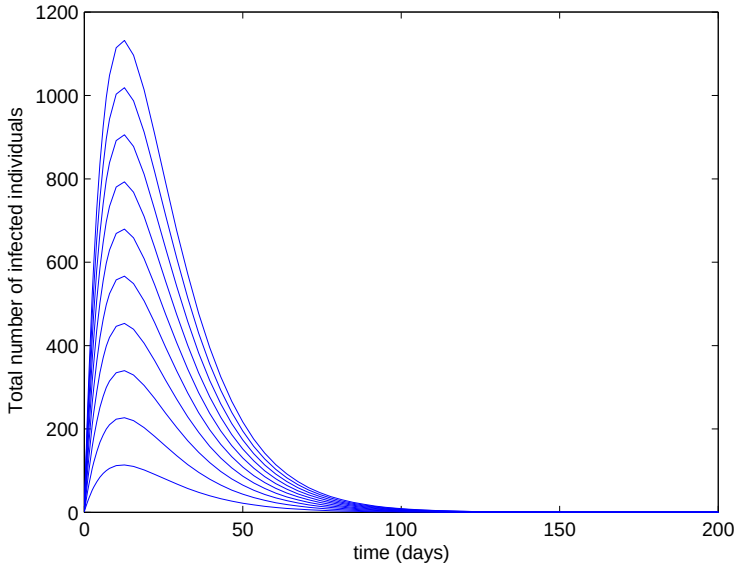


Figure 4.2: Simulations of the model (4.3), showing the total number of infected individuals as a function of time. Parameter values used are as given in Table 4.2, with $\tau = 20$ and $\beta = 0.15$ (so that, $\mathcal{R}_0^S = 0.7150 < 1$ ($\tau > \tau_c^S$)).

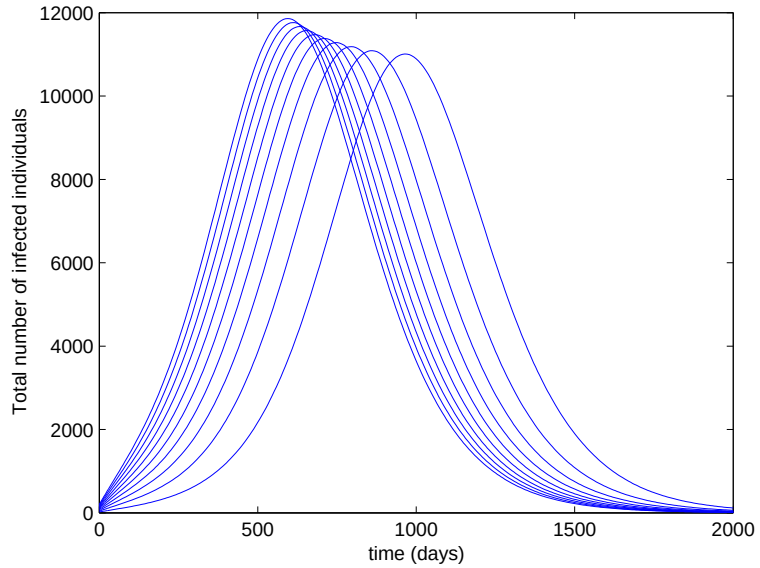


Figure 4.3: Simulations of the model (4.3), showing the total number of infected individuals as a function of time. Parameter values used are as given in Table 4.2, with $\tau = 18$ and $\beta = 0.1$ (so that, $\mathcal{R}_0^S = 1.0298 > 1$ ($\tau < \tau_c^S$)).

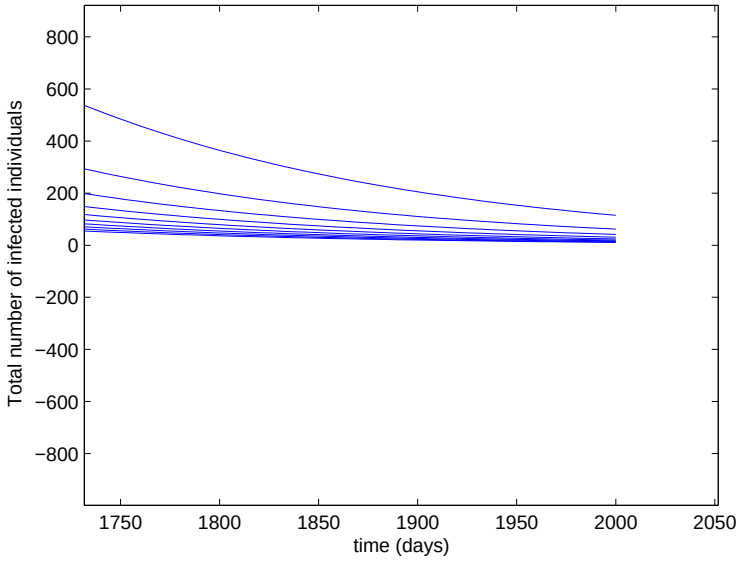


Figure 4.4: Blow up of the tail end of Figure 4.3.

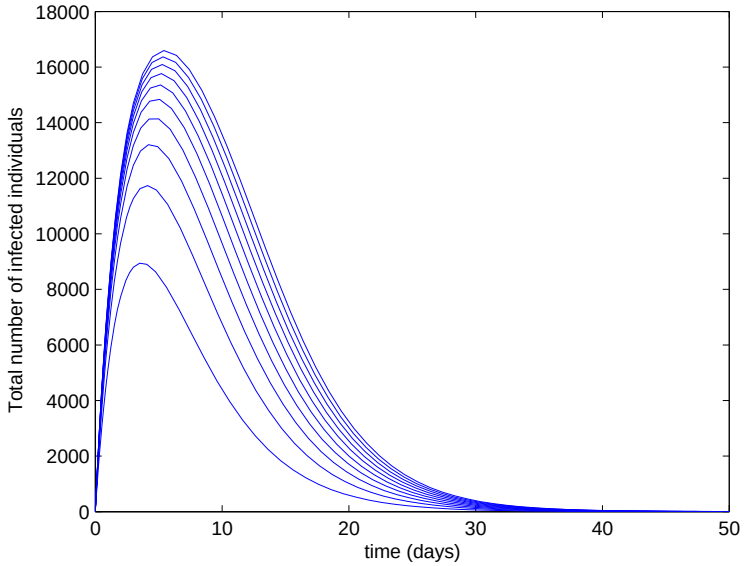


Figure 4.5: Simulations of the model (4.15), showing the total number of infected individuals as a function of time. Parameter values used are as given in Table 4.2, with $\tau = 20$ and $\beta = 0.0025809$ (so that, $\mathcal{R}_0^H = 0.1599 < 1$ ($\tau > \tau_c^H$)).

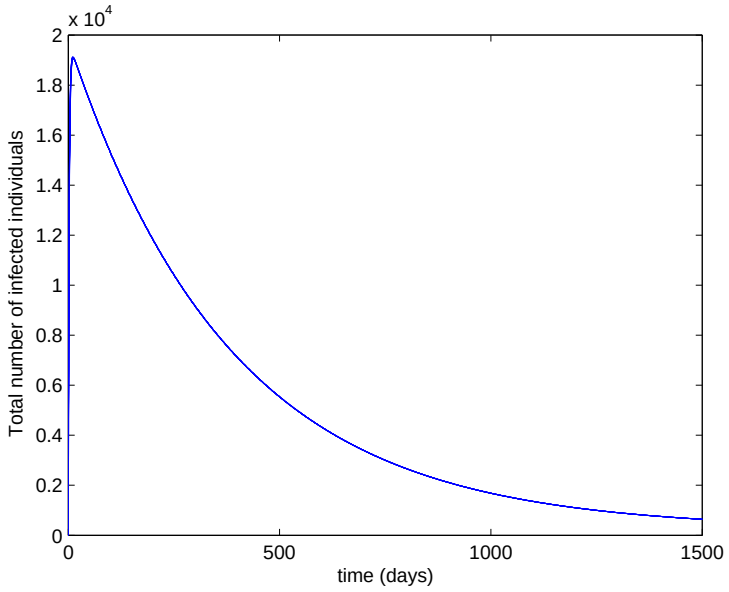


Figure 4.6: Simulations of the model (4.15), showing the total number of infected individuals as a function of time. Parameter values used are as given in Table 4.2, with $\tau = 10$ and $\beta = 0.0025809$ (so that, $\mathcal{R}_0^H = 2.3741 > 1$ ($\tau < \tau_c^H$)).

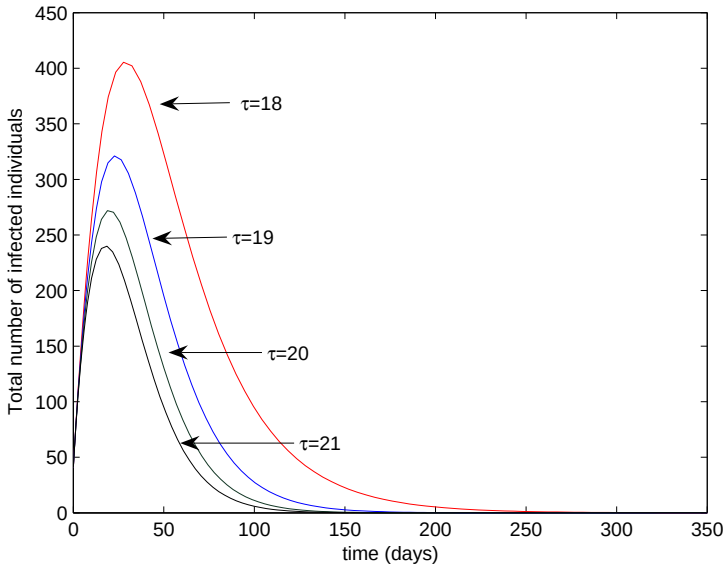


Figure 4.7: Simulations of the model (4.15) showing the total number of infected individuals for various values of τ. Parameter values used are as given in Table 4.2, with $\beta = 0.15$.

Chapter 5

Quarantine/Isolation Model in a Periodic Environment

5.1 Introduction

It is well known that some infectious diseases, such as measles, mumps and chickenpox, exhibit periodic fluctuations in their transmission dynamics. For instance, the city of New York recorded yearly outbreaks of chickenpox and mumps, and a biennial pattern of measles outbreaks, between 1929-1970 [17, 65]. Furthermore, contact rates may vary during a time period due to a number of factors, such as environmental (weather changes; emergence of insects caused by seasonal variation) and the fact that children are in school during certain months etc. [21]. London and Yorke [65] showed such variations in contact rates by studying data for mumps, chickenpox and measles. Other diseases show seasonal behavior as well (see, for instance, [19, 24, 25, 45, 65]).

As noted by Cooke and Kaplan [17], since periodic fluctuation in contact rate is crucial to a number of diseases, it is instructive to carry out a rigorous mathematical study to theoretically evaluate the effect of such fluctuations on the transmission dynamics of the relevant diseases in a population in the presence of the basic public health

control measures (quarantine and isolation). However, as noted by McLeod *et al.* [67], such basic control measures are gradually refined during the course of a disease outbreak (as more data and knowledge about the epidemiology and biology of the disease becomes available). Thus, it is reasonable to incorporate the effect of periodicity in disease transmission models that involve the use of such control measures (quarantine and isolation). The aim of this chapter is to theoretically assess the role of periodicity on the transmission dynamics of a disease that is controllable using quarantine and isolation.

5.2 Model Formulation and Basic Properties

The model to be considered is that for the transmission dynamics of an infectious disease, in the presence of quarantine of exposed individuals and isolation of infectious individuals, and is given by the following non-autonomous system of differential equations [76]:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi + \psi R(t) - \frac{\beta(t)S(t)[I(t)+\eta(t)H(t)]}{N(t)} - \mu S(t),\\
\frac{dE}{dt} &= \frac{\beta(t)S(t)[I(t)+\eta(t)H(t)]}{N(t)} - [\kappa(t)+\sigma(t)+\mu]E(t),\\
\frac{dI}{dt} &= \kappa(t)E(t) - [\gamma_1(t)+\phi(t)+\mu+\delta_1]I(t),\\
\frac{dQ}{dt} &= \sigma(t)E(t) - [\alpha(t)+\mu]Q(t),\\
\frac{dH}{dt} &= \alpha(t)Q(t) + \phi(t)I(t) - [\gamma_2(t)+\mu+\delta_2]H(t)\\
\frac{dR}{dt} &= \gamma_1(t)I(t) + \gamma_2(t)H(t) - (\psi+\mu)R(t),
\end{aligned} \tag{5.1}$$

where, S, E, I, Q, H, R denote, respectively, the populations of susceptible, exposed, infectious, quarantined, hospitalized and recovered individuals at time t, so that the

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

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

Furthermore, the parameter Π represents recruitment rate into the population, $\beta(t)$ is the contact rate, ψ is the rate of loss of infection-acquired immunity, $\eta(t)$ is a time-dependent modification parameter for the reduction in infectiousness of hospitalized individuals in relation to infectious individuals in class I. Exposed individuals are quarantined at a rate α. They develop symptoms at a rate $\kappa(t)$. Quarantined and infectious individuals are hospitalized at the rates $\alpha(t)$ and $\phi(t)$, respectively. The parameters $\gamma_1(t)$ and $\gamma_2(t)$ represent the recovery rates of infectious and hospitalized individuals, respectively, while μ is the natural death rate. Finally, δ_1 and δ_2 are disease-induced death rates for infectious and hospitalized individuals, respectively (a flow diagram of the model (5.1) is given in Figure 5.1; and the associated variables and parameters are described and estimated in Tables 5.1 and 3.2).

Table 5.1: Description of variables and parameters of the model (5.2).

Variable	Description
$S(t)$	Population of susceptible individuals
$E(t)$	Population of exposed individuals
$I(t)$	Population of infected individuals
$Q(t)$	Population of quarantined individuals
$H(t)$	Population of hospitalized individuals
$R(t)$	Population of recovered individuals
Parameter	Description
Π	Recruitment rate
β	Effective contact rate
η	Modification parameter for reduction in infectiousness of hospitalized individuals
κ	Progression rate from exposed to infectious class
σ	Quarantine rate of exposed individuals
α	Hospitalization rate for quarantined individuals
ϕ	Hospitalization rate for infectious individuals
ψ	Rate of loss of infection-acquired immunity
γ_1	Recovery rate for infectious individuals
γ_2	Recovery rate for hospitalized individuals
δ_1	Disease-induced death rate for infectious individuals
δ_2	Disease-induced death rate for hospitalized individuals
μ	Natural death rate

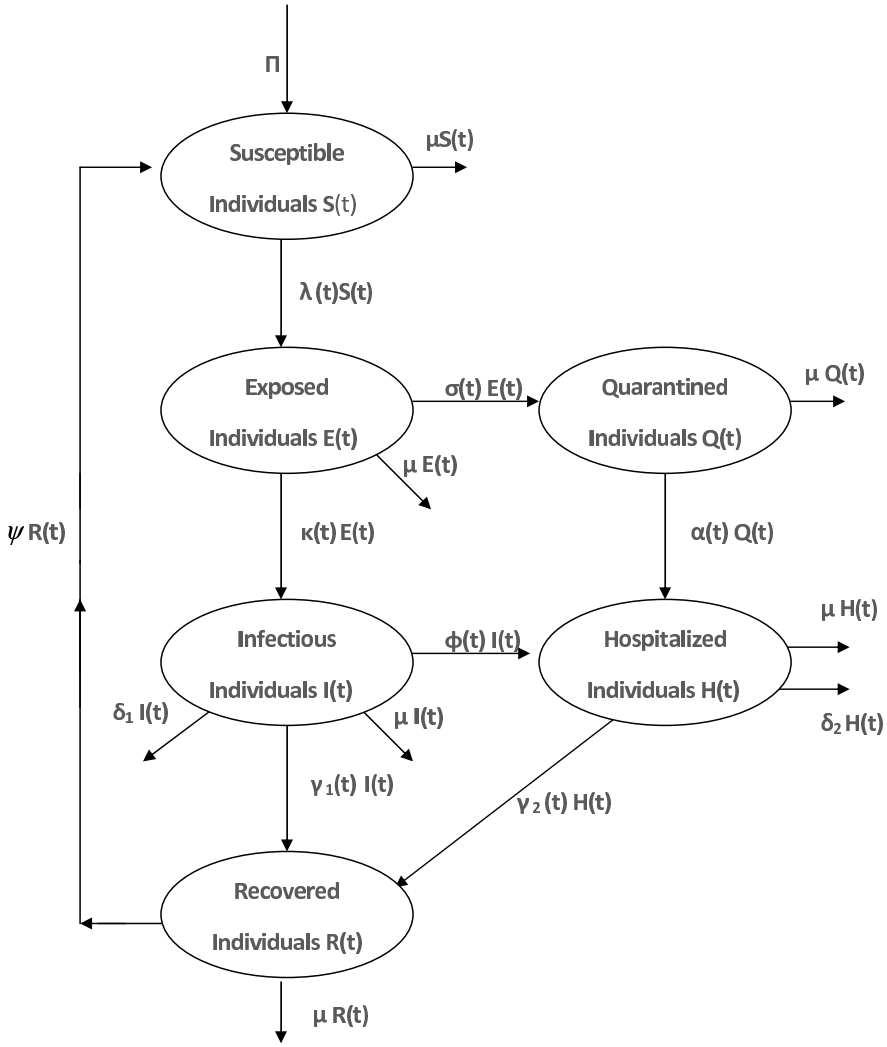


Figure 5.1: Flow diagram for the non-autonomous model (5.2).

The non-autonomous quarantine/isolation model (5.1) is an extension of the autonomous quarantine/isolation model (3.2), by considering some of the model parameters (namely, $\beta, \eta, \kappa, \sigma, \phi, \gamma_1, \gamma_2$ and α) to be periodic positive continuous functions in t, with period ω for some $\omega > 0$ (unlike in the autonomous model (3.2), where all the model parameters are assumed to be constant). It should be stated that the non-autonomous system (5.1) reduces to the autonomous model (3.2) when $\beta(t) = \beta,\ \eta(t) = \eta,\ \kappa(t) = \kappa,\ \phi(t) = \phi,\ \alpha(t) = \alpha,\ \gamma_1(t) = \gamma_1,\ \gamma_2(t) = \gamma_2$ and $\sigma(t) = \sigma$.

Using the equality, $N = S + E + I + Q + H + R$, the system (5.1) can be re-written

as:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi + \psi[N(t) - S(t) - E(t) - I(t) - Q(t) - H(t)] - \frac{\beta(t)S(t)[I(t) + \eta(t)H(t)]}{N(t)} - \mu S(t), \\
\frac{dE}{dt} &= \frac{\beta(t)S(t)[I(t) + \eta(t)H(t)]}{N(t)} - [\kappa(t) + \sigma(t) + \mu]E(t), \\
\frac{dI}{dt} &= \kappa(t)E(t) - [\gamma_1(t) + \phi(t) + \mu + \delta_1]I(t), \\
\frac{dQ}{dt} &= \sigma(t)E(t) - [\alpha(t) + \mu]Q(t), \\
\frac{dH}{dt} &= \alpha(t)Q(t) + \phi(t)I(t) - [\gamma_2(t) + \mu + \delta_2]H(t), \\
\frac{dN}{dt} &= \Pi - \delta_1 I - \delta_2 H - \mu N.
\end{aligned} \tag{5.2}$$

Basic properties

The basic properties of the model (5.2) will now be studied. We claim the following:

Lemma 5.1. *System* (5.2) *has a unique and bounded solution with the initial value* $(S^0, E^0, I^0, Q^0, H^0, N^0) \in X = \{(S, E, I, Q, H, N) \in \mathbb{R}^6_+ : N \geq S + E + I + Q + H\}$.

Further, the compact set

$$\mathcal{D} = \{(S, E, I, Q, H, N) \in X : N \leq \Pi/\mu\}$$

is positively-invariant for the model (5.2) *and attracts all positive orbits in* X.

Proof. Following [62], let $g \in (\mathbb{R}^6_+, \mathbb{R})$ be defined by:

$$g(S, E, I, Q, H, R) = \begin{cases} 0 & \text{if } (S, E, I, Q, H, R) = (0, 0, 0, 0, 0, 0); \\ \dfrac{S(I + \eta(t)H)}{S + E + I + Q + H + R}, & \text{otherwise.} \end{cases}$$

Thus, the function $g(S, E, I, Q, H, R)$ is continuous on $\mathbb{R}^6_+$. Furthermore, it can be shown that $g(S, E, I, Q, H, R)$ is globally Lipschitz on $\mathbb{R}^6_+$ (with Lipschitz constant $L =$

6). Theorem 5.2.1 of [82] can then be applied to show that, for any $(S^0, E^0, I^0, Q^0, H^0, N^0) \in \mathbb{R}^6_+$, the system (5.2) has a unique local non-negative solution (S, E, I, Q, H, N) with

$$[S(0), E(0), I(0), Q(0), H(0), N(0)] = (S^0, E^0, I^0, Q^0, H^0, N^0).$$

It follows from the last equation of the system (5.2) that

$$\frac{dN}{dt} = \Pi - \delta_1 I - \delta_2 H - \mu N \leq \Pi - \mu N,$$

from which it is clear that the associated linear differential equation,

$$\frac{dN}{dt} = \Pi - \mu N,$$

has a unique equilibrium $N^* = \Pi/\mu$, which is GAS. Finally, it can be shown, using comparison theorem (Theorem 2.8), that $N(t)$ is bounded. Thus, the solution of the system (5.2) exists globally on the interval $[0, \infty)$. □

5.3 Stability of Disease-Free Solution (DFS)

5.3.1 Local stability

The concept of the *basic reproduction number* (or *basic reproduction ratio*) of a disease transmission model in a periodic environment has been addressed by a number of authors, most recently by Bacaër *et al.* [4, 5, 6] and Wang and Zhao [91]. The methodology in [91] will be followed to compute the reproduction ratio associated with the non-autonomous system (5.2).

The DFS of the system (5.2), obtained by setting the derivatives in (5.2) to zero, is given by

$$\mathcal{E}_0 = (S_0, E_0, I_0, Q_0, H_0, N_0) = \left(\frac{\Pi}{\mu}, 0, 0, 0, 0, \frac{\Pi}{\mu}\right). \tag{5.3}$$

The equations for the rates of change of the infected components (E, I, Q, H) of the linearized version of the system (5.2), at the DFS $(\mathcal{E}_0)$, are given by:

$$\begin{aligned}
\frac{dE}{dt} &= \beta(t)[I(t) + \eta(t)H(t)] - [\kappa(t) + \sigma(t) + \mu]E(t),\\
\frac{dI}{dt} &= \kappa(t)E(t) - [\gamma_1(t) + \phi(t) + \mu + \delta_1]I(t),\\
\frac{dQ}{dt} &= \sigma(t)E(t) - [\alpha(t) + \mu]Q(t),\\
\frac{dH}{dt} &= \alpha(t)Q(t) + \phi(t)I(t) - [\gamma_2(t) + \mu + \delta_2]H(t).
\end{aligned}$$

Using the notation in [91], the next generation matrix $F(t)$ (of new infection terms) and the M-matrix $V(t)$ (of the remaining transition terms) associated with the model (5.2) are given, respectively, by

$$F(t) = \begin{pmatrix} 0 & \beta(t) & 0 & \eta(t)\beta(t) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

and,

$$V(t) = \begin{pmatrix} \kappa(t) + \sigma(t) + \mu & 0 & 0 & 0 \\ -\kappa(t) & \gamma_1(t) + \phi(t) + \mu + \delta_1 & 0 & 0 \\ -\sigma(t) & 0 & \alpha(t) + \mu & 0 \\ 0 & -\phi(t) & -\alpha(t) & \gamma_2(t) + \mu + \delta_2 \end{pmatrix}.$$

Following [91], let Φ_M be the monodromy matrix of the linear ω-periodic system

$$\frac{dZ}{dt} = M(t)Z,$$

and $\rho(\Phi_M(\omega))$ be the spectral radius of $\Phi_M(\omega)$. Further, let

$$Y(t,s), \;\; t \geq s,$$

be the evolution operator of the linear ω-periodic system

$$\frac{dy}{dt} = -V(t)y.$$

In other words, for each $s \in \mathbb{R}$, the associated 4×4 matrix, $Y(t,s)$, satisfies

$$\frac{dY(t,s)}{dt} = -V(t)Y(t,s) \;\; \forall t \geq s, \quad Y(s,s) = I.$$

It is further assumed that $\phi(s)$ (ω-periodic in s) is the initial distribution of infectious individuals. That is, $F(s)\phi(s)$ is the rate at which new infections are produced by infected individuals who were introduced into the population at time s [91]. Since $t \geq s$, it follows then that $Y(t,s)F(s)\phi(s)$ represents the distribution of those infected individuals who were newly-infected at time s, and remain infected at time t.

Hence, the cumulative distribution of new infections at time t, produced by all infected individuals ($\phi(s)$) introduced at a prior time $s = t$, is given by

$$\Psi(t) = \int_{-\infty}^{t} Y(t,s)F(s)\phi(s)ds = \int_{0}^{\infty} Y(t,t-a)F(t-a)\phi(t-a)da.$$

Let $\mathbb{C}_\omega$ be the ordered Banach space of all ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^4$, which is equipped with maximum norm $\|.\|$ and positive cone

$$\mathbb{C}_\omega^+ = \{\phi \in \mathbb{C}_\omega : \;\; \phi(t) \geq 0, \;\; \forall t \in \mathbb{R}\}.$$

Define a linear operator $L : \mathbb{C}_\omega \to \mathbb{C}_\omega$ by [91]

$$(L\phi)(t) = \int_0^\infty Y(t, t-a)F(t-a)\phi(t-a)da \quad \forall t \in \mathbb{R}, \phi \in \mathbb{C}_\omega.$$

The reproduction ratio ($\mathcal{R}_0$) is then given by the spectral radius of L, denoted by $\rho(L)$. That is, $\mathcal{R}_0 = \rho(L)$ [91]. The system (5.2) satisfies the Assumptions A1-A7 in Appendix A (see Appendix B). Thus, using Theorem 2.2 in [91], the following result is established.

Lemma 5.2. *The DFS of the model* (5.2)*, given by* (5.3)*, is locally-asymptotically stable if* $\mathcal{R}_0 < 1$*, and unstable if* $\mathcal{R}_0 > 1$.

It is worth noting that, for the special case of the model (5.2) with $\beta(t) = \beta, \eta(t) = \eta, \kappa(t) = \kappa, \phi(t) = \phi, \alpha(t) = \alpha, \gamma_1(t) = \gamma_1, \gamma_2(t) = \gamma_2$ and $\sigma(t) = \sigma$, the matrices $F(t)$ and $V(t)$, respectively, become

$$F_a = \begin{pmatrix} 0 & \beta & 0 & \eta\beta \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

and,

$$V_a = \begin{pmatrix} \kappa+\sigma+\mu & 0 & 0 & 0 \\ -\kappa & \gamma_1+\phi+\mu+\delta_1 & 0 & 0 \\ -\sigma & 0 & \alpha+\mu & 0 \\ 0 & -\phi & -\alpha & \gamma_2+\mu+\delta_2 \end{pmatrix},$$

so that,

$$\mathcal{R}_0 = \rho(L) = \rho(F_a V_a^{-1})$$
$$= \frac{\beta[\kappa(\mu+\alpha)(\mu+\gamma_2(t)+\delta_2)+\eta\phi\kappa(\mu+\alpha)+\alpha\eta\sigma(\mu+\delta_1+\gamma_1+\phi)]}{(\mu+\kappa+\sigma)(\mu+\delta_1+\gamma_1+\phi)(\mu+\alpha)(\mu+\gamma_2+\delta_2)},$$

which is exactly the same expression obtained for the reproduction number ($\mathcal{R}_c$) of the corresponding autonomous quarantine/isolation model (3.2) given in Section 3.3.

To compute the reproduction ratio $\mathcal{R}_0$, associated with the non-autonomous model (5.2), Theorem 2.1 in [91], reported below, will be used.

Theorem 5.1. *(Wang and Zhao [91]). Let $W(t,\lambda)$ $t \geq 0$ be the standard fundamental matrix of*

$$\frac{dw}{dt} = \left(-V(t) + \frac{1}{\lambda}F(t)\right) w, \quad w \in \mathbb{R}^n, \lambda \in (0,\infty),$$

with $W(0,\lambda) = I$. The following statements are valid:

(i) If $\rho(W(\omega,\lambda)) = 1$ has a positive solution λ_0, then λ_0 is an eigenvalue of L, and hence $\mathcal{R}_0 > 0$;

(ii) If $\mathcal{R}_0 > 0$, then $\lambda = \mathcal{R}_0$ is the unique solution of $\rho(W(\omega,\lambda)) = 1$;

(iii) $\mathcal{R}_0 = 0$ if and only if $\rho(W(\omega,\lambda)) < 1$ for all $\lambda > 0$.

The computation for $\mathcal{R}_0$ is then carried out *via* the following steps [91]:

(a) First of all, for a given value of λ, the matrix $W(\omega,\lambda)$ is numerically computed using a standard numerical integrator (such as the forward-Euler or Runge-Kutta finite-difference method [55]);

(b) Then, the spectral radius $\rho(W(\lambda))$ is calculated;

(c) Let $f(\lambda) = \rho(W(\lambda)) - 1$. Then, a root-finding method (such as the bisection method [55]) is used to find the zero of f;

(d) Let $[\mathcal{R}_0]$ be the reproduction number of the corresponding autonomous system, obtained from the averaging of the system (5.2). That is,

$$[\mathcal{R}_0] = \frac{\bar{\beta}[\bar{\kappa}(\mu+\bar{\alpha})(\mu+\bar{\gamma_2}(t)+\delta_2)+\bar{\eta}\bar{\phi}\bar{\kappa}(\mu+\bar{\alpha})+\bar{\alpha}\bar{\eta}\bar{\sigma}(\mu+\delta_1+\bar{\gamma_1}+\bar{\phi})]}{(\mu+\bar{\kappa}+\bar{\sigma})(\mu+\delta_1+\bar{\gamma_1}+\bar{\phi})(\mu+\bar{\alpha})(\mu+\bar{\gamma_2}+\delta_2)},$$

where,

$$\bar{\beta} = \frac{1}{\omega}\int_0^\omega \beta(t)dt, \quad \bar{\eta} = \frac{1}{\omega}\int_0^\omega \eta(t)dt, \quad \bar{\kappa} = \frac{1}{\omega}\int_0^\omega \kappa(t)dt, \quad \bar{\phi} = \frac{1}{\omega}\int_0^\omega \phi(t)dt$$

$$\bar{\sigma} = \frac{1}{\omega}\int_0^\omega \sigma(t)dt, \quad \bar{\alpha} = \frac{1}{\omega}\int_0^\omega \alpha(t)dt, \quad \bar{\gamma_1} = \frac{1}{\omega}\int_0^\omega \gamma_1(t)dt, \quad \bar{\gamma_2} = \frac{1}{\omega}\int_0^\omega \gamma_2(t)dt;$$

(e) Let $\beta(t)$ be defined by $\beta(t) = \beta_0\left(1.1 + \sin(\frac{\pi(t+1)}{6})\right)$ [62], and the other parameters are as given in Table 3.2 (it should be mentioned that the parameter values chosen in Table 3.2 are largely relevant to the transmission dynamics of severe acute respiratory syndrome (SARS)[15, 16, 23, 38, 48, 61, 64, 67, 73, 90, 93]).

Figure 5.2 shows the curves of the reproduction ratio ($\mathcal{R}_0$) and the average reproduction number $[\mathcal{R}_0]$ as function of β_0. It is clear from this figure that the average reproduction number $[\mathcal{R}_0]$ is either equal or greater than the reproduction ratio for values of β_0 considered. This conclusion is also drawn in [62]. The epidemiological implication of the result in Lemma 5.2 implies that the disease can be eliminated from the community (when $\mathcal{R}_0 < 1$) if the initial sizes of the sub-populations of the model are in the basin of attraction of the DFS ($\mathcal{E}_0$). To ensure that disease elimination is independent of the initial sizes of sub-populations, it is necessary to show that the DFS is globally-asymptotically stable if $\mathcal{R}_0 < 1$. This is explored below.

5.3.2 Global stability

Theorem 5.2. *The DFS of the model* (5.2)*, given by* (5.3)*, is GAS in* $\mathcal{D}$ *whenever* $\mathcal{R}_0 < 1$.

Proof. It is sufficient to prove that $\mathcal{E}_0$ is globally-attractive if $\mathcal{R}_0 < 1$, since it is shown (Lemma 5.2) that $\mathcal{E}_0$ is asymptotically-stable if $\mathcal{R}_0 < 1$. First of all, using the fact that $S(t) \leq N(t)$ for all $t \geq 0$ in $\mathcal{D}$, the non-autonomous system (5.2) can be re-written as

$$\begin{aligned}
\frac{dE}{dt} &\leq \beta(t)[I(t) + \eta(t)H(t))] - [\kappa(t) + \mu]E(t), \\
\frac{dI}{dt} &= \kappa(t)E(t) - [\gamma_1(t) + \phi(t) + \mu + \delta_1]I(t), \\
\frac{dQ}{dt} &= \sigma(t)E(t) - [\alpha(t) + \mu]Q(t), \\
\frac{dH}{dt} &= \alpha(t)Q(t) + \phi(t)I(t) - [\gamma_2(t) + \mu + \delta_2]H(t).
\end{aligned} \tag{5.4}$$

The equations in (5.4), with equality used in place of the inequality, can be re-written in terms of the matrices $F(t)$ and $V(t)$, as follows:

$$\frac{dW}{dt} = [F(t) - V(t)]W(t). \tag{5.5}$$

It follows from Lemma 2.1 in [102] that there exists a positive ω-periodic function, $w(t)$, such that

$$W(t) = e^{\theta t}w(t), \quad \text{with } \theta = \frac{1}{\omega}\ln\rho[\phi_{\mathrm{F-V}}(\omega)],$$

is a solution of (5.5). However, $\mathcal{R}_0 < 1$ implies that $\rho(\phi_{F-V}(\omega)) < 1$ (by Theorem 2.2 in [91]). Hence, θ is a negative constant. Thus, $W(t) \to 0$ as $t \to \infty$. This implies that the trivial solution of system (5.5), given by $W(t) = 0$, is GAS.

For any non-negative initial solution $(E(0), I(0), Q(0), H(0))^T$ of the system (5.5), there exists a sufficiently large $M^* > 0$ such that

$$(E(0), I(0), Q(0), H(0))^T \leq M^* w(0).$$

Thus, by comparison theorem (Theorem 2.8), it follows that

$$(E(t), I(t), Q(t), H(t)) \leq M^* W(t), \quad \text{for all } \ t > 0,$$

where, $M^*W(t)$ is also a solution of (5.5). Hence, $(E(t), I(t), Q(t), H(t)) \to (0, 0, 0, 0)$ as $t \to \infty$. Finally, by Theorem 1.2 in [85], it follows that $N(t) \to \Pi/\mu$ and $S(t) \to \Pi/\mu$ as $t \to \infty$. In summary,

$$\lim_{t\to\infty} [S(t), E(t), I(t), Q(t), H(t), N(t)] \to \mathcal{E}_0, \quad \text{whenever } \ \mathcal{R}_0 < 1.$$

□

The epidemiological implication of Theorem 5.2 is that the combined use of quarantine and isolation can lead to disease elimination in the community (periodic environment) if they can bring (and keep) the threshold quantity, $\mathcal{R}_0$, to a value less than unity (i.e., the condition $\mathcal{R}_0 < 1$ is necessary and sufficient for disease elimination in the periodic environment). Figure 5.3 depicts the numerical results obtained by simulating the model (5.2) using various initial conditions for the case $\mathcal{R}_0 < 1$. It is evident from this figure that all solutions converged to the DFS, $\mathcal{E}_0$ (in line with Theorem 5.2). It is worth mentioning that the DFE of the corresponding autonomous qurantine/isolation model, given by (3.2), was also shown to be globally-asymptotically stable when the associated reproduction number is less than unity (see Theorem 3.2). Thus, this study shows that adding periodicity to the corresponding autonomous quarantine/isolation model (3.2) does not alter the stability properties of the associated disease-free equilibrium of the autonomous model (3.2).

5.4 Uniform-persistence of Periodic Solutions

In this section, the persistence of the infectious population, above a certain positive level for a long time, will be explored. That is, condition(s) for which the disease becomes endemic in the population (periodic environment) will be derived.

Theorem 5.3. *If the reproduction ratio $\mathcal{R}_0 > 1$, then there exists $\epsilon > 0$ such that any solution $(S(t), E(t), Q(t), H(t), N(t))$ of the system (5.2) with initial value $(S^0, E^0, I^0, Q^0, H^0, N^0) \in \{(S, E, I, Q, H, N) \in X : E > 0, I > 0, Q > 0, H > 0\}$ satisfies*

$$\liminf_{t\to\infty} I \geq \epsilon, \quad \liminf_{t\to\infty} E \geq \epsilon, \quad \liminf_{t\to\infty} Q \geq \epsilon, \quad \textit{and} \quad \liminf_{t\to\infty} H \geq \epsilon.$$

Proof. The proof is based on using persistence theory (see, for instance, [102, 104]). This typically entails defining a Poincaré map for the system (5.2), and then showing that the map is bounded, positively-invariant and uniformly-persistent (see also [9, 43, 82, 84, 102, 104]). This is done as follows.

Construction of the Poincaré map

Define,

$$X_0 = \{(S, E, I, Q, H, N) \in X : E > 0, I > 0, Q > 0, H > 0\}, \quad \partial X_0 = X \setminus X_0.$$

Let $P : X \to X$ be the Poincaré map associated with system (5.2). That is,

$$P(x^0) = u(\omega, x^0), \quad \forall x^0 \in X,$$

where, $u(t, x^0)$ is the unique solution of the system (5.2) with $u(0, x^0) = x^0$. It follows that

$$P^m(S^0, E^0, I^0, Q^0, H^0, N^0) = u(m\omega, (S^0, E^0, I^0, Q^0, H^0, N^0)), \quad \forall m \geq 0.$$

It can be shown that the regions X and X_0 (defined in Sections 5.2 and 5.3.2, respectively) are positively-invariant as follows. Let $(S^0, E^0, I^0, Q^0, H^0, N^0) \in X_0$. It follows from the first equation of the system (5.2) that

$$\begin{aligned} S(t) &= e^{-\int_0^t b(s_1)ds_1} \left\{ S^0 + \int_0^t [\Pi + \psi k(s_2)]\, e^{\int_0^{s_2} b(s_1)ds_1} ds_2 \right\}, \\ &\geq \Pi e^{-\int_0^t b(s_1)ds_1} \left\{ \int_0^t e^{\int_0^{s_2} b(s_1)ds_1} ds_2 \right\} > 0, \ \forall t > 0, \end{aligned} \tag{5.6}$$

where,

$$b(t) = \psi + \mu + \frac{\beta(t)[I(t) + \eta(t)H(t)]}{N(t)} \ \text{ and } \ k(s_2) = N(s_2) - E(s_2) - I(s_2) - Q(s_2) - H(s_2).$$

It should be noted that $N(t) \geq S(t) > 0$ for all $t > 0$. Further, since the matrix

$$J = \begin{pmatrix} -[\kappa(t) + \sigma(t) + \mu] & \frac{\beta(t)S}{N} & 0 & \frac{\eta(t)\beta(t)S}{N} \\ \kappa & -([\gamma_1(t) + \phi(t) + \mu + \delta_1] & 0 & 0 \\ \sigma(t) & 0 & -[\alpha(t) + \mu] & 0 \\ 0 & \phi(t) & \alpha(t) & -[\gamma_2(t) + \mu + \delta_2] \end{pmatrix} \tag{5.7}$$

is irreducible and cooperative (see Section 2.3), it follows that $(E, I, Q, H)^T \gg 0 \ \ \forall t > 0$ (see Theorem 2.5). Thus, X and X_0 are positively-invariant, as required. Furthermore, it is clear that ∂X_0 is relatively-close in X. Hence, it follows from Lemma 5.1 that the discrete-time system $\{P^m\}$ has a global attractor in X.

To prove that P is uniformly-persistent with respect to $(X_0, \partial X_0)$, it is necessary to show that P is weakly uniformly-persistent (since X and X_0 are positively-invariant). Following [102], let

$M_\partial = \{(S^0, E^0, I^0, Q^0, H^0, N^0) \in \partial X_0 : P^m(S^0, E^0, I^0, Q^0, H^0, N^0) \in \partial X_0, \forall m \geq 0\}$.

Lemma 5.3.

$$M_\partial = \{(S, 0, 0, 0, 0, N) \in X : S \geq 0, N \geq 0\}. \tag{5.8}$$

Proof. It suffices to prove that for any $(S^0, E^0, I^0, Q^0, H^0, N^0) \in M_\partial$, then $E(m\omega) = I(m\omega) = Q(m\omega) = H(m\omega) = 0, \forall m \geq 0$. This is shown by contradiction as follows [102]. Assume that there exists an $m_1 \geq 0$ such that $(E(m_1\omega), I(m_1\omega), Q(m_1\omega), H(m_1\omega))^T > 0$. Since $S(t) > 0, \ \forall t > 0$, it follows that (by replacing the initial time 0 with $m_1\omega$)

$$N(t) \geq S(t) > 0, \ \ \forall t > m_1\omega.$$

Similarly, by Theorem 2.5 (as generalized to non-autonomous systems), it follows that

$$(E(t), I(t), Q(t), H(t)) \gg 0 \ \ \forall t > m_1\omega,$$

which contradicts the fact that $M_\partial \subset X_0$. Thus, there is no $m_1 \geq 0$ such that $(E(m_1\omega), I(m_1\omega), Q(m_1\omega), H(m_1\omega))^T > 0$. Hence, the definition (5.8) holds. Thus, there is exactly one fixed-point, $\mathcal{E}_0 = (\Pi/\mu, 0, 0, 0, 0, \Pi/\mu)$, of P in M_∂. □

Weakly uniformly-persistence

Lemma 5.4. *P is weakly uniformly-persistent with respect to $(X_0, \partial X_0)$. That is, there exists $\epsilon^* > 0$ such that*

$$\lim_{m\to\infty} \sup d(P^m(S^0, E^0, I^0, Q^0, H^0, N^0), \mathcal{E}_0) \geq \epsilon^*, \ \ \forall (S^0, E^0, I^0, Q^0, H^0, N^0) \in X_0. \tag{5.9}$$

Proof. The proof is based on using the method in [102]. Assume, by contradiction, that the inequality (5.9) does not hold. Then,

$$\lim_{m\to\infty} \sup d(P^m(S^0, E^0, I^0, Q^0, H^0, N^0), \mathcal{E}_0) < \epsilon^*,$$

for some $(S^0, E^0, I^0, Q^0, H^0, N^0) \in X_0$ and all $\epsilon^* > 0$. Without loss of generality, let

$$d(P^m(S^0, E^0, I^0, Q^0, H^0, N^0), \mathcal{E}_0) < \epsilon^* \text{ for all } m \geq 0.$$

Hence, by the continuity of the solutions of the system (5.2) with respect to the initial values,

$$\|u(t, P^m(S^0, E^0, I^0, Q^0, H^0, N^0)) - u(t, \mathcal{E}_0)\| < \epsilon, \ \ \forall m \geq 0, \quad \forall t \in [0, \omega] \text{ for some } \epsilon > 0.$$

It follows, by the properties of the Poincaré map (see Section 2.7), for any $t \geq 0$ such that $t = m\omega + \acute{t}$ (where $\acute{t} \in [0, \omega)$ and m is the largest positive integer less than or equal to $\frac{t}{\omega}$), that

$$\|u(t, (S^0, E^0, I^0, Q^0, H^0, N^0)) - u(t, \mathcal{E}_0)\|$$

$$= \|u(\acute{t}, P^m(S^0, E^0, I^0, Q^0, H^0, N^0)) - u(\acute{t}, \mathcal{E}_0)\|$$

$$< \epsilon, \quad \forall t \geq 0.$$

Hence, it follows that

$$E(t) < \epsilon, I(t) < \epsilon, Q(t) < \epsilon, H(t) < \epsilon, \forall t \geq 0. \tag{5.10}$$

Noting the inequalities in (5.10), the equation for $\dfrac{dS}{dt}$ in (5.2) can be expressed as:

$$\frac{dS}{dt} \geq \Pi - \frac{\beta(t)S[\epsilon + \eta(t)\epsilon]}{N} + \psi(N - S - 4\epsilon) - \mu S,$$

$$\geq \Pi - \epsilon\beta(t)(1 + \eta(t)) - 4\psi\epsilon - \mu S. \tag{5.11}$$

Consider, next, the auxiliary (with equality) equation of the system (5.11)

$$\frac{d\hat{S}(t)}{dt} = \Pi - \epsilon\beta(t)[1 + \eta(t)] - 4\psi\epsilon - \mu\hat{S(t)}. \tag{5.12}$$

Thus, the system (5.12) has a unique periodic solution ($\hat{S}^*(t, \epsilon)$). It can be shown that $\hat{S}^*(t, \epsilon)$ is globally-attractive on $\mathbb{R}_+$ as follows. The equation (5.12) has a unique periodic solution given by

$$\hat{S}^*(t, \epsilon) = e^{-\mu t}\left\{\hat{S}^*(0, \epsilon) + \int_0^t e^{\mu s}[\Pi - \epsilon\beta(s)(1 + \eta(s)) - 4\psi\epsilon]ds\right\}, \tag{5.13}$$

where, $\hat{S}^*(0, \epsilon)$ is found by substituting $t = \omega$ in (5.13) (and noting that $\hat{S}^*(\omega, \epsilon) = \hat{S}^*(0, \epsilon)$). Hence,

$$\hat{S}^*(0, \epsilon) = \frac{\int_0^\omega e^{\mu s}\{\Pi - \epsilon\beta(s)[1 + \eta(s)] - 4\psi\epsilon\}ds}{e^{\mu\omega} - 1}.$$

Clearly, $|\hat{S}(t, \epsilon) - \hat{S}^*(t, \epsilon)| \to 0$ as $t \to \infty$. Thus, $\hat{S}^*(t, \epsilon)$ is globally attractive on $\mathbb{R}_+$.

It can be seen, from the form of $\hat{S}^*(0, \epsilon)$, that $\hat{S}^*(0, \epsilon)$ is continuous in ϵ. Hence, fixed values of ϵ, ν, small enough, can be chosen such that

$$\hat{S}^*(t, \epsilon) > S_* - \nu, \ \ \forall t \in [0, \omega],$$

where $S_* = \pi/\mu$ is the unique steady-state solution of the equation $\dfrac{d\bar{S}}{dt} = \Pi - \mu\bar{S}$,

which is globally-attractive in $\mathbb{R}_+$.

By the periodicity of $\hat{S}^*(t,\epsilon)$, together with the fact $S_* - \nu$ is constant, it follows that the inequality

$$\hat{S}^*(t,\epsilon) > S_* - \nu$$

holds for sufficiently small ϵ and ν and $t \geq 0$. Since the periodic solution $\hat{S}^*(t,\epsilon)$, of equation (5.12), is globally-attractive on $\mathbb{R}_+$, and $\hat{S}^*(t,\epsilon) > S_* - \nu$, it follows that $S(t) > S_* - \nu$ for sufficiently large t. Furthermore, it is clear from the last equation of the system (5.2) that

$$N(t) \leq \frac{\Pi}{\mu} + \nu, \text{ for sufficiently large } t.$$

Similarly, it follows from the second, third, fourth and fifth equations of the system (5.2), for sufficiently large t, that

$$\begin{aligned}
\frac{dE}{dt} &\geq \beta(t)\left(1 - \frac{2\nu}{\Pi/\mu + \nu}\right)[I + \eta(t)H] - (\kappa(t) + \mu)E(t),\\
\frac{dI}{dt} &= \kappa(t)E(t) - [\gamma_1(t) + \phi(t) + \mu + \delta_1]I(t),\\
\frac{dQ}{dt} &= \sigma(t)E(t) - [\alpha(t) + \mu]Q(t),\\
\frac{dH}{dt} &= \alpha(t)Q(t) + \phi(t)I(t) - [\gamma_2(t) + \mu + \delta_2]H(t).
\end{aligned} \tag{5.14}$$

Consider, now, the case when the inequality in (5.14) is replaced by equality, giving

$$\frac{d\hat{E}}{dt} = \beta(t)\left(1 - \tfrac{2\nu}{\Pi/\mu+\nu}\right)\left[\hat{I}(t) + \eta(t)\hat{H}(t)\right] - [\kappa(t) + \mu]\hat{E}(t). \tag{5.15}$$

It follows from Lemma 2.1 in [102] that there exists a positive, ω-periodic function

$(\bar{E}(t), \bar{I}(t), \bar{Q}(t), \bar{H}(t))^T$ such that

$$(\hat{E}(t), \hat{I}(t), \hat{Q}(t), \hat{H}(t))^T = e^{\zeta t}(\bar{E}(t), \bar{I}(t), \bar{Q}(t), \bar{H}(t))^T,$$

is a solution of system (5.15), where

$$\zeta = \frac{1}{\omega} \ln \rho(\Phi_{F-V-M_\nu}(\omega)),$$

and,

$$M_\nu = \begin{pmatrix} 0 & \dfrac{2\nu\beta(t)}{\Pi/\mu + \nu} & 0 & \dfrac{2\nu\eta(t)\beta(t)}{\Pi/\mu + \nu} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Since $\mathcal{R}_0 > 1$ implies that $\rho(\Phi_{F-V}(\omega)) > 1$, a small enough $\nu > 0$ can be chosen such that $\rho(\Phi_{F-V-M_\nu}(\omega)) > 1$. That is, ζ is a positive constant.

Let $t = n\omega$ and n be a non-negative integer. Hence,

$$(\hat{E}(n\omega), \hat{I}(n\omega), \hat{Q}(n\omega), \hat{H}(n\omega))^T = e^{\zeta n\omega}(\bar{E}(n\omega), \bar{I}(n\omega), \bar{Q}(n\omega), \bar{H}(n\omega))^T \to (\infty, \infty, \infty, \infty)^T,$$

as $n \to \infty$, since $\omega\zeta > 0$ and $(\bar{E}(t), \bar{I}(t), \bar{Q}(t), \bar{H}(t))^T > 0$. For any non-negative initial condition $(E(0), I(0), Q(0), H(0))^T$, of system (5.14), there exists $m^* > 0$ sufficiently small such that

$$(E(0), I(0), Q(0), H(0))^T \geq m^*(\bar{E}(0), \bar{I}(0), \bar{Q}(0), \bar{H}(0))^T.$$

It follows, by comparison theorem (Theorem 2.8), that

$$(E(t), I(t), Q(t), H(t))^T \geq m^*(E(t), I(t), Q(t), H(t))^T, \text{ for all } t > 0.$$

Thus,

$$E(n\omega) \to \infty, I(n\omega) \to \infty, Q(n\omega) \to \infty \text{ and } H(n\omega) \to \infty,$$

which contradicts the inequalities given in (5.10). Hence, P is weakly uniformly-persistent with respect to $(X_0, \partial X_0)$.

□

Uniform-persistence of solutions

It follows from Theorems 2.13 and 2.14 that P is uniformly-persistent with respect to $(X_0, \partial X_0)$. Furthermore, by Theorem 2.15, the solutions of the system (5.2) are uniformly-persistent with respect to $(X_0, \partial X_0)$. That is, there exists $\epsilon > 0$ such that any solution $(S(t), E(t), I(t), Q(t), H(t), N(t))$ of the system (5.2) with initial value $(S^0, E^0, I^0, Q^0, H^0, N^0) \in X_0$ satisfies

$$\liminf_{t\to\infty} I \geq \epsilon, \ \liminf_{t\to\infty} E \geq \epsilon, \ \liminf_{t\to\infty} Q \geq \epsilon, \text{ and } \liminf_{t\to\infty} H \geq \epsilon.$$

□

The epidemiological implication of Theorem 5.3 is that the disease will persist in the population if $\mathcal{R}_0 > 1$.

5.5 Existence and Stability of Periodic Solution

In this section, the possible existence and stability of non-trivial periodic solutions of the system (5.2) will be explored. Theorem 2.16 will be used to achieve this objective.

Theorem 5.4. *The system* (5.2) *(or, equivalently,* (5.1)*) has a periodic solution in* X_0*, which is GAS in* X_0 *whenever* $\mathcal{R}_0 > 1$ *and* $sign(S - S^*) = sign(E - E^*) =$

$sign(I - I^*) = sign(Q - Q^*) = sign(H - H^*) = sign(R - R^*)$.

Proof. The proof of the existence part is based on the method in [102]. It follows from Lemma 5.1 that the solutions of the model (5.2) are ultimately-bounded. Thus, P is point-dissipative on $\mathbb{R}^6_+$ and $P : \mathbb{R}^6_+ \to \mathbb{R}^6_+$. Furthermore, P is uniformly-persistent with respect to $(X_0, \partial X_0)$ whenever $\mathcal{R}_0 > 1$ (Theorem 5.3). Then, it follows from Theorem 2.16 that P has a fixed-point

$$[S^*(t), E^*(t), I^*(t), Q^*(t), H^*(t), N^*(t)] \in Int(\mathbb{R}^6_+).$$

Hence, $[S^*(t), E^*(t), I^*(t), Q^*(t), H^*(t), N^*(t)]$ is a positive ω-periodic solution of the system (5.2). This shows the existence part.

For the stability part, it is convenient to consider the system (5.1) (since it is also equivalent to the system (5.2)). Let,

$$\mathcal{E}_1 = [S^*(t), E^*(t), I^*(t), Q^*(t), H^*(t), R^*(t)],$$

be a positive ω-periodic solution of the system (5.1). To prove that the periodic solution is globally-asymptotically stable, consider the following Lyapunov function (Lyapunov functions of this type have been used in the literature, such as [96, 101]):

$$\begin{aligned} G = &|S(t) - S^*(t)| + |E(t) - E^*(t)| + |I(t) - I^*(t)| + |Q(t) - Q^*(t)| \\ &+ |H(t) - H^*(t)| + |R(t) - R^*(t)|, \end{aligned}$$

where $[S^*(t), E^*(t), I^*(t), Q^*(t), H^*(t), R^*(t)]$ is any solution of the system (5.1).

The right derivative, D^+G, of G, along the solutions of (5.1), is given by:

$$\begin{aligned}
D^+G =& sign\,[S(t)-S^*(t)]\,\{\psi[R(t)-R^*(t)]-\lambda(t)S(t)-\mu[S(t)-S^*(t)]+\lambda^*(t)S^*(t)\}\\
&+sign\,[E(t)-E^*(t)]\,\{\lambda(t)S(t)-[\kappa(t)+\sigma(t)+\mu][E(t)-E^*(t)]-\lambda^*(t)S^*(t)\}\\
&+sign\,[I(t)-I^*(t)]\,\{\kappa(t)[E(t)-E^*(t)]-[\gamma_1(t)+\phi(t)+\mu+\delta_1][I(t)-I^*(t)]\}\\
&+sign\,[Q(t)-Q^*(t)]\,\{\sigma(t)[E(t)-E^*(t)]-[\alpha(t)+\mu][Q(t)-Q^*(t)]\}\\
&+sign\,[H(t)-H^*(t)]\,\big\{\alpha(t)[Q(t)-Q^*(t)]+\phi(t)[I(t)-I^*(t)]\\
&\quad-[\gamma_2(t)+\mu+\delta_2][H(t)-H^*(t)]\big\}+sign\,[R(t)-R^*(t)]\,\big\{\gamma_1(t)[I(t)-I^*(t)]\\
&\quad+\gamma_2(t)[H(t)-H^*(t)]-(\psi+\mu)[R(t)-R^*(t)]\big\}
\end{aligned}$$

with,

$$\lambda(t)=\frac{\beta(t)S(t)[I(t)+\eta(t)H(t)]}{N(t)}\quad\text{and}\quad\lambda^*(t)=\frac{\beta(t)S^*(t)[I^*(t)+\eta(t)H^*(t)]}{N^*(t)}.$$

Using the fact that $sign(S-S^*)=sign(E-E^*)=sign(I-I^*)=sign(Q-Q^*)=sign(H-H^*)=sign(R-R^*)$, it follows that

$$\begin{aligned}
D^+G =& -\mu\,|S(t)-S^*(t)|-\mu\,|E(t)-E^*(t)|-(\mu+\delta_1)\,|I(t)-I^*(t)|-\mu\,|Q(t)-Q^*(t)|\\
&-(\mu+\delta_2)\,|H(t)-H^*(t)|-\mu\,|R(t)-R^*(t)|\,,\\
\\
&\leq -\mu\,|S(t)-S^*(t)|-\mu\,|E(t)-E^*(t)|-\mu\,|I(t)-I^*(t)|-\mu\,|Q(t)-Q^*(t)|\\
&-\mu\,|H(t)-H^*(t)|-\mu\,|R(t)-R^*(t)|\,,\\
\\
&=-\mu G(t).
\end{aligned}$$

Hence, $\lim_{t\to\infty} G(t)=0$. Thus, the non-trivial periodic solution, $\mathcal{E}_1$, of (5.1) is GAS in X_0

whenever $\mathcal{R}_0 > 1$ and $sign(S - S^*) = sign(E - E^*) = sign(I - I^*) = sign(Q - Q^*) = sign(H - H^*) = sign(R - R^*)$. □

Theorem 5.4 guarantees the persistence of the disease in the population whenever $\mathcal{R}_0 > 1$ and $sign(S - S^*) = sign(E - E^*) = sign(I - I^*) = sign(Q - Q^*) = sign(H - H^*) = sign(R - R^*)$. It should be stated that the condition $sign(S - S^*) = sign(E - E^*) = sign(I - I^*) = sign(Q - Q^*) = sign(H - H^*) = sign(R - R^*)$ is somewhat restrictive (but it is necessary for the proof to work). Figure 5.4 shows a time series plot of the total number of infected individuals for two sets of initial conditions. It should be mentioned that the solutions did not converge to zero as they appear to in Figure 5.4 (see Figure 5.5 for a depiction of the zoomed version of the tail end of Figure 5.4). Figures 5.4 and 5.5 clearly show convergence of the solutions to the non-trivial periodic solution for the case $\mathcal{R}_0 > 1$ (in line with Theorem 5.4). Phase portraits of the solutions are also provided (Figure 5.6). Figure 5.7 shows the fixed-points of the Poincaré map associated with the system (5.2). The fixed-points of the Poincaré map are numerically computed as follows:

(i) For each value of β_0, the model is run 5000 times, and the transient solutions are removed by discarding the first 4900 iterates;

(ii) An arbitrary point (typically the first local maximum) is picked out of the remaining 100 iterates;

(iii) A time period of 12 days (arbitrarily) is selected;

(iv) The fixed-points of the Poincaré map are plotted, starting from the first local maximum.

For all the 8 iterations carried out, the local maxima (corresponding to each period) are the same (as plotted in Figure 5.7). Furthermore, it is clear from Figure 5.7 that for $\beta_0 < \beta_{0c}$ (i.e., $\mathcal{R}_0 < 1$), the map has a unique trivial fixed-point (corresponding

to the trivial solution, DFS.) Furthermore, for $\beta_0 > \beta_{0c}$ (i.e., $\mathcal{R}_0 > 1$), the map has a unique non-trivial fixed-point (corresponding to the non-trivial periodic solution). Hence, the system (5.2) undergoes a forward (transcritical) bifurcation at $\beta_0 = \beta_{0c}$ (for the parameter values used in the simulations, this bifurcation occurs at the point $\beta_0 = \beta_{0c} \backsimeq 0.112$). It should be recalled from Figure 5.2 that, for $\beta_0 = \beta_{0c} \backsimeq 0.112, \mathcal{R}_0 \backsimeq 1$ (which is in line with the simulation results depicted in Figure 5.7). A detailed bifurcation diagram of the periodic solution is given in Figure 5.8 (this figure is plotted using the same approach as that of Figure 5.7, except that the absolute minimum and maximum of the number of infectious individuals in class I, denoted by $I_{\min}$ and $I_{\max}$, are depicted). Clearly, Figure 5.8 shows that β_0 must exceed a critical value for the disease to persist in the population ($\beta_0 > \beta_{0c} = 0.112$).

Additional numerical simulations of the model (5.2) suggest that the family of periodic solutions ($\mathcal{E}_1$) is GAS in X_0 whenever $\mathcal{R}_0 > 1$. This suggests the following conjecture.

Conjecture. *The periodic solution ($\mathcal{E}_1$), of the system* (5.2)*, is GAS in X_0 whenever $\mathcal{R}_0 > 1$.*

5.6 Summary

This chapter addresses the problem of assessing the impact of periodicity on the transmission dynamics of a disease that is controllable using quarantine and isolation. The model given in Chapter 3 is extended to incorporate the effect of periodicity. The resulting non-autonomous model is rigorously analysed and also numerically simulated using data consistent with the 2003 SARS outbreaks. The main findings of this chapter are summarized below:

(i) The non-autonomous model (5.2) has a globally-asymptotically stable disease-free solution whenever the associated reproduction ratio ($\mathcal{R}_0$) of the model is less

than unity (Theorem 5.2);

(ii) The model has a positive periodic solution whenever the reproduction ratio ($\mathcal{R}_0$) exceeds unity (Theorem 5.4);

(iii) Any solution of the model (5.2) is uniformly-persistent whenever the reproduction ratio ($\mathcal{R}_0$) exceeds unity (Theorem 5.3);

(iv) The model (5.2) has a globally-asymptotically stable non-trivial periodic solution for a special case (Theorem 5.4);

(v) Numerical simulations of the model show that the associated average basic reproduction number is always greater than the basic reproduction ratio (Figure 5.2).

In summary, the theoretical analyses of this chapter show that adding periodicity to the non-autonomous quarantine/isolation model (3.2) does not really alter the transmission dynamics of the disease (*vis-a-vis* the persistence or elimination of the disease). In both the autonomous and the non-autonomous quarantine/isolation models considered, the disease dies out if the associated reproduction threshold is less than unity, and persists if the threshold exceeds unity.

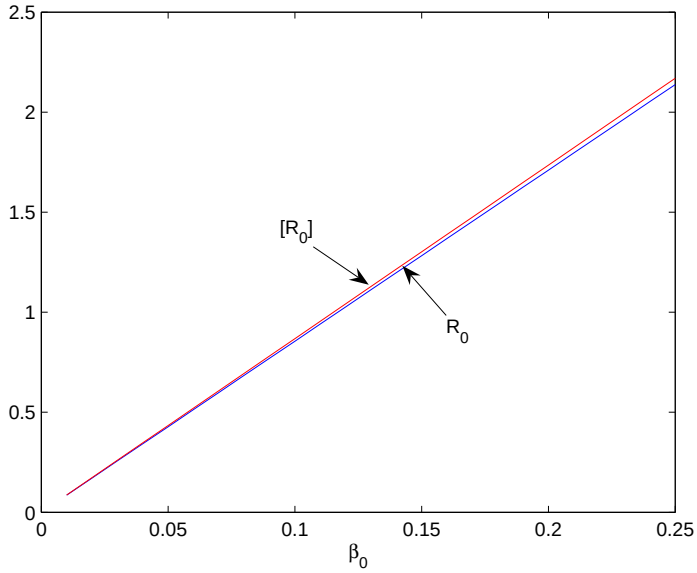


Figure 5.2: Simulation of the model (5.2) showing the basic reproduction ratio $\mathcal{R}_0$. and the average basic reproduction number $[\mathcal{R}_0]$ as a function of $\beta_0 \in [0.01, 0.25]$. Parameter values used are as given in Table 3.2.

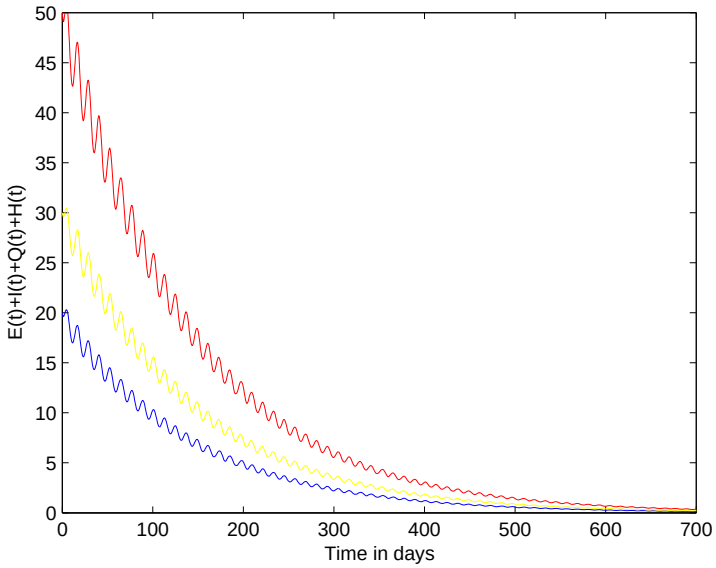


Figure 5.3: Simulation of the model (5.2) showing the total number of infected individuals as a function of time for $\mathcal{R}_0 < 1$. Parameter values used are as given in Table 3.2, with $\beta_0 = 0.1$, (so that, $\mathcal{R}_0 = 0.8551$.)

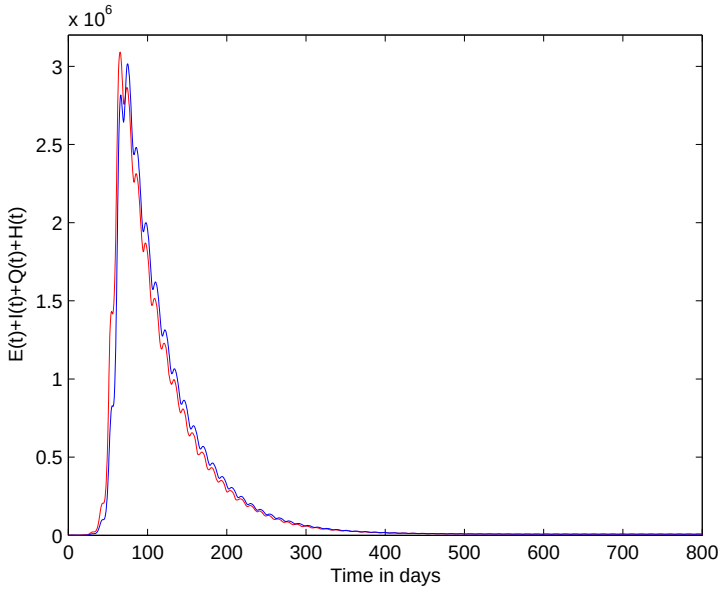


Figure 5.4: Simulations of the model (5.2) showing the total number of infected individuals as a function of time . Parameter values used are as given in Table 3.2, with $\beta_0 = 1$ (so that, $\mathcal{R}_0 > 1$).

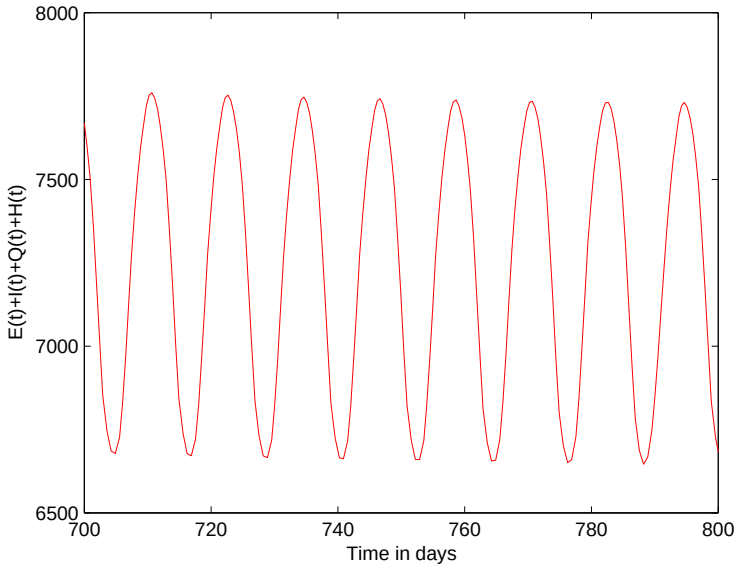


Figure 5.5: Blow up of the tail end of Figure 5.4.

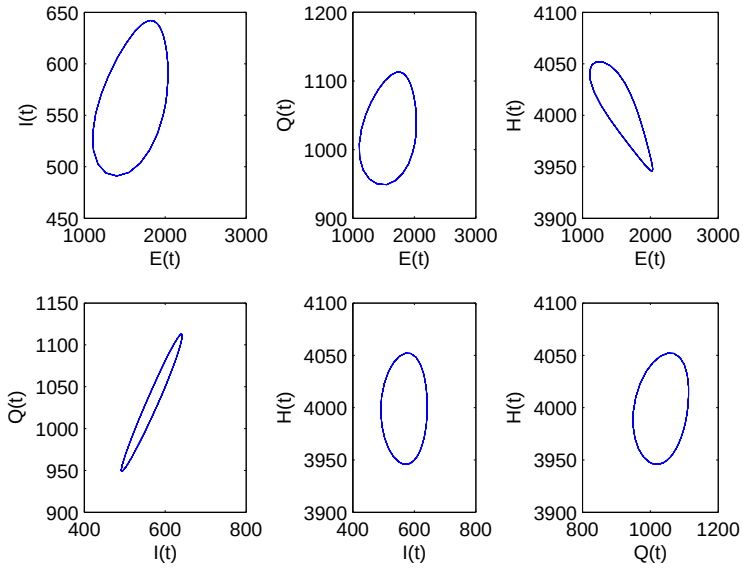


Figure 5.6: Phase portraits of the model (5.2). Parameter values used are as given in Table 3.2, with $\beta_0 = 1.6$ (so that, $\mathcal{R}_0 > 1$).

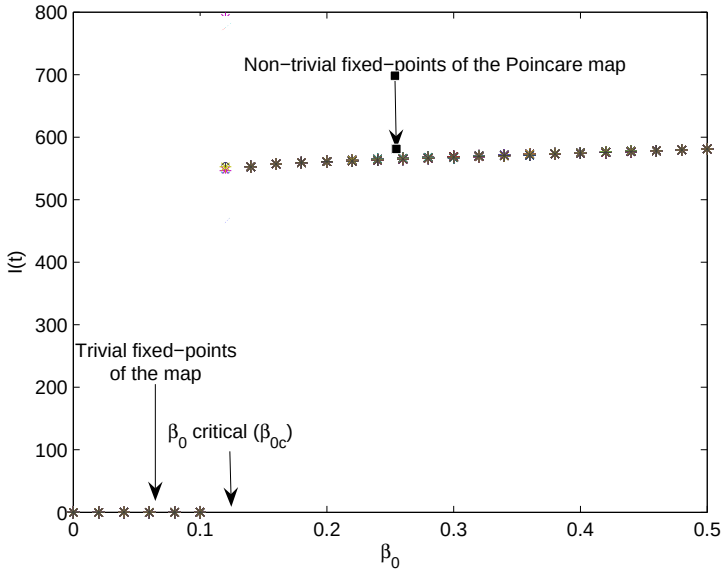


Figure 5.7: Simulations of the model (5.2) showing the fixed-points the Poincaré map as β_0 varies from 0 to 0.5. Parameter values used are as given in Table 3.2.

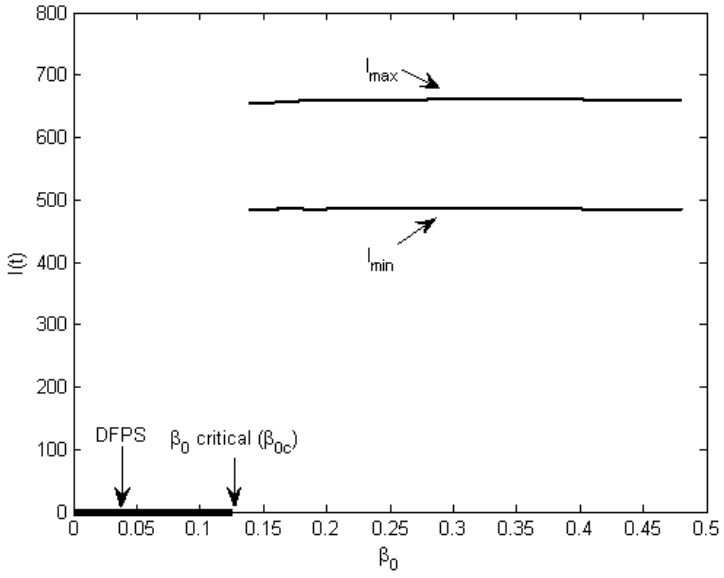


Figure 5.8: Bifurcation diagram of the non-trivial periodic solution showing the number of infectious individuals in class I as a function of $\beta_0 \in [0, 0.5]$. Parameter values used are as given in Table 3.2.

Chapter 6

Quarantine/Isolation Model with an Imperfect Vaccine

6.1 Introduction and Model Formulation

The purpose of this chapter is to qualitatively (and quantitatively) assess the combined impact of quarantine, isolation and an imperfect vaccine in the control of the spread of a communicable disease in a population. Such non-pharmaceutical [14] and pharmaceutical [88] interventions have been applied (singly or in combinations) to control the spread of a number of diseases, such as SARS [73] and the 2009 swine influenza pandemic [36]. This chapter is based on the use of a new deterministic model, which extends the quarantine/isolation model (3.2) by incorporating an imperfect vaccine.

The model is designed by splitting the total human population at time t, denoted by $N(t)$; into mutually-exclusive compartments of unvaccinated susceptible ($S(t)$), vaccinated susceptible ($V(t)$), unvaccinated exposed ($E(t)$), exposed vaccinated ($E_V(t)$), unvaccinated infectious ($I(t)$), vaccinated infectious ($I_V(t)$), quarantined un- vaccinated ($Q(t)$), vaccinated quarantined ($Q_V(t)$), unvaccinated hospitalized ($H(t)$), vaccinated hospitalized ($H_V(t)$), unvaccinated recovered ($R(t)$) and vaccinated recovered

($R_V(t)$) individuals, so that (it should be mentioned that the terms "susceptible" and "unvaccinated susceptible" are used interchangeably)

$$N(t) = S(t)+V(t)+E(t)+E_V(t)+I(t)+I_V(t)+Q(t)+Q_V(t)+H(t)+H_V(t)+R(t)+R_V(t).$$

The equations of the model are obtained as follows. Individuals are recruited into the population (assumed susceptible) at a rate Π. A fraction, ρ, of these newly-recruited individuals, are vaccinated. Further, susceptible individuals are vaccinated at a rate ζ, and the vaccine is assumed to wane at a rate ψ. Unvaccinated susceptible individuals may acquire infection, following effective contact with infectious individuals at a rate λ, where

$$\lambda = \frac{\beta(I + \nu_1 I_V + \eta H + \nu_2 H_V)}{N}. \tag{6.1}$$

In (6.1), the parameter β is the effective contact rate, while $0 \leq \eta < 1$ is the modification parameter which accounts for the assumed reduction in disease transmission by unvaccinated hospitalized individuals (in the H class) in comparison to non-hospitalized infectious individuals (in the I class), and $0 \leq \nu_1, \nu_2 < 1$ are the modification parameters accounting for the vaccine-induced reduction of infectiousness for vaccinated individuals (in the I_V and H_V classes) in comparison to unvaccinated infectious individuals (in the I and H classes). Furthermore, it is assumed that the vaccine is imperfect, so that vaccinated individuals can acquire break-through infection at a reduced rate $(1 - \varepsilon)\lambda$, where $0 < \varepsilon < 1$ represents the vaccine efficacy. The populations of unvaccinated and vaccinated susceptible individuals are decreased by natural death, at a rate μ.

Thus, the rates of change of the populations of susceptible and vaccinated individuals are given, respectively, by

$$\frac{dS}{dt} = (1-\rho)\Pi + \psi V - \lambda S - (\zeta + \mu)S,$$
$$\frac{dV}{dt} = \rho\Pi + \zeta S - (1-\varepsilon)\lambda V - (\psi + \mu)V.$$

The population of unvaccinated exposed individuals is generated by the infection of susceptible individuals (at the rate λ) and is decreased by the development of disease symptoms (at a rate κ), quarantine (at a rate σ) and natural death (at the rate μ), so that

$$\frac{dE}{dt} = \lambda S - (\kappa + \sigma + \mu)E.$$

Similarly, the population of exposed vaccinated individuals is generated by the breakthrough infection of vaccinated individuals (at the rate $(1-\varepsilon)\lambda$) and is decreased by the development of disease symptoms (at a rate $\theta_1\kappa$, where $0 < \theta_1 < 1$ accounts for the reduction in the rate of development of symptoms for vaccinated exposed individuals in relation to unvaccinated individuals), quarantine (at a rate σ_1) and natural death (at the rate μ), so that

$$\frac{dE_V}{dt} = (1-\varepsilon)\lambda V - (\theta_1\kappa + \sigma_1 + \mu)E_V.$$

The population of infectious unvaccinated individuals is generated by the development of symptoms of unvaccinated exposed individuals (at the rate κ). It is decreased by natural recovery (at a rate γ_1), hospitalization (at a rate ϕ), natural death (at the rate μ) and disease-induced death (at a rate δ_1). This gives

$$\frac{dI}{dt} = \kappa E - (\gamma_1 + \phi + \mu + \delta_1)I.$$

The population of vaccinated infectious individuals is generated at the rate $\theta_1\kappa$, and is

decreased by natural recovery (at a rate $\theta_2\gamma_1$, where $\theta_2 > 1$ accounts for the assumption that vaccinated infectious individuals recover at a faster rate in comparison to unvaccinated infectious individuals), hospitalization (at a rate $\theta_3\phi$, where $0 < \theta_3 < 1$, represents the relative reduction in hospitalization rate of vaccinated infectious individuals in comparison to unvaccinated infectious individuals), natural death (at the rate μ) and disease-induced death (at a rate $\theta_4\delta_1$, where $0 < \theta_4 < 1$ accounts for the assumption that vaccinated individuals have reduced disease-induced mortality in comparison to unvaccinated infectious individuals, so that

$$\frac{dI_V}{dt} = \theta_1\kappa E_V - (\theta_2\gamma_1 + \theta_3\phi + \mu + \theta_4\delta_1)I_V.$$

Unvaccinated exposed individuals are quarantined at the rate σ. The population of unvaccinated quarantined individuals is decreased by hospitalization (at a rate α) and natural death (at the rate μ). Thus,

$$\frac{dQ}{dt} = \sigma E - (\alpha + \mu)Q.$$

Similarly, exposed vaccinated individuals are quarantined at the rate σ_1. The population of quarantined vaccinated individuals is decreased by hospitalization (at a rate $\theta_5\alpha$, where $0 < \theta_5 < 1$ accounts for the assumption that quarantined vaccinated individuals are hospitalized at a slower rate in comparison to unvaccinated quarantined individuals) and natural death (at the rate μ). Thus,

$$\frac{dQ_V}{dt} = \sigma_1 E_V - (\theta_5\alpha + \mu)Q_V.$$

The population of unvaccinated hospitalized individuals is generated by the hospitalization of unvaccinated quarantined individuals (at the rate α) and unvaccinated symptomatic individuals (at the rate ϕ). This population is decreased by recovery (at

a rate γ_2), natural death (at the rate μ) and disease-induced death (at a rate $\delta_2 < \delta_1$). It is assumed that hospitalized individuals (vaccinated or unvaccinated) have reduced disease-induced mortality rate in comparison to non-hospitalized infectious individuals because of the hospital care (e.g., treatment) given to individuals in the former (hospitalized) class. Hence,

$$\frac{dH}{dt} = \alpha Q + \phi I - (\gamma_2 + \mu + \delta_2)H.$$

Similarly, the population of vaccinated hospitalized individuals is generated by the hospitalization of vaccinated quarantined individuals (at the rate $\theta_5\alpha$) and vaccinated infectious individuals (at the rate $\theta_3\phi$). It is decreased by recovery (at a rate $\theta_6\gamma_2$, where $\theta_6 > 1$ accounts for the assumption that vaccinated infectious individuals recover at a faster rate than unvaccinated infectious individuals), natural death (at the rate μ) and disease-induced death (at a rate $\theta_7\delta_2 < \theta_4\delta_1$, where $0 < \theta_7 < 1$ accounts for the assumed reduction of disease-related mortality of vaccinated hospitalized individuals in comparison to unvaccinated hospitalized individuals). Thus,

$$\frac{dH_V}{dt} = \theta_5\alpha Q_V + \theta_3\phi I_V - (\theta_6\gamma_2 + \mu + \theta_7\delta_2)H_V.$$

The population of unvaccinated recovered individuals is generated by the recovery of unvaccinated non-hospitalized and unvaccinated hospitalized infectious individuals (at the rates γ_1 and γ_2, respectively). It is decreased by natural death (at the rate μ), so that

$$\frac{dR}{dt} = \gamma_1 I + \gamma_2 H - \mu R.$$

Finally, the population of recovered vaccinated individuals is generated by the recovery of vaccinated non-hospitalized and vaccinated hospitalized infectious individuals (at the

rates $\theta_2\gamma_1$ and $\theta_6\gamma_2$, respectively). This population is decreased by natural death (at the rate μ), so that

$$\frac{dR_V}{dt} = \theta_2\gamma_1 I_V + \theta_6\gamma_2 H_V - \mu R_V.$$

Unlike in the basic quarantine/isolation model (3.2), it is assumed (for mathematical tractability) that recovered individuals acquire permanent immunity against re-infection (so that recovered individuals do not return to the susceptible class). Combining the aforementioned derivations and assumptions, it follows that the model for the transmission dynamics of an infectious disease, in the presence of an imperfect vaccine, quarantine of exposed individuals and isolation of infectious individuals, is given by the following non-linear system of differential equations (a flow diagram is given in Figure 6.1; and the associated variables and parameters are described in Tables 6.1 and 6.2):

$$
\begin{aligned}
\frac{dS}{dt} &= (1-\rho)\Pi + \psi V - \lambda S - (\zeta+\mu)S,\\
\frac{dV}{dt} &= \rho\Pi + \zeta S - (1-\varepsilon)\lambda V - (\psi+\mu)V,\\
\frac{dE}{dt} &= \lambda S - (\kappa+\sigma+\mu)E,\\
\frac{dE_V}{dt} &= (1-\varepsilon)\lambda V - (\theta_1\kappa+\sigma_1+\mu)E_V,\\
\frac{dI}{dt} &= \kappa E - (\gamma_1+\phi+\mu+\delta_1)I,\\
\frac{dI_V}{dt} &= \theta_1\kappa E_V - (\theta_2\gamma_1+\theta_3\phi+\mu+\theta_4\delta_1)I_V,\\
\frac{dQ}{dt} &= \sigma E - (\alpha+\mu)Q,\\
\frac{dQ_V}{dt} &= \sigma_1 E_V - (\theta_5\alpha+\mu)Q_V,\\
\frac{dH}{dt} &= \alpha Q + \phi I - (\gamma_2+\mu+\delta_2)H,\\
\frac{dH_V}{dt} &= \theta_5\alpha Q_V + \theta_3\phi I_V - (\theta_6\gamma_2+\mu+\theta_7\delta_2)H_V,\\
\frac{dR}{dt} &= \gamma_1 I + \gamma_2 H - \mu R,\\
\frac{dR_V}{dt} &= \theta_2\gamma_1 I_V + \theta_6\gamma_2 H_V - \mu R_V.
\end{aligned}
\tag{6.2}
$$

Table 6.1: Description of variables and parameters of the model (6.2).

Variable	Description
$S(t)$	Population of unvaccinated susceptible individuals
$V(t)$	Population of vaccinated susceptible individuals
$E(t)$	Population of unvaccinated exposed individuals
$E_V(t)$	Population of exposed vaccinated individuals
$I(t)$	Population of unvaccinated infectious (symptomatic) individuals
$I_V(t)$	Population of infectious vaccinated individuals
$Q(t)$	Population of unvaccinated quarantined individuals
$Q_V(t)$	Population of quarantined vaccinated individuals
$H(t)$	Population of unvaccinated hospitalized individuals
$H_V(t)$	Population of hospitalized vaccinated individuals
$R(t)$	Population of unvaccinated recovered individuals
$R_V(t)$	Population of recovered vaccinated individuals

Parameter	Description
Π	Recruitment rate
β	Effective contact rate
μ	Natural death rate
ρ	Fraction of newly-recruited individuals vaccinated
η	Modification parameter for reduction in infectiousness of hospitalized individuals
ν_1, ν_2	Modification parameters for reduction in infectiousness of vaccinated infectious and hospitalized individuals
ε	Efficacy of vaccine
ζ	Vaccination rate of susceptible individuals
ψ	Waning rate of vaccine
κ	Progression rate from exposed to infectious class
σ	Quarantine rate for exposed individuals
σ_1	Quarantine rate for vaccinated exposed individuals
α	Hospitalization rate for quarantined individuals
ϕ	Hospitalization rate for infectious individuals
γ_1	Recovery rate for non-hospitalized infectious individuals
γ_2	Recovery rate for hospitalized individuals
δ_1	Disease-induced death rate for non-hospitalized infectious individuals
δ_2	Disease-induced death rate for hospitalized individuals
$\theta_1, \cdots, \theta_7$	Modification parameters

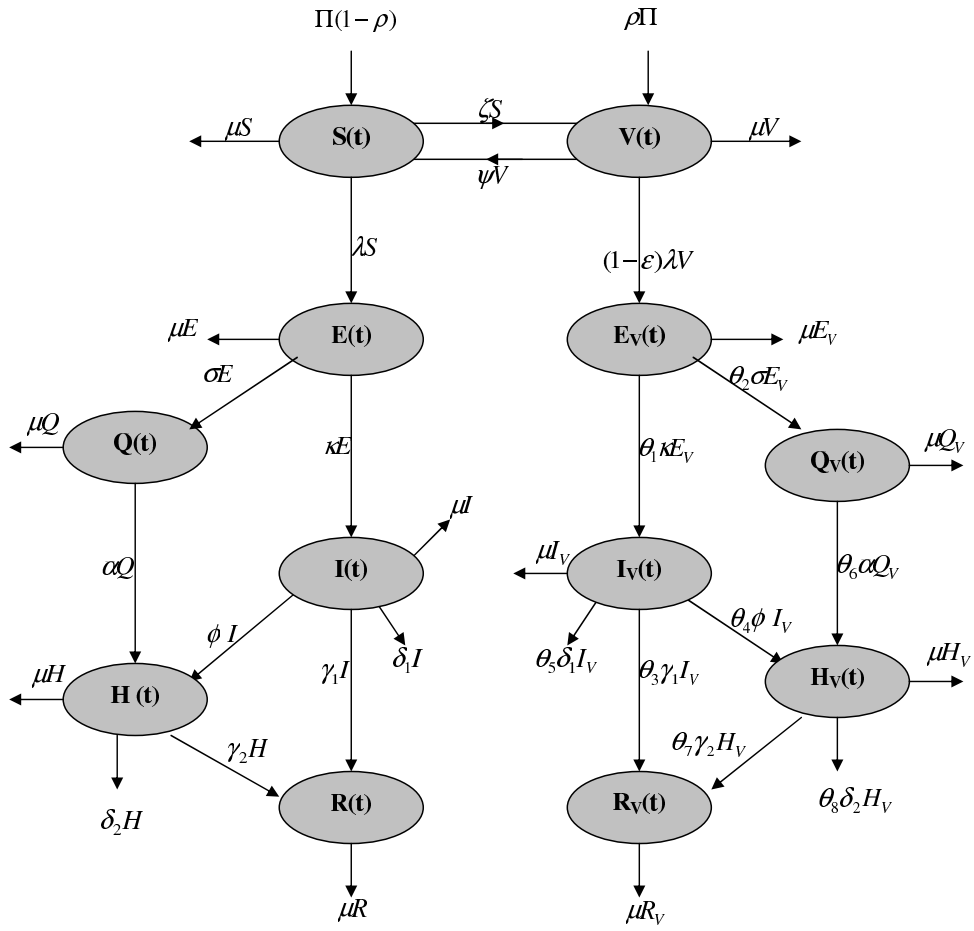


Figure 6.1: Flow diagram of the model (6.2).

The model (6.2) is a an extension of the SEIQHR model (3.2), by including six compartments for the vaccinated individuals (namely, V, E_V, Q_V, I_V, H_V and R_V). The main objective of this chapter is to carry out a detailed rigorous qualitative analysis of the model (6.2), and determine whether or not adding an imperfect vaccine to the quarantine/isolation model (3.2) alters its qualitative (equilibrium) dynamics. It is worth emphasizing that the model (6.2) considers an imperfect vaccine with a number of therapeutic characteristics, such as:

(i) the vaccine blocks infection (with efficacy $0 < \varepsilon < 1$);

(ii) the vaccine reduces transmissibility in break-through infections (at rates $\nu_1\beta$ and $\nu_2\beta$ for infectious individuals in the I_V and H_V classes, respectively; with $0 < \nu_1, \nu_2 < 1$);

(iii) the vaccine slows the development of disease symptoms in exposed vaccinated individuals (at a rate $\theta_1\kappa$, with $0 < \theta_1 < 1$);

(iv) the vaccine reduces disease-induced mortality in break-through infections (at the rates $\theta_4\delta_1$ and $\theta_7\delta_2$ for I_V and H_V individuals, respectively; with $0 < \theta_4, \theta_7 < 1$);

(v) the vaccine increases rate of recovery in break-through infections (at rate $\theta_2\gamma_1$ and $\theta_6\gamma_2$, for I_V and H_V individuals, respectively; with $\theta_2 > 1$ and $\theta_6 > 1$);

(vi) the vaccine reduces hospitalization rate in break-through infections (at rates $\theta_5\alpha$ and $\theta_3\sigma$ for Q_V and I_V individuals, respectively; with $0 < \theta_3, \theta_5 < 1$).

6.2 Basic Properties

Since the model (6.2) monitors human populations, all its associated parameters are non-negative. The following results can be established using the approach in Section 3.2.

Theorem 6.1. *The variables of the model* (6.2) *are non-negative for all time. In other words, solutions of the model system* (6.2) *with positive initial data will remain positive for all time* $t > 0$.

Lemma 6.1. *The closed set*

$$\mathcal{D} = \Bigg\{ (S, V, E, E_V, I, I_V, Q, Q_V, H, H_V, R, R_V) \in \mathbb{R}_+^{12} : \\ S + V + E + E_V + I + I_V + Q + Q_V + H + H_V + R + R_V \leq \frac{\Pi}{\mu} \Bigg\}$$

is positively-invariant for the model (6.2).

6.3 Local Stability of Disease-free Equilibrium

The DFE of the model (6.2) is given by

$$\begin{aligned}\mathcal{E}_0 &= (S^*,\ V^*,\ E^*,\ E_V^*,\ I^*,\ I_V^*,\ Q^*,\ Q_V^*,\ H^*,\ H_V^*,\ R^*,\ R_V^*)\\ &= \left(\frac{\Pi[(1-\rho)\mu+\psi]}{\mu(\mu+\psi+\zeta)}, \frac{\Pi(\rho\mu+\zeta)}{\mu(\mu+\psi+\zeta)}\ ,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0\right).\end{aligned} \tag{6.3}$$

The local stability of $\mathcal{E}_0$ will be explored using the next generation operator method [21, 87]. Using the notation in [87], the non-negative matrix, F, of the new infection terms, and the M-matrix, G, of the transition terms associated with the model (6.2), are given, respectively, by

$$F = \begin{pmatrix} 0 & 0 & \beta\omega_1 & \nu_1\beta\omega_1 & 0 & 0 & \eta\beta\omega_1 & \nu_2\eta\beta\omega_1 \\ 0 & 0 & (1-\varepsilon)\beta\omega_2 & (1-\varepsilon)\nu_1\beta\omega_2 & 0 & 0 & (1-\varepsilon)\eta\beta\omega_2 & (1-\varepsilon)\nu_2\eta\beta\omega_2 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and,

$$G = \begin{pmatrix} k_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & k_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\kappa & 0 & k_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\theta_1\kappa & 0 & k_4 & 0 & 0 & 0 & 0 \\ -\sigma & 0 & 0 & 0 & k_5 & 0 & 0 & 0 \\ 0 & -\sigma_1 & 0 & 0 & 0 & k_6 & 0 & 0 \\ 0 & 0 & -\phi & 0 & -\alpha & 0 & k_7 & 0 \\ 0 & 0 & 0 & -\theta_3\phi & 0 & -\theta_5\alpha & 0 & k_8 \end{pmatrix},$$

where,

$$\omega_1 = \frac{(1-\rho)\mu + \psi}{\mu + \psi + \zeta}, \quad \omega_2 = \frac{\rho\mu + \zeta}{\mu + \psi + \zeta}, \quad k_1 = \kappa + \sigma + \mu, \quad k_2 = \theta_1\kappa + \sigma_1 + \mu,$$
$$k_3 = \gamma_1 + \phi + \mu + \delta_1, \quad k_4 = \theta_2\gamma_1 + \theta_3\phi + \mu + \theta_4\delta_1, \quad k_5 = \alpha + \mu,$$
$$k_6 = \theta_5\alpha + \mu, \quad k_7 = \gamma_2 + \mu + \delta_2, \quad k_8 = \theta_6\gamma_2 + \mu + \theta_7\delta_2.$$

It follows that the *control reproduction number* [2, 44], denoted by $\mathcal{R}_{vac} = \rho(FG^{-1})$, is given by

$$\mathcal{R}_{vac} = \frac{\beta(1-\varepsilon)\omega_2[\nu_1\theta_1\kappa k_1k_3k_5k_6k_7k_8 + \nu_2\eta\theta_1\kappa\theta_3\phi k_1k_3k_5k_6k_7 + \nu_2\eta\sigma_1\theta_5\alpha k_1k_3k_4k_5k_7]}{k_1k_2k_3k_4k_5k_6k_7k_8}$$
$$+ \frac{\beta\omega_1[\kappa k_2k_4k_5k_6k_7k_8 + \eta\phi\kappa k_2k_4k_5k_6k_8 + \eta\alpha\sigma k_2k_3k_4k_6k_8]}{k_1k_2k_3k_4k_5k_6k_7k_8}.$$

Using Theorem 2.10, the following result is established.

Lemma 6.2. *The DFE of the model* (6.2)*, given by* (6.3)*, is locally-asymptotically stable if* $\mathcal{R}_{vac} < 1$*, and unstable if* $\mathcal{R}_{vac} > 1$*.*

The quantity $\mathcal{R}_{vac}$ measures the average number of new infections generated by a single infectious individual in a population where a certain fraction of the susceptible

population are vaccinated. Lemma 6.2 implies that the disease can be eliminated from the community (when $\mathcal{R}_{vac} < 1$) if the initial sizes of the sub-populations of the model are in the basin of attraction of the DFE ($\mathcal{E}_0$).

6.3.1 Backward bifurcation

In this section, the existence of endemic equilibria of the model (6.2) is established. Let,

$$\mathcal{E}_1 = (S^{**},\ V^{**},\ E^{**},\ E_V^{**},\ I^{**},\ I_V^{**},\ Q^{**},\ Q_V^{**},\ H^{**},\ H_V^{**},\ R^{**},\ R_V^{**})$$

represent any arbitrary EEP of the model (6.2). Further, define

$$\lambda^{**} = \frac{\beta(I^{**} + \nu_1 I_V^{**} + \eta H^{**} + \nu_2 \eta H_V^{**})}{N^{**}} \tag{6.4}$$

(the force of infection of the model (6.2) at steady-state). It follows, by solving the equations in (6.2) at steady-state, that

$$\begin{aligned}
S^{**} &= \frac{\Pi[\psi + (1-\rho)\{\mu + (1-\varepsilon)\}]}{(1-\varepsilon)\lambda^2 + [(1-\varepsilon)(\mu+\zeta) + \mu + \psi]\lambda + \mu(\zeta + \psi + \mu)},\\
V^{**} &= \frac{\Pi[\rho\lambda + \rho\mu + \zeta]}{(1-\varepsilon)\lambda^2 + [(1-\varepsilon)(\mu+\zeta) + \mu + \psi]\lambda + \mu(\zeta + \psi + \mu)},\\
E^{**} &= \frac{\lambda^{**}S^{**}}{k_1}, \quad E_V^{**} = \frac{(1-\varepsilon)\lambda^{**}V^{**}}{k_2},\\
I^{**} &= \frac{\lambda^{**}S^{**}\kappa}{k_1k_3}, \quad I_V^{**} = \frac{(1-\varepsilon)\lambda^{**}V^{**}\theta_1\kappa}{k_2k_4},\\
Q^{**} &= \frac{\lambda^{**}S^{**}\sigma}{k_1k_5}, \quad Q_V^{**} = \frac{(1-\varepsilon)\lambda^{**}V^{**}\sigma_1}{k_2k_6},\\
H^{**} &= \frac{\lambda^{**}S^{**}(\alpha\sigma k_3 + \kappa\phi k_5)}{k_1k_3k_5k_7}, \quad H_V^{**} = \frac{(1-\varepsilon)\lambda^{**}V^{**}(\theta_5\alpha\sigma_1 k_4 + \theta_1\kappa\theta_3\phi k_6)}{k_2k_4k_6k_8},\\
R^{**} &= \frac{\lambda^{**}S^{**}(\gamma_1\kappa k_5k_7 + \gamma_2\alpha\sigma k_3 + \gamma_2\phi\kappa k_5)}{\mu k_1k_3k_5k_7},\\
R_V^{**} &= \frac{(1-\varepsilon)\lambda^{**}V^{**}(\theta_2\gamma_1\theta_1\kappa k_6k_8 + \theta_6\gamma_2\theta_5\alpha\sigma_1 k_4 + \theta_6\gamma_2\theta_3\phi\theta_1\kappa k_6)}{\mu k_2k_4k_6k_8}.
\end{aligned} \tag{6.5}$$

Substituting the expressions in (6.5) into (6.4) shows that the non-zero equilibria of the model satisfy the following quadratic equation (in terms of λ^{**}):

$$a_0(\lambda^{**})^2 + a_1\lambda^{**} + a_2 = 0, \tag{6.6}$$

where,

$$
\begin{aligned}
a_0 &= k_2k_4k_6k_8(1-\varepsilon)(1-\rho)(\sigma\, k_3k_7\mu + \gamma_1\kappa\, k_5k_7 + \kappa\, k_7k_5\mu + \mu\,\alpha\,\sigma\, k_3) \\
&+ k_2k_4k_6k_8(1-\varepsilon)(1-\rho)(k_3k_5k_7\mu + \gamma_2\phi\, k_5\kappa + \mu\,\phi\, k_5\kappa + \gamma_2\alpha\,\sigma\, k_3) \\
&+ \rho k_1k_3k_5k_7(1-\varepsilon)(\mu\,\theta_4\phi\, k_6\theta_1\kappa + \mu\,\theta_1\kappa\, k_6k_8 + \theta_7\gamma_2\theta_6\alpha\,\theta_2\sigma\, k_4 + \theta_7\gamma_2\theta_4\phi\, k_6\theta_1\kappa) \\
&+ \rho k_1k_3k_5k_7(1-\varepsilon)(\theta_3\gamma_1\theta_1\kappa\, k_6k_8 + \mu\, k_4k_6k_8 + \mu\,\theta_2\sigma\, k_4k_8 + \mu\,\theta_6\alpha\,\theta_2\sigma\, k_4),
\end{aligned}
$$

$$
\begin{aligned}
a_1 &= -\beta\mu(1-\varepsilon)\Big[\eta\kappa\phi k_2k_4k_5k_6k_8(1-\rho) + \nu_2\rho\eta\theta_5\alpha\sigma_1k_1k_3k_4k_5k_7 + \eta\sigma\alpha k_2k_3k_4k_6k_8(1-\rho) \\
&+ \nu_1\rho\theta_1\kappa k_1k_3k_5k_6k_7k_8 + \nu_2\eta\rho\theta_1\kappa\theta_3\phi k_1k_3k_5k_6k_7 + \kappa k_2k_4k_5k_6k_7k_8(1-\rho)\Big] \\
&+ k_1k_3k_5k_7(1-\varepsilon)\Big[\mu\zeta\theta_1\kappa\theta_3\phi k_6(1-\rho) + \mu\zeta\sigma_1\theta_5\alpha k_4(1-\rho) + \rho\mu\theta_1\kappa k_4k_6(\mu+\zeta) \\
&+ \rho\mu k_4k_6k_8(\mu+\zeta) + \mu k_2k_4k_6k_8(1-\rho)(1+\zeta) + \mu\zeta\theta_1\kappa k_6k_8(1-\rho) + \zeta\theta_1\kappa\theta_2\gamma_1k_6k_8(1-\rho) \\
&+ \mu\zeta\sigma_1k_4k_8(1-\rho) + \mu\rho\sigma_1k_4k_8(\mu+\zeta) + \sigma_1\theta_5\alpha\theta_6\gamma_2k_4 + \mu\rho\theta_1\kappa\theta_3\phi k_6(\mu+\zeta) \\
&+ \mu\rho\sigma_1\theta_5\alpha k_4(\mu+\zeta) + \zeta\theta_1\kappa\theta_3\phi\theta_6\gamma_2k_6(1-\rho) + \rho\theta_1\kappa\theta_3\phi\theta_6\gamma_2k_6(\mu+\zeta) \\
&+ \rho\theta_1\kappa\theta_2\gamma_1k_6k_8(\mu+\zeta) + \rho\sigma_1\theta_5\alpha\theta_6\gamma_2k_4(\mu+\zeta)\Big] \\
&+ k_2k_4k_6k_8\Big[\mu\rho k_1k_3k_5k_7 + \mu\rho\psi\sigma k_3k_5 + \mu\rho\psi\alpha\sigma k_3 + \mu\sigma k_3k_7(1-\rho)(\mu+\psi) + \mu\rho\phi\kappa\phi k_5 \\
&+ \mu\kappa k_5k_7(\mu+\psi)(1-\rho) + \mu\rho\psi\kappa k_5k_7 + \mu\sigma\alpha k_3(\mu+\psi)(1-\rho) + \gamma_1\kappa k_5k_7(\mu+\psi)(1-\rho) \\
&+ \rho\psi\kappa\gamma_1k_5k_7 + \mu k_3k_5k_7(\mu+\psi)(1-\rho) + \mu\phi\kappa k_5(\mu+\psi)(1-\rho) + \gamma_2\alpha\sigma k_3(\mu+\psi)(1-\rho) \\
&+ \rho\psi\alpha\sigma\gamma_2k_3 + \rho\psi\kappa\phi\gamma_2k_5 + \mu\rho\psi k_3k_5k_7 + (1-\rho)(\mu+\psi\kappa\phi\gamma_2k_5)\Big],
\end{aligned}
$$

$$
a_2 = \mu k_1k_2k_3k_4k_5k_6k_7k_8(\mu+\zeta+\psi)(1-\mathcal{R}_{vac}).
$$

The endemic equilibria of the model (6.2) can then be obtained by solving for λ^{**} from (6.6), and substituting the positive values of λ^{**} into the expressions in (6.5). The quadratic equation (6.6) can be analyzed for the possibility of multiple endemic

equilibria when $\mathcal{R}_{vac} < 1$. It should be noted that the coefficient, a_0, of the quadratic (6.6) is always positive and a_2 is positive (negative) if $\mathcal{R}_{vac}$ is less (greater) than unity. Hence, the following result is established.

Theorem 6.2. *The model* (6.2) *has*

(i) a unique endemic equilibrium if $a_2 < 0 \Leftrightarrow \mathcal{R}_{vac} > 1$;

(ii) a unique endemic equilibrium if ($a_1 < 0$ *and* $a_2 = 0$) *or* $a_1^2 - 4a_0a_2 = 0$;

(iii) two endemic equilibria if $a_2 > 0, a_1 < 0$ *and* $a_1^2 - 4a_0a_2 > 0$;

(iv) no endemic equilibrium otherwise.

Thus, it is clear from Case (i) of Theorem 6.2 that the model (6.2) has a unique EEP (of the form $\mathcal{E}_1$) whenever $\mathcal{R}_{vac} > 1$. Furthermore, Case (iii) of Theorem 6.2 indicates the possibility of backward bifurcation, where a LAS DFE co-exists with a LAS endemic equilibrium when the associated reproduction number $\mathcal{R}_{vac}$; is less than unity (see, for instance, [27, 35, 80] for discussions on backward bifurcation) in the model (6.2). The epidemiological importance of the phenomenon of backward bifurcation is that the classical requirement of having $\mathcal{R}_{vac} < 1$ is, although necessary, not sufficient for disease elimination. In this case, disease elimination will depend upon the initial sizes of the sub-populations of the model. To check for the possibility of backward bifurcation in (6.2), the discriminant $a_1^2 - 4a_0a_2$ of the quadratic (6.6), is set to zero and the result solved for the critical value of $\mathcal{R}_{vac}$ (denoted by $\mathcal{R}_{vac}^c$). This gives:

$$\mathcal{R}_{vac}^c = 1 - \frac{a_1^2}{4a_0\mu k_1k_2k_3k_4k_5k_6k_7k_8(\mu + \zeta + \psi)},$$

from which it can be shown that backward bifurcation occurs for values of $\mathcal{R}_{vac}$ such that $\mathcal{R}_{vac}^c < \mathcal{R}_{vac} < 1$ (see also [27, 35, 80]). This phenomenon is numerically illustrated

by simulating the model (6.2) with the following set of parameter value (these parameter values may not all be realistic epidemiologically; the reader may refer to the study in [60] for discussions on whether or not backward bifurcation can occur using a realistic set of parameter values): $\Pi = 136,\ \beta = 1.4,\ \ \mu = 0.001,\ \zeta = 0.06,\ \psi = 0.0001,\ \kappa = 0.00016,\ \theta_1 = 0.7\ \theta_4 = 0.9,\ \sigma_1 = 0.09,\ \theta_5 = 0.9,\ \theta_2 = 1,\ \theta_6 = 1,\ \theta_3 = 0.01,\ \theta_7 = 1,\ \delta_1 = 0.001,\ \delta_2 = 0.01,\ \nu_1 = 0.9,\ \rho = 0.1,\ \varepsilon = 10^{-7},\ \alpha = 1,\ \phi = 1,\ \gamma_1 = 0.01,\ \gamma_2 = 0.1,\ \eta = 1,\ \nu_2 = 1,\ \sigma = 1$ (so that, $\mathcal{R}^c_{vac} = 0.5673706974 < \mathcal{R}_{vac} = 0.6719831393 < 1$). The result obtained, depicted in Figure 6.2, shows that the model has a DFE and two endemic equilibria (one of the endemic equilibria is LAS, the other is unstable (saddle) and the DFE is LAS). This figure clearly shows the coexistence of two stable equilibria when $\mathcal{R}^c_{vac} < \mathcal{R}_{vac} < 1$, confirming that the model (6.2) exhibits backward bifurcation at $\mathcal{R}_{vac} = 1$.

It should be stated that the backward bifurcation phenomenon of the model (6.2) is only illustrated numerically. A more rigorous proof, based on using center manifold theory (see, for instance, [11, 13, 35, 87]), is given in Appendix C. In particular, Theorem 2.4 will be used to theoretically establish the presence of the backward bifurcation phenomenon of the model (6.2). It should be recalled that no such backward bifurcation phenomenon exists in the corresponding quarantine/isolation model (3.2) (without vaccine). Thus, the analyses of this chapter show that adding vaccination to the quarantine/isolation model (3.2) alters its qualitative properties (by inducing the phenomenon of backward bifurcation).

6.3.2 Non-existence of backward bifurcation

In this section, some scenarios where the backward bifurcation property of the model can be lost are explored. The following cases are considered.

Case 1: Use of perfect vaccination ($\varepsilon = 1$)

Consider the model (6.2) with a perfect vaccine (so that, $\varepsilon = 1$). In this case, the coefficients a_0, a_1 and a_2 of the quadratic equation (6.6) reduce to $a_0 = 0, a_1 > 0$ and $a_2 \geq 0$ whenever $\tilde{\mathcal{R}}_{vac} = \mathcal{R}_{vac}|_{\varepsilon=1} \leq 1$. Thus, for this case, the quadratic equation (6.6) has one solution ($\lambda^{**} = \frac{-c}{b} \leq 0$.) Therefore, the model (6.2) with a perfect vaccine has no positive endemic equilibrium whenever $\tilde{\mathcal{R}}_{vac} < 1$. This rules out the possibility of backward bifurcation in this case (since backward bifurcation requires the existence of at least two endemic equilibria whenever $\tilde{\mathcal{R}}_{vac} \leq 1$ [27, 35, 80]). Furthermore, it can be shown that, for the case when $\varepsilon = 1$, the DFE ($\mathcal{E}_0$) of the model (6.2) is globally-asymptotically stable under some conditions, as shown below.

Setting $\varepsilon = 1$ in the model (6.2) gives the following reduced model (it should be noted from (6.2) that, for the case when $\varepsilon = 1$, $(E_V, I_V, Q_V, H_V, R_V) \to (0, 0, 0, 0, 0)$ as $t \to \infty$; hence, these variables are omitted from the asymptotic analysis of the model for the special case with $\varepsilon = 1$):

$$\begin{aligned}
\frac{dS}{dt} &= (1-p)\Pi - \lambda_1 S - (\zeta + \mu)S, \\
\frac{dV}{dt} &= p\Pi + \zeta S - \mu V, \\
\frac{dE}{dt} &= \lambda_1 S - (\kappa + \sigma + \mu)E, \\
\frac{dI}{dt} &= \kappa E - (\gamma_1 + \phi + \mu + \delta_1)I, \\
\frac{dQ}{dt} &= \sigma E - (\alpha + \mu)Q, \\
\frac{dH}{dt} &= \alpha Q + \phi I - (\gamma_2 + \mu + \delta_2)H, \\
\frac{dR}{dt} &= \gamma_1 I + \gamma_2 H - \mu R,
\end{aligned} \tag{6.7}$$

with the associated force of infection $\lambda = \lambda_1$, where

$$\lambda_1 = \lambda|_{\epsilon=1} = \frac{\beta(I + \eta H)}{S + V + E + I + Q + H + R}. \tag{6.8}$$

It can be shown that the reproduction number associated with the reduced model (6.7), with (6.8), is given by

$$\tilde{\mathcal{R}}_{vac} = \mathcal{R}_{vac}|_{\epsilon=1} = \frac{\beta\omega_1(\kappa k_5 k_7 + \eta\phi\kappa k_5 + \eta\alpha\sigma k_3)}{k_1 k_3 k_5 k_7}. \tag{6.9}$$

Define,

$$\mathcal{D}_1 = \left\{(S, V, E, I, Q, H, R) \in \mathbb{R}^7_+ : S + V + E + I + Q + H + R \leq \frac{\Pi}{\mu}\right\}.$$

The model (6.7) has a DFE, given by $\mathcal{E}_{01} = (S^*, V^*, 0, 0, 0, 0, 0)$.

Theorem 6.3. *The DFE ($\mathcal{E}_{01}$) of the reduced model* (6.7)*, with* (6.8)*, is GAS in $\mathcal{D}_1$ whenever $\tilde{\mathcal{R}}_{vac} \leq \omega_1 < 1$.*

Proof. Consider the following Lyapunov function (this is the same Lyapunov function used in the proof of the GAS of the DFE of the quarantine/isolation model (3.2)):

$$\mathcal{F} = \left(\frac{k_7\tilde{\mathcal{R}}_{vac}}{\omega_1\eta\beta}\right) E + \left(\frac{k_7 + \eta\phi}{k_3\eta}\right) I + \left(\frac{\alpha}{k_5}\right) Q + H,$$

with Lyapunov derivative given by

$$\dot{\mathcal{F}} = \left(\frac{k_7\tilde{\mathcal{R}}_{vac}}{\omega_1\eta\beta}\right)\dot{E} + \left(\frac{k_7+\eta\phi}{k_3\eta}\right)\dot{I} + \left(\frac{\alpha}{k_5}\right)\dot{Q} + \dot{H},$$

$$= \frac{k_7\tilde{\mathcal{R}}_{vac}}{\omega_1\eta\beta}\left[\frac{\beta S(I+\eta H)}{N} - k_1E\right] + \left(\frac{k_7+\eta\phi}{k_3\eta}\right)(\kappa E - k_3 I) + \left(\frac{\alpha}{k_5}\right)(\sigma E - k_5 Q)$$
$$+ \alpha Q + \phi I - k_7 H,$$

$$\leq \frac{k_7\tilde{\mathcal{R}}_{vac}}{\omega_1\eta}(I+\eta H) - \frac{k_1k_7\tilde{\mathcal{R}}_{vac}}{\omega_1\eta\beta}E + \frac{\kappa(k_7+\eta\phi)}{k_3\eta}E - \frac{(k_7+\eta\phi)}{\eta}I + \frac{\alpha\sigma}{k_5}E$$
$$+ \phi I - k_7 H, \quad \text{since } S \leq N \text{ in } \mathcal{D}_1,$$

$$= \left[\frac{-k_1k_7\tilde{\mathcal{R}}_{vac}}{\omega_1\eta\beta} + \frac{\kappa(k_7+\eta\phi)}{k_3\eta} + \frac{\alpha\sigma}{k_5}\right]E + \left(\phi + \frac{k_7\tilde{\mathcal{R}}_{vac}}{\omega_1\eta} - \frac{k_7+\eta\phi}{\eta}\right)I + k_7\left(\frac{\tilde{\mathcal{R}}_{vac}}{\omega_1} - 1\right)H,$$

$$= \frac{k_7}{\eta}\left(\frac{\tilde{\mathcal{R}}_{vac}}{\omega_1} - 1\right)(I+\eta H) \leq 0 \text{ whenever } \tilde{\mathcal{R}}_{vac} \leq \omega_1 < 1.$$

Since all the parameters and variables of the model (6.2) are non-negative (Theorem 6.1), it follows that $\dot{\mathcal{F}} \leq 0$ for $\tilde{\mathcal{R}}_{vac} \leq \omega_1$ (it should be noted that $\omega_1 = \frac{S^*}{N^*} < 1$) with $\dot{\mathcal{F}} = 0$ if and only if $E = I = Q = H = 0$. Hence, $\mathcal{F}$ is a Lyapunov function on $\mathcal{D}_1$. Thus, it follows, by the LaSalle's Invariance Principle (Theorem 2.6), that

$$(E, I, Q, H) \to (0, 0, 0, 0) \text{ as } t \to \infty. \tag{6.10}$$

Since $\limsup_{t\to\infty} I = 0$ and $\limsup_{t\to\infty} H = 0$ (from (6.10)), it follows that, for sufficiently small small $\varpi^* > 0$, there exist constants $M_1 > 0$ and $M_2 > 0$ such that $\limsup_{t\to\infty} I \leq \varpi^*$ for all $t > M_1$ and $\limsup_{t\to\infty} H \leq \varpi^*$ for all $t > M_2$. Hence, it follows from the seventh equation of the model (6.7) that, for $t > \max\{M_1, M_2\}$,

$$\dot{R} \leq \gamma_1 \varpi^* + \gamma_2 \varpi^* - \mu R.$$

Thus, by comparison theorem (Theorem 2.8),

$$R^\infty = \limsup_{t\to\infty} R \leq \frac{\gamma_1 \varpi^* + \gamma_2 \varpi^*}{\mu},$$

so that, by letting $\varpi^* \to 0$,

$$R^\infty = \limsup_{t\to\infty} R \leq 0. \tag{6.11}$$

Similarly (by using $\liminf_{t\to\infty} I = 0$ and $\liminf_{t\to\infty} H = 0$), it can be shown that

$$R_\infty = \liminf_{t\to\infty} R \geq 0. \tag{6.12}$$

Thus, it follows from (6.11) and (6.12) that

$$R_\infty \geq 0 \geq R^\infty.$$

Hence,

$$\lim_{t\to\infty} R = 0. \tag{6.13}$$

Similarly, it can be shown that

$$\lim_{t\to\infty} S(t) = \frac{\Pi[(1-\rho)\mu + \psi]}{\mu(\mu + \psi + \zeta)} = S^*, \ \lim_{t\to\infty} V(t) = \frac{\Pi(\rho\mu + \zeta)}{\mu(\mu + \psi + \zeta)} = V^*. \tag{6.14}$$

Thus, by combining equations (6.10), (6.13) and (6.14), it follows that every solution of the equations in the model (6.7), with initial conditions in $\mathcal{D}_1$, approaches $\mathcal{E}_0$ as $t \to \infty$ (for $\tilde{\mathcal{R}}_{vac} \leq \omega_1 < 1$). □

Thus, these analyses show that the backward bifurcation property of the model 6.2 can be removed if the vaccine offer 100% protection against infection (i.e., $\varepsilon = 1$).

Case 2: Mass action incidence

Consider the model (6.2) with $0 < \varepsilon < 1$ and the associated disease-induced mortality rates set to zero (so that, $\delta_1 = \delta_2 = 0$). Substituting $\delta_1 = \delta_2 = 0$ into the model (6.2) shows that $dN/dt = \Pi - \mu N$, so that $N \to \Pi/\mu$ as $t \to \infty$. Thus, Π/μ is an upper bound of $N(t)$ provided that $N(0) \leq \Pi/\mu$. Further, if $N(0) > \Pi/\mu$, then $N(t)$ will decrease to this level. Finally, using $N = \Pi/\mu$ in (6.1) gives

$$\lambda = \beta_1(I + \nu_1 I_V + \eta H + \nu_2 \eta H_V), \text{where } \beta_1 = \frac{\beta\mu}{\Pi}. \tag{6.15}$$

It should be mentioned that using (6.15) in the model (6.2) reduces the model (6.2) (which is originally a standard incidence model) to a mass action model (as discussed in Section 1.2). It is convenient to define the region:

$$\hat{\mathcal{D}} = \{(S, V, E, E_V, I, I_V, Q, Q_V, H, H_V, R, R_V) \in \mathcal{D} : S \leq S^*,\ V \leq V^*\}.$$

It can be shown that the associated reproduction number of the model (6.2), with (6.15), is given by

$$\begin{aligned}
\mathcal{R}_{vac}^m &= \mathcal{R}_{vac}|_{\delta_1=\delta_2=0}, \\
&= \frac{\beta_1(1-\varepsilon)V^*[\nu_1\theta_1\kappa k_1\tilde{k_3}k_5k_6\tilde{k_7}\tilde{k_8} + \nu_2\eta\theta_1\kappa\theta_3\phi k_1\tilde{k_3}k_5k_6\tilde{k_7} + \nu_2\eta\sigma_1\theta_5\alpha k_1\tilde{k_3}\tilde{k_4}k_5\tilde{k_7}]}{k_1k_2\tilde{k_3}\tilde{k_4}k_5k_6\tilde{k_7}\tilde{k_8}} \\
&+ \frac{\beta_1 S^*[\kappa k_2\tilde{k_4}k_5k_6\tilde{k_7}\tilde{k_8} + \eta\phi\kappa k_2\tilde{k_4}k_5k_6\tilde{k_8} + \eta\alpha\sigma k_2\tilde{k_3}\tilde{k_4}k_6\tilde{k_8}]}{k_1k_2\tilde{k_3}\tilde{k_4}k_5k_6\tilde{k_7}\tilde{k_8}},
\end{aligned}$$

where, now, $\tilde{k_3} = \gamma_1 + \phi + \mu, \quad \tilde{k_4} = \theta_2\gamma_1 + \theta_3\phi + \mu, \quad \tilde{k_7} = \gamma_2 + \mu$ and $\tilde{k_8} = \theta_6\gamma_2 + \mu$.

It can be shown, using the technique in Section 6.3.1, that the non-zero equilibria of the model (6.2) with (6.15) satisfy the following quadratic equation (in terms of $\lambda^{**} = \beta_1(I^{**} + \nu_1 I^{**}V + \eta H^{**} + \nu_2\eta H_V^{**})$)

$$b_0(\lambda^{**})^2 + b_1\lambda^{**} + b_2 = 0, \tag{6.16}$$

where,

$$\begin{aligned} b_0 &= (1-\varepsilon), \\ b_1 &= 1 - \frac{(1-\rho)(1-\varepsilon)A_1 + \rho A_2}{(1-\varepsilon)l_1 + l_2}, \\ b_2 &= \mu(\mu+\zeta+\psi)(1-\mathcal{R}_{vac}^m), \end{aligned} \tag{6.17}$$

with,

$$\begin{aligned} A_1 &= \frac{\Pi\beta_1[\eta\sigma\alpha\tilde{k_3} + \kappa k_5\tilde{k_7} + \eta\phi\kappa k_5]}{k_1\tilde{k_3}k_5\tilde{k_7}}, \\ A_2 &= \frac{(1-\varepsilon)\Pi\beta_1[nu_2\eta\sigma_1\theta_5\alpha\tilde{k_4} + \nu_1\theta_1\kappa k_6\tilde{k_8} + \nu_2\eta\theta_1\kappa\theta_3\phi k_6]}{k_2\tilde{k_4}k_6\tilde{k_8}}, \\ l_1 &= (\zeta+\mu), \quad l_2 = (\psi+\mu). \end{aligned}$$

The threshold quantity $\mathcal{R}_{vac}^m$ can be re-written as

$$\mathcal{R}_{vac}^m = \frac{(1-\rho)\mu + \psi}{\mu(\mu+\zeta+\psi)}A_1 + \frac{\rho\mu+\zeta}{\mu(\mu+\zeta+\psi)}A_2.$$

Further, to show that the coefficient b_1 in (6.17) is always positive when $\mathcal{R}_{vac}^m \leq 1$, it is sufficient to show that $\frac{(1-\rho)(1-\varepsilon)A_1 + \rho A_2}{(1-\varepsilon)l_1 + l_2} \leq 1$. When $\mathcal{R}_{vac}^m \leq 1$.

Let $\mathcal{R}_{vac}^m \leq 1$. It follows that

$$A_1 \leq \frac{\mu(\mu+\zeta+\psi)}{(1-\rho)\mu+\psi} \text{ and } A_2 \leq \frac{\mu(\mu+\zeta+\psi)}{\rho\mu+\zeta}.$$

Hence,

$$\frac{(1-\rho)(1-\varepsilon)A_1+\rho A_2}{(1-\varepsilon)l_1+l_2} \leq \frac{\mu(1-\rho)(1-\varepsilon)(\mu+\zeta+\psi)}{[(1-\varepsilon)l_1+l_2][(1-\rho)\mu+\psi]} + \frac{\rho\mu(\mu+\zeta+\psi)}{(\rho\mu+\zeta)[(1-\varepsilon)l_1+l_2]},$$

$$= \frac{\mu(1-\rho)(1-\varepsilon)(\mu+\zeta+\psi)(\rho\mu+\zeta)+\rho\mu(\mu+\zeta+\psi)[(1-\rho)\mu+\psi]}{(\rho\mu+\zeta)[(1-\rho)\mu+\psi][(1-\varepsilon)l_1+l_2]}.$$

It can be shown, after some algebraic manipulations, that

$$\begin{aligned}
&\mu(1-\rho)(1-\varepsilon)(\mu+\zeta+\psi)(\rho\mu+\zeta)+\rho\mu(\mu+\zeta+\psi)[(1-\rho)\mu+\psi] \\
&-(\rho\mu+\zeta)[(1-\rho)\mu+\psi][(1-\varepsilon)l_1+l_2] \\
&\\
&=[(1-\rho)-1](1-\varepsilon)\zeta\mu\psi+[(1-\varepsilon)-1]\rho\mu\zeta\psi \\
&+(\rho-1)(1-\rho)\mu^2\zeta+[(1-\rho)-1](1-\varepsilon)\rho\mu^2\psi-(1-\varepsilon)\psi\zeta^2-\mu\zeta\psi \\
&-(1-\rho)\mu\zeta\psi-\zeta\psi^2 \leq 0,
\end{aligned}$$

so that,

$$\frac{(1-\rho)(1-\varepsilon)A_1+\rho A_2}{(1-\varepsilon)l_1+l_2} \leq 1.$$

Hence, $b_1 \leq 0$ whenever $\mathcal{R}^m_{vac} \leq 1$. In other words, for $\mathcal{R}^m_{vac} \leq 1$, the coefficients b_0, b_1 and b_2 of the quadratic equation (6.16) are non-negative. Thus, for this case (with $\mathcal{R}^m_{vac} \leq 1$,) the quadratic equation (6.16) has no positive root. Therefore, the model (6.2) has no positive endemic equilibrium whenever $\mathcal{R}^m_{vac} < 1$ (which rules out backward bifurcation in this case). This result is summarized below.

Theorem 6.4. *The model* (6.2)*, with* (6.15)*, has no endemic equilibrium if* $\mathcal{R}_{vac}^{m} \leq 1$.

The following result can be claimed.

Theorem 6.5. *The DFE of the model* (6.2)*, with* (6.15)*, is GAS in* $\hat{\mathcal{D}}$ *whenever* $\mathcal{R}_{vac}^{m} \leq 1$.

Proof. Consider the following Lyapunov function:

$$\begin{aligned}\mathcal{F} = &\frac{\tilde{k_8}}{\tilde{k_7}\nu_2}\left[\left(\frac{\kappa k_5\tilde{k_7} + \kappa\eta\phi k_5 + \eta\alpha\sigma\tilde{k_3}}{k_1\tilde{k_3}k_5\eta}\right)E + \left(\frac{\tilde{k_7}+\eta\phi}{\tilde{k_3}\eta}\right)I + \left(\frac{\alpha}{k_5}\right)Q + H\right] \\ &+ \left(\frac{\nu_1\theta_1\kappa k_6\tilde{k_8} + \nu_2\eta\theta_3\phi + \theta_1\kappa k_6 + \nu_2\eta\theta_5\alpha\sigma_1\tilde{k_4}}{k_2\tilde{k_4}k_6\nu_2\eta}\right)E_V + \left(\frac{\nu_1\tilde{k_8}+\nu_2\eta\theta_3\phi}{\nu_2\eta\tilde{k_4}}\right)I_V \\ &+ \left(\frac{\theta_5\alpha}{k_6}\right)Q_V + H_V,\end{aligned}$$

with Lyapunov derivative given by,

$$\begin{aligned}\dot{\mathcal{F}} = &\frac{\tilde{k_8}}{\tilde{k_7}\nu_2}\left[\left(\frac{\kappa k_5\tilde{k_7} + \kappa\eta\phi k_5 + \eta\alpha\sigma\tilde{k_3}}{k_1\tilde{k_3}k_5\eta}\right)\dot{E} + \left(\frac{\tilde{k_7}+\eta\phi}{\tilde{k_3}\eta}\right)\dot{I} + \left(\frac{\alpha}{k_5}\right)\dot{Q} + \dot{H}\right] \\ &+ \left(\frac{\nu_1\theta_1\kappa k_6\tilde{k_8} + \nu_2\eta\theta_3\phi + \theta_1\kappa k_6 + \nu_2\eta\theta_5\alpha\sigma_1\tilde{k_4}}{k_2\tilde{k_4}k_6\nu_2\eta}\right)\dot{E_V} + \left(\frac{\nu_1\tilde{k_8}+\nu_2\eta\theta_3\phi}{\nu_2\eta\tilde{k_4}}\right)\dot{I_V} \\ &+ \left(\frac{\theta_5\alpha}{k_6}\right)\dot{Q_V} + \dot{H_V}.\end{aligned} \tag{6.18}$$

The first four terms of $\dot{\mathcal{F}}$ can be simplified as follows:

$$\begin{aligned}
&\frac{\tilde{k_8}}{\tilde{k_7}\nu_2}\left[\left(\frac{\kappa k_5\tilde{k_7}+\kappa\eta\phi k_5+\eta\alpha\sigma\tilde{k_3}}{k_1\tilde{k_3}k_5\eta}\right)\dot{E}+\left(\frac{\tilde{k_7}+\eta\phi}{\tilde{k_3}\eta}\right)\dot{I}+\left(\frac{\alpha}{k_5}\right)\dot{Q}+\dot{H}\right],\\
&=\frac{\tilde{k_8}}{\tilde{k_7}\nu_2}\left[\left(\frac{\kappa k_5\tilde{k_7}+\kappa\eta\phi k_5+\eta\alpha\sigma\tilde{k_3}}{k_1\tilde{k_3}k_5\eta}\right)(\lambda S-k_1E)+\left(\frac{\tilde{k_7}+\eta\phi}{\tilde{k_3}\eta}\right)(\kappa E-\tilde{k_3}I)\right]\\
&+\frac{\tilde{k_8}}{\tilde{k_7}\nu_2}\left\{\left(\frac{\alpha}{k_5}\right)(\sigma E-k_5Q)+\alpha Q+\phi I-\tilde{k_7}H\right\},\\
&=\frac{\tilde{k_8}}{\tilde{k_7}\nu_2}\left(\frac{\kappa k_5\tilde{k_7}+\kappa\eta\phi k_5+\eta\alpha\sigma\tilde{k_3}}{k_1\tilde{k_3}k_5\eta}\right)\lambda S-\frac{\tilde{k_8}}{\nu_2\eta}(I+\eta H),\\
&=\frac{\tilde{k_8}}{\eta\nu_2}\left[\left(\frac{\kappa k_5\tilde{k_7}+\kappa\eta\phi k_5+\eta\alpha\sigma\tilde{k_3}}{k_1\tilde{k_3}k_5\tilde{k_7}}\right)\lambda S-(I+\eta H)\right]\\
&\leq\frac{\tilde{k_8}}{\eta\nu_2}\left[\left(\frac{\kappa k_5\tilde{k_7}+\kappa\eta\phi k_5+\eta\alpha\sigma\tilde{k_3}}{k_1\tilde{k_3}k_5\tilde{k_7}}\right)\lambda S^*-(I+\eta H)\right],\ \text{ since }\ S\leq S^*\ \text{ in }\ \hat{\mathcal{D}}.
\end{aligned}\tag{6.19}$$

Similarly, by using $V\leq V^*$ in $\hat{\mathcal{D}}$, the last four terms of $\dot{\mathcal{F}}$ can be simplified as follows:

$$\begin{aligned}
&\left(\frac{\nu_1\theta_1\kappa k_6\tilde{k_8}+\nu_2\eta\theta_3\phi+\theta_1\kappa k_6+\nu_2\eta\theta_5\alpha\sigma_1\tilde{k_4}}{k_2\tilde{k_4}k_6\nu_2\eta}\right)\dot{E_V}+\left(\frac{\nu_1\tilde{k_8}+\nu_2\eta\theta_3\phi}{\nu_2\eta\tilde{k_4}}\right)\dot{I_V}\\
&+\left(\frac{\theta_5\alpha}{k_6}\right)\dot{Q_V}+\dot{H_V},\\
&\leq\frac{\tilde{k_8}}{\eta\nu_2}\left[\left(\frac{\nu_1\theta_1\kappa k_6\tilde{k_8}+\nu_2\eta\theta_3\phi+\theta_1\kappa k_6+\nu_2\eta\theta_5\alpha\sigma_1\tilde{k_4}}{k_2\tilde{k_4}k_6\tilde{k_8}}\right)\lambda V^*-(\nu_1I_V+\nu_2H_V)\right].
\end{aligned}\tag{6.20}$$

Using (6.19) and (6.20) in (6.18) gives:

$$\begin{aligned}
\dot{\mathcal{F}}&\leq\frac{\tilde{k_8}}{\eta\nu_2}\left[\left(\frac{\kappa k_5\tilde{k_7}+\kappa\eta\phi k_5+\eta\alpha\sigma\tilde{k_3}}{k_1\tilde{k_3}k_5\tilde{k_7}}\right)\lambda S^*-(I+\eta H)\right]\\
&+\frac{\tilde{k_8}}{\eta\nu_2}\left[\left(\frac{\nu_1\theta_1\kappa k_6\tilde{k_8}+\nu_2\eta\theta_3\phi+\theta_1\kappa k_6+\nu_2\eta\theta_5\alpha\sigma_1\tilde{k_4}}{k_2\tilde{k_4}k_6\tilde{k_8}}\right)\lambda V^*-(\nu_1I_V+\nu_2H_V)\right]\\
&=\frac{\tilde{k_8}\lambda}{\eta\nu_2\beta_1}(\mathcal{R}_{vac}^m-1)\leq 0,\ \text{ whenever }\ \mathcal{R}_{vac}^m\leq 1.
\end{aligned}$$

Since all the parameters and variables of the model (6.2) are non-negative, it follows that $\dot{\mathcal{F}} \leq 0$ for $\mathcal{R}_{vac}^m \leq 1$. Furthermore, $\dot{\mathcal{F}} = 0$ if and only if $E = E_V = I = I_V = Q = Q_V = H = H_V = 0$. Hence, $\mathcal{F}$ is a Lyapunov function on $\hat{\mathcal{D}}$. Thus, it follows, by the LaSalle's Invariance Principle (Theorem 2.6), that

$$(E, E_V, I, I_V, Q, Q_V, H, H_V) \to (0, 0, 0, 0, 0, 0, 0, 0) \text{ as } t \to \infty. \tag{6.21}$$

Furthermore, it follows from (6.21) that $\limsup_{t\to\infty} I = \liminf_{t\to\infty} I = 0$ and $\limsup_{t\to\infty} H = \liminf_{t\to\infty} H = 0$. Thus, for sufficiently small $\varpi^* > 0$, there exist constants $M_1, M_2 > 0$ such that $\limsup_{t\to\infty} I \leq \varpi^*$ for all $t > M_1$ and $\limsup_{t\to\infty} H \leq \varpi^*$ for all $t > M_2$. Hence, it follows from the eleventh equation of the model (6.2) that, for $t > \max\{M_1, M_2\}$,

$$\dot{R} \leq \gamma_1 \varpi^* + \gamma_2 \varpi^* - \mu R.$$

Thus, by comparison theorem (Theorem 2.8),

$$R^\infty = \limsup_{t\to\infty} R \leq \frac{\gamma_1 \varpi^* + \gamma_2 \varpi^*}{\mu},$$

so that, by letting $\varpi^* \to 0$,

$$R^\infty = \limsup_{t\to\infty} R \leq 0. \tag{6.22}$$

Similarly (by using $\liminf_{t\to\infty} I = 0$ and $\liminf_{t\to\infty} H = 0$), it can be shown that

$$R_\infty = \liminf_{t\to\infty} R \geq 0. \tag{6.23}$$

Thus, it follows from (6.22) and (6.23) that

$$R_\infty \geq 0 \geq R^\infty.$$

Hence,

$$\lim_{t\to\infty} R = 0. \tag{6.24}$$

Similarly, it can be shown that

$$\lim_{t\to\infty} S(t) = S^*,\ \lim_{t\to\infty} V(t) = V^*,\ \text{and}\ \lim_{t\to\infty} R_V(t) = 0. \tag{6.25}$$

Thus, by combining equations (6.21), (6.24) and (6.25), it follows that every solution of the equations in the model (6.2), with initial conditions in $\hat{\mathcal{D}}$, approaches $\mathcal{E}_0$ as $t \to \infty$ (for $\mathcal{R}^m_{vac} \leq 1$). □

Hence, the model (6.2) cannot undergo backward bifurcation when the standard incidence function is replaced by the mass action incidence function (since Theorem 6.4 shows that, in this case, the model has no endemic equilibrium when $\mathcal{R}^m_{vac} < 1$; and Theorem 6.5 shows that the associated DFE of the model (6.2) with $\delta_1 = \delta_2 = 0$, is GAS when $\mathcal{R}^m_{vac} \leq 1$). Figure 6.3 depicts the numerical results obtained by simulating the model (6.2) with $\delta_1 = \delta_2 = 0$, using various initial conditions, for the case when $\mathcal{R}^m_{vac} < 1$. It is clear from this figure that all initial solutions converged to the DFE, $\mathcal{E}_0$ (in line with Theorem 6.5).

In summary, the aforementioned analyses show that the vaccine-induced backward bifurcation phenomenon of the model (6.2) can be removed by doing any of the following:

(i) using a perfect vaccine (with efficacy 100%); or

(ii) ignoring disease-induced mortality in the model (this is equivalent to replacing the standard incidence function in the model with a mass action incidence function).

6.4 Global Stability of EEP

In this section, the global stability of the endemic equilibrium of the model (6.2) is given for the special case where the vaccine does not wane ($\psi = 0$), no continuous vaccination ($\zeta = 0$; but there is cohort vaccination of newly-recruited susceptible individuals ($\rho \neq 0$)), unvaccinated hospitalized individuals do not transmit infection ($\eta = 0$) and the associated disease- induced mortality is negligible (i.e., $\delta_1 = \delta_2 = 0$).

Substituting $\psi = \zeta = \eta = \delta_1 = \delta_2 = 0$ into the model (6.2) gives:

$$\begin{aligned}
\frac{dS}{dt} &= (1-p)\Pi - \lambda S - \mu S,\\
\frac{dV}{dt} &= p\Pi - (1-\varepsilon)\lambda V - \mu V,\\
\frac{dE}{dt} &= \lambda S - (\kappa + \sigma + \mu)E,\\
\frac{dE_V}{dt} &= (1-\varepsilon)\lambda V - (\theta_1\kappa + \sigma_1 + \mu)E_V,\\
\frac{dI}{dt} &= \kappa E - (\gamma_1 + \phi + \mu)I,\\
\frac{dI_V}{dt} &= \theta_1\kappa E_V - (\theta_2\gamma_1 + \theta_3\phi + \mu)I_V,\\
\frac{dQ}{dt} &= \sigma E - (\alpha + \mu)Q,\\
\frac{dQ_V}{dt} &= \sigma_1 E_V - (\theta_5\alpha + \mu)Q_V,\\
\frac{dH}{dt} &= \alpha Q + \phi I - (\gamma_2 + \mu)H,\\
\frac{dH_V}{dt} &= \theta_5\alpha Q_V + \theta_3\phi I_V - (\theta_6\gamma_2 + \mu)H_V,\\
\frac{dR}{dt} &= \gamma_1 I + \gamma_2 H - \mu R,\\
\frac{dR_V}{dt} &= \theta_2\gamma_1 I_V + \theta_6\gamma_2 H_V - \mu R_V,
\end{aligned} \tag{6.26}$$

where, now,

$$\lambda = \frac{\beta(I + \nu_1 I_V)}{N}. \tag{6.27}$$

It should be recalled that setting $\delta_1 = \delta_2 = 0$ in (6.2) implies that $N \to \Pi/\mu$ as $t \to \infty$. Using $N = \Pi/\mu$ in (6.27) gives

$$\lambda = \beta_1(I + \nu_1 I_V), \text{where } \beta_1 = \frac{\beta\mu}{\Pi}. \tag{6.28}$$

It can be shown that the associated reproduction number of the reduced model (6.26), with (6.28), is given by

$$\mathcal{R}_{vac}^{mr} = \frac{\beta_1(1-\varepsilon)\rho\Pi\nu_1\theta_1\kappa}{\mu k_2 \tilde{k_4}} + \frac{\beta_1(1-\rho\Pi)\kappa}{\mu k_1 \tilde{k_3}}.$$

Furthermore, it is easy to show, using the technique in Section 6.3.1, that the reduced model, (6.26) with (6.28), has a unique EEP, of the form

$$\mathcal{E}_2 = (S^{***},\ V^{***},\ E^{***},\ E_V^{***},\ I^{***},\ I_V^{***},\ Q^{***},\ Q_V^{***},\ H^{***},\ H_V^{***},\ R^{***},\ R_V^{***}),$$

whenever $\mathcal{R}_{vac}^{mr} > 1$.

Lemma 6.3. *The reduced model* (6.26)*, with* (6.28)*, has a unique positive endemic equilibrium, of the form* $\mathcal{E}_2$*, whenever* $\mathcal{R}_{vac}^{mr} > 1$.

It is convenient to define the region

$$\mathcal{D}_0 = \Big\{(S, V, E, E_V, I, I_V, Q, Q_V, H, H_V, R, R_V) \in \mathcal{D} : \\ E = E_V = I = I_V = Q = Q_V = H = H_V = R = R_V = 0\Big\}.$$

Theorem 6.6. *The unique endemic equilibrium of the reduced model* (6.26)*, with* (6.28)*, given by* $\mathcal{E}_2$*, is GAS in* $\mathcal{D} \setminus \mathcal{D}_0$ *if* $\mathcal{R}_{vac}^{mr} > 1$.

Proof. Consider the reduced model (6.26), with (6.28). Let $\mathcal{R}_{vac}^{mr} > 1$, so that the associated unique endemic equilibrium exists (Lemma 6.3). Further, consider the following non-linear Lyapunov function for the sub-system consisting of the first six equations of (6.26):

$$\begin{aligned}
\mathcal{F} &= (1-\varepsilon)\beta_1 V^{***} I^{***} \left[S - S^{***} - S^{***} \ln\left(\frac{S}{S^{***}}\right) + E - E^{***} - E^{***} \ln\left(\frac{E}{E^{***}}\right) \right] \\
&+ (1-\varepsilon)\beta_1 V^{***} I^{***} \frac{k_1}{\kappa} \left[I - I^{***} - I^{***} \ln\left(\frac{I}{I^{***}}\right) \right] \\
&+ \nu_1 \beta_1 S^{***} I_V^{***} \left[V - V^{***} - V^{***} \ln\left(\frac{V}{V^{***}}\right) + E_V - E_V^{***} - E_V^{***} \ln\left(\frac{E_V}{E_V^{***}}\right) \right] \\
&+ \nu_1 \beta_1 S^{***} I_V^{***} \frac{k_2}{\theta_1 \kappa} \left[I_V - I_V^{***} - I_V^{***} \ln\left(\frac{I_V}{I_V^{***}}\right) \right],
\end{aligned}$$

with Lyapunov derivative,

$$\begin{aligned}
\dot{\mathcal{F}} &= (1-\varepsilon)\beta_1 V^{***} I^{***} \left[\dot{S} - \frac{S^{***}}{S}\dot{S} + \dot{E} - \frac{E^{***}}{E}\dot{E} + \frac{k_1}{\kappa}\left(\dot{I} - \frac{I^{***}}{I}\dot{I} \right) \right] \\
&+ \nu_1 \beta_1 S^{***} I_V^{***} \left[\dot{V} - \frac{V^{***}}{V}\dot{V} + \dot{E_V} - \frac{E_V^{***}}{E_V}\dot{E_V} + \frac{k_2}{\theta_1 \kappa}\left(\dot{I_V} - \frac{I_V^{***}}{I_V}\dot{I_V} \right) \right],
\end{aligned}$$

so that (using the first six equations of (6.26)),

$$\begin{aligned}
\dot{\mathcal{F}} &= c\beta_1 V^{***} I^{***} \left[\Pi_1 - \beta_1 S(I + \nu_1 I_V) - \mu S - \frac{S^{***}}{S}\left(\Pi_1 - \beta_1 S(I + \nu_1 I_V) - \mu S \right) \right] \\
&+ c\beta_1 V^{***} I^{***} \left[\beta_1 S(I + \nu_1 I_V) - k_1 E - \frac{E^{***}}{E}\left(\beta_1 S(I + \nu_1 I_V) - k_1 E \right) \right] \\
&+ c\beta_1 V^{***} I^{***} \frac{k_1}{\kappa} \left[\kappa E - \tilde{k_3} I - \frac{I^{***}}{I}\left(\kappa E - \tilde{k_3} I \right) \right] \\
&+ \nu_1 \beta_1 S^{***} I_V^{***} \left[\Pi_2 - c\beta_1 V(I + \nu_1 I_V) - \mu V - \frac{V^{***}}{V}\left(\Pi_2 - c\beta_1 V(I + \nu_1 I_V) - \mu V \right) \right] \\
&+ \nu_1 \beta_1 S^{***} I_V^{***} \left[c\beta_1 V(I + \nu_1 I_V) - k_2 E_V - \frac{E_V^{***}}{E_V}\left(c\beta_1 V(I + \nu_1 I_V) - k_2 E_V \right) \right] \\
&+ \nu_1 \beta_1 S^{***} I_V^{***} \frac{k_2}{\theta_1 \kappa} \left[\theta_1 \kappa E_V - \tilde{k_4} I_V - \frac{I_V^{***}}{I_V}\left(\theta_1 \kappa E_V - \tilde{k_4} I_V \right) \right],
\end{aligned} \tag{6.29}$$

where,

$$c = 1 - \varepsilon, \quad \Pi_1 = (1-\rho)\Pi \text{ and } \Pi_2 = \rho\Pi.$$

It can be shown from (6.26) that, at endemic steady-state $\mathcal{E}_2$,

$$\Pi_1 = \beta_1(I^{***} + \nu_1 I_V^{***})S^{***} + \mu S^{***}, \;\; \Pi_2 = c\beta_1(I^{***} + \nu_1 I_V^{***})V^{***} + \mu V^{***},$$

$$k_1 = \frac{\beta_1(I^{***} + \nu_1 I_V^{***})S^{***}}{E^{***}}, \;\; k_2 = \frac{c\beta_1(I^{***} + \nu_1 I_V^{***})V^{***}}{E_V^{***}}, \tag{6.30}$$

$$\tilde{k_3} I^{***} = \frac{\kappa}{k_1}\beta_1(I^{***} + \nu_1 I_V^{***})S^{***}, \;\; \tilde{k_4} I_V^{***} = \frac{\theta_1\kappa}{k_2} c\beta_1(I^{***} + \nu_1 I_V^{***})V^{***}.$$

Using the first two relations of (6.30) in equation (6.29), and simplifying, gives

$$\begin{aligned}
\dot{\mathcal{F}} &= c\beta_1 V^{***} I^{***} \left[\beta_1(I^{***} + \nu_1 I_V^{***})S^{***} + \mu S^{***} - \mu S\right] \\
&+ c\beta_1 V^{***} I^{***} \left\{-\frac{S^{***}}{S}\left[\beta_1(I^{***} + \nu_1 I_V^{***})S^{***} + \mu S^{***} - \beta_1 S(I + \nu_1 I_V) - \mu S\right]\right\} \\
&+ c\beta_1 V^{***} I^{***} \left[-\frac{E^{***}}{E}\left(\beta_1 S(I + \nu_1 I_V) - k_1 E\right) + \frac{k_1}{\kappa}\left\{-\tilde{k_3} I - \frac{I^{***}}{I}\left(\kappa E - \tilde{k_3} I\right)\right\}\right] \\
&+ \nu_1\beta_1 S^{***} I_V^{***} \left[c\beta_1(I^{***} + \nu_1 I_V^{***})V^{***} + \mu V^{***} - \mu V\right] \\
&+ \nu_1\beta_1 S^{***} I_V^{***} \left\{-\frac{V^{***}}{V}\left[c\beta_1(I^{***} + \nu_1 I_V^{***})V^{***} + \mu V^{***} - c\beta_1 V(I + \nu_1 I_V) - \mu V\right]\right\} \\
&+ \nu_1\beta_1 S^{***} I_V^{***} \left\{-\frac{E_V^{***}}{E_V}\left(c\beta_1 V(I + \nu_1 I_V) - k_2 E_V\right) + \frac{k_2}{\theta_1\kappa}\left[-\tilde{k_4} I_V - \frac{I_V^{***}}{I_V}\left(\theta_1\kappa E_V - \tilde{k_4} I_V\right)\right]\right\},
\end{aligned}$$

so that,

$$
\begin{aligned}
\dot{\mathcal{F}} &= c\mu\beta_1 V^{***}S^{***}I^{***}\left(2-\frac{S^{***}}{S}-\frac{S}{S^{***}}\right)+\nu_1\mu\beta_1 V^{***}S^{***}I_V^{***}\left(2-\frac{V^{***}}{V}-\frac{V}{V^{***}}\right)\\
&+\left(c\beta_1^2 S^{***}V^{***}I^{***}+\nu_1 c\beta_1^2 S^{***}V^{***}I_V^{***}-\frac{k_1\tilde{k_3}}{\kappa}c\beta_1 V^{***}I^{***}\right)I\\
&+\left(\nu_1 c\beta_1^2 S^{***}V^{***}I^{***}+\nu_1^2 c\beta_1^2 S^{***}V^{***}I_V^{***}-\frac{k_2\tilde{k_4}}{\theta_1\kappa}\nu_1\beta_1 S^{***}I_V^{***}\right)I_V\\
&+c\beta_1^2 S^{***}V^{***}I^{***}(I^{***}+\nu_1 I_V^{***})-c\beta_1^2 V^{***}I^{***}\frac{(S^{***})^2}{S}(I^{***}+\nu_1 I_V^{***})\\
&-c\beta_1^2 V^{***}I^{***}\frac{E^{***}}{E}S(I+\nu_1 I_V)+k_1 c\beta_1 V^{***}I^{***}E^{***}-c\beta_1 V^{***}I^{***}\frac{k_1 E I^{***}}{I}\\
&+c\beta_1 V^{***}I^{***}\frac{k_1\tilde{k_3}}{\kappa}I^{***}+\nu_1 c\beta_1^2 S^{***}V^{***}I_V^{***}(I^{***}+\nu_1 I_V^{***})-\nu_1 c\beta_1^2 S^{***}I_V^{***}\frac{(V^{***})^2}{V}(I^{***}+\nu_1 I_V^{***})\\
&-\nu_1 c\beta_1^2 S^{***}I_V^{***}\frac{E_V^{***}}{E_V}V(I+\nu_1 I_V)+k_2\nu_1\beta_1 S^{***}I_V^{***}E_V^{***}\\
&-\nu_1\beta_1 S^{***}I_V^{***}\frac{k_2 E_V I_V^{***}}{I_V}+\nu_1\beta_1 S^{***}I_V^{***}\frac{k_2\tilde{k_4}}{\theta_1\kappa}I_V^{***}.
\end{aligned}
\tag{6.31}
$$

It can be shown from the last two relations of (6.30) that

$$
\begin{aligned}
&c\beta_1^2 S^{***}V^{***}I^{***}+\nu_1 c\beta_1^2 S^{***}V^{***}I_V^{***}-\frac{k_1\tilde{k_3}}{\kappa}c\beta_1 V^{***}I^{***}=0,\\
&\nu_1 c\beta_1^2 S^{***}V^{***}I^{***}+\nu_1^2 c\beta_1^2 S^{***}V^{***}I_V^{***}-\frac{k_2\tilde{k_4}}{\theta_1\kappa}\nu_1\beta_1 S^{***}I_V^{***}=0.
\end{aligned}
\tag{6.32}
$$

Substituting (6.32) in (6.31) gives

$$
\begin{aligned}
\dot{\mathcal{F}} &= c\mu\beta_1 V^{***}S^{***}I^{***}\left(2-\frac{S^{***}}{S}-\frac{S}{S^{***}}\right)+\nu_1\mu\beta_1 V^{***}S^{***}I_V^{***}\left(2-\frac{V^{***}}{V}-\frac{V}{V^{***}}\right)\\
&+c\beta_1^2 S^{***}V^{***}I^{***}(I^{***}+\nu_1 I_V^{***})-c\beta_1^2 V^{***}I^{***}\frac{(S^{***})^2}{S}(I^{***}+\nu_1 I_V^{***})\\
&-c\beta_1^2 V^{***}I^{***}\frac{E^{***}}{E}S(I+\nu_1 I_V)+k_1 c\beta_1 V^{***}I^{***}E^{***}-c\beta_1 V^{***}I^{***}\frac{k_1 EI^{***}}{I}\\
&+c\beta_1 V^{***}I^{***}\frac{k_1\tilde{k_3}}{\kappa}I^{***}+\nu_1 c\beta_1^2 S^{***}V^{***}I_V^{***}(I^{***}+\nu_1 I_V^{***})-\nu_1 c\beta_1^2 S^{***}I_V^{***}\frac{(V^{***})^2}{V}(I^{***}+\nu_1 I_V^{***})\\
&-\nu_1 c\beta_1^2 S^{***}I_V^{***}\frac{E_V^{***}}{E_V}V(I+\nu_1 I_V)+k_2\nu_1\beta_1 S^{***}I_V^{***}E_V^{***}-\nu_1\beta_1 S^{***}I_V^{***}\frac{k_2 E_V I_V^{***}}{I_V}\\
&+\nu_1\beta_1 S^{***}I_V^{***}\frac{k_2\tilde{k_4}}{\theta_1\kappa}I_V^{***}.
\end{aligned}
\tag{6.33}
$$

Using the last four relations of (6.30) in equation (6.33) gives

$$
\begin{aligned}
\dot{\mathcal{F}} &= c\mu\beta_1 V^{***}S^{***}I^{***}\left(2-\frac{S^{***}}{S}-\frac{S}{S^{***}}\right)+\nu_1\mu\beta_1 V^{***}S^{***}I_V^{***}\left(2-\frac{V^{***}}{V}-\frac{V}{V^{***}}\right)\\
&+c\beta_1^2 S^{***}V^{***}I^{***}(I^{***}+\nu_1 I_V^{***})-c\beta_1^2 V^{***}I^{***}\frac{(S^{***})^2}{S}(I^{***}+\nu_1 I_V^{***})\\
&-c\beta_1^2 V^{***}I^{***}\frac{E^{***}}{E}S(I+\nu_1 I_V)+c\beta_1^2 S^{***}V^{***}I^{***}(I^{***}+\nu_1 I_V^{***})\\
&-c\beta_1^2 V^{***}I^{***}S^{***}(I^{***}+\nu_1 I_V^{***})\frac{EI^{***}}{IE^{***}}+c\beta_1^2 S^{***}V^{***}I^{***}(I^{***}+\nu_1 I_V^{***})\\
&+\nu_1 c\beta_1^2 S^{***}V^{***}I_V^{***}(I^{***}+\nu_1 I_V^{***})-\nu_1 c\beta_1^2 S^{***}I_V^{***}\frac{(V^{***})^2}{V}(I^{***}+\nu_1 I_V^{***})\\
&-\nu_1 c\beta_1^2 S^{***}I_V^{***}\frac{E_V^{***}}{E_V}V(I+\nu_1 I_V)+k_2\nu_1 c\beta_1^2 S^{***}V^{***}I_V^{***}(I^{***}+\nu_1 I_V^{***})\\
&-\nu_1 c\beta_1^2 S^{***}V^{***}I_V^{***}(I^{***}+\nu_1 I_V^{***})\frac{E_V I_V^{***}}{E_V^{***}I_V}+\nu_1 c\beta_1^2 S^{***}V^{***}I_V^{***}(I^{***}+\nu_1 I_V^{***}).
\end{aligned}
$$

Thus,

$$\dot{\mathcal{F}} = c\mu\beta_1 V^{***}S^{***}I^{***}\left(2 - \frac{S^{***}}{S} - \frac{S}{S^{***}}\right) + \nu_1\mu\beta_1 V^{***}S^{***}I_V^{***}\left(2 - \frac{V^{***}}{V} - \frac{V}{V^{***}}\right)$$
$$+ c\beta_1^2 S^{***}V^{***}(I^{***})^2\left(3 - \frac{S^{***}}{S} - \frac{E^{***}SI}{ES^{***}I^{***}} - \frac{EI^{***}}{IE^{***}}\right)$$
$$+ \nu_1^2 c\beta_1^2 S^{***}V^{***}(I_V^{***})^2\left(3 - \frac{V^{***}}{V} - \frac{E_V^{***}VI_V}{E_V I_V^{***}V^{***}} - \frac{E_V I_V^{***}}{E_V^{***}I_V}\right)$$
$$+ \nu_1 c\beta_1^2 S^{***}V^{***}I^{***}I_V^{***}\left(6 - \frac{S^{***}}{S} - \frac{E^{***}SI_V}{ES^{***}I_V^{***}} - \frac{EI^{***}}{E^{***}I} - \frac{V^{***}}{V} - \frac{E_V^{***}VI}{E_V V^{***}I^{***}} - \frac{E_V I_V^{***}}{E_V^{***}I_V}\right).$$

Finally, since the arithmetic mean exceeds the geometric mean, then

$$\left(2 - \frac{S^{***}}{S} - \frac{S}{S^{***}}\right) \leq 0, \quad \left(2 - \frac{V^{***}}{V} - \frac{V}{V^{***}}\right) \leq 0,$$
$$\left(3 - \frac{S^{***}}{S} - \frac{SIE^{***}}{S^{***}I^{***}E} - \frac{EI^{***}}{IE^{***}}\right) \leq 0, \quad \left(3 - \frac{V^{***}}{V} - \frac{E_V^{***}VI_V}{E_V I_V^{***}V^{***}} - \frac{E_V I_V^{***}}{E_V^{***}I_V}\right) \leq 0,$$
$$\left(6 - \frac{S^{***}}{S} - \frac{E^{***}SI_V}{ES^{***}I_V^{***}} - \frac{EI^{***}}{E^{***}I} - \frac{V^{***}}{V} - \frac{E_V^{***}VI}{E_V V^{***}I^{***}} - \frac{E_V I_V^{***}}{E_V^{***}I_V}\right) \leq 0.$$

Further, since all the model parameters are non-negative, it follows that $\dot{\mathcal{F}} \leq 0$ for $\mathcal{R}_{vac}^{mr} > 1$. Thus, $\mathcal{F}$ is a Lyapunov function of the sub-system consisting of the first six equations of the model (6.26) on $\mathcal{D} \setminus \mathcal{D}_0$. Therefore, it follows, by the LaSalle's Invariance Principle [41], that

$$\begin{aligned} &\lim_{t\to\infty} S(t) = S^{***}, \ \lim_{t\to\infty} V(t) = V^{***}, \ \lim_{t\to\infty} E(t) = E^{***}, \\ &\lim_{t\to\infty} I(t) = I^{***}, \ \lim_{t\to\infty} E_V(t) = E_V^{***}, \ \lim_{t\to\infty} I_V(t) = I_V^{***}. \end{aligned} \tag{6.34}$$

It is clear from (6.34) that $\limsup_{t\to\infty} E = E^{***}$. Thus, for sufficiently small small $\varpi > 0$, there exists a constant $n_1 > 0$ such that $\limsup_{t\to\infty} E \leq E^{***} + \varpi$ for all $t > n_1$. It follows from the seventh equation of the model (6.26) that, for $t > n_1$,

$$\dot{Q} \leq \sigma(E^{***} + \varpi) - (\alpha + \mu)Q.$$

Thus, by comparison theorem (Theorem 2.8),

$$Q^{\infty} = \limsup_{t\to\infty} Q \leq \frac{\sigma(E^{***} + \varpi)}{\alpha + \mu},$$

so that, by letting $\varpi \to 0$,

$$Q^{\infty} = \limsup_{t\to\infty} Q \leq \frac{\sigma E^{***}}{\alpha + \mu}. \tag{6.35}$$

Similarly (by using $\liminf_{t\to\infty} E = E^{***}$), it can be shown that

$$Q_{\infty} = \liminf_{t\to\infty} Q \geq \frac{\sigma E^{***}}{\alpha + \mu}. \tag{6.36}$$

Thus, it follows from (6.35) and (6.36) that

$$Q_{\infty} \geq \frac{\sigma E^{***}}{\alpha + \mu} \geq Q^{\infty}.$$

Hence,

$$\lim_{t\to\infty} Q = \frac{\sigma E^{***}}{\alpha + \mu} = Q^{***}. \tag{6.37}$$

Similarly, it can be shown that

$$\begin{aligned} &\lim_{t\to\infty} H(t) = H^{***},\ \lim_{t\to\infty} Q_V(t) = Q_V^{***},\ \lim_{t\to\infty} H_V(t) = H_V^{***}, \\ &\lim_{t\to\infty} R(t) = R^{***},\ \lim_{t\to\infty} R_V(t) = R_V^{***}. \end{aligned} \tag{6.38}$$

Thus, by combining (6.34), (6.37) and (6.38), it follows that every solution to the equations of the reduced model (6.26) with (6.28), with initial conditions in $\mathcal{D} \setminus \mathcal{D}_0$, approaches the unique endemic equilibrium of the reduced system (6.26) with (6.28)

as $t \to \infty$ for $\mathcal{R}_{vac}^{mr} > 1$. □

The above result (Theorem 6.6) shows that, for this special case (with $\psi = \zeta = \eta = \delta_1 = \delta_2 = 0$), the disease will persist in the population whenever the associated reproduction number ($\mathcal{R}_{vac}^{mr}$) exceeds unity. Figure 6.4A depicts the simulation results of the model (6.26) for the case when $\mathcal{R}_{vac}^{mr} > 1$, showing convergence to an EEP (in line with Theorem 6.6; a blow up of Figure 6.4A is given in Figure 6.4B to confirm that the solutions, indeed, converged to the EEP). Further extensive numerical simulations suggest that the endemic equilibrium ($\mathcal{E}_1$) of the model (6.2) is GAS in $\mathcal{D}\backslash\mathcal{D}_0$, whenever $\mathcal{R}_{vac} > 1$. Hence, the following conjecture is suggested.

Conjecture 6.1. *The unique endemic equilibrium of the model* (6.2)*, given by* $\mathcal{E}_1$*, is GAS in* $\mathcal{D} \setminus \mathcal{D}_0$*, whenever* $\mathcal{R}_{vac} > 1$*.*

6.5 Assessment of Vaccinae Impact

In this section, the potential impact of the imperfect vaccine is assessed by carrying out threshold analysis on the associated reproduction number ($\mathcal{R}_{vac}^{m}$) as follows (it should be recalled that $\mathcal{R}_{vac}^{m}$ is the reproduction number associated with the model (6.2) in the absence of disease-induced mortality; in this case, the requirement $\mathcal{R}_{vac}^{m} \leq 1$ is sufficient for disease elimination, as confirmed by Theorem 6.5). First of all, the quantity $\mathcal{R}_{vac}^{m}$ is expressed as a function of the fraction of susceptible individuals vaccinated at steady-state, denoted by $\mathcal{T} = \frac{V^*}{N^*}$, given by:

$$\mathcal{R}_{vac}^{m}(\mathcal{T}) = \frac{\beta(1-\mathcal{T})(\kappa k_5 \tilde{k}_7 + \eta\phi\kappa k_5 + \eta\sigma\alpha\tilde{k}_3)}{k_1\tilde{k}_3 k_5 \tilde{k}_7} + \frac{\beta(1-\varepsilon)\mathcal{T}(\nu_1\theta_1\kappa k_6\tilde{k}_8 + \nu_2\eta\theta_1\kappa\theta_3\phi k_6 + \nu_2\eta\sigma_1\theta_5\alpha\tilde{k}_4)}{k_2\tilde{k}_4 k_6 \tilde{k}_8}.$$

Differentiating $\mathcal{R}_{vac}^{m}$ partially with respect to $\mathcal{T}$ gives

$$\frac{\partial \mathcal{R}^m_{vac}}{\partial \mathcal{T}} = \frac{-\beta(\kappa k_5 \tilde{k}_7 + \eta\phi\kappa k_5 + \eta\sigma\alpha\tilde{k}_3)}{k_1\tilde{k}_3 k_5 \tilde{k}_7} + \frac{\beta(1-\varepsilon)(\nu_1\theta_1\kappa k_6\tilde{k}_8 + \nu_2\eta\theta_1\kappa\theta_3\phi k_6 + \nu_2\eta\sigma_1\theta_5\alpha\tilde{k}_4)}{k_2\tilde{k}_4 k_6 \tilde{k}_8}. \tag{6.39}$$

The critical (threshold) value of vaccine efficacy (denoted by ε_c) needed to ensure positive population-level vaccine impact (in reducing disease burden in the community) can be obtained by setting the right-hand side of equation (6.39) to zero and solving for ε (it should be mentioned that disease burden is typically measured in terms of the number of new infections, hospitalizations and disease-induced mortality). This gives:

$$\varepsilon_c = 1 - \frac{(\kappa k_5 \tilde{k}_7 + \eta\phi\kappa k_5 + \eta\sigma\alpha\tilde{k}_3)k_2\tilde{k}_4 k_6\tilde{k}_8}{(\nu_1\theta_1\kappa k_6\tilde{k}_8 + \nu_2\eta\theta_1\kappa\theta_3\phi k_6 + \nu_2\eta\sigma_1\theta_5\alpha\tilde{k}_4)k_1\tilde{k}_3 k_5\tilde{k}_7}.$$

It follows then that $\frac{\partial \mathcal{R}^m_{vac}}{\partial \mathcal{T}} < 0$ whenever $\varepsilon > \varepsilon_c$. That is, $\mathcal{R}^m_{vac}$ is a decreasing function of the fraction of susceptible individuals vaccinated at steady-state ($\mathcal{T}$) whenever $\varepsilon > \varepsilon_c$. Thus, the above analysis shows that the vaccine will have a positive population-level impact in reducing disease burden whenever $\varepsilon > \varepsilon_c$, and will not otherwise. This result is summarized below:

Lemma 6.4. *Consider the model* (6.2) *with* $\delta_1 = \delta_2 = 0$. *The vaccine will have:*

(i) a positive population-level impact if $\varepsilon > \varepsilon_c$;

(ii) no population-level impact if $\varepsilon = \varepsilon_c$;

(iii) negative population-level impact if $\varepsilon < \varepsilon_c$.

A plot of the reproduction number ($\mathcal{R}^m_{vac}$) as a function of the fraction of susceptible individuals vaccinated at steady-state ($\mathcal{T}$) is given in Figure 6.5, for the cases where $\varepsilon > \varepsilon_c$ and $\varepsilon < \varepsilon_c$. This figure shows that, for the case when $\varepsilon > \varepsilon_c$, the reproduction

threshold, $\mathcal{R}_{vac}^m$, decreases as $\mathcal{T}$ increases. On other hand, $\mathcal{R}_{vac}^m$ increases with increasing values of $\mathcal{T}$ for the case when $\varepsilon < \varepsilon_c$ (these results are in line with Lemma 6.4).

Alternatively, the vaccine impact can be measured by rewriting $\mathcal{R}_{vac}^m$ as

$$\mathcal{R}_{vac}^m = \mathcal{R}_0 \left[1 - \frac{V^*}{N^*}\left(1 - \frac{\mathcal{R}_{0v}}{\mathcal{R}_0}\right)\right], \tag{6.40}$$

where,

$$\mathcal{R}_0 = \frac{\beta(\kappa k_5 \tilde{k}_7 + \eta\phi\kappa k_5 + \eta\sigma\alpha\tilde{k}_3)}{k_1\tilde{k}_3 k_5 \tilde{k}_7}, \tag{6.41}$$

and V^* and S^* are as defined in Section 6.3. The quantity, $\mathcal{R}_0$, is the reproduction number of the model (6.2) with $\delta_1 = \delta_2 = 0$ in the absence of vaccination. Furthermore,

$$\mathcal{R}_{0v} = \frac{\beta(1-\varepsilon)(\nu_1\theta_1\kappa k_6\tilde{k}_8 + \nu_2\eta\theta_1\kappa\theta_3\phi k_6 + \nu_2\eta\sigma_1\theta_5\alpha\tilde{k}_4)}{k_2\tilde{k}_4 k_6 \tilde{k}_8} \tag{6.42}$$

is the reproduction number when every individual in the population is vaccinated [7, 27].

Let,

$$\chi = \frac{V^*}{N^*}\left(1 - \frac{\mathcal{R}_{0v}}{\mathcal{R}_0}\right). \tag{6.43}$$

It should be noted from the expression in (6.43) that if $\mathcal{R}_{0v} < \mathcal{R}_0$, then the vaccine impact factor, χ, is positive, so that the vaccine will reduce $\mathcal{R}_{vac}^m$ (hence, the vaccine will have positive community-wide impact in this case disease burden). On the other hand, if $\mathcal{R}_{0v} > \mathcal{R}_0$, then the vaccine will have negative community-wide impact (i.e., it will increase disease burden) since $\chi < 0$ in this case. Finally, if $\mathcal{R}_{0v} = \mathcal{R}_0$ (so that, $\chi = 0$), then the vaccine will have no community-wide impact. These results are summarized below.

Theorem 6.7. *Consider the model* (6.2) *with* $\delta_1 = \delta_2 = 0$. *The vaccine will have:*

(i) a positive community-wide impact if $\chi > 0$ *(*$\mathcal{R}_{0v} < \mathcal{R}_0$*);*

(ii) no impact if $\chi = 0$ *(*$\mathcal{R}_{0v} = \mathcal{R}_0$*);*

(iii) negative community-wide impact if $\chi < 0$ *(*$\mathcal{R}_{0v} > \mathcal{R}_0$*).*

The above result (Theorem 6.7) is numerically illustrated, by depicting the cumulative number of new cases of infection as a function of time, in Figures 6.6 and 6.7. Figure 6.6 shows the case with $\varepsilon > \varepsilon_c$ ($\chi > 0$), from which it is clear that the use of the imperfect vaccine induces a positive community-wide impact (since the cumulative number of new cases of infection in the presence of the vaccine is less than that in the absence of vaccination). However, for the case when $\varepsilon < \varepsilon_c$ ($\chi < 0$), the use of an imperfect vaccine causes a detrimental community-wide impact (since, in this case, the cumulative number of new cases exceeds that for the case when vaccination is not implemented (Figure 6.7)).

A contour plot of $\mathcal{R}^m_{vac}$, as a function of the fraction of susceptible individuals vaccinated at steady-state ($\mathcal{T}$) and the vaccine efficacy (ε), is depicted in Figure 6.8. It is clear from Figure 6.8 that effective disease elimination is feasible if the fraction of individuals vaccinated at steady-state ($\mathcal{T}$) and vaccine efficacy (ε) are high enough. For example, if the vaccine is 70% effective ($\varepsilon = 0.7$), vaccinating 50% of the susceptible population at steady-state ($\mathcal{T} = 0.5$) will be sufficient to eliminate the disease.

Further numerical simulations were carried out to assess the impact of the singular use of the quarantine/isolation strategy (in the absence of the imperfect vaccine). The following levels of quarantine/isolation effectiveness are considered (arbitrarily):

(i) low effectiveness level of the quarantine/isolation strategy ($\phi = 0.05,\ \sigma = 0.05,\ \delta_1 = \delta_2 = 0$; so that, $\mathcal{R}_0 = 1.1138$);

(ii) moderate effectiveness level of the quarantine/isolation strategy ($\phi = 0.1,\ \sigma = 0.1,\ \delta_1 = \delta_2 = 0$; so that, $\mathcal{R}_0 = 0.9815$);

(iii) high effectiveness level of the quarantine/isolation strategy ($\phi = 1,\ \sigma = 1,\ \delta_1 = \delta_2 = 0$; so that, $\mathcal{R}_0 = 0.8491$).

In other words, it is assumed that the moderately effective quarantine/isolation strategy is twice as effective as the low effective quarantine/isolation strategy. Furthermore, the high quarantine/isolation effective strategy is ten times more effective than the moderately effective quarantine/isolation strategy (as mentioned above, these choices are made arbitrarily).

The simulation results obtained, depicted in Figure 6.9, show a decrease in the cumulative number of new cases of infection with increasing effectiveness level of the quarantine/isolation strategy. For instance, while the low effectiveness strategy results in about over 250,000 cumulative new cases over 2 years (Figure 6.9A), the moderate and high effectiveness levels of the quarantine/isolation strategy resulted in only 4,000 and 1,000 new cases, over the same time period, respectively (Figure 6.9B). Thus, based on the parameter values used in these simulations, the singular use of the quarantine/isolation strategy could lead to the effective control (or elimination) of the disease if its effectiveness level is moderately high enough (since both the moderate and the high effectiveness level of the quarantine/isolation strategy guaranteed that the associated reproduction number, $\mathcal{R}^m_{vac}$, is less than unity so that, by Theorem 6.5, the disease will be eliminated from the community).

Furthermore, simulations for the universal strategy, where the quarantine/isolation strategy is combined with a vaccination strategy, are also carried out. Here, too, three effectiveness levels are considered (arbitrarily), as follows:

(i) low effectiveness level of the universal strategy ($\phi = 0.05,\ \sigma = 0.05,\ \sigma_1 = 0.05,\ \zeta = 0.05,\ \rho = 0.25,\ \delta_1 = \delta_2 = 0$; so that, $\mathcal{R}^m_{vac} = 0.7593$);

(ii) moderate effectiveness level of the universal strategy $\phi = 0.1,\ \sigma = 0.1,\ \sigma_1 = 0.1,\ \zeta = 0.1,\ \rho = 0.4,\ \delta_1 = \delta_2 = 0$; so that, $\mathcal{R}^m_{vac} = 0.5380$);

(iii) high effectiveness level of the universal strategy ($\phi = 1,\ \sigma = 1,\ \sigma_1 = 1\zeta = 1,\ \rho = 0.5,\ \delta_1 = \delta_2 = 0$; so that, $\mathcal{R}^m_{vac} = 0.2355$).

Clearly, each of the three levels of the universal strategy reduces the associated reproduction number, $\mathcal{R}^m_{vac}$, to a value less than unity (so that, by Theorem 6.5, the disease will be eliminated from the community under each of the aforementioned universal strategy scenarios). Figure 6.10 shows the simulation results obtained for the various effectiveness level of the universal strategy. This figure shows a dramatic decrease in the cumulative number of new cases in comparison to the corresponding number of cases recorded using the quarantine/isolation strategy alone (depicted in Figure 6.9). For instance, while the low effectiveness level of the universal strategy resulted in 1800 cases over 2 years (note that the corresponding number of cases for the quarantine/isolation strategy only is about 250,000), the moderate and high effectiveness levels of the universal strategy resulted in 600 and 200 new cases, over the same time period, respectively.

These simulations show that, while a moderately high effectiveness level is required if only quarantine/isolation is used, even the low effectiveness level of the universal strategy (considered in this chapter) will guarantee elimination of the disease from the community. Figure 6.11A shows that the disease can be eliminated after about 200 days using the high effectiveness level of the universal strategy (the time to disease elimination increases with decreasing effectiveness level of the universal strategy (see Figure 6.11B and Figure 6.11C)). In other words, the prospect of disease elimination from the community is greatly enhanced if the universal strategy is used.

6.6 Summary

In this chapter, a new deterministic model for disease transmission in a population, subject to the use of quarantine (of asymptomatic cases) and isolation (of symptomatic

cases) and an imperfect vaccine, is designed and rigorously analyzed. The analyses of the model, which consists of twelve mutually-exclusive epidemiological compartments, shows the following:

(i) The model undergoes the phenomenon of backward bifurcation when the associated reproduction number ($\mathcal{R}_{vac}$) is less than unity (Theorem 6.2). The presence of this phenomenon, which does not arise if the vaccine is 100% effective or if the standard incidence function is replaced by mass action incidence function in the model formulation (Theorems 6.3 and 6.5), implies that the effective control of the spread of the disease, using an imperfect vaccine (in addition to quarantine and isolation), depends on the initial sizes of the sub-populations of the model (when $\mathcal{R}_{vac} < 1$);

(ii) The disease-free equilibrium of the model is shown to be globally-asymptotically stable under any of the following scenarios (Theorems 6.3 and 6.5):

  (a) if the vaccine is perfect (i.e., the vaccine is 100% effective);

  (b) if there is no disease-induced mortality;

(iii) The model has a unique endemic equilibrium whenever the associated reproduction threshold ($\mathcal{R}_{vac}$) exceeds unity (Theorem 6.2). The unique endemic equilibrium of the model is shown to be globally-asymptotically stable for a special case (Theorem 6.6);

(iv) An imperfect vaccine could have positive or negative population-level impact, depending on the value of some associated threshold quantities (expressed in terms of a critical vaccine efficacy, ε_c, or a vaccine impact factor, χ) (Lemma 6.4 and Theorem 6.7).

Numerical simulations of the model (6.2), with $\delta_1 = \delta_2 = 0$, suggest the following:

(a) the singular use of quarantine/isolation strategy may lead to the effective control of the disease (or elimination) if its effectiveness level is moderately high enough;

(b) the combined use of the quarantine/isolation strategy with a vaccination strategy will eliminate the disease, even for the low efficacy level of the universal strategy (considered in this chapter).

Overall, the analyses in this chapter show that adding a vaccine to the quarantine/isolation model (3.2) alters its asymptotic dynamics (by inducing the phenomenon of backward bifurcation). The prospect of disease control using quarantine/isolation, as a single control strategy, is bright provided its effectiveness level is moderately high enough. The use of a universal strategy, involving the use of quarantine, isolation and an imperfect vaccine, will lead to disease elimination (even for the low effectiveness level considered in the simulations).

Table 6.2: Estimated values for the parameters of the model (6.2)

Parameters	Values (per day)	Sources
Π	136	[38]
β	[0.1, 0.2]	[38]
μ	0.0000351	[38]
γ_1	0.03521	[15]
γ_2	0.042553	[15]
δ_1	0.04227	[59]
δ_2	0.027855	[15]
κ	0.156986	[23]
α	0.156986	[23]
ϕ	0.20619	[15]
σ	0.1	[38]
σ_1	0.06	Assumed
ψ	0.0666	Assumed
η	0.6	Assumed
ν_1	0.9	Assumed
ν_2	0.8	Assumed
ε	[0,1]	Variable
ζ	0.7	Assumed
θ_1	0.6	Assumed
θ_2	1.4	Assumed
θ_3	0.7	Assumed
θ_4	0.6	Assumed
θ_5	0.5	Assumed
θ_6	1.4	Assumed
θ_7	0.7	Assumed

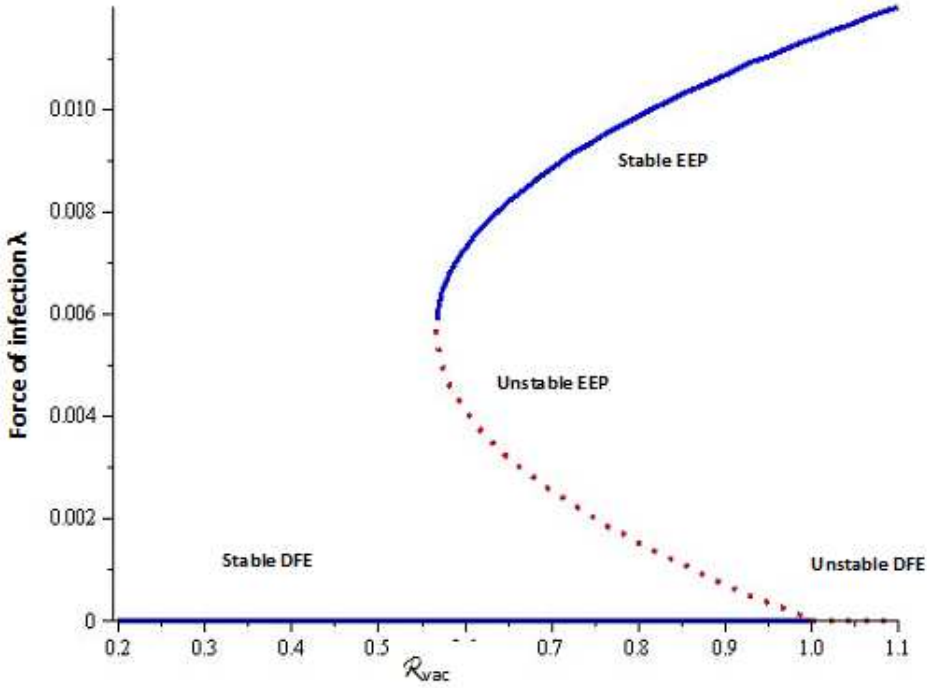


Figure 6.2: Backward bifurcation diagram for the model (6.2). Parameter values used are: $\Pi = 136,\ \beta = 1.4,\ \ \mu = 0.001,\ \zeta = 0.06,\ \psi = 0.0001,\ \kappa = 0.00016,\ \theta_1 = 0.7\ \theta_4 = 0.9,\ \sigma_1 = 0.09,\ \theta_5 = 0.9,\ \theta_2 = 1,\ \theta_6 = 1,\ \theta_3 = 0.01,\ \theta_7 = 1,\ \delta_1 = 0.001,\ \delta_2 = 0.01,\ \nu_1 = 0.9,\ \rho = 0.1,\ \varepsilon = 10^{-7},\ \alpha = 1,\ \phi = 1,\ \gamma_1 = 0.01,\ \gamma_2 = 0.1,\ \eta = 1,\ \nu_2 = 1,\ \sigma = 1$ (so that, $\mathcal{R}^c_{vac} = 0.5673706974 < \mathcal{R}_{vac} = 0.6719831393 < 1$).

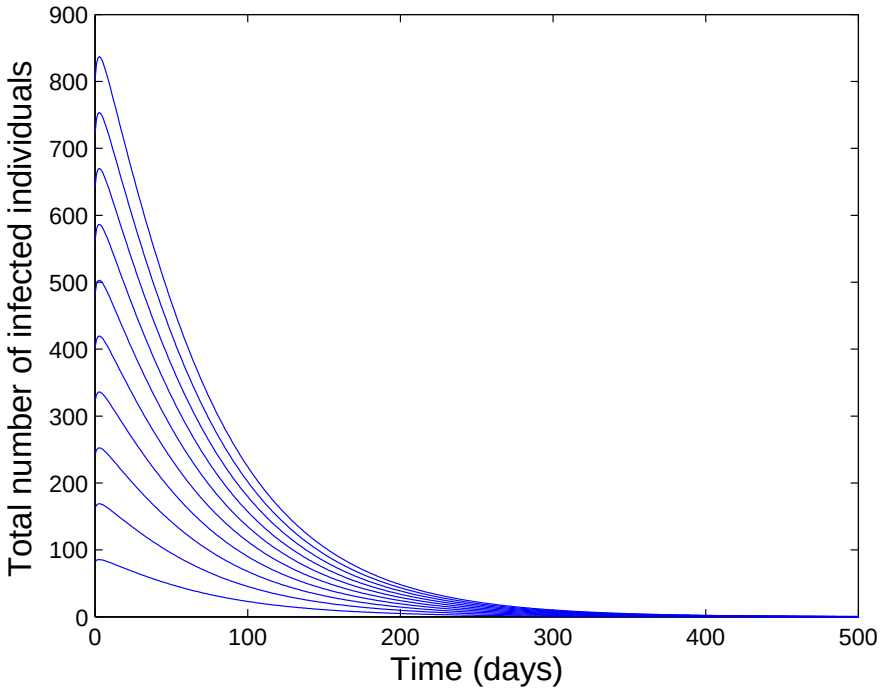
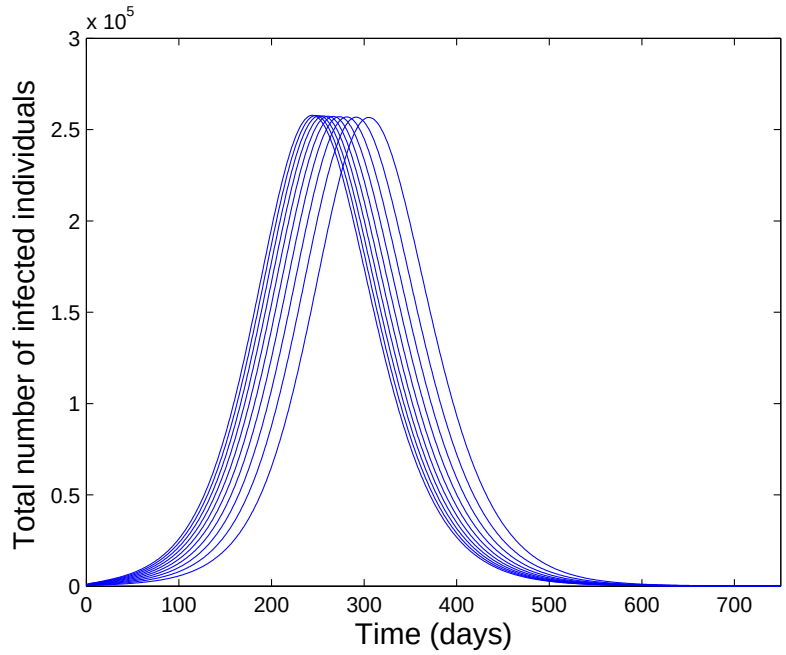


Figure 6.3: Simulation of the model (6.2) with $\delta_1 = \delta_2 = 0$ showing the total number of infected individuals as a function of time for the case when $\mathcal{R}_{vac}^m < 1$. Parameter values used are as given in Table 6.2, with $\beta = 0.15$ (so that, $\mathcal{R}_{vac}^m = 0.6206$).

(A)



(B)

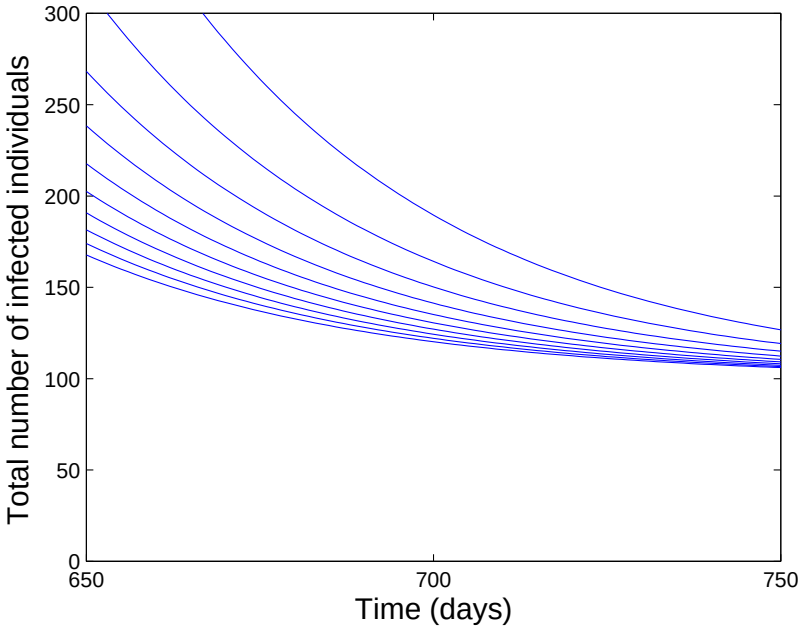
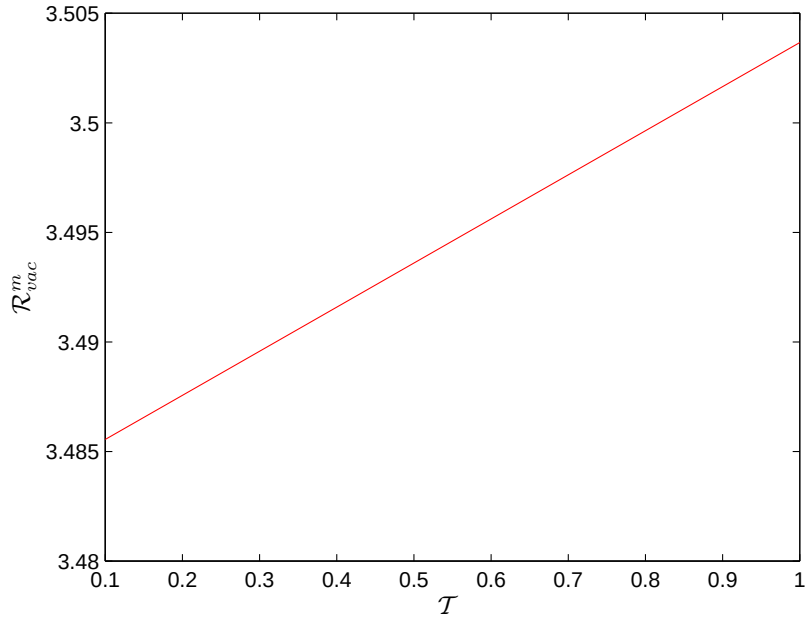


Figure 6.4: Simulation of the model (6.26) showing the total number of infected individuals as a function of time for $\mathcal{R}_{vac}^{mr} > 1$. (A) Convergence to an EEP. (B) Blow up of tail end of Figure 6.4A. Parameter values used are as given in Table 6.2, with $\beta = 0.5, \psi = \zeta = \eta = \delta_1 = \delta_2 = 0$ (so that, $\mathcal{R}_{vac}^{mr} = 1.2260$).

(A)



(B)

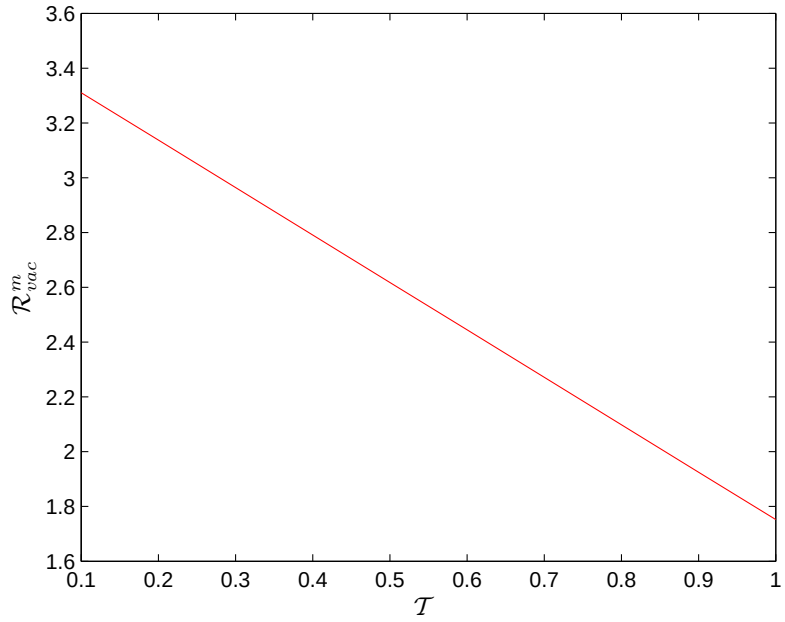


Figure 6.5: Simulations of the model (6.2) with $\delta_1 = \delta_2 = 0$ showing the reproduction number ($\mathcal{R}^m_{vac}$) as a function of the fraction of susceptible individuals vaccinated at steady-state ($\mathcal{T}$). Parameter values used are as given in Table 6.2, with (A): $\beta = 0.3, \theta_2 = \theta_6 = 1.1, \delta_1 = \delta_2 = 0$ and $\varepsilon = 0.001$ (so that, $0.001 = \varepsilon < \varepsilon_c = 0.0058$); (B): $\varepsilon = 0.5$ (so that, $0.5 = \varepsilon > \varepsilon_c = 0.0058$).

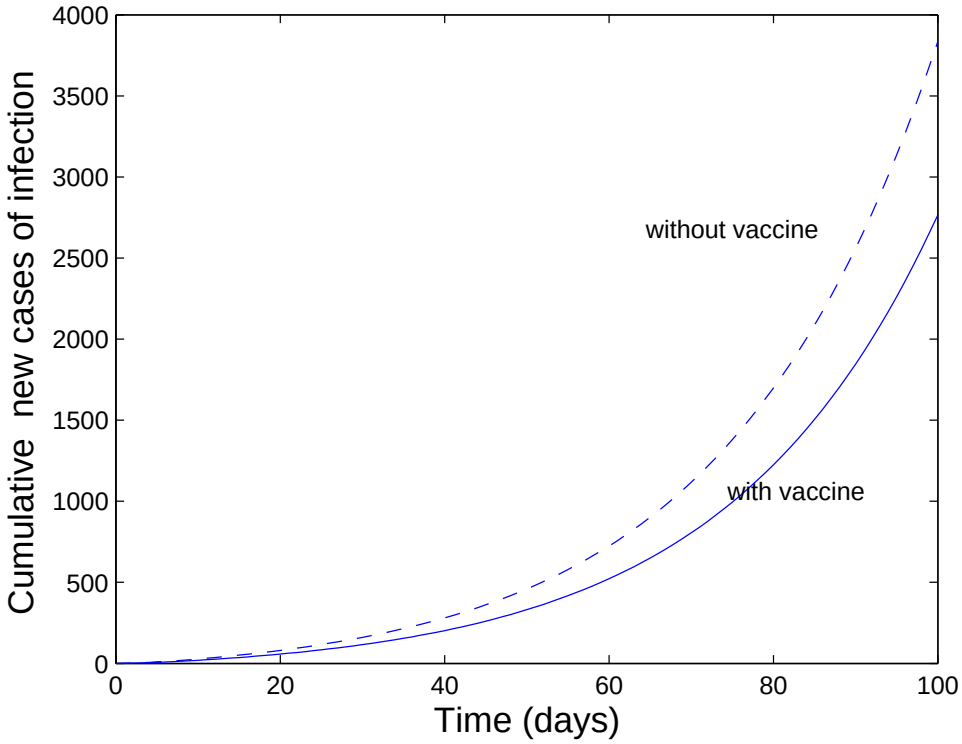


Figure 6.6: Simulations of the model (6.2), showing the cumulative number of new cases of infection as a function of time in the presence or absence of vaccination. Parameter values used are as given in Table 6.2, with $\beta = 0.3, \theta_2 = \theta_6 = 1.1, \delta_1 = \delta_2 = 0$ and $\varepsilon = 0.5$ (so that, $\chi = 0.4538 > 0, 0.5 = \varepsilon > \varepsilon_c = 0.0058$ and the vaccine has a positive population-level impact).

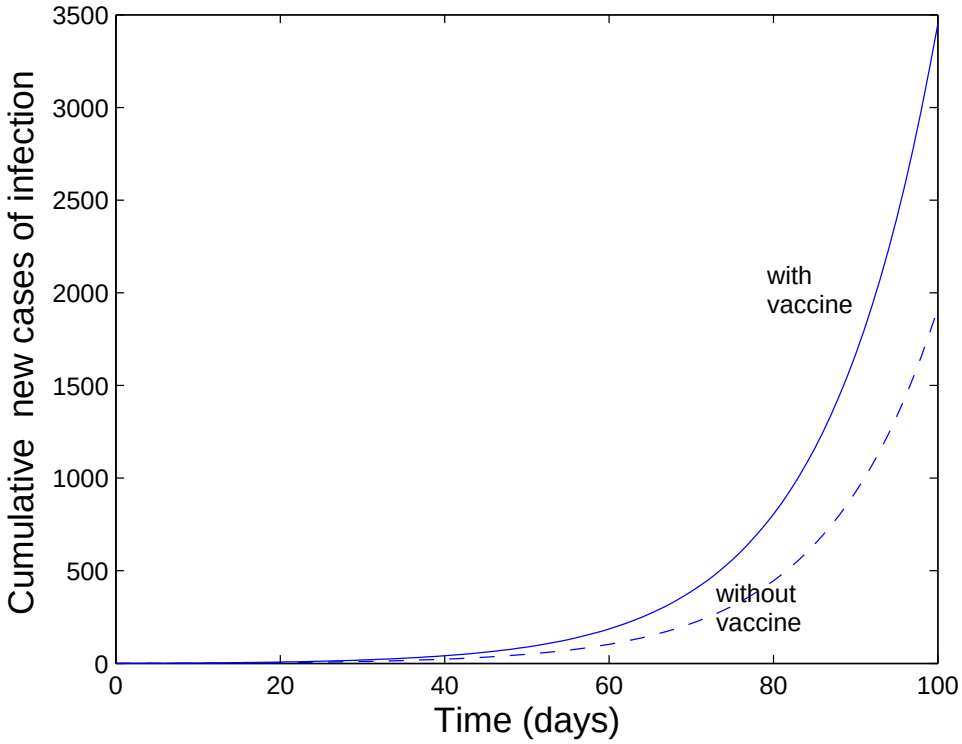


Figure 6.7: Simulations of the model (6.2), showing the cumulative number of new cases of infection as a function of time in the presence or absence of vaccination. Parameter values used are as given in Table 6.2, with $\beta = 0.3, \theta_2 = \theta_6 = 1.1, \delta_1 = \delta_2 = 0$ and $\varepsilon = 0.001$ (so that, $\chi = -0.0053 < 0$, $0.001 = \varepsilon < \varepsilon_c = 0.0058$, and the vaccine has a negative population-level impact).

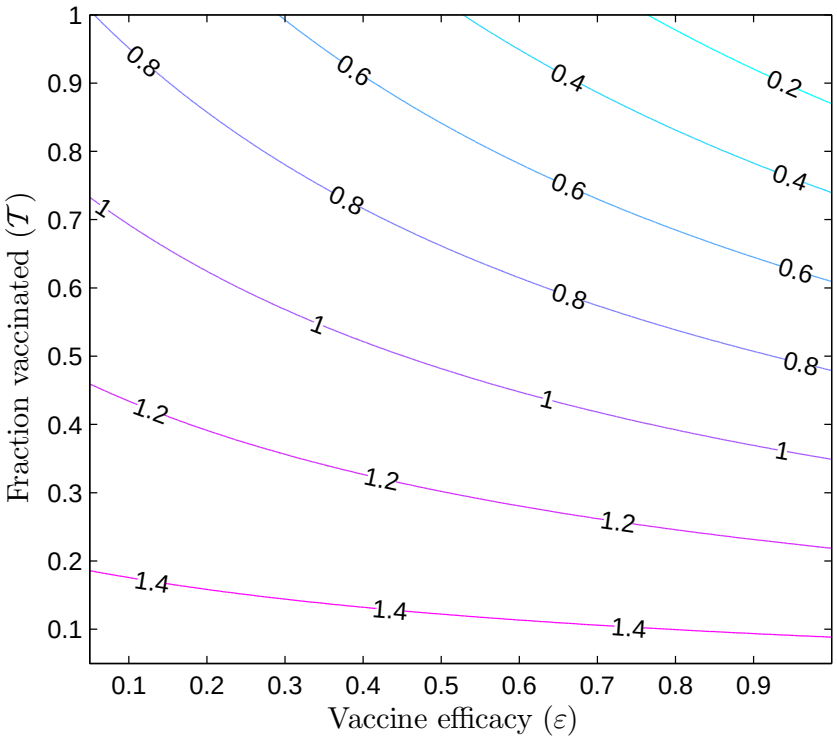
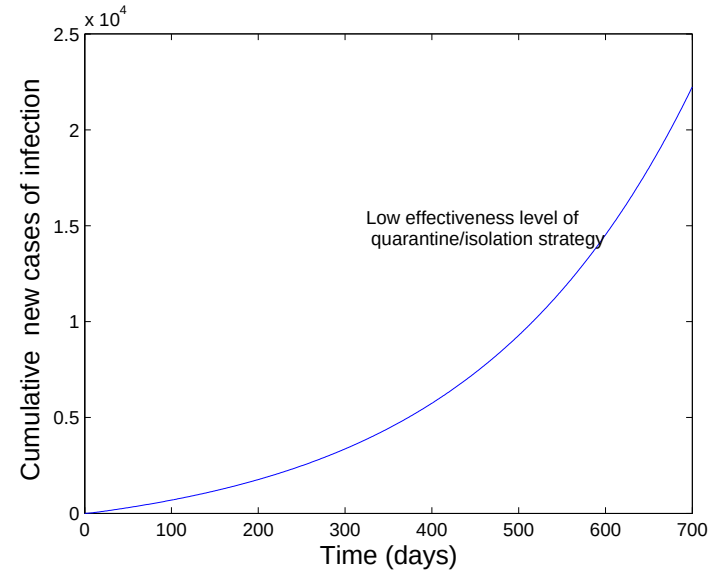


Figure 6.8: Simulation of the model (6.2), showing contour plots of $\mathcal{R}^m_{vac}$ as a function of vaccine efficacy (ε) and the fraction of susceptible individuals vaccinated at steady- state ($\mathcal{T}$). Parameter values used are as given in Table 6.2, with $\beta = 0.15$ and $\delta_1 = \delta_2 = 0$.

(A)



(B)

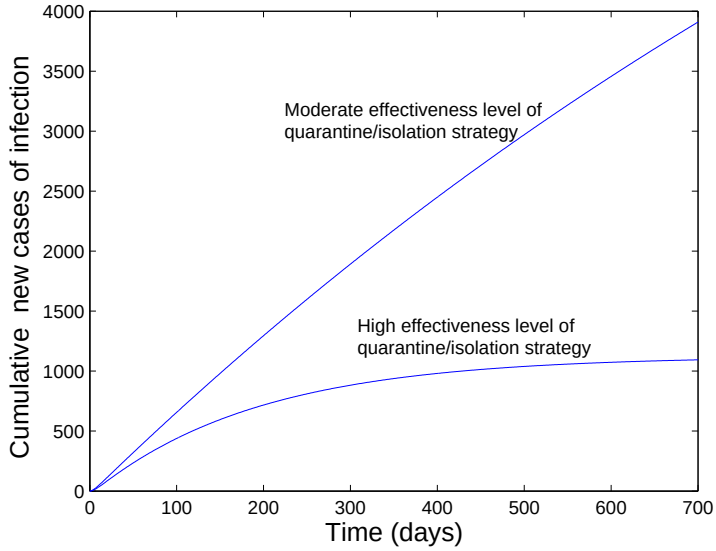


Figure 6.9: Simulations of the model (6.2) with $\delta_1 = \delta_2 = 0$, showing the cumulative number of new cases of infection for various effectiveness levels of the quarantine/isolation strategy in the absence of vaccination. Parameter values used are as given in Table 6.2 with all vaccine-related parameters set to zero. (A) Low effectiveness levels of quarantine/isolation strategy: $\beta = 0.06; \phi = 0.05; \sigma = 0.05$ (so that, $\mathcal{R}_0 = 1.1138$). (B) Moderate effectiveness levels of quarantine/isolation strategy: $\beta = 0.06; \phi = 0.1; \sigma = 0.1$ (so that, $\mathcal{R}_0 = 0.9815$) and high effectiveness levels of quarantine/isolation strategy: $\beta = 0.06; \phi = 1; \sigma = 1$ (so that, $\mathcal{R}_0 = 0.8491$).

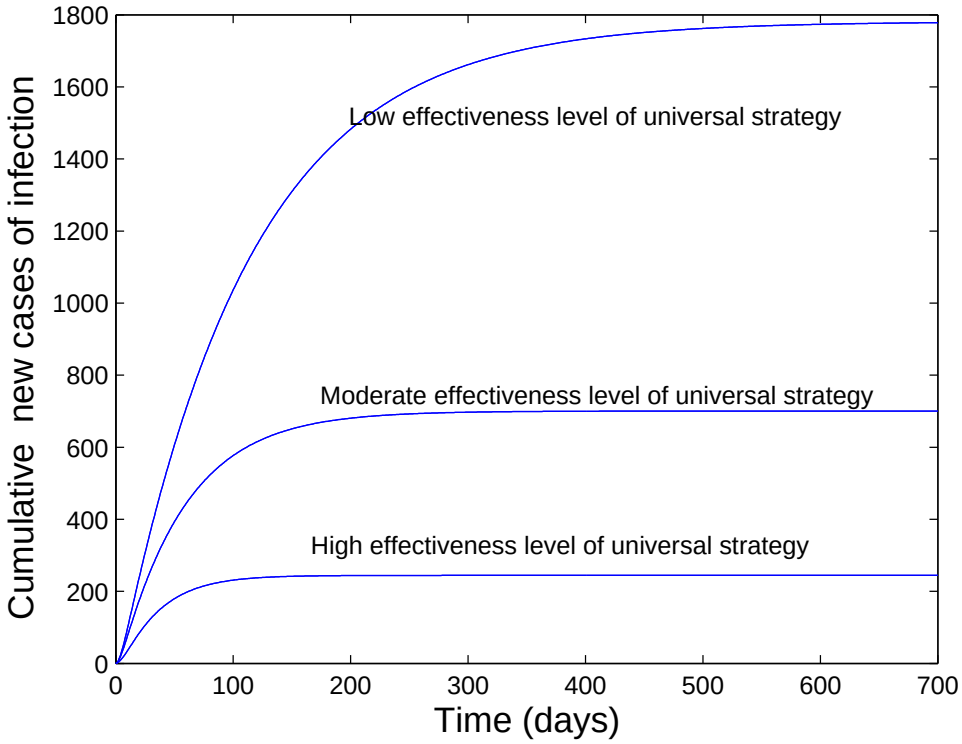


Figure 6.10: simulations of the model (6.2) with $\delta_1 = \delta_2 = 0$, showing the cumulative number of new cases of infection for various effectiveness levels of the universal strategy. Parameter values used are as given in Table 6.2, with: (i) low effectiveness level of universal strategy: $\beta = 0.06; \phi = 0.05, \sigma = 0.05, \sigma_1 = 0.05, \zeta = 0.05, \rho = 0.25$ (so that, $\mathcal{R}^m_{vac} = 0.7593$); (ii) moderate effectiveness level of universal strategy: $\beta = 0.06; \phi = 0.1, \sigma = 0.1, \sigma_1 = 0.1, \zeta = 0.1, \rho = 0.4$ (so that, $\mathcal{R}^m_{vac} = 0.5380$); (iii) high effectiveness level of universal strategy: $\beta = 0.06; \phi = 1, \sigma = 1, \sigma_1 = 1, \zeta = 1, \rho = 0.5$ (so that, $\mathcal{R}^m_{vac} = 0.2355$).

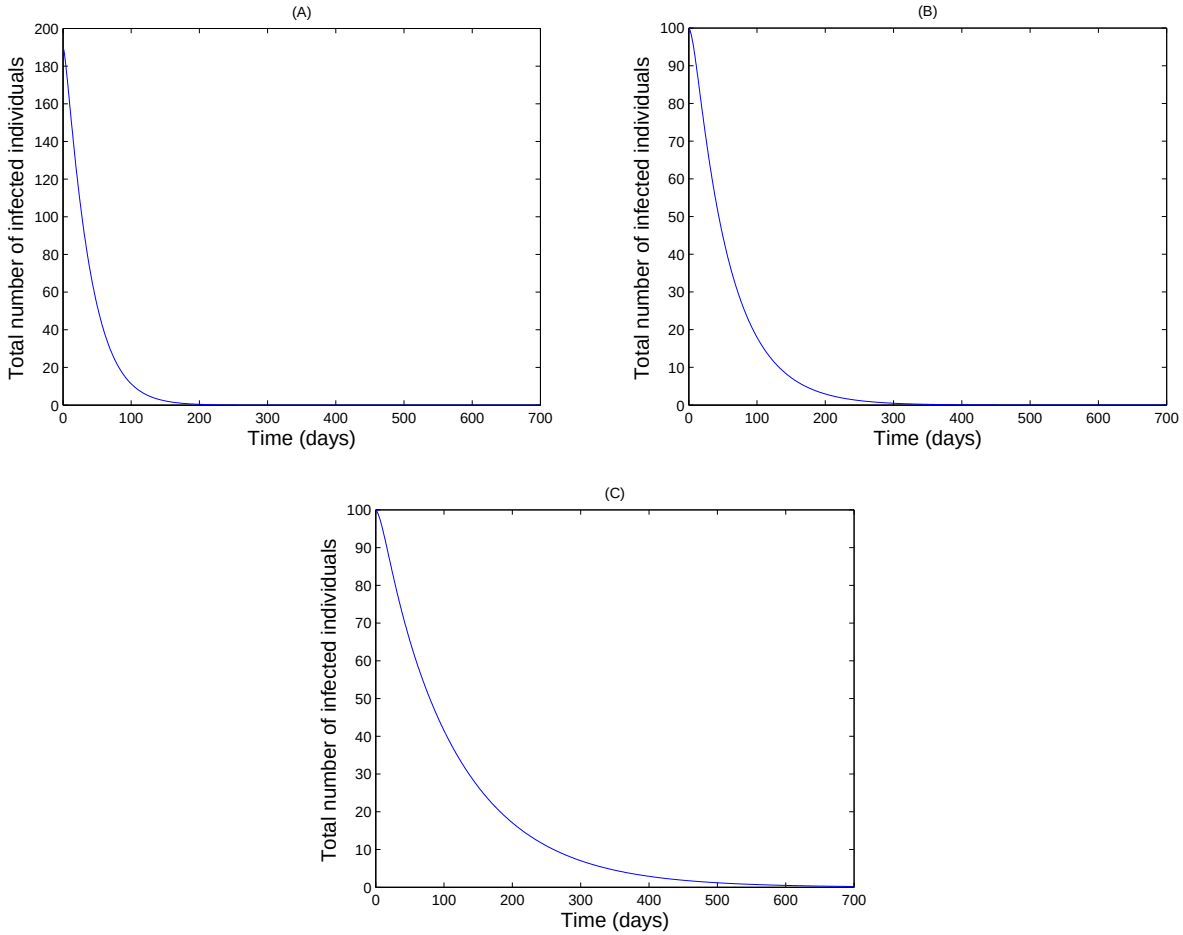


Figure 6.11: simulations of the model (6.2) with $\delta_1 = \delta_2 = 0$, showing the time needed to eliminate the disease for various effectiveness levels of the universal strategy. Parameter values used are as given in Table 6.2, with: (A) high effectiveness level of universal strategy: $\beta = 0.06; \phi = 1, \sigma = 1, \sigma_1 = 1, \zeta = 1, \rho = 0.5$ (so that, $\mathcal{R}^m_{vac} = 0.2355$); (B) moderate effectiveness level of universal strategy: $\beta = 0.06; \phi = 0.1, \sigma = 0.1, \sigma_1 = 0.1, \zeta = 0.1, \rho = 0.4$ (so that, $\mathcal{R}^m_{vac} = 0.5380$); (C) low effectiveness level of universal strategy: $\beta = 0.06; \phi = 0.05, \sigma = 0.05, \sigma_1 = 0.05, \zeta = 0.05, \rho = 0.25$ (so that, $\mathcal{R}^m_{vac} = 0.7593$).

Chapter 7

Quarantine/Isolation Model with Multiple Disease Stages

7.1 Introduction

Many of the models used in studying the effect of quarantine and isolation in combatting the spread of a communicable disease tend to be built based on the assumption that the average waiting time in the associated disease stages is exponentially distributed (see, for instance, [48, 77]). However, some recent studies [32, 92] show that it may be more realistic to use gamma distribution assumptions for the average waiting time in the disease stages (rather than the exponential distribution assumption). Furthermore, Feng *et al.* [32] showed that quarantine and isolation models that assume exponential distribution (for the disease stages) may not be suitable for diseases with relatively long latent and/or infectious periods for the case when isolation is not completely effective (i.e., for the case where isolated individuals can transmit infection).

The purpose of this chapter is to provide a rigorous qualitative analysis of a new deterministic model for transmission dynamics of a communicable disease, subject to the use of quarantine and isolation, where the average waiting times in the associated

infected classes are assumed to have gamma distribution. The model to be designed extends the SEIQHR model (3.2) by considering multiple stages of the exposed, infectious, quarantined and hospitalized individuals (however, unlike in the model (3.2), it's assumed here that hospitalized individuals do not transmit infection). Diseases like HIV [80] and influenza [26] are known to have multiple disease (infection) stages.

7.2 Model Formulation and Basic Properties

The total population at time t, denoted by $N(t)$, is sub-divided into six disjoint classes of susceptible ($S(t)$), exposed ($E(t)$; with m exposed stages), quarantined ($Q(t)$; with m quarantined stages), infectious ($I(t)$; with n infectious stages), hospitalized ($H(t)$; with n hospitalized stages) and recovered ($R(t)$) individuals, so that

$$N(t) = S(t) + \sum_{i=1}^{m} E_i(t) + \sum_{j=1}^{n} I_j(t) + \sum_{i=1}^{m} Q_i(t) + \sum_{j=1}^{n} H_j(t) + R(t).$$

The susceptible population is increased by the recruitment of individuals into the community (assumed susceptible), at a rate Π. Susceptible individuals may acquire infection, following effective contact with infectious individuals (in any of the n infectious stages) at a rate λ, where

$$\lambda = \frac{\beta \sum_{j=1}^{n} I_j}{N}. \tag{7.1}$$

It is assumed that infected individuals in the E_i, Q_i (with $i = 1, 2, \cdots, m$) and H_j (with $j = 1, 2, \cdots, n$) classes do not transmit infection (i.e., it is assumed that exposed individuals do not transmit infection, and that quarantine and isolation measures are implemented in a perfect manner, so that quarantined and isolated individuals do not transmit infection). Although some of these assumptions may not be entirely realistic

in some epidemiological settings, such as in the transmission dynamics of influenza (where transmission by infected individuals without disease symptoms occurs), they help in making the mathematical analysis of the resulting large system of non-linear differential equations more tractable. Furthermore, in (7.1), the parameter β is the effective contact rate (contact capable of leading to infection). The population of susceptible individuals is further decreased by natural death (at a rate μ), and increased when recovered individuals lose their infection-acquired immunity (at a rate ψ). Thus, the rate of change of the susceptible population is given by

$$\frac{dS}{dt} = \Pi + \psi R - \lambda S - \mu S.$$

The population of exposed individuals in stage 1 (E_1) is generated by the infection of susceptible individuals (at the rate λ). This population is decreased by progression to the next exposed stage (E_2; at a rate $a_1\alpha$), quarantine (at a rate σ_1) and natural death (at the rate μ), so that

$$\frac{dE_1}{dt} = \lambda S - (a_1\alpha + \sigma_1 + \mu)E_1.$$

The population of exposed individuals in stage i (with $2 \leq i \leq m$) is generated by the progression of individuals in stage E_{i-1} into the stage i (at a rate $a_{i-1}\alpha$). It is decreased by progression to the next exposed stage (at a rate $a_i\alpha$), quarantine (at a rate σ_i) and natural death (at the rate μ), so that

$$\frac{dE_i}{dt} = a_{i-1}\alpha E_{i-1} - (a_i\alpha + \sigma_i + \mu)E_i;\ i = 2, \cdots, m.$$

The population of infectious individuals in stage 1 is generated when exposed individuals in the final (m) stage develop symptoms (at the rate $a_m\alpha$). It is decreased by progression to the next infectious stage (I_2; at a rate $d_1\kappa$), hospitalization (at a rate

ϕ_1), natural death (at the rate μ) and disease-induced death (at a rate δ_1). This gives

$$\frac{dI_1}{dt} = a_m \alpha E_m - (d_1\kappa + \phi_1 + \mu + \delta_1)I_1.$$

The population of infectious individuals in stage j (with $2 \leq j \leq n$) is generated by progression of individuals in stage $j-1$ (at a rate $d_{j-1}\kappa$). It is decreased by progression to the next infectious stage (at a rate $d_j\kappa$), hospitalization (at a rate ϕ_j), natural death (at the rate μ) and disease-induced death (at a rate δ_j). Individuals in the final (n) stage of infectiousness recover (at a rate $\gamma_1 = d_n\kappa$). Thus,

$$\frac{dI_j}{dt} = d_{j-1}\kappa I_{j-1} - (d_j\kappa + \phi_j + \mu + \delta_j)I_j;\ j = 2, \cdots, n-1,$$

and,

$$\frac{dI_n}{dt} = d_{n-1}\kappa I_{n-1} - (\phi_n + \gamma_1 + \mu + \delta_n)I_n.$$

Exposed individuals in stage 1 are quarantined at the rate σ_1. The population of quarantined individuals in stage 1 is decreased by progression to the next quarantined stage (at a rate $b_1\alpha$) and natural death (at the rate μ). Thus,

$$\frac{dQ_1}{dt} = \sigma_1 E_1 - (b_1\alpha + \mu)Q_1.$$

Similarly, the population of quarantined individuals in stage i (with $2 \leq i \leq m-1$) is generated by the quarantine of exposed individuals in stage E_i (at the rate σ_i) and the progression of quarantined individuals in stage Q_{i-1} into the stage Q_i (at a rate $b_{i-1}\alpha$). It is decreased by progression to the next quarantined stage (at a rate $b_i\alpha$) and natural death (at the rate μ). Thus,

$$\frac{dQ_i}{dt} = \sigma_i E_i + b_{i-1}\alpha Q_{i-1} - (b_i\alpha + \mu)Q_i\ ;\ i = 2, \cdots, m.$$

It should be mentioned that the parameters σ_i $(i = 1, 2, \cdots, m)$ can be used to model the progressive refinement of quarantine measures in the population, by assuming smaller values of σ_i at the beginning and higher values for later stages (e.g., for $m = 3$, we can assume smaller values for σ_1 and σ_2, but a higher value for σ_3; so that, $\sigma_1 < \sigma_2 < \sigma_3$).

The population of hospitalized individuals in stage 1 is generated by the hospitalization of quarantined individuals in the final stage (m; at the rate $b_m\alpha$) and infectious individuals in stage 1 (at the rate ϕ_1). It is decreased by progression to the next hospitalized stage (at a rate $c_1\kappa$), natural death (at the rate μ), and disease-induced death (at a rate δ_{n+1}). Thus,

$$\frac{dH_1}{dt} = b_m\alpha Q_m + \phi_1 I_1 - (c_1\kappa + \mu + \delta_{n+1})H_1.$$

The population of hospitalized individuals in stage j (with $2 \leq j \leq n$) is generated by the hospitalization of infectious individuals in stage j (I_j) (at the rate ϕ_j) and the progression of hospitalized individuals in stage $j-1$ (H_{j-1}) into the H_j class (at a rate $c_{j-1}\kappa$). It is decreased by the progression to the next hospitalized stage (at a rate $c_j\kappa$), natural death (at the rate μ) and disease-induced death (at a rate δ_{n+j}). Individuals in the final n stage of hospitalized recover (at a rate $\gamma_2 = c_n\kappa$). Thus,

$$\frac{dH_j}{dt} = \phi_j I_j + c_{j-1}\kappa H_{j-1} - (c_j\kappa + \mu + \delta_{n+j})H_j;\ j = 2, \cdots, n-1,$$

and,

$$\frac{dH_n}{dt} = \phi_n I_n + c_{n-1}\kappa H_{n-1} - (\gamma_2 + \mu + \delta_{2n})H_n.$$

As in the case of the quarantine measures discussed above, the parameters ϕ_i $(i = 1, \cdots, n)$ can also be used to model the progressive refinement of isolation (in hospital;

so that, for $n = 3$, we can have $\phi_1 < \phi_2 < \phi_3$). Finally, the population of recovered individuals is generated by the recovery of non-hospitalized and hospitalized infectious individuals in the final n stage (at the rates γ_1 and γ_2, respectively). It is decreased by the loss of natural immunity (at the rate ψ) and natural death (at the rate μ), so that

$$\frac{dR}{dt} = \gamma_1 I_n + \gamma_2 H_n - (\psi + \mu)R.$$

It should be stated that, in the above formulation, a_i, b_i, c_j, d_j $(i = 1, 2, \cdots, m;\ j = 1, 2, \cdots, n)$ are constants. Furthermore, it is assumed that the distributions of the exposed, quarantined, infectious and hospitalized periods are exponential, given by

$$\begin{aligned} p_{E_i}(s) &= a_i \alpha e^{-a_i \alpha s}, \\ p_{I_j}(s) &= d_i \kappa e^{-d_i \kappa s}, \\ p_{Q_i}(s) &= b_i \alpha e^{-b_i \alpha s}, \\ p_{H_j}(s) &= c_j \kappa e^{-c_j \kappa s} \ \text{ for } i = 1, \cdots, m \ \text{ and } j = 1, \cdots, n. \end{aligned} \tag{7.2}$$

In (7.2), $T_{E_i} = 1/a_i\alpha$, $T_{I_j} = 1/d_j\kappa$, $T_{Q_i} = 1/b_i\alpha$ and $T_{H_j} = 1/c_j\kappa$ are the mean exposed, quarantined, infectious and hospitalized periods, respectively. The relations in (7.2) are such that:

$$\sum_{i=1}^{m} \frac{1}{a_i \alpha} = \sum_{i=1}^{m} \frac{1}{b_i \alpha} = \frac{1}{\alpha} \ \text{ and } \ \sum_{j=1}^{n} \frac{1}{c_j \kappa} = \sum_{j=1}^{n} \frac{1}{d_j \kappa} = \frac{1}{\kappa}. \tag{7.3}$$

That is, the respective mean time spent in a given infected compartment (e.g., $1/\kappa$ for the hospitalized compartment, H) is shared among the various stages in that compartment. In other words, the time period $1/\kappa$ is distributed equally (if $c_1 = c_2 = \cdots = c_n = n$) or unequally (if $c_1 \neq c_2 \neq \cdots \neq c_n \neq n$) between all the H_j $(j = 1, 2, \cdots, n)$

stages. Hence, this formulation extends the formulation in [32], where these periods are equally distributed among the relevant stages (for all the infected compartments, E, Q, I, H), by allowing for equal or unequal distribution of the average sojourn times in the asymptomatic ($1/\alpha$) and symptomatic ($1/\kappa$) compartments. In line with [32], it is assumed that the mean exposed and quarantined periods are the same ($1/\alpha$) and the mean infectious and hospitalized periods are the same ($1/\kappa$).

Let,

$$E = \sum_{i=1}^{m} \frac{a_i E_i}{m}, \quad I = \sum_{j=1}^{n} \frac{d_j I_j}{n}, \quad Q = \sum_{i=1}^{m} \frac{b_i Q_i}{m} \quad \text{and} \quad H = \sum_{j=1}^{n} \frac{c_j H_j}{n}. \tag{7.4}$$

It follows from (7.2) and (7.4), using the properties of gamma distribution ([49]; see also Section 2.10 for a brief description), that the compartments E, I, Q and H indeed have gamma distributions, given, respectively, by

$$\begin{aligned}
p_E(s) &= \frac{(m\alpha)^m e^{-m\alpha s} s^{m-1}}{\Gamma(m)}; \quad m \geq 1, \\
p_I(s) &= \frac{(n\kappa)^n e^{-n\kappa s} s^{n-1}}{\Gamma(n)}; \quad n \geq 1, \\
p_Q(s) &= \frac{(m\alpha)^m e^{-m\alpha s} s^{m-1}}{\Gamma(m)}; \quad m \geq 1, \\
p_H(s) &= \frac{(n\kappa)^n e^{-n\kappa s} s^{n-1}}{\Gamma(n)}; \quad n \geq 1,
\end{aligned}$$

where the associated exposed, infectious, quarantined and hospitalized periods are

given, respectively, by (see also [32, 100])

$$T_E = \frac{1}{\alpha},$$
$$T_I = \frac{1}{\kappa},$$
$$T_Q = \frac{1}{\alpha},$$
$$T_H = \frac{1}{\kappa}.$$

It should be mentioned that the above formulation ((7.3) and (7.4)) reduces to that given in [32] by setting $a_i = b_i = m$ (for $i = 1, \cdots, m$) and $c_j = d_j = n$ (for $j = 1, \cdots, n$). In other words, it should be emphasized that the main distinction between the gamma distribution formulation in this chapter and that in [32] is that, here, it is assumed that the average sojourn periods in each of the four compartments, E, I, Q, and H, given by $1/\alpha, 1/\kappa, 1/\alpha$ and $1/\kappa$, respectively, are distributed (not necessarily equally) among the various sub stages (whereas, these periods are distributed equally at each related stage in [32]). Eichner *et al.* [26] considered 9 latent and 19 infectious stages to model the transmission dynamics of pandemic influenza.

It is worth stating that although the sums defined in (7.4) are gamma distributed, the actual (true) total number of infected individuals, $E_{\text{true}}, I_{\text{true}}, Q_{\text{true}}$ and H_{true}, given, respectively, by

$$E_{\text{true}} = \sum_{i=1}^{m} E_i, \quad I_{\text{true}} = \sum_{j=1}^{n} I_j, \quad Q_{\text{true}} = \sum_{i=1}^{m} Q_i \quad \text{and} \quad H_{\text{true}} = \sum_{j=1}^{n} H_j, \tag{7.5}$$

are not necessarily gamma distributed. However, the different sums in (7.4) have the same means, with their respective sums given in (7.5), but different variances.

Thus, putting all these formulations and assumptions together, it follows that the model for the transmission dynamics of an infectious disease in the presence of exposed,

quarantine, infectious and isolation periods, subject to gamma distributed sojourn periods, is given by the following non-linear system of differential equations (a flow diagram of the model is given in Figure 7.1; and the associated variables and parameters are described in Table 7.1):

$$
\begin{aligned}
\frac{dS}{dt} &= \Pi + \psi R - \lambda S - \mu S, \\
\frac{dE_1}{dt} &= \lambda S - (\sigma_1 + a_1\alpha + \mu)E_1, \\
\frac{dE_2}{dt} &= a_1\alpha E_1 - (\sigma_2 + a_2\alpha + \mu)E_2, \\
\frac{dE_j}{dt} &= a_{j-1}\alpha E_{j-1} - (\sigma_j + a_j\alpha + \mu)E_j;\ j = 3, \cdots, m, \\
\frac{dI_1}{dt} &= a_m\alpha E_m - (\phi_1 + d_1\kappa + \mu + \delta_1)I_1, \\
\frac{dI_2}{dt} &= d_1\kappa I_1 - (\phi_2 + d_2\kappa + \mu + \delta_2)I_2, \\
\frac{dI_j}{dt} &= d_{j-1}\kappa I_{j-1} - (\phi_j + d_j\kappa + \mu + \delta_j)I_j;\ j = 3, \cdots, n-1, \\
\frac{dI_n}{dt} &= d_{n-1}\kappa I_{n-1} - (\phi_n + d_n\kappa + \mu + \delta_n)I_n, \\
\frac{dQ_1}{dt} &= \sigma_1 E_1 - (b_1\alpha + \mu)Q_1, \\
\frac{dQ_2}{dt} &= \sigma_2 E_2 + b_1\alpha Q_1 - (b_2\alpha + \mu)Q_2, \\
\frac{dQ_j}{dt} &= \sigma_j E_j + b_{j-1}\alpha Q_{j-1} - (b_j\alpha + \mu)Q_j;\ j = 3, \cdots, m, \\
\frac{dH_1}{dt} &= b_m\alpha Q_m + \phi_1 I_1 - (c_1\kappa + \mu + \delta_{n+1})H_1, \\
\frac{dH_2}{dt} &= \phi_2 I_2 + c_1\kappa H_1 - (c_2\kappa + \mu + \delta_{n+2})H_2, \\
\frac{dH_j}{dt} &= \phi_j I_j + c_{j-1}\kappa H_{j-1} - (c_j\kappa + \mu + \delta_{n+j})H_j;\ j = 3, \cdots, n-1, \\
\frac{dH_n}{dt} &= \phi_n I_n + c_{n-1}\kappa H_{n-1} - (c_n\kappa + \mu + \delta_{2n})H_n, \\
\frac{dR}{dt} &= \gamma_1 I_n + \gamma_2 H_n - (\psi + \mu)R.
\end{aligned}
\tag{7.6}
$$

Table 7.1: Description of variables and parameters of the model (7.6).

Variable	Description
$S(t)$	Population of susceptible individuals
$E_i(t)$	Population of exposed individuals in i^{th} exposed stage $(i = 1, \cdots, m)$
$I_j(t)$	Population of infected individuals in j^{th} infectious stage $(j = 1, \cdots, n)$
$Q_i(t)$	Population of quarantined individuals in i^{th} quarantined stage $(i = 1, \cdots, m)$
$H_j(t)$	Population of hospitalized individuals in j^{th} hospitalized stage $(j = 1, \cdots, n)$
$R(t)$	Population of recovered individuals
Parameter	Description
Π	Recruitment rate
μ	Natural death rate
β	Effective contact rate
$d_j\kappa$	Progression rate from infectious stage j to $j+1$ $(j = 1, \cdots, n)$
$c_j\kappa$	Progression rate from hospitalized stage j to $j+1$ $(j = 1, \cdots, n)$
σ_i	Quarantine rate of exposed individuals on i^{th} exposed stage $(i = 1, \cdots, m)$
$a_i\alpha$	Progression rate from exposed stage i to $i+1$ $(i = 1, \cdots, m-1)$
$a_m\alpha$	Progression rate to first infectious class of exposed individuals in stage m
$b_i\alpha$	Progression rate from quarantined stage i to $i+1$ $(i = 1, \cdots, m-1)$
$b_m\alpha$	Progression rate to first hospitalized class of quarantined individuals in stage m
ϕ_j	Hospitalization rate for infectious individuals in j^{th} infectious stage $(j = 1, \cdots, n)$
ψ	Rate of loss of infection-acquired immunity
γ_1	Recovery rate for infectious individuals in stage n
γ_2	Recovery rate for hospitalized individuals in stage n
$\delta_j (1 \leq j \leq n)$	Disease-induced death rate for individuals in j^{th} infectious stage
$\delta_j (n+1 \leq j \leq 2n)$	Disease-induced death rate for individuals in $(n-j)^{th}$ hospitalized stage

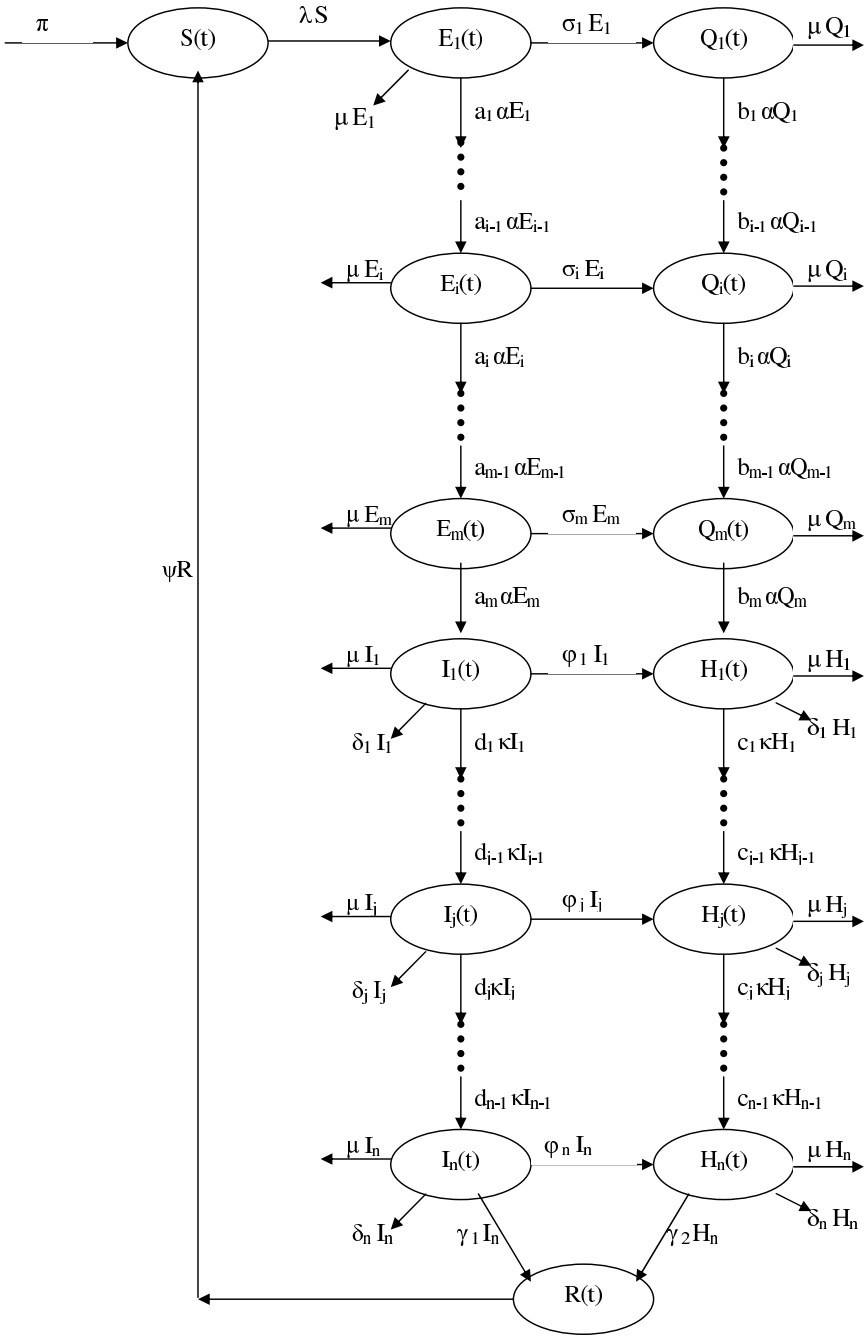


Figure 7.1: Flow diagram of the model (7.6).

The model (7.6) extends the multi-stage model given in [32], by:

(i) including a term for the loss of infection-acquired immunity (at the rate ψ). Al-

though the numerical simulations to be carried out in this chapter are largely based on the 2003 SARS outbreaks (which was a single season epidemic), the model (7.6) is robust enough to enable the assessment of the transmission dynamics of any arbitrary disease where the infection-acquired immunity is lost either during a single season or in multiple seasons (such as the case of influenza, malaria, and some childhood diseases);

(ii) including disease-induced death (at rates $\delta_i;\ i = 1, 2, \cdots, 2n$). Most diseases, such as HIV, malaria, influenza, TB, etc., have significant disease-induced mortality. Hence, it is crucial that this feature is incorporated in their modeling studies;

(iii) assuming the average sojourn periods in the exposed, quarantined, infectious and hospitalized classes are distributed (not necessarily equally) among the various stages (these periods are assumed to be equally distributed among each of the aforementioned four infected compartments in [32]). Although, to our knowledge, there is no definitive epidemiological data to suggest that these periods are equally or unequally distributed, the model (7.6) is general enough to allow for the assessment of each of the two cases;

(iv) assuming varied rates of quarantine and isolation in each quarantine and isolation stage (same rates are used in [32] in all quarantine and isolation stages). This assumption allows for the assessment of progressive refinement of quarantine and isolation measures (this was evident during 2003 SARS outbreaks [38, 59]).

The model (7.6) is denoted by GD1 for comparison purposes.

It is worth emphasizing that the model (7.6) reduces to the model in [32] by setting $\psi = \delta_1 = \delta_2 = \cdots = \delta_{2n} = 0$, $a_1 = a_2 = \cdots = a_m = b_1 = b_2 = \cdots = b_m = m$, $c_1 = c_2 = \cdots = c_n = d_1 = d_2 = \cdots = d_n = n$, $\phi_1 = \cdots = \phi_n = \phi$ and $\sigma_1 = \cdots = \sigma$. Also, the

model (7.6) is an extension of the model (3.2) by considering m stages for the exposed ($E_i;\ i = 1, 2, \cdots, m$) and quarantined ($Q_i; i = 1, 2, \cdots, m$) individuals, and n stages for the infectious ($I_j; j = 1, 2, \cdots, n$) and the hospitalized ($H_j; j = 1, 2, \cdots, n$) individuals (i.e., the model (7.6) reduces to the model (3.2) by setting $n = m = 1$, taking into account the assumption that hospitalized individuals do not transmit infection; this assumption is relaxed in the model (3.2)).

In addition to formulating the model in terms of gamma-distributed average waiting times for the associated disease stages, this chapter contributes by way of carrying out a detailed rigorous mathematical analysis of the model (7.6). In particular, global asymptotic stability results for the equilibria of the model will be proven (under certain conditions). Furthermore, the model (7.6) is used to evaluate the impact of quarantine and isolation in combatting the spread of a given communicable disease (such as SARS). This chapter offers not only important extensions to the model presented in [32], it also contributes by extending some of the mathematical results presented in [32] (particularly, by giving global stability proof of the associated endemic equilibrium of the extended model (7.6)). The following results can be established using the approach in Section 3.2

Theorem 7.1. *The state variables of the model* (7.6) *are non-negative for all time. In other words, solutions of the model system* (7.6) *with positive initial data will remain positive for all time* $t > 0$.

Lemma 7.1. *The closed set*

$$\mathcal{D} = \Bigg\{ (S, E_1, \cdots, E_m, I_1, \cdots, I_n, Q_1, \cdots, Q_m, H_1, \cdots, H_n, R) \in \mathbb{R}_+^{2(m+n+1)} : S + \sum_{i=1}^{m} (E_i + Q_i) + \sum_{j=1}^{n} (I_j + H_j) + R \leq \frac{\Pi}{\mu} \Bigg\} \text{ is positively-invariant for the model (7.6).} \tag{7.7}$$

7.3 Stability of Disease-free Equilibrium

7.3.1 Local stability

The DFE of the model (7.6) is given by

$$\begin{aligned}\Omega_0 &= (S^*,\ E_1^*,\ \cdots,\ E_m^*,\ I_1^*,\ \cdots,\ I_n^*,\ Q_1^*,\ \cdots,\ Q_m^*,\ H_1^*,\ \cdots,\ H_n^*,\ R^*)\\ &= (\Pi/\mu,\ 0,\ \cdots,\ 0).\end{aligned} \tag{7.8}$$

The local stability of Ω_0 will be explored using the next generation operator method [21, 87]. Using the notation in [87], the non-negative matrix, F, of the new infection terms, and the M-matrix, V, of the transition terms associated with the model (7.6), are given, respectively, by

$$F = \begin{pmatrix} A_F & B_F & C_F \end{pmatrix},$$

and,

$$V = \begin{pmatrix} A_V & B_V \\ C_V & D_V \end{pmatrix},$$

where, A_F is $2(m+n)\times m$ zero matrix, C_F, B_V are $2(m+n)\times(m+n), (m+n)\times(m+n)$ zero matrices, respectively. Furthermore, B_F is a $2(m+n)\times n$ matrix, given by

$$B_F = \begin{pmatrix} \beta & \beta & \cdots & \beta \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & & \vdots \\ 0 & 0 & \cdots & 0 \end{pmatrix}.$$

The matrices, A_V, C_V and D_V are $(m+n)\times(m+n)$ are given, respectively, by

$$A_V = \begin{pmatrix} k_1 & & & & & & & & \\ -a_1\alpha & k_2 & & & & & & & \\ & -a_2\alpha & k_3 & & & & & & \\ & & \ddots & \ddots & & & & & \\ & & & -a_m\alpha & k_{m+1} & & & & \\ & & & & -d_1\kappa & k_{m+2} & & & \\ & & & & & -d_2\kappa & k_{m+3} & & \\ & & & & & & \ddots & \ddots & \\ & & & & & & & -d_{n-1}\kappa & k_{m+n} \end{pmatrix},$$

$$C_V = \begin{pmatrix} -\sigma_1 & & & & & & & \\ & -\sigma_2 & & & & & & \\ & & \ddots & & & & & \\ & & & -\sigma_m & & & & \\ & & & & -\phi_1 & & & \\ & & & & & -\phi_2 & & \\ & & & & & & \ddots & \\ & & & & & & & -\phi_n \end{pmatrix},$$

and,

$$D_V = \begin{pmatrix} k_{m+n+1} & & & & & & & & & \\ -b_1\alpha & k_{m+n+2} & & & & & & & & \\ & -b_2\alpha & k_{m+n+3} & & & & & & & \\ & & \ddots & \ddots & & & & & & \\ & & & -b_m\alpha & k_{2m+n+1} & & & & & \\ & & & & -c_1\kappa & k_{2m+n+2} & & & & \\ & & & & & -c_2\kappa & k_{2m+n+3} & & & \\ & & & & & & \ddots & \ddots & & \\ & & & & & & & -c_{n-1}\kappa & k_{2(m+n)} \end{pmatrix},$$

with,

$$k_j = \begin{cases} \sigma_j + a_j\alpha + \mu; & 1 \le j \le m; \\ \phi_{j-m} + d_{j-m}\kappa + \mu + \delta_{j-m}; & m+1 \le j \le m+n; \\ b_{j-(m+n)}\alpha + \mu; & n+m+1 \le j \le 2m+n; \\ c_{j-(2m+n)}\kappa + \mu + \delta_{j-2m}; & 2m+n+1 \le j \le 2(m+n). \end{cases}$$

Let,

$$\begin{aligned} A_l &= \alpha^{m-l+1} \prod_{i=l}^{m} a_i, \quad l = 1, 2, \cdots, m; \\ B_l &= \prod_{i=l}^{m+n-1} k_i, \quad l = 1, 2, \cdots, m+n-1; \text{with } (B_{m+n} = 1); \\ D_l &= \frac{A_l}{B_l}; \quad l = 1, 2, \cdots, m; D_{m+1} = \frac{1}{B_{m+1}}; \end{aligned} \tag{7.9}$$

$$C_{p,q} = \kappa^{p-1} \prod_{i=1}^{p-1} d_{i+q-1} + \prod_{s=2}^{p} k_{m+s+q-1} + \sum_{t=1}^{p-2} \kappa^t \prod_{i=1}^{t} d_{i+q-1} \prod_{s=2+t}^{p} k_{m+s+q-1};$$

$$\text{for } (p = 3, \cdots, n;\ q = n + 1 - p); C_{1,n} = 1 \text{ and } C_{2,n-1} = \kappa d_{n-1} + k_{m+n}.$$

It follows that the *control reproduction number* [2, 44], denoted by $\mathcal{R}_c = \rho(FV^{-1})$, where ρ is the spectral radius, is given by

$$\mathcal{R}_c = \frac{\beta D_1 C_{n,1}}{k_{m+n}}.$$

Using Theorem 2.10, the following result is established.

Lemma 7.2. *The DFE of the model* (7.6)*, given by* (7.8)*, is locally-asymptotically stable if* $\mathcal{R}_c < 1$*, and unstable if* $\mathcal{R}_c > 1$*.*

The quantity $\mathcal{R}_c$ measures the average number of new infections generated by a single infectious individual introduced into a completely susceptible population. Lemma 7.2 implies that the disease can be eliminated from the community (when $\mathcal{R}_c < 1$) if the initial sizes of the sub-populations of the model are in the basin of attraction of the DFE (Ω_0). To ensure that disease elimination is independent of the initial sizes of sub-populations, it is necessary to show that the DFE is globally-asymptotically stable if $\mathcal{R}_c < 1$. This is explored below.

7.3.2 Global stability

Theorem 7.2. *The DFE of the model* (7.6)*, given by* (7.8)*, is GAS in* $\mathcal{D}$ *whenever* $\mathcal{R}_c \leq 1$*.*

Proof. Consider the following Lyapunov function (with the coefficients B, C and D as

defined in (7.9)):

$$\mathcal{F} = \left(\frac{k_{m+n}\mathcal{R}_c}{\beta}\right) E_1 + C_{n,1}D_2E_2 + \sum_{j=3}^{m} C_{n,1}D_jE_j + \sum_{j=1}^{n-1}\left(\frac{C_{n-j+1,j}}{B_{m+j}}\right) I_j + I_n$$

with Lyapunov derivative given by,

$$\dot{\mathcal{F}} = \left(\frac{k_{m+n}\mathcal{R}_c}{\beta}\right) \dot{E}_1 + C_{n,1}D_2\dot{E}_2 + \sum_{j=3}^{m} C_{n,1}D_j\dot{E}_j + \sum_{j=1}^{n-1}\left(\frac{C_{n-j+1,j}}{B_{m+j}}\right) \dot{I}_j + \dot{I}_n,$$

$$= \left(\frac{k_{m+n}\mathcal{R}_c}{\beta}\right) \left(\begin{array}{l} \beta S\sum_{j=1}^{n} I_j \\ \hline N \end{array} - k_1E_1\right) + C_{n,1}D_2\left(a_1\alpha E_1 - k_2E_2\right)$$

$$+ \sum_{j=3}^{m-1} C_{n,1}D_j\left(a_{j-1}\alpha E_{j-1} - k_jE_j\right) + C_{n,1}D_m\left(a_{m-1}\alpha E_{m-1} - k_mE_m\right)$$

$$+ \frac{C_{n,1}}{B_{m+1}}\left(a_m\alpha E_m - k_{m+1}I_1\right) + \sum_{j=2}^{n-1}\frac{C_{n-j+1,j}}{B_{m+j}}\left(d_{j-1}\kappa I_{j-1} - k_{m+j}I_j\right) + d_{n-1}\kappa I_{n-1} - k_{m+n}I_n,$$

$$\leq k_{m+n}\mathcal{R}_c\sum_{j=1}^{n} I_j - \left(\frac{k_1k_{m+n}\mathcal{R}_c}{\beta}\right) E_1 + C_{n,1}D_2\left(a_1\alpha E_1 - k_2E_2\right)$$

$$+ \sum_{j=3}^{m-1} C_{n,1}D_j\left(a_{j-1}\alpha E_{j-1} - k_jE_j\right) + C_{n,1}D_m\left(a_{m-1}\alpha E_{m-1} - k_mE_m\right)$$

$$+ \frac{C_{n,1}}{B_{m+1}}\left(a_m\alpha E_m - k_{m+1}I_1\right) + \sum_{j=2}^{n-1}\frac{C_{n-j+1,j}}{B_{m+j}}\left(d_{j-1}\kappa I_{j-1} - k_{m+j}I_j\right)$$

$$+ d_{n-1}\kappa I_{n-1} - k_{m+n}I_n, \qquad \text{since } S \leq N \text{ in } \mathcal{D},$$

$$= k_{m+n}\mathcal{R}_c \sum_{j=1}^{n} I_j + \left(-\frac{k_1 k_{m+n}\mathcal{R}_c}{\beta} + C_{n,1}D_2 a_1\alpha\right) E_1 + \sum_{j=3}^{m+1} C_{n,1}D_j a_{j-1}\alpha E_{j-1}$$
$$- \sum_{j=2}^{m} C_{n,1}D_j k_j E_j + \sum_{j=2}^{n} \frac{C_{n-j+1,j}}{B_{m+j}} d_{j-1}\kappa I_{j-1} - \sum_{j=1}^{n-1} \frac{C_{n-j+1,j}}{B_{m+j}} k_{m+j} I_j - k_{m+n} I_n,$$

$$= k_{m+n}\mathcal{R}_c \sum_{j=1}^{n} I_j + \sum_{j=2}^{m} C_{n,1}\left(D_{j+1}a_j\alpha - D_j k_j\right) E_j + \sum_{j=1}^{n-1}\left(\frac{d_j\kappa C_{n-j,j+1}}{B_{m+j+1}} - \frac{k_{m+j}C_{n-j+1,j}}{B_{m+j}}\right) I_j$$
$$- k_{m+n} I_n.$$

It can be shown, after some lengthy algebraic manipulations, that

$$D_{j+1}a_j\alpha - D_j k_j = 0,$$

and,

$$\frac{d_j\kappa C_{n-j,j+1}}{B_{m+j+1}} - \frac{k_{m+j}C_{n-j+1,j}}{B_{m+j}} = -k_{m+n}.$$

Hence,

$$\dot{\mathcal{F}} \leq k_{m+n}\left(\mathcal{R}_c - 1\right)\sum_{j=1}^{n} I_j \leq 0 \quad \text{for } \mathcal{R}_c \leq 1.$$

Since all the parameters of the model (7.6) and variables are non-negative, it follows that $\dot{\mathcal{F}} \leq 0$ for $\mathcal{R}_c \leq 1$ with $\dot{\mathcal{F}} = 0$ if and only if $I_1 = I_2 = \cdots = I_n = 0$. Hence, $\mathcal{F}$ is a Lyapunov function on $\mathcal{D}$. Therefore, by the LaSalle's Invariance Principle (Theorem 2.6),

$$\begin{aligned} &\lim_{t\to\infty} E_i(t) = 0, \text{ for all } i = 1, \cdots, m; \\ &\lim_{t\to\infty} I_j(t) = 0, \text{ for all } j = 1, \cdots, n. \end{aligned} \tag{7.10}$$

It is clear from (7.10) that $\limsup_{t\to\infty} E_1 = 0$. Thus, for sufficiently small small $\varpi_1 > 0$, there exists a constant $N_1 > 0$ such that $\limsup_{t\to\infty} E_1 \leq \varpi_1$ for all $t > N_1$. It follows from the $(m+n+2)th$ equation of the model (7.6) that, for $t > N_1$,

$$\dot{Q}_1 \leq \sigma_1 \varpi_1 - k_{m+n+1} Q_1.$$

Thus, by comparison theorem (Theorem 2.8),

$$Q_1^{\infty} = \limsup_{t\to\infty} Q_1 \leq \frac{\sigma_1 \varpi_1}{k_{m+n+1}},$$

so that, by letting $\varpi_1 \to 0$,

$$Q_1^{\infty} = \limsup_{t\to\infty} \ Q_1 \leq 0. \tag{7.11}$$

Similarly (by using $\liminf_{t\to\infty} E_1 = 0$), it can be shown that

$$Q_{1\infty} = \liminf_{t\to\infty} Q_1 \geq 0. \tag{7.12}$$

Thus, it follows from (7.11) and (7.12) that

$$Q_{1\infty} \geq 0 \geq Q_1^{\infty}.$$

Hence,

$$\lim_{t\to\infty} Q_1 = 0. \tag{7.13}$$

Similarly, it can be shown that

$$\begin{aligned}
&\lim_{t\to\infty} Q_i(t) = 0, \text{ for all } i = 2, \cdots, m, \\
&\lim_{t\to\infty} H_j(t) = 0, \text{ for all } j = 1, \cdots, n, \\
&\lim_{t\to\infty} R(t) = 0 \text{ and } \lim_{t\to\infty} S(t) = \Pi/\mu.
\end{aligned} \tag{7.14}$$

Thus, by combining (7.10), (7.13) and (7.14), it follows that every solution of the equations in the model (7.6), with initial conditions in $\mathcal{D}$, approaches the DFE, Ω_0, as $t \to \infty$ when $\mathcal{R}_c \leq 1$. □

The epidemiological implication of the above result is that the combined use of quarantine and isolation can lead to disease elimination if they can bring (and keep) the threshold quantity, $\mathcal{R}_c$, to a value less than or equal unity (i.e., the condition $\mathcal{R}_c \leq 1$ is necessary and sufficient for disease elimination). Figure 7.2 depicts numerical results obtained by simulating the model (7.6), with $m = 2$ and $n = 3$, using various initial conditions for the case $\mathcal{R}_c < 1$. It is clear from this figure that all solutions converged to the DFE, Ω_0 (in line with Theorem 7.2). It should be mentioned that, unless otherwise stated, the numerical simulations of the model (7.6) are carried out using the parameter values in Tables 3.2 and 7.2. These parameter values are consistent with those associated with the 2003 SARS outbreaks [15, 23, 38, 59]. It is worth mentioning that the progressive refinement of quarantine and isolation measures is incorporated in all numerical simulations in this chapter (unless otherwise stated) by using smaller values of σ_1 and σ_2, in comparison to σ_3; and also smaller values of ϕ_1 and ϕ_2, in relation to ϕ_3 (see Table 7.2).

Table 7.2: Quarantine and hospitalization rates for different disease stages

Number of stages	Quarantine rates	Hospitalization rates
$m = n = 1$	$\sigma_1 = 0.1$	$\phi_1 = 0.20619$
$m = n = 2$	$\sigma_1 = 0.05,\ \ \sigma_2 = 0.1$	$\phi_1 = 0.1\ \ \phi_2 = 0.20619$
$m = n = 3$	$\sigma_1 = 0.03333,\ \ \sigma_2 = 0.05,\ \ \sigma_3 = 0.1$	$\phi_1 = 0.0666,\ \ \phi_2 = 0.1,\ \ \phi_3 = 0.20619$

Table 7.3: Distribution of exposed and infectious periods for the model (7.6)

Number of stages	Values of a_i, b_i, c_i, d_i
$m = n = 1$	$a_1 = b_1 = 1,\ c_1 = d_1 = 1$
$m = n = 2$	$a_1 = b_1 = 1.5,\ a_2 = b2 = 3,\ c_1 = d_1 = 1.5,\ c_2 = d_2 = 3$
$m = n = 3$	$a_1 = b_1 = 2,\ a_2 = b2 = 3,\ a_3 = b_3 = 6,\ c_1 = d_1 = 2,\ c_2 = d_2 = 3,\ c_3 = d_3 = 6$

7.4 Existence and Stability of Endemic Equilibrium

In this section, the possible existence and stability of endemic (positive) equilibria of the model (7.6) will be explored.

7.4.1 Existence

Let $\Omega_1 = (S^{**}, E_1^{**}, E_2^{**}, \cdots, E_m^{**}, I_1^{**}, I_2^{**}, \cdots, I_n^{**}, Q_1^{**}, Q_2^{**}, \cdots, Q_m^{**}, H_1^{**}, H_2^{**}, \cdots, H_n^{**}, R^{**})$ represent any arbitrary endemic equilibrium of the model (7.6).

Solving the equations of the model at endemic steady-state gives

$$S^{**} = \frac{\Pi + \psi R^{**}}{\lambda^{**} + \mu}, \quad E_1^{**} = \frac{\lambda^{**} S^{**}}{k_1}, \quad E_j^{**} = \frac{a_{j-1}\alpha E_{j-1}^{**}}{k_j} \text{ for } j = 2, \cdots, m,$$

$$I_1^{**} = \frac{a_m \alpha E_m^{**}}{k_{m+1}}, \quad I_2^{**} = \frac{d_1 \kappa I_1^{**}}{k_{m+2}}, \quad I_j^{**} = \frac{d_{j-1}\kappa I_{j-1}^{**}}{k_{m+j}} \text{ for } j = 3, \cdots, n,$$

$$Q_1^{**} = \frac{\sigma_1 E_1^{**}}{k_{m+n+1}}, \quad Q_j^{**} = \frac{\sigma_j E_j^{**} + b_{j-1}\alpha Q_{j-1}^{**}}{k_{m+n+j}} \text{ for } j = 2, \cdots, m, \tag{7.15}$$

$$H_1^{**} = \frac{\phi_1 I_1^{**} + b_n \alpha Q_n^{**}}{k_{2m+n+1}}, \quad H_j^{**} = \frac{\phi_j I_j^{**} + c_{j-1}\kappa H_{j-1}^{**}}{k_{2m+n+j}} \text{ for } j = 2, \cdots, n,$$

$$R^{**} = \frac{\gamma_1 I_n^{**} + \gamma_2 H_n^{**}}{\psi + \mu}.$$

The force of infection λ, given by (7.1), can be expressed at endemic steady-state as

$$\lambda^{**} = \frac{\beta \sum_{j=1}^{n} I_j^{**}}{N^{**}}. \tag{7.16}$$

As in the case of the model (3.2), for instance, the expressions in (7.15) are re-written in terms of $\lambda^{**}S^{**}$, for mathematical convenience, as below:

$$E_1^{**} = \frac{\lambda^{**} S^{**}}{k_1}, \quad E_j^{**} = \left(\frac{\alpha^{j-1}}{k_1} \prod_{l=2}^{j} \frac{a_{l-1}}{k_l} \right) \lambda^{**} S^{**}, \text{ for } j = 2, \cdots, m,$$

$$I_1^{**} = \left(\frac{\alpha^m}{k_1} \prod_{l=2}^{m+1} \frac{a_{l-1}}{k_l} \right) \lambda^{**} S^{**}, \quad I_j^{**} = \left(\frac{\alpha^m \kappa^{j-1}}{k_1} \prod_{l=2}^{m+1} \frac{a_{l-1}}{k_l} \prod_{l=2}^{j} \frac{d_{l-1}}{k_{m+j}} \right) \lambda^{**} S^{**}, \text{ for } j = 2, \cdots, n,$$

$$Q_1^{**} = \frac{\sigma_1 \lambda^{**} S^{**}}{k_1 k_{m+n+1}} = p_1 \lambda^{**} S^{**}, \quad Q_j^{**} = p_j \lambda^{**} S^{**}, \text{ for } j = 2, \cdots, m, \tag{7.17}$$

$$H_1^{**} = \left(\frac{\alpha^m \phi_1}{k_1 k_{2m+n+1}} \prod_{l=2}^{m+1} \frac{a_{l-1}}{k_l} + \frac{b_m \alpha p_m}{k_{2m+n+1}} \right) \lambda^{**} S^{**} = q_1 \lambda^{**} S^{**}, \quad H_j^{**} = q_j \lambda^{**} S^{**}, \text{ for } j = 2, \cdots, n,$$

$$R^{**} = \left(\frac{\alpha^m \kappa^{n-1} \gamma_1}{k_1(\psi + \mu)} \prod_{l=2}^{m+1} \frac{a_{l-1}}{k_l} \prod_{l=2}^{n} \frac{d_{l-1}}{k_{m+n}} + \frac{q_n \gamma_2}{\psi + \mu} \right) \lambda^{**} S^{**},$$

where,

$$p_1 = \frac{\sigma_1}{k_1 k_{m+n+1}}, \quad q_1 = \frac{\alpha^m \phi_1}{k_1 k_{2m+n+1}} \prod_{l=2}^{m+1} \frac{a_{l-1}}{k_l} + \frac{b_m \alpha p_m}{k_{2m+n+1}},$$

$$p_j = \frac{b_{j-1} \alpha p_{j-1}}{k_{m+n+j}} + \frac{\sigma_i \alpha^{j-1}}{k_{m+n+j} k_1} \prod_{l=2}^{j} \frac{a_{l-1}}{k_l}, \text{ for } j = 2, \cdots, m,$$

and,

$$q_j = \frac{c_{j-1} \kappa q_{j-1}}{k_{2m+n+j}} + \frac{\phi_j \alpha^m \kappa^{j-1}}{k_1 k_{2m+n+j}} \prod_{l=2}^{m+1} \frac{a_{l-1}}{k_l} \prod_{l=2}^{j} \frac{d_{l-1}}{k_{m+j}}, \text{ for } j = 2, \cdots, n.$$

Substituting the expressions in (7.17) into (7.16) gives

$$\begin{aligned} &\lambda^{**} S^{**} + \frac{\lambda^{**} S^{**} \lambda^{**}}{k_1} + \sum_{i=2}^{m} \left(\frac{\alpha^{j-1}}{k_1} \prod_{l=2}^{j} \frac{a_{l-1}}{k_l} \right) \lambda^{**} S^{**} \lambda^{**} + \left(\frac{\alpha^m}{k_1} \prod_{l=2}^{m+1} \frac{a_{l-1}}{k_l} \right) \lambda^{**} S^{**} \lambda^{**} \\ &+ \sum_{j=2}^{n} \left(\frac{\alpha^m \kappa^{j-1}}{k_1} \prod_{l=2}^{m+1} \frac{a_{l-1}}{k_l} \prod_{l=2}^{j} \frac{d_{l-1}}{k_{m+j}} \right) \lambda^{**} S^{**} \lambda^{**} + \sum_{i=1}^{m} q_i \lambda^{**} S^{**} \lambda^{**} + \sum_{j=1}^{n} p_j \lambda^{**} S^{**} \lambda^{**} \\ &+ \left(\frac{\alpha^m \kappa^{n-1} \gamma_1}{k_1(\psi + \mu)} \prod_{l=2}^{m+1} \frac{a_{l-1}}{k_l} \prod_{l=2}^{n} \frac{d_{l-1}}{k_{m+n}} + \frac{q_n \gamma_2}{\psi + \mu} \right) \lambda^{**} S^{**} \lambda^{**} \end{aligned} \tag{7.18}$$

$$= \beta \left[\frac{\alpha^m}{k_1} \prod_{l=2}^{m+1} \frac{a_{l-1}}{k_l} + \sum_{j=2}^{n} \left(\frac{\alpha^m \kappa^{j-1}}{k_1} \prod_{l=2}^{m+1} \frac{a_{l-1}}{k_l} \prod_{l=2}^{j} \frac{d_{l-1}}{k_{m+j}} \right) \right] \lambda^{**} S^{**}.$$

Dividing each term in (7.18) by $\lambda^{**} S^{**}$(and noting that, at the endemic steady-state,

$\lambda^{**}S^{**} \neq 0$) gives

$$1 + W\lambda^{**} = \mathcal{R}_c,$$

where,

$$W = \frac{1}{k_1} + \sum_{i=2}^{m+1} \frac{\alpha^{j-1}}{k_1} \prod_{l=2}^{j} \frac{a_{l-1}}{k_l} + \sum_{j=2}^{n} \frac{\alpha^m \kappa^{j-1}}{k_1} \prod_{l=2}^{m+1} \frac{a_{l-1}}{k_l} \prod_{l=2}^{j} \frac{d_{l-1}}{k_{m+j}} + \sum_{i=1}^{m} q_i + \sum_{j=1}^{n} p_j$$
$$+ \frac{\alpha^m \kappa^{n-1} \gamma_1}{k_1(\psi + \mu)} \prod_{l=2}^{m+1} \frac{a_{l-1}}{k_l} \prod_{l=2}^{n} \frac{d_{l-1}}{k_{m+n}} + \frac{q_n \gamma_2}{\psi + \mu} \geq 0.$$

Hence,

$$\lambda^{**} = \frac{\mathcal{R}_c - 1}{W} > 0, \text{ whenever } \mathcal{R}_c > 1. \tag{7.19}$$

The components of Ω_1 can then be obtained by substituting the unique value of λ^{**} given in (7.19) into the expressions in (7.17). Thus, the following result is established.

Lemma 7.3. *The model* (7.6) *has a unique endemic equilibrium, given by* Ω_1*, whenever* $\mathcal{R}_c > 1$.

7.4.2 Local stability

Define,

$$\mathcal{D}_0 = \Big\{ (S, E_1, E_2, \cdots, E_m, I_1, I_2, \cdots, I_n, Q_1, Q_2, \cdots, Q_m, H_1, H_2, \cdots, H_n, R) \in \mathcal{D} :$$
$$E_i = I_j = Q_i = H_j = R = 0; \text{ for } i = 1, \cdots, m, \ j = 1, \cdots, n \Big\},$$

the stable manifold of the DFE (Ω_0). Further, let,

$$\mathcal{R}_{cr} = \mathcal{R}_c|_{\delta_1=\delta_2=\cdots=\delta_{2n}=0} = \frac{\beta\tilde{D_1}\tilde{C_{n,1}}}{f_{m+n}},$$

where,

$$\tilde{D_1} = \frac{\alpha^m \prod_{i=l}^{m} a_i}{\prod_{i=l}^{m+n-1} f_i} \text{ and } \tilde{C_{n,1}} = \kappa^{n-1}\prod_{i=1}^{p-1} d_i + \prod_{s=2}^{n} f_{m+s} + \sum_{t=1}^{n-2}\kappa^t \prod_{i=1}^{t} d_i \prod_{s=2+t}^{n} f_{m+s}, \quad (7.20)$$

with,

$$f_j = \begin{cases} \sigma_j + a_j\alpha + \mu; & 1 \leq j \leq m; \\ \phi_{j-m} + d_{j-m}\kappa + \mu; & m+1 \leq j \leq m+n; \\ b_{j-(m+n)}\alpha + \mu; & n+m+1 \leq j \leq 2m+n; \\ c_{j-(2m+n)}\kappa + \mu; & 2m+n+1 \leq j \leq 2(m+n). \end{cases}$$

Theorem 7.3. *The unique endemic equilibrium of the model* (7.6) *is LAS if* $\mathcal{R}_{cr} > 1$.

The proof is given in Appendix D.

The epidemiological implication of Theorem 7.3 is that the disease will persist in the population if $\mathcal{R}_c > 1$. Simulation results for the model (7.6), depicted in Figure 7.3 (for the case when $m = 2$, $n = 3$, and $\delta_1 = \delta_2 = \cdots = \delta_{2n} = 0$, so that $\mathcal{R}_c > 1$) using numerous initial conditions, show convergence of the solutions to the endemic equilibrium (in line with Theorem 7.3).

7.4.3 Global stability for special case

Here, the global stability of the endemic equilibrium of the model (7.6) is given for the special case where the recovered individuals do not lose their infection-acquired

immunity (i.e., $\psi = 0$) and the associated disease-induced mortality in all classes is negligible (so that, $\delta_1 = \delta_2 = \cdots \delta_{2n} = 0$). The model (7.6), with $\psi = \delta_1 = \delta_2 = \cdots = \delta_{2n} = 0$, then reduces to:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \lambda S - \mu S, \\
\frac{dE_1}{dt} &= \lambda S - f_1 E_1, \\
\frac{dE_2}{dt} &= a_1 \alpha E_1 - f_2 E_2, \\
\frac{dE_j}{dt} &= a_{j-1} \alpha E_{j-1} - f_j E_j;\ j = 3, \cdots, m, \\
\frac{dI_1}{dt} &= a_m \alpha E_m - f_{m+1} I_1, \\
\frac{dI_j}{dt} &= d_{j-1} \kappa I_{j-1} - f_{m+j} I_j;\ j = 2, \cdots, n, \\
\frac{dQ_1}{dt} &= \sigma_1 E_1 - f_{m+n+1} Q_1, \\
\frac{dQ_j}{dt} &= \sigma_j E_j + b_{j-1} \alpha Q_{j-1} - f_{m+n+j} Q_j;\ j = 2, \cdots, m, \\
\frac{dH_1}{dt} &= b_m \alpha Q_m + \phi_1 I_1 - f_{2m+n+1} H_1, \\
\frac{dH_j}{dt} &= \phi_j I_j + c_{j-1} \kappa H_{j-1} - f_{2m+n+j} H_j;\ j = 2, \cdots, n, \\
\frac{dR}{dt} &= \gamma_1 I_n + \gamma_2 H_n - \mu R.
\end{aligned} \tag{7.21}$$

Adding the equations of the reduced model (7.21) gives $dN/dt = \Pi - \mu N$. Hence, $N \to \Pi/\mu$ as $t \to \infty$. Thus, Π/μ is an upper bound of $N(t)$ provided that $N(0) \leq \Pi/\mu$. Further, if $N(0) > \Pi/\mu$, then $N(t)$ will decrease to this level. Using $N = \Pi/\mu$ in (7.1) gives a limiting (mass action) system given by (7.21), with

$$\lambda = \beta_1 \sum_{j=1}^{n} I_j, \text{where } \beta_1 = \frac{\beta \mu}{\Pi}. \tag{7.22}$$

It can be shown that the associated reproduction number of the reduced model, (7.21) with (7.22), is given by

$$\mathcal{R}_{cr} = \frac{\beta \tilde{D}_1 \tilde{C_{n,1}}}{f_{m+n}},$$

where, $\tilde{D}_1 = \dfrac{\alpha^m \prod_{i=l}^{m} a_i}{\prod_{i=l}^{m+n-1} f_i}$ and $\tilde{C_{n,1}} = \kappa^{n-1} \prod_{i=1}^{p-1} d_i + \prod_{s=2}^{n} f_{m+s} + \sum_{t=1}^{n-2} \kappa^t \prod_{i=1}^{t} d_i \prod_{s=2+t}^{n} f_{m+s}$.

It is easy to show, using the technique in Section 7.4.1, that the reduced model, given by (7.21) with (7.22), has a unique EEP whenever $\mathcal{R}_{cr} > 1$.

Lemma 7.4. *The reduced model, given by* (7.21) *with* (7.22)*, has a unique endemic equilibrium whenever* $\mathcal{R}_{cr} > 1$.

Furthermore, the following result is claimed (see Appendix E for the proof).

Theorem 7.4. *The unique endemic equilibrium of the reduced model, given by* (7.21) *with* (7.22)*, is GAS in* $\mathcal{D} \setminus \mathcal{D}_0$ *if* $\mathcal{R}_{cr} > 1$.

Figure 7.4 depicts the cumulative number of new infections as a function of quarantine rates, from which it is evident that the cumulative number of new infections decreases with increasing quarantine rate. A similar result is obtained by increasing the isolation rate (Figure 7.5). It should be mentioned that the simulation results in Figures 7.4 and 7.5 are consistent with those reported in [32]. Although the global asymptotic stability result given in Appendix E is for a special case (with $\psi = \delta_1 = \delta_2 = \cdots = \delta_{2n} = 0$), further extensive numerical simulations suggest that the endemic equilibrium Ω_1, of the full model (7.6), is GAS in $\mathcal{D} \setminus \mathcal{D}_0$ whenever $\mathcal{R}_c > 1$. Hence, the following conjecture is made.

Conjecture. *The unique endemic equilibrium of the model* (7.6)*, denoted by* Ω_1*, is GAS in* $\mathcal{D} \setminus \mathcal{D}_0$ *if* $\mathcal{R}_c > 1$.

The effect of the number of disease stages for the exposed (m) and infectious (n) classes is monitored by simulating the model (7.6) with various values of $m = n$. The results obtained, depicted in Figure 7.6, show an increase in the cumulative number of disease-related mortality with increasing values of $m = n$.

Simulations for the cumulative number of probable SARS cases observed during the 2003 outbreaks in the Greater Toronto Area (GTA) of Canada are also carried out. The results obtained, for the case $m = n = 3$, are compared with those obtained using the exponentially-distributed (ED) equivalent of the model (7.6) (i.e., model (7.6) with $m = n = 1$) and another gamma-distributed version of the model (7.6) with $m = n = 3$, denoted by GD2, where the average sojourn time in each of the exposed, quarantined, hospitalized and infectious stages is shared equally among each associated disease stage (this is similar to the model given in [32]). It should be mentioned that, in such a setting, the standard ED model has the associated reproduction number given by $\mathcal{R}_c = 0.6506$. Similarly, the GD2 and GD1 models have $\mathcal{R}_c = 0.6962$ and $\mathcal{R}_c = 0.9858$, respectively. Furthermore, about 250 probable SARS cases were reported for the GTA (see Figure 2 in [38]). The simulation results obtained, depicted in Figure 7.7, show that while the ED and GD2 models under-estimated the observed number of probable cases, the GD1 model (7.6) gave a very good estimate of the observed data. It should be mentioned that the GD2 model is also competitive if the quarantine and isolation rates are distributed (unequally) to incorporate their progressive refinement (as in the case of the model GD1).

Similar comparisons are made for the cumulative number of cases recorded for the Hong Kong 2003 SARS outbreaks (approximately 1750 cases were recorded in Hong Kong [38]). Here, too, the GD1 model is more competitive (Figure 7.8). For these simulations, the ED, GD1 and GD2 models have $\mathcal{R}_c$ given by 0.7345, 0.9710 and 0.7861, respectively. It should be emphasized, however, that the reason why the GD1 model gives different results, compared to the GD2 model (for instance), is that the

values of σ_1 and σ_2, and also ϕ_1 and ϕ_2, used in the simulations of the GD1 model are different from the quarantine (σ) and isolation (ϕ) rates used in the simulations of the GD2 model. While the values $\sigma_1 = 0.0333$, $\sigma_2 = 0.05$, $\sigma_3 = 0.1$ and $\phi_1 = 0.0666$, $\phi_2 = 0.1$, $\phi_3 = 0.20619$ were used in the simulations of the GD1 model (to account for the gradual refinement of quarantine and isolation), the values $\sigma_1 = \sigma_2 = \sigma_3 = 0.1$ and $\phi_1 = \phi_2 = \phi_3 = 0.20619$ were used in the simulations of the GD2 model (that's why the $\mathcal{R}_c$ value for the GD1 model is 0.9710, while that of the GD2 model is 0.7861 for this setting).

The effect of the distribution of sojourn times for the symptomatic period ($1/\kappa$) is monitored by simulating the GD1 model (7.6) with the parameters in Table 3.2 for the case where the periods are either same or varied in each stage (i.e., the case where $d_j = n = c_j$ versus the case where $d_j \neq n \neq c_j$). In both cases, the same numerical simulation results were obtained (Figure 7.9). In other words, distributing the average sojourn times equally or unequally between the sub stages of the symptomatic classes (I and H) does not alter the numerical simulation results obtained. The effect of the distribution of sojourn times in the asymptomatic classes (E and Q; given by $1/\alpha$) is also monitored by simulating the model with the parameters in Table 3.2 for three different scenarios. An asymptomatic period $1/\alpha = 6$ days is chosen, and distributed as follows:

(I) 2.5 days in E_1 and Q_1 classes (i.e., $1/a_1\alpha = 1/b_1\alpha = 2.5$ days), 2 days in E_2 and Q_2 classes (i.e., $1/a_2\alpha = 1/b_2\alpha = 2$ days) and 1.5 days in E_3 and Q_3 classes (i.e., $1/a_3\alpha = 1/b_3\alpha = 1.5$ days);

(II) 2 days in E_1 and Q_1 classes (i.e., $1/a_1\alpha = 1/b_1\alpha = 2$ days), 2 days in E_2 and Q_2 classes (i.e., $1/a_2\alpha = 1/b_2\alpha = 2$ days) and 2 days in E_3 and Q_3 classes (i.e., $1/a_3\alpha = 1/b_3\alpha = 2$ days);

(III) 1.5 days in E_1 and Q_1 classes (i.e., $1/a_1\alpha = 1/b_1\alpha = 1.5$ days), 2 days in E_2 and

Q_2 classes (i.e., $1/a_2\alpha = 1/b_2\alpha = 2$ days) and 2.5 days in E_3 and Q_3 classes (i.e., $1/a_3\alpha = 1/b_3\alpha = 2.5$ days).

The simulation results obtained (depicted in Figure 7.10) clearly show that if the asymptomatic period is distributed such that more time is spent in the early stages of the asymptomatic (latent and quarantine) classes (i.e., more time is spent in the E_1, E_2, Q_1, Q_2 classes in comparison to in the E_3 and Q_3 classes), the cumulative number of new cases is higher than for the cases where the asymptomatic period is distributed equally among the stages, or if more time is spent in the later asymptomatic stages. In other words, unlike for the case of the sojourn time spent in the symptomatic classes (I and H), the way the sojourn time is distributed in the asymptomatic compartments (E and Q) affects the cumulative number of new cases.

7.5 Summary

A new deterministic model for disease transmission, subject to the use of quarantine and isolation, is presented and rigorously analyzed. The model, which is based on the assumption that the mean waiting periods in all infected classes obey a gamma distribution, adopts a standard incidence formulation for the infection rate. An important feature of this model is that it allows for equal, or unequal, distribution of the average sojourn time in each of the associated infected compartment. Furthermore, it allows for the gradual refinement of quarantine and isolation measures (this was the case during the 2003 SARS outbreaks).

The main theoretical findings of this chapter are given below:

(i) The model (7.6) has a globally-asymptotically stable disease-free equilibrium whenever the associated reproduction number ($\mathcal{R}_c$) is less than unity (Theorem 7.2);

(ii) The model has a unique endemic equilibrium whenever the reproduction number exceeds unity (Lemma 7.3);

(iii) The unique endemic equilibrium of the model is shown to be locally and then globally-asymptotically stable for some special cases (Theorems 7.3 and 7.4).

Numerical simulations of the model (7.6), using data related to the 2003 SARS outbreaks, show the following:

(a) The cumulative number of new cases of infection decreases with increasing quarantine or isolation rate;

(b) the cumulative number of disease-related mortality increases with increasing number of disease stages (m and n);

(c) unlike the ED and GD2 models, the model (7.6) gives numerical results that are consistent with the 2003 SARS outbreaks data for the GTA and Hong Kong;

(d) distributing the average sojourn time equally or unequally between the respective symptomatic classes does not alter the numerical simulation result obtained (i.e, the cumulative number of new cases);

(e) if the asymptomatic period is distributed such that more time is spent in the early asymptomatic (latent and quarantine) stages, the cumulative number of new cases is higher than for the cases where the period is distributed equally among the asymptomatic stages or if more time is spent in the later asymptomatic stages.

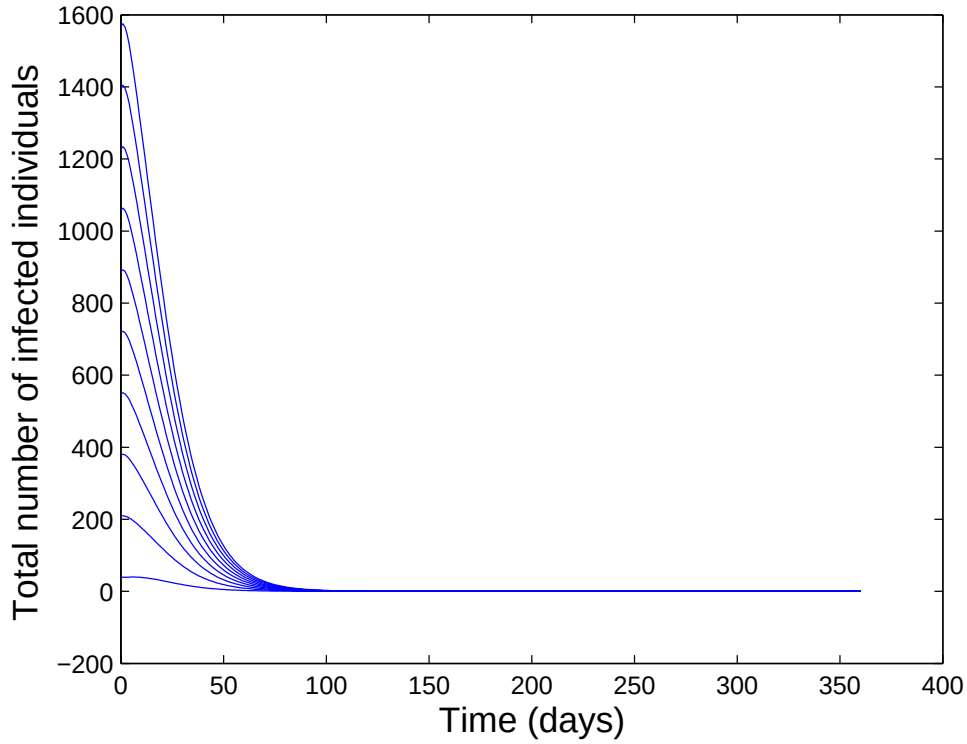


Figure 7.2: Simulation of the model (7.6) showing the total number of infected individuals as a function of time for $\mathcal{R}_c < 1$. Parameter values used are as given in Tables 3.2 and 7.2, with $\beta = 0.2$, $m = 2$, $n = 3$, $a_1 = b_1 = 1.5$, $a_2 = b_2 = 3$, $c_1 = d_1 = c_2 = d_2 = c_3 = d_3 = 3$ (so that, $\mathcal{R}_c = 0.4610$).

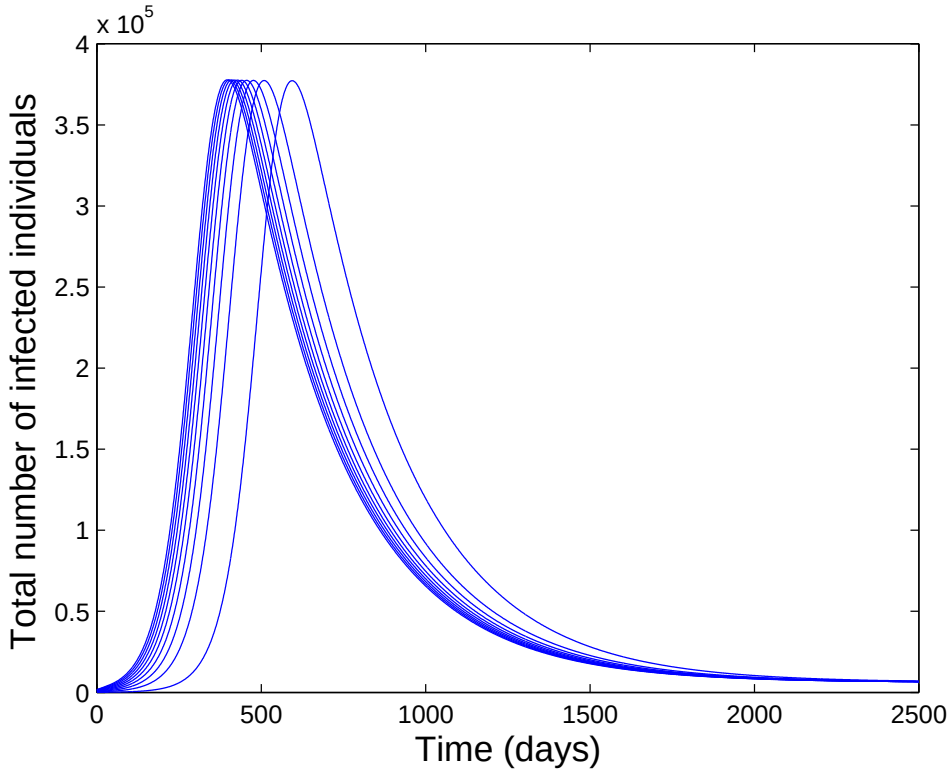


Figure 7.3: Simulation of the model (7.6) showing the total number of infected individuals as a function of time for $\mathcal{R}_c > 1$. Parameter values used are as given in Tables 3.2 and 7.2, with $\beta = 0.5$, $m = 2$, $n = 3$, $a_1 = b_1 = 1.5$, $a_2 = b_2 = 3$, $c_1 = d_1 = c_2 = d_2 = c_3 = d_3 = 3$ (so that, $\mathcal{R}_c = 1.1526$).

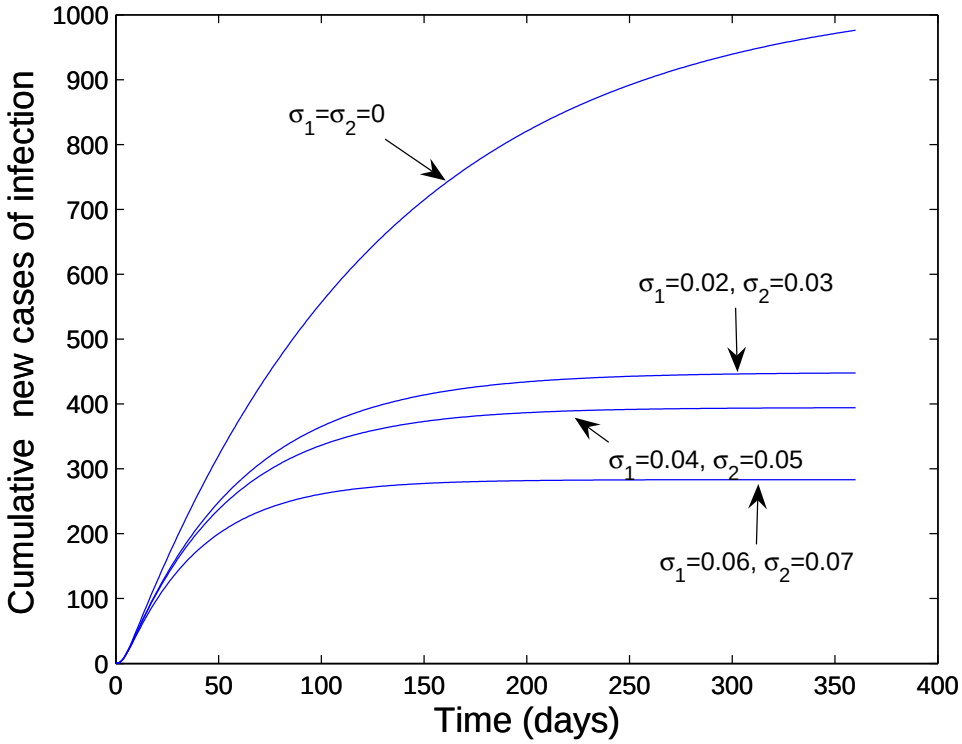


Figure 7.4: Numerical simulations of the model (7.6) showing the cumulative number of new infections for various values of the quarantine parameters (σ_1 and σ_2). Parameter values used are as given in Table 3.2, with $\beta = 0.15$, $m = 2$, $n = 3$, $a_1 = b_1 = 1.5$, $a_2 = b_2 = 3$ $c_1 = d_1 = c_2 = d_2 = c_3 = d_3 = 3$ and the isolation rates are as given in Table 7.2.

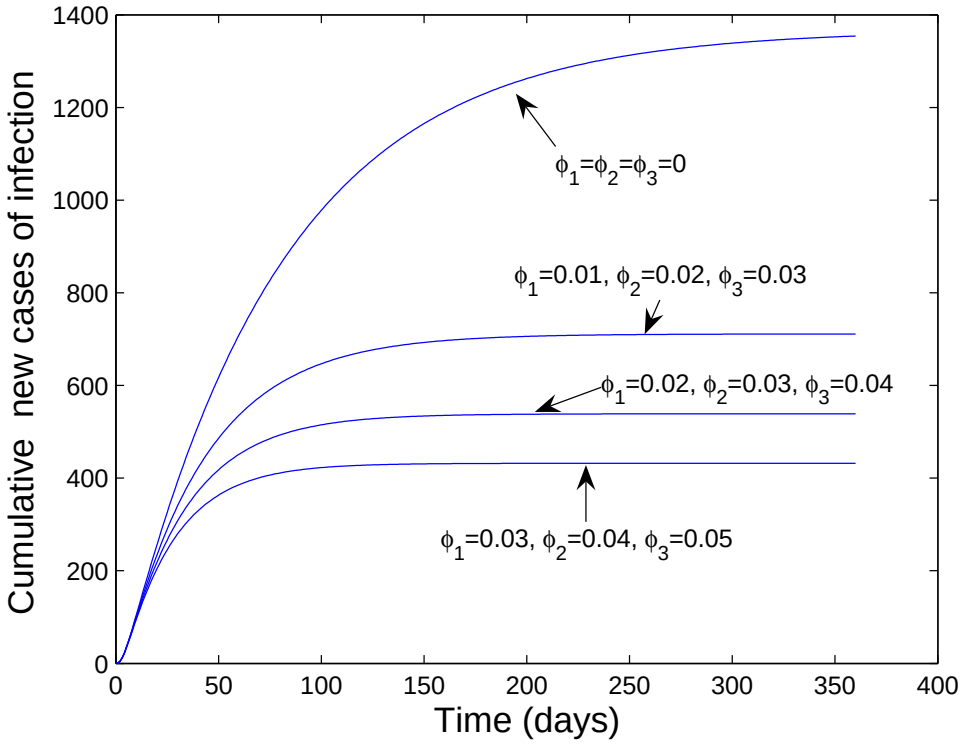


Figure 7.5: Numerical simulations of the model (7.6) showing the cumulative number of new infections for various values of the isolation parameters (ϕ_1, ϕ_2 and ϕ_3). Parameter values used are as in Table 3.2, with $\beta = 0.15$, $m = 2$, $n = 3$, $a_1 = b_1 = 1.5$, $a_2 = b_2 = 3$ $c_1 = d_1 = c_2 = d_2 = c_3 = d_3 = 3$ and the quarantine rates are as given in Table 7.2.

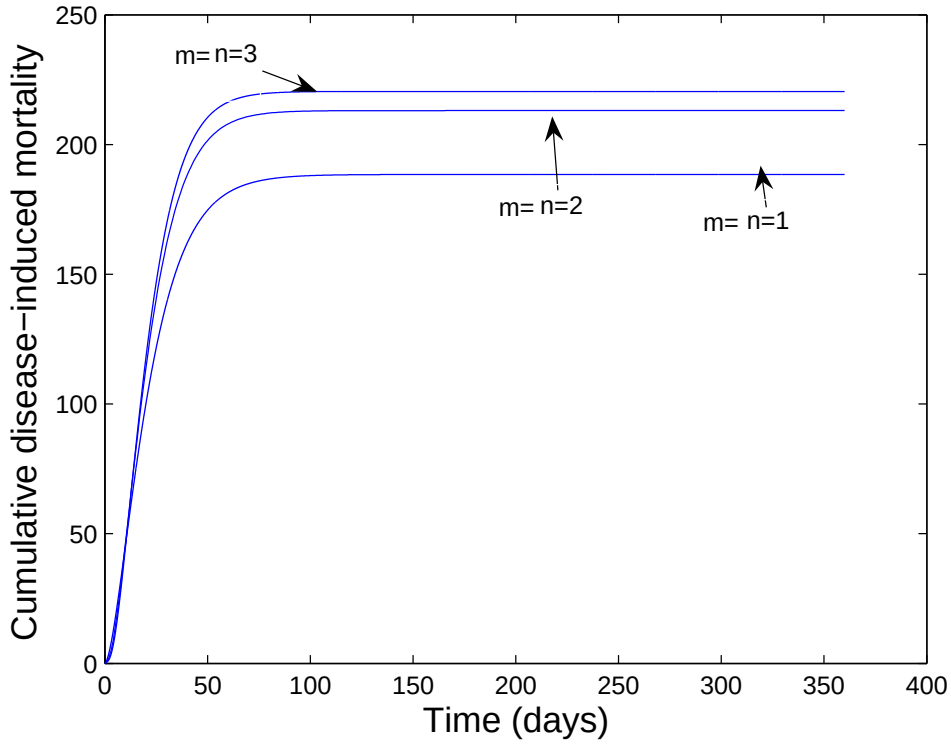


Figure 7.6: Numerical simulations of the model (7.6) showing the cumulative number of disease-induced mortality for various disease stages ($m = n$). Parameter values used are as given in Tables 3.2, 7.2 and 7.3, with $\beta = 0.15$.

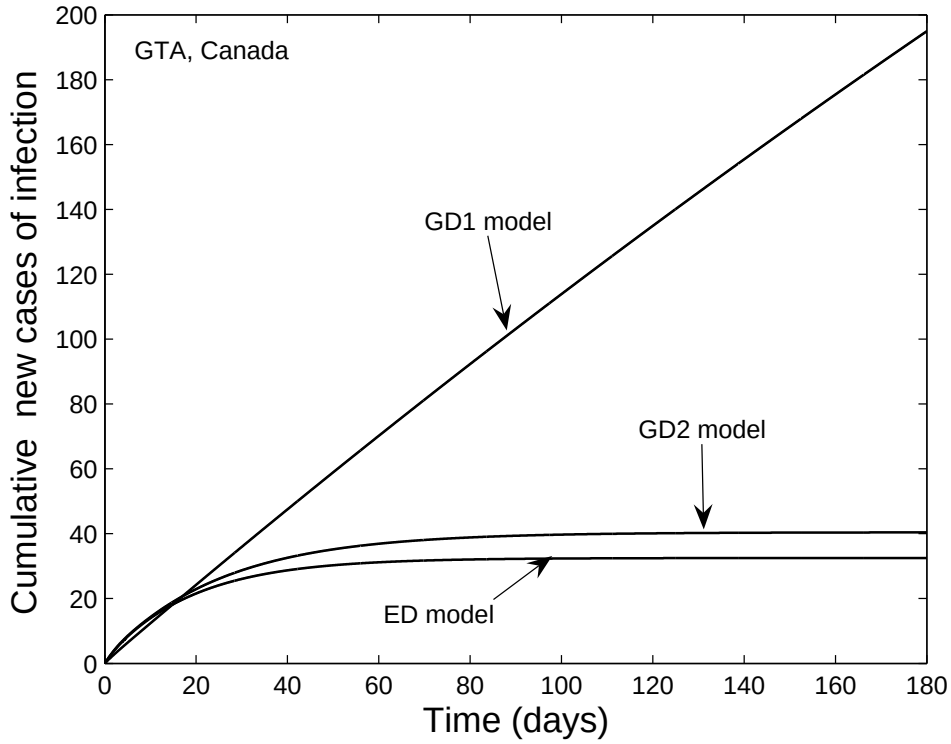


Figure 7.7: Numerical simulations of the model (7.6) showing the cumulative number of probable SARS for the GTA generated using the GD1, GD2 and ED models. Parameter values used are as given in Tables 3.2, 7.2 and 7.3. with $\beta = 0.2,\ \psi = 0$. GD1 model: $m = n = 3$, GD2 model: $m = n = 3$; $\sigma_1 = \sigma_2 = \sigma_3 = 0.1$ and $\phi_1 = \phi_2 = \phi_3 = 0.20619$. ED model: $m = n = 1$.

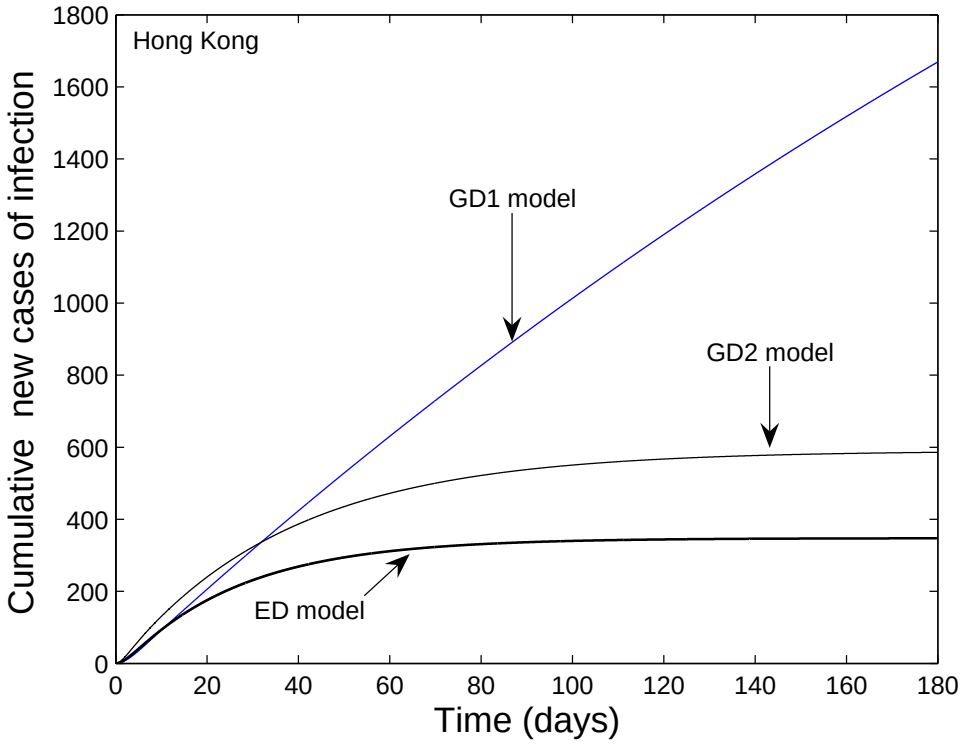


Figure 7.8: Numerical simulations of the model (7.6) showing the cumulative number of probable SARS for the Hong Kong generated using the GD1, GD2 and ED models. Parameter values used are as given in Tables 3.2, 7.2 and 7.3, with $\beta = 0.2, \psi = 0$ and $\Pi = 122$. GD1 model: $m = n = 3$. GD2 model: $m = n = 3$. $\sigma_1 = \sigma_2 = \sigma_3 = 0.1$ and $\phi_1 = \phi_2 = \phi_3 = 0.20619$. ED model: $m = n = 1$.

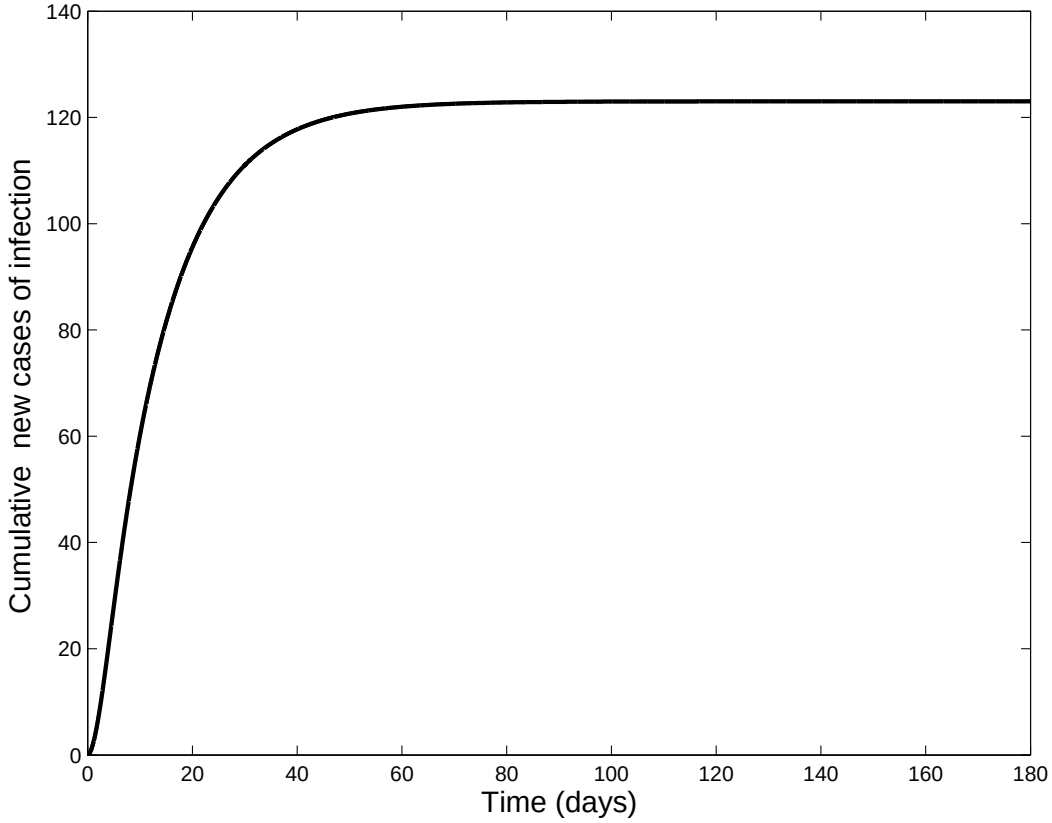


Figure 7.9: Numerical simulations of the model (7.6) showing the cumulative number of new cases for various distributions of the symptomatic period $(1/\kappa)$ using different values of $c_1 = d_1,\ c_2 = d_2,$ and $\mathrm{c}_3 = \mathrm{d}_3$. Parameter values used are as given in Table 3.2, with $\beta = 0.2,\ \psi = 0,\ \sigma_1 = \sigma_2 = \sigma_3 = 0.1$ and $\phi_1 = \phi_2 = \phi_3 = 0.20619$.

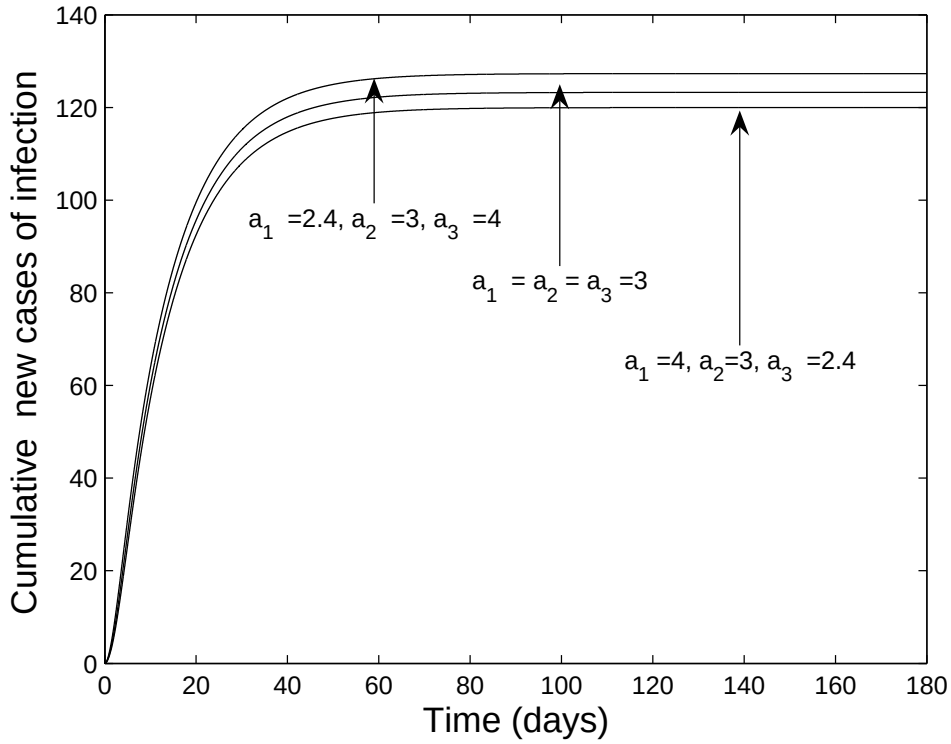


Figure 7.10: Numerical simulations of the model (7.6) showing the cumulative number of new cases for various distributions of the asymptomatic period $(1/\alpha)$ using different values of $a_1 = b_1,\ a_2 = b_2,$ and $\mathrm{a}_3 = \mathrm{b}_3$. Parameter values used are as given in Table 3.2, with $\beta = 0.2,\ \psi = 0,\ \sigma_1 = \sigma_2 = \sigma_3 = 0.1$ and $\phi_1 = \phi_2 = \phi_3 = 0.20619$.

Chapter 8

Summary of Contributions and Future Work

The main contributions of this thesis can be classified into three main categories, namely, model formulation, mathematical analysis and contributions to public health. These categories are summarized as follows.

8.1 Model Formulation

A deterministic model for assessing the combined impact of quarantine (of asymptomatic cases) and isolation (of symptomatic cases) on curtailing the spread of a communicable disease is considered. In addition to using standard incidence in modelling the infection rates, the basic model allows for the loss of infection-acquired immunity (so that individuals who recovered from infection can become susceptible again). The thesis contains four new models which extend the basic model described above, for the transmission dynamics of a disease that is controllable using quarantine and isolation, as follows:

(i) A new quarantine/isolation model, that incorporates time delay as well as two

different incidence functions (Holling type II and standard incidence) is designed in Chapter 4;

(ii) The basic model (in Chapter 3) is extended to incorporate the effect of periodicity in the transmission dynamics of the disease. The resulting non-autonomous model is presented in Chapter 5;

(iii) A new quarantine/isolation model with an imperfect vaccine is constructed in Chapter 6;

(iv) A new quarantine/isolation model that allows for multiple latent and infectious stages, as well as gamma-distributed waiting times in these stages, is designed in Chapter 7.

8.2 Mathematical Analysis

A major contribution of the thesis is the detailed qualitative analyses carried out (using a robust collection of non-linear dynamical systems theories and techniques) of all the models presented in this thesis (this is particularly noteworthy considering the relatively large size and non-linearity of the models considered). Some of the main mathematical results are summarized below.

Chapter 3

Rigorous qualitative analysis of the SEIQHRS model, which takes the form of a deterministic system of nonlinear differential equations with standard incidence, reveals that it has a globally-asymptotically stable disease-free equilibrium whenever its associated reproduction number ($\mathcal{R}_c$) is less than unity. Further, the model has a unique endemic equilibrium when the threshold quantity exceeds unity. Using a Krasnoselskii sublinearity trick, it is shown that the unique endemic equilibrium is locally-asymptotically

stable when it exists (for a special case). A non-linear Lyapunov function of Volterra type is used, in conjunction with the LaSalle's Invariance Principle, to show that the endemic equilibrium is globally-asymptotically stable for a special case. These analyses show that the disease will be eliminated from the community if the use of quarantine and isolation can bring $\mathcal{R}_c$ to a value less than unity.

Chapter 4

The problem of the asymptomatic dynamics of a quarantine/isolation model with time delay is considered, subject to two incidence functions (namely standard incidence and Holling type II incidence function). Rigorous qualitative analysis of the model shows that it exhibits essentially the same (equilibrium) dynamics regardless of which of the two incidence functions is used. In particular, for each of the two incidence functions, the model has a globally-asymptotically stable disease-free equilibrium whenever the associated reproduction threshold quantity is less than unity. Further, it has a unique endemic equilibrium when the threshold quantity exceeds unity. For the case with Holling type II incidence function, it is shown that the unique endemic equilibrium of the model (by using Comparison Theorem) is globally-asymptotically stable for a special case. The permanence of the disease is also established for the model with Holling type II incidence function. Furthermore, it is shown that adding time delay to, and/or replacing the standard incidence function with the Holling type II incidence function in, the corresponding autonomous quarantine/isolation model with standard incidence (considered in Chapter 3, for the case where recovered individuals do not lose their infection-acquired immunity and hospitalized individuals do not transmit infection) does not alter the qualitative dynamics of the autonomous system (with respect to the elimination or persistence of the disease).

Chapter 5

In this chapter, the model presented in Chapter 3 is extended to include the effect of periodicity on the transmission dynamics of the disease. Rigorous analysis of the resulting model reveals that it has a globally-asymptotically stable disease-free solution whenever its associated basic reproduction ratio is less than unity. Furthermore, using persistence theory, it is shown that the model has a globally-asymptotically stable family of positive periodic solutions for a special case. These analyses show that adding periodicity to the autonomous quarantine/isolation model (3.2) does not alter its qualitative dynamics (with respect to the elimination or persistence of the disease).

Chapter 6

The potential impact of an imperfect vaccine in combatting the spread of a disease, in the presence of quarantine and isolation is rigorously assessed by extending and analysing the model in Chapter 3 to include an imperfect vaccine. Using center manifold theorem, the new (12-dimensional) model is shown to undergo the phenomenon of backward bifurcation, where a stable disease-free equilibrium co-exists with a stable endemic equilibrium when the associated reproduction threshold is less than unity. It is shown that the backward bifurcation phenomenon can be removed if the vaccine is perfect or if mass action incidence is used, instead of standard incidence, in the model formulation. Thus, this chapter shows that adding vaccination to the quarantine/isolation model in Chapter 3 alters its qualitative properties (since the model in Chapter 3 did not exhibit backward bifurcation). Further, the model has a unique endemic equilibrium when the reproduction threshold quantity exceeds unity. A nonlinear Lyapunov function, of Goh-Volterra type, is used to show that the endemic equilibrium is globally-asymptotically stable for a special case.

Chapter 7

In this chapter, a new ($2(m+n+1)$-dimensional) quarantine/isolation model which incorporates multiple latent and infectious periods (as well as gamma-distributed waiting times in these compartments) is designed and rigorously analysed. A linear Lyapunov function is used, in conjunction with the LaSalle's Invariance Principle, to show that the disease-free equilibrium of the model is globally-asymptotically stable whenever its associated reproduction number is less than unity. Further, the model has a unique endemic equilibrium when the threshold quantity exceeds unity. Using a Krasnoselskii sub-linearity trick, it is shown that the unique endemic equilibrium is locally-asymptotically stable for a special case. A nonlinear Lyapunov function of Volterra type is used, in conjunction with the LaSalle's Invariance Principle, to show that the endemic equilibrium is also globally-asymptotically stable for a special case. This chapter shows that adding multiple latent and infectious stages, as well as gamma-distributed waiting times in these stages, does not alter the dynamics of the basic quarantine/isolation model considered in Chapter 3, for the case where recovered individuals do not lose their infection-acquired immunity (with respect to the persistence or elimination of the disease).

8.3 Public Health

The study provides some important epidemiological insights into the impact of quarantine/isolation on the control of a communicable disease, including the following:

(i) The level of transmission by individuals isolated in hospitals play an important role in determining the qualitative impact of the two control measures (the use of quarantine and isolation could offer a detrimental population-level impact if the isolation-related transmission is high enough);

(ii) The disease burden decreases with increasing time delay (incubation period);

(iii) The singular use of a quarantine/isolation strategy may lead to the effective disease control (or elimination) if its effectiveness level is at least moderately high enough. The combine use of the quarantine/isolation strategy with a vaccination strategy will eliminate the communicable disease being studied, even for the low efficacy level of the universal strategy considered in this thesis. It is further shown that the imperfect vaccine could induce a positive or negative population-level impact depending on the size (or sign) of a certain associated epidemiological threshold;

(iv) Owing to the phenomenon of backward bifurcation in the quarantine/isolation/vaccination model considered in Chapter 6, it is shown that, in this setting, effective disease control (or elimination) depends on the initial sizes of the sub-populations of the model;

(v) The cumulative number of new cases of infection decreases with increasing quarantine or isolation rate;

(vi) The cumulative number of new cases of infection is higher if the asymptomatic period is distributed such that most of the period is spent in the early stages of the asymptomatic compartments in comparison to the cases where the average time period is equally distributed among the associated stages or if most of the time period is spent in the later (final) stages of the asymptomatic compartments. Distributing the average sojourn time in the asymptomatic infectious classes equally or unequally does not effect the cumulative number of new cases.

8.4 Future Work

The work in this thesis can be extended in numerous directions, including:

(i) Establishing the global dynamics of the endemic equilibria of the models (without considering any special cases);

(ii) Investigating the uniqueness and stability of the periodic solution associated with the non-autonomous model in Chapter 5;

(iii) Studying the cost-effectiveness and optimal control of quarantine and isolation measures in controlling the spread of a disease in a population;

(iv) Carrying out detailed uncertainty and sensitivity analyses in the models (to study the effect of such uncertainties on some of the simulation results obtained);

(v) Modelling the impact of quarantine and isolation in a multi-patch setting (such as for the case of the spread of animal diseases, like foot-and-mouth disease).

Appendices

Appendix A: Basic Reproduction Ratio in Periodic Environment

In this appendix, the theory of basic reproduction ratio for disease transmission models in a periodic environment, developed by Wang and Zhao [91], is described.

Suppose that the disease compartments are divided into infected compartments (labeled by $i = 1, 2, \cdots, m$) and uninfected compartments (labeled by $i = m+1, \cdots, n$). Define X_s to be the set of all disease-free states:

$$X_s := \{x \geq 0 : x_i = 0, \text{ for all } i = 1, 2, \cdots, m\}.$$

Let $\mathcal{F}_i(t, x)$ be the input rate of newly infected individuals in the ith compartment, $\mathcal{V}_i^+(t, x)$ be the input rate of individuals and $\mathcal{V}_i^-(t, x)$ be the rate of transfer of individuals out of compartment i. Thus, the disease transmission model is governed by a non-autonomous ordinary differential system:

$$\frac{d}{dt}x(t) = \mathcal{F}(t, x(t)) - \mathcal{V}(t, x(t)) = f(t, x(t)), \tag{A.1}$$

where, $\mathcal{V}_i(t, x) = \mathcal{V}_i^-(t, x) - \mathcal{V}_i^+(t, x)$, $f = (f_1, f_2, \cdots, f_n)$.

Assume the following:

(A1) For each $1 \leq i \leq n$, $\mathcal{F}_i(t,x)$, $\mathcal{V}_i^+(t,x)$ and $\mathcal{V}_i^-(t,x)$ are non-negative, continuous on $\mathbb{R} \times \mathbb{R}_+^n$ and continuously differential with respect to x.

(A2) There exists a real number $\omega > 0$, such that $\mathcal{F}_i(t,x)$, $\mathcal{V}_i^+(t,x)$ and $\mathcal{V}_i^-(t,x)$ are ω-periodic in t.

(A3) If $x_i = 0$, then $\mathcal{V}_i^- = 0$ for $i = 1, \cdots, m$.

(A4) $\mathcal{F}_i = 0$ for $i > m$.

(A5) if $x \in X_s$, then $\mathcal{F}_i = \mathcal{V}_i^+ = 0$ for $i = 1, \cdots, m$.

It is further assumed that the model (A.1) has a disease-free solution, given by

$$x^0(t) = \{(0, \cdots, 0, x_{m+1}^0(t), \cdots, x_n^0(t))^T \text{ with } x_i^0(t) > 0, m+1 \leq i \leq n \text{ for all } t\}.$$

Define, an $(n-m) \times (n-m)$ matrix

$$M(t) = \left(\frac{\partial f_i(t,x^0)}{\partial x_j}\right)_{m+1 \leq i,j \leq n},$$

and the $m \times m$ matrices

$$V(t) = \left(\frac{\partial \mathcal{F}_i(t,x^0)}{\partial x_j}\right)_{1 \leq i,j \leq m}, \quad F(t) = \left(\frac{\partial \mathcal{F}_i(t,x^0)}{\partial x_j}\right)_{1 \leq i,j \leq m}.$$

Let $\Phi_M(t)$ be the monodromy matrix of the linear ω-periodic system $\dfrac{dz}{dt} = M(t)z$. Further, it is assumed that

(A6) $\rho(\Phi_M(\omega)) < 1$, where $\rho(\Phi_M(\omega))$ is the spectral radius of $\Phi_M(\omega)$.

(A7) $\rho(\Phi_{-V}(\omega)) < 1$.

Let,

$$Y(t,s), \;\; t \geq s,$$

be the evolution operator of the linear ω-periodic system

$$\frac{dy}{dt} = -V(t)y.$$

In other words, for each $s \in \mathbb{R}$, the associated $m \times m$ matrix $Y(t,s)$ satisfies

$$\frac{dY(t,s)}{dt} = -V(t)Y(t,s) \;\; \forall t \geq s, \quad Y(s,s) = I.$$

It is further assumed that $\phi(s)$ (ω-periodic in s) is the initial distribution of infectious individuals. That is, $F(s)\phi(s)$ is the rate at which new infections are produced by infected individuals who were introduced into the population at time s [91]. Since $t \geq s$, it follows then that $Y(t,s)F(s)\phi(s)$ represents the distribution of those infected individuals who were newly-infected at time s, and remain infected at time t.

Hence, the cumulative distribution of new infections at time t, produced by all infected individuals ($\phi(s)$) introduced at a prior time $s = t$, is given by

$$\Psi(t) = \int_{-\infty}^{t} Y(t,s)F(s)\phi(s)ds = \int_{0}^{\infty} Y(t,t-a)F(t-a)\phi(t-a)da.$$

Let $\mathbb{C}_\omega$ be the ordered Banach space of all ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^4$, which is equipped with maximum norm $\|.\|$ and positive cone

$$\mathbb{C}_\omega^+ = \{\phi \in \mathbb{C}_\omega : \;\; \phi(t) \geq 0, \;\; \forall t \in \mathbb{R}\}.$$

Define a linear operator $L : \mathbb{C}_\omega \to \mathbb{C}_\omega$ by [91]

$$(L\phi)(t) = \int_0^\infty Y(t, t-a)F(t-a)\phi(t-a)da \quad \forall t \in \mathbb{R}, \phi \in \mathbb{C}_\omega.$$

The reproduction ratio (denoted by $\mathcal{R}_0$) is then given by the spectral radius of L, denoted by $\rho(L)$. That is, $\mathcal{R}_0 = \rho(L)$ [91].

Appendix B: Verification of Assumptions A1-A7 in Appendix A

The assumptions are verified following the approach in [91]. Using the notation in Appendix A, the system (5.1) can be re-written as:

$$\frac{d}{dt}x(t) = \mathcal{F}(t, x(t)) - \mathcal{V}(t, x(t)) = f(t, x(t)), \tag{B.1}$$

where,

$$x = \begin{pmatrix} S \\ E \\ I \\ Q \\ H \\ R \end{pmatrix}, \quad \mathcal{F} = \begin{pmatrix} 0 \\ \frac{\beta(t)S(t)[I(t)+\eta(t)H(t)]}{N(t)} \\ \kappa E \\ \sigma E \\ \alpha Q \\ 0 \end{pmatrix},$$

and,

$$\mathcal{V} = \begin{pmatrix} -\Pi - \psi R + \dfrac{\beta(t)S(t)[I(t)+\eta(t)H(t)]}{N(t)} + \mu S \\ (\kappa(t)+\sigma(t)+\mu)E \\ (\gamma_1+\phi+\mu+\delta_1)I \\ (\alpha(t)+\mu)Q \\ (\gamma_2+\mu+\delta_2)H \\ -\gamma_1 I - \gamma_2 H + (\psi+\mu)R \end{pmatrix}.$$

Further, let,

$$\mathcal{V}^+ = \begin{pmatrix} \Pi + \psi R \\ 0 \\ 0 \\ 0 \\ 0 \\ \gamma_1 I + \gamma_2 H \end{pmatrix} \quad \text{and} \quad \mathcal{V}^- = \begin{pmatrix} \dfrac{\beta(t)S(t)[I(t)+\eta(t)H(t)]}{N(t)} + \mu S \\ (\kappa(t)+\sigma(t)+\mu)E \\ (\gamma_1+\phi+\mu+\delta_1)I \\ (\alpha(t)+\mu)Q \\ (\gamma_2+\mu+\delta_2)H \\ (\psi+\mu)R \end{pmatrix}.$$

It is easy to see that $\mathcal{V} = \mathcal{V}^- - \mathcal{V}^+$. The functions $\mathcal{F}, \mathcal{V}^+$ and $\mathcal{V}^-$ satisfy the following:

(A1) For each $1 \leq i \leq 6$, $\mathcal{F}_i(t,x)$, $\mathcal{V}_i^+(t,x)$ and $\mathcal{V}_i^-(t,x)$ are non-negative, continuous on $\mathbb{R} \times \mathbb{R}_+^6$ and continuously differential with respect to x, (since each function denotes a direct non-negative transfer of individuals).

(A2) By assumption (note that it is assumed that some of the model parameters are ω-periodic functions), there exists a real number $\omega > 0$, such that $\mathcal{F}_i(t,x)$, $\mathcal{V}_i^+(t,x)$ and $\mathcal{V}_i^-(t,x)$ are ω-periodic in t.

(A3) If $x_i = 0$, then $\mathcal{V}_i^- = 0$ for $i = 2,3,4,5$.

(A4) $\mathcal{F}_i = 0$ for $i = 1,6$.

(A5) Define $X_s = \{x \geq 0 : \ x_i = 0 \text{ for } i = 2, 3, 4, 5\}$. It is clear that if $x \in X_s$, then $\mathcal{F}_i = \mathcal{V}_i^+ = 0$ for $i = 2, 3, 4, 5$.

System (5.1) has a disease-free periodic solution $x^* = (x_1^*, x_2^*, x_3^*, x_4^*, x_5^*, x_6^*) = (\pi/\mu, 0, 0, 0, 0, 0)$. Define a 2×2 matrix

$$M(t) = \left(\frac{\partial f_i(t, x^*)}{\partial x_j} \right)_{i,j=1,6}.$$

It follows from (B.1), and the definitions of the matrices $\mathcal{F}$ and $\mathcal{V}$, that

$$M(t) = \begin{bmatrix} -\mu & \psi \\ 0 & -(\mu + \psi) \end{bmatrix}.$$

(A6) Since $M(t)$ is a diagonalizable matrix with negative eigenvalues, then

$$\rho(\Phi_M(\omega)) < 1.$$

(A7) Similarly, $-V(t)$ is a diagonalizable matrix with negative eigenvalues. Hence,

$$\rho(\Phi_{-V}(\omega)) < 1.$$

Appendix C: Backward Bifurcation in Model (6.2)

Proof. Consider the model (6.2). It is convenient to make the following change of variables. Let,

$$S = x_1,\ V = x_2,\ E = x_3,\ E_V = x_4,\ I = x_5,\ I_V = x_6,$$
$$Q = x_7,\ Q_V = x_8,\ H = x_9,\ H_V = x_{10},\ R = x_{11},\ R_V = x_{12},$$

so that,

$$N = x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8 + x_9 + x_{10} + x_{11} + x_{12}.$$

Further, let $X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10}, x_{11}, x_{12})^T$. Thus, the model (6.2) can be re-written in the form $\frac{dX}{dt} = F(X)$, with $F = (f_1; f_2; f_3; f_4; f_5; f_6; f_7; f_8; f_9; f_{10}; f_{11}; f_{12})^T$, as follows:

$$
\begin{aligned}
\frac{dx_1}{dt} &= f_1 = (1-\rho)\Pi - \frac{\beta(x_5+\nu_1 x_6 + x_9 + \nu_2 x_{10})x_1}{x_1+x_2+x_3+x_4+x_5+x_6+x_7+x_8+x_9+x_{10}+x_{11}+x_{12}} \\
&\quad + \psi x_2 - (\mu+\zeta), \\
\frac{dx_2}{dt} &= f_2 = \rho\Pi - \frac{(1-\varepsilon)\beta(x_5+\nu_1 x_6 + x_9 + \nu_2 x_{10})x_2}{x_1+x_2+x_3+x_4+x_5+x_6+x_7+x_8+x_9+x_{10}+x_{11}+x_{12}} \\
&\quad + \zeta x_1 - (\mu+\psi), \\
\frac{dx_3}{dt} &= f_3 = \frac{\beta(x_5+\nu_1 x_6 + x_9 + \nu_2 x_{10})x_1}{x_1+x_2+x_3+x_4+x_5+x_6+x_7+x_8+x_9+x_{10}+x_{11}+x_{12}} - k_1 x_3, \\
\frac{dx_4}{dt} &= f_4 = \frac{(1-\varepsilon)\beta(x_5+\nu_1 x_6 + x_9 + \nu_2 x_{10})x_2}{x_1+x_2+x_3+x_4+x_5+x_6+x_7+x_8+x_9+x_{10}+x_{11}+x_{12}} - k_2 x_4, \\
\frac{dx_5}{dt} &= f_5 = \kappa x_3 - k_3 x_5, \\
\frac{dx_6}{dt} &= f_6 = \theta_1 \kappa x_4 - k_4 x_6, \\
\frac{dx_7}{dt} &= f_7 = \sigma x_3 - k_5 x_7, \\
\frac{dx_8}{dt} &= f_8 = \sigma_1 x_4 - k_6 x_8, \\
\frac{dx_9}{dt} &= f_9 = \alpha x_7 + \phi x_5 - k_7 x_9, \\
\frac{dx_{10}}{dt} &= f_{10} = \theta_5 \alpha x_7 + \theta_3 \phi x_6 - k_8 x_{10}, \\
\frac{dx_{11}}{dt} &= f_{11} = \gamma_1 x_5 + \gamma_2 x_9 - \mu x_{11}, \\
\frac{dx_{12}}{dt} &= f_{11} = \theta_2 \gamma_1 x_6 + \theta_6 \gamma_2 x_{10} - \mu x_{11}.
\end{aligned}
\tag{C.1}
$$

The Jacobian of the system (C.1), at the associated DFE (given by $\mathcal{E}_0$, in (6.3)) is given by

$$
J(\mathcal{E}_0) = [M_{12\times 6} \;\; U_{12\times 6}]
$$

where,

$$
M = \begin{pmatrix}
-(\zeta+\mu) & \psi & 0 & 0 & -\dfrac{\beta x_1^*}{x_1^*+x_2^*} & -\dfrac{\beta\nu_1 x_1^*}{x_1^*+x_2^*} \\
\zeta & -(\psi+\mu) & 0 & 0 & -\dfrac{(1-\varepsilon)\beta x_2^*}{x_1^*+x_2^*} & -\dfrac{(1-\varepsilon)\beta\nu_1 x_2^*}{x_1^*+x_2^*} \\
0 & 0 & -k_1 & 0 & \dfrac{\beta x_1^*}{x_1^*+x_2^*} & \dfrac{\beta\nu_1 x_1^*}{x_1^*+x_2^*} \\
0 & 0 & 0 & -k_2 & \dfrac{(1-\varepsilon)\beta x_2^*}{x_1^*+x_2^*} & \dfrac{(1-\varepsilon)\beta\nu_1 x_2^*}{x_1^*+x_2^*} \\
0 & 0 & \kappa & 0 & -k_3 & 0 \\
0 & 0 & 0 & \theta_1\kappa & 0 & -k_4 \\
0 & 0 & \sigma & 0 & 0 & 0 \\
0 & 0 & 0 & \sigma_1 & 0 & 0 \\
0 & 0 & 0 & 0 & \phi & 0 \\
0 & 0 & 0 & 0 & 0 & \theta_3\phi \\
0 & 0 & 0 & 0 & \gamma_1 & 0 \\
0 & 0 & 0 & 0 & 0 & \theta_2\gamma_1
\end{pmatrix},
$$

$$U = \begin{pmatrix} 0 & 0 & -\dfrac{\beta\eta x_1^*}{x_1^*+x_2^*} & -\dfrac{\beta\eta\nu_2 x_1^*}{x_1^*+x_2^*} & 0 & 0 \\ 0 & 0 & -\dfrac{(1-\varepsilon)\beta\eta x_2^*}{x_1^*+x_2^*} & -\dfrac{(1-\varepsilon)\beta\eta\nu_2 x_2^*}{x_1^*+x_2^*} & 0 & 0 \\ 0 & 0 & \dfrac{\beta\eta x_1^*}{x_1^*+x_2^*} & \dfrac{\beta\eta\nu_2 x_1^*}{x_1^*+x_2^*} & 0 & 0 \\ 0 & 0 & \dfrac{(1-\varepsilon)\beta\eta x_2^*}{x_1^*+x_2^*} & \dfrac{(1-\varepsilon)\beta\eta\nu_2 x_2^*}{x_1^*+x_2^*} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ -k_5 & 0 & 0 & 0 & 0 & 0 \\ 0 & -k_6 & 0 & 0 & 0 & 0 \\ \alpha & 0 & -k_7 & 0 & 0 & 0 \\ 0 & \theta_5\alpha & 0 & -k_8 & 0 & 0 \\ 0 & 0 & \gamma_2 & 0 & -\mu & 0 \\ 0 & 0 & 0 & \theta_6\gamma_2 & 0 & -\mu \end{pmatrix}.$$

Consider the case when $\mathcal{R}_{vac} = 1$ (where $\mathcal{R}_{vac}$ is as defined in Section 6.3). Suppose, further, that β is chosen as a bifurcation parameter. Solving for β from $\mathcal{R}_{vac} = 1$, gives

$$\beta^* = \frac{k_1k_2k_3k_4k_5k_6k_7k_8}{B_1 + B_2},$$

where,

$$B_1 = \omega_2 k_1 k_3 k_5 k_7 (1-\varepsilon)(\nu_1\theta_1\kappa k_6 k_8 + \nu_2\eta\theta_3\phi\theta_1\kappa k_6 + \nu_2\eta\theta_5\alpha\sigma_1 k_4),$$

$$B_2 = \omega_1 k_2 k_4 k_6 k_8 (\kappa k_5 k_7 + \eta\phi\kappa k_5 + \eta\alpha\sigma k_3).$$

It is worth stating that the transformed system (C.1), with $\beta = \beta^*$, has a hyperbolic

equilibrium point (that is, the linearized system has a simple eigenvalue with zero real part and all other eigenvalues have negative real part). Hence, the center manifold theorem can be used to analyze the dynamics of (C.1) near $\beta = \beta^*$. It can be shown that the right eigenvector of $J(\mathcal{E}_0)|_{\beta=\beta^*}$ is given by $\mathbf{w} = (w_1, w_2, \cdots, w_{11}, w_{12})^T$, where,

$$
\begin{aligned}
w_1 &= \frac{k_2 w_4 + (\mu+\psi)w_2}{\zeta}, \quad w_2 = \left[\frac{-\zeta}{\mu(\mu+\zeta+\psi)}\right]\left[k_1 w_3 + \frac{k_2 w_4(\mu+\zeta)}{\zeta}\right], \\
w_3 &= \frac{\beta(x_1^* w_5 + \nu_1 x_1^* w_6 + \eta x_1^* w_9 + \nu_2 \eta x_1^* w_{10})}{k_1(x_1^* + x_2^*)}, \qquad w_7 = \frac{\sigma w_3}{k_5}, \\
w_4 &= \frac{(1-\varepsilon)\beta(x_2^* w_5 + \nu_1 x_2^* w_6 + \eta x_2^* w_9 + \nu_2 \eta x_2^* w_{10})}{k_2(x_1^* + x_2^*)}, \quad w_8 = \frac{\sigma_1 w_4}{k_6}, \\
w_{11} &= \frac{\gamma_1 w_5 + \gamma_2 w_9}{\mu}, \quad w_{12} = \frac{\theta_2\gamma_1 w_6 + \theta_6\gamma_2 w_{10}}{\mu}, \\
w_5 &= w_5 > 0, \quad w_6 = w_6 > 0, \quad w_9 = w_9 > 0, \quad w_{10} = w_{10} > 0.
\end{aligned}
$$

Similarly, $J(\mathcal{E}_0)|_{\beta=\beta^*}$ has a left eigenvector $\mathbf{v} = (v_1, v_2, \cdots, v_{11}, v_{12})$, where,

$$
\begin{aligned}
&v_1 = 0, \;\; v_2 = 0, \;\; v_3 = \frac{\kappa v_5 + \sigma v_7}{k_1}, \quad v_4 = \frac{\theta_1\kappa + \theta_5\sigma v_8}{k_2}, \;\; v_5 = v_5 > 0, \quad v_6 = v_6 > 0, \\
&v_7 = \frac{\alpha v_9}{k_5}, \quad v_8 = \frac{\theta_5\alpha v_{10}}{k_6} \quad v_9 = v_9 > 0, \quad v_{10} = v_{10} > 0, \quad v_{11} = 0, \quad v_{12} = 0.
\end{aligned}
$$

Consequently, it follows that the bifurcation coefficients, a and b (defined in Theo-

rem 2.4) are given, respectively, by

$$\begin{aligned} a &= \sum_{k,i,j=1}^{12} v_k w_i w_j \frac{\partial^2 f_k(0,0)}{\partial x_i \partial x_j} \\ &= -(1-\varepsilon)v_4 x_2^*(w_1 + w_3 + w_4 + w_5 + w_6 + w_7 + w_8 + w_9 + w_{10} + w_{11} + w_{12}) \\ &+ w_2 x_1^*(1-\varepsilon)v_4 + w_1 x_2^* v_3 - x_1^* v_3(w_2 + w_3 + w_4 + w_5 + w_6 + w_7 + w_8 + w_9 \\ &+ w_{10} + w_{11} + w_{12}), \end{aligned} \tag{C.2}$$

$$b = \sum_{k,i=1}^{12} v_k w_i \frac{\partial^2 f_k(0,0)}{\partial x_i \partial \beta^*} = \frac{(v_3 x_1^* + (1-\varepsilon)v_4 x_2^*)(\eta w_9 + w_5 + w_6 v_1 + \eta w_{10} v_2)}{x_1^* + x_2^*} > 0.$$

Since the coefficient b is always positive, it follows from Theorem 2.4 that the system (C.1) will undergo backward bifurcation if the coefficient a, given in (C.2), is positive. This result is summarized below. □

Theorem 1. *The transformed model* (C.1)*, or equivalently* (6.2)*, exhibits backward bifurcation at* $\mathcal{R}_{vac} = 1$ *whenever the bifurcation parameter* a*, given in* (C.2)*, is positive.*

Appendix D: Proof of Theorem 7.3

Proof. Consider the model (7.6) with $\delta_1 = \delta_2 = \cdots = \delta_{2n} = 0$. In such a case, the reproduction number $\mathcal{R}_c$ reduces to $\mathcal{R}_{cr}$. The proof is based on using a Krasnoselskii sub-linearity trick (see [46, 85], and also [28, 29]). First of all, setting $\delta_1 = \delta_2 = \cdots = \delta_{2n} = 0$ in (7.6) shows that $dN/dt = \Pi - \mu N$, so that $N \to \Pi/\mu = N^{**}$ as $t \to \infty$. Using $N = N^{**}$, the substitution $S = N^{**} - \sum_{i=1}^{m}(E_i + Q_i) - \sum_{j=1}^{n}(I_j + H_j) - R$ is then used to re-write the model (7.6) as:

$$
\begin{aligned}
\frac{dE_1}{dt} &= \frac{\beta \sum_{j=1}^{n} I_j \left[N^{**} - \sum_{i=1}^{m}(E_i + Q_i) - \sum_{j=1}^{n}(I_j + H_j) - R \right]}{N^{**}} - f_1 E_1, \\
\frac{dE_2}{dt} &= a_1 \alpha E_1 - f_2 E_2, \\
\frac{dE_j}{dt} &= a_{j-1} \alpha E_{j-1} - f_j E_j;\ j = 3, \cdots, m, \\
\frac{dI_1}{dt} &= a_m \alpha E_m - f_{m+1} I_1, \\
\frac{dI_j}{dt} &= d_{j-1} \kappa I_{j-1} - f_{m+j} I_j;\ j = 2, \cdots, n, \\
\frac{dQ_1}{dt} &= \sigma_1 E_1 - f_{m+n+1} Q_1, \\
\frac{dQ_j}{dt} &= \sigma_j E_j + b_{j-1} \alpha Q_{j-1} - f_{m+n+j} Q_j;\ j = 2, \cdots, m, \\
\frac{dH_1}{dt} &= b_m \alpha Q_m + \phi_1 I_1 - f_{2m+n+1} H_1, \\
\frac{dH_j}{dt} &= \phi_j I_j + c_{j-1} \kappa H_{j-1} - f_{2m+n+j} H_j;\ j = 2, \cdots, n, \\
\frac{dR}{dt} &= \gamma_1 I_n + \gamma_2 H_n - (\psi + \mu) R.
\end{aligned}
\tag{D.1}
$$

Linearizing the model (D.1) around the endemic equilibrium, Ω_1 (defined in Section 7.4) gives

$$
\begin{aligned}
\frac{dE_1}{dt} &= (-r_1 - f_1)E_1 - r_1 \sum_{i=2}^{m} E_i + (r_2 - r_1) \sum_{j=1}^{n} I_j - r_1 \sum_{i=1}^{m} Q_i - r_1 \sum_{j=1}^{n} H_j - r_1 R, \\
\frac{dE_2}{dt} &= a_1 \alpha E_1 - f_2 E_2, \\
\frac{dE_j}{dt} &= a_{j-1} \alpha E_{j-1} - f_j E_j;\ j = 3, \cdots, m, \\
\frac{dI_1}{dt} &= a_m \alpha E_m - f_{m+1} I_1, \\
\frac{dI_j}{dt} &= d_{j-1} \kappa I_{j-1} - f_{m+j} I_j;\ j = 2, \cdots, n, \\
\frac{dQ_1}{dt} &= \sigma_1 E_1 - f_{m+n+1} Q_1, \\
\frac{dQ_j}{dt} &= \sigma_j E_j + b_{j-1} \alpha Q_{j-1} - f_{m+n+j} Q_j;\ j = 2, \cdots, m, \\
\frac{dH_1}{dt} &= b_m \alpha Q_m + \phi_1 I_1 - f_{2m+n+1} H_1, \\
\frac{dH_j}{dt} &= \phi_j I_j + c_{j-1} \kappa H_{j-1} - f_{2m+n+j} H_j;\ j = 2, \cdots, n, \\
\frac{dR}{dt} &= \gamma_1 I_n + \gamma_2 H_n - (\psi + \mu) R,
\end{aligned}
\tag{D.2}
$$

where, $r_1 = \dfrac{\beta \sum_{j=1}^{m} I_j}{N^{**}}$ and $r_2 = \beta S^{**}/N^{**}$.

It follows that the Jacobian of the system (D.2), evaluated at Ω_1, is given by

$$
J(\Omega_1) = \begin{pmatrix} A_J & B_J \\ C_J & D_J \end{pmatrix},
$$

where A_J, is an $(m+n) \times (m+n)$ matrix, B_J is an $(m+n) \times (m+n+1)$ matrix, C_J is an $(m+n+1) \times (m+n)$ matrix and D_J is an $(m+n+1) \times (m+n+1)$ matrix, given by

$$A_J = \begin{pmatrix} -f_1 - r_1 & -r_1 & -r_1 & \cdots & -r_1 & r_2 - r_1 & r_2 - r_1 & \cdots & r_2 - r_1 & r_2 - r_1 \\ a_1\alpha & -f_2 & & & & & & & & \\ & a_2\alpha & -f_3 & & & & & & & \\ & & \ddots & \ddots & & & & & & \\ & & & a_{m-1}\alpha & -f_m & & & & & \\ & & & & a_m\alpha & -f_{m+1} & & & & \\ & & & & & d_1\kappa & -f_{m+2} & & & \\ & & & & & & d_2\kappa & -f_{m+3} & & \\ & & & & & & & \ddots & \ddots & \\ & & & & & & & & d_{n-1}\kappa & -f_{m+n} \end{pmatrix},$$

$$B_J = \begin{pmatrix} -r_1 & -r_1 & \cdots & -r_1 \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & & \vdots \\ 0 & 0 & \cdots & 0 \end{pmatrix}, \quad C_J = \begin{pmatrix} \sigma_1 & & & & & & & & & \\ & \sigma_2 & & & & & & & & \\ & & \ddots & & & & & & & \\ & & & \sigma_m & & & & & & \\ & & & & \phi_1 & & & & & \\ & & & & & \phi_2 & & & & \\ & & & & & & \ddots & & & \\ & & & & & & & \phi_n & & \\ & & & & & & & \gamma_1 & & \end{pmatrix},$$

and,

$$D_J = \begin{pmatrix} -f_{m+n+1} & & & & & & & & \\ b_1\alpha & -f_{m+n+2} & & & & & & & \\ & \ddots & \ddots & & & & & & \\ & & b_m\alpha & -f_{2m+n+1} & & & & & \\ & & & c_1\kappa & -f_{2m+n+2} & & & & \\ & & & & \ddots & \ddots & & & \\ & & & & & c_{n-1}\kappa & -f_{2(m+n)} & & \\ & & & & & & \gamma_2 & -(\psi+\mu) & \end{pmatrix}.$$

Assume that the system (D.2) has solution of the form

$$\mathbf{Z}(t) = \mathbf{Z}_0 e^{\omega t}, \tag{D.3}$$

with $\mathbf{Z}_0 = (Z_1, Z_2, \cdots, Z_{2(m+n)+1}), \omega, Z_i \in \mathbb{C}(i = 1, 2, \cdots, 2(m+n)+1)$. Substituting a solution of the form (D.3) into the system (D.2) gives

$$
\begin{aligned}
\omega Z_1 &= (-r_1 - f_1)Z_1 - r_1 \sum_{i=2}^{m} Z_i + [r_2 - r_1] \sum_{j=m+1}^{m+n} Z_j - r_1 \sum_{i=m+n+1}^{2(m+n+1)} Z_i, \\
\omega Z_2 &= a_1 \alpha Z_1 - k_2 Z_2, \\
\omega Z_j &= a_{j-1} \alpha Z_{j-1} - k_j Z_j;\ j = 3, \cdots, m, \\
\omega Z_{m+1} &= a_m \alpha Z_m - k_{m+1} Z_{m+1}, \\
\omega Z_{m+j} &= d_{j-1} \kappa Z_{m+j-1} - k_{m+j} Z_{m+j};\ j = 2, \cdots, n, \\
\omega Z_{m+n+1} &= \sigma_1 Z_1 - k_{m+n+1} Z_{m+n+1}, \\
\omega Z_{m+n+j} &= \sigma_j Z_j + b_{j-1} \alpha Z_{m+n+j-1} - k_{m+n+j} Z_{m+n+j};\ j = 2, \cdots, m, \\
\omega Z_{2m+n+1} &= b_m \alpha Z_{2m+n} + \phi_1 Z_{m+1} - k_{2m+n+1} Z_{2m+n+1}, \\
\omega Z_{2m+n+j} &= \phi_j Z_{m+j} + c_{j-1} \kappa Z_{2m+n+j-1} - k_{2m+n+j} Z_{2m+n+j};\ j = 2, \cdots, n, \\
\omega Z_{2(m+n)+1} &= \gamma_1 Z_{m+n} + \gamma_2 Z_{2(m+n)} - (\psi + \mu) Z_{2(m+n)+1}.
\end{aligned}
\tag{D.4}
$$

System (D.4) is simplified as follows. First, all the negative terms in the last nine equations of (D.4) are moved to the respective left-hand sides. Secondly, the (resulting) last nine equations are then re-written in terms of Z_1 and substituted into the first equation of (D.4), and all its negative terms are moved to the right-hand side. Doing all these lead to the following system:

$$
[1 + F_i(\omega)]\, Z_i = (MZ)_i, \quad \text{for } i = 1, 2, \cdots, 2(m+n), \tag{D.5}
$$

where,

$$F_1(\omega) = \frac{\omega}{k_1} + \frac{r_1}{f_1}\left(1 + \sum_{i=2}^{m+1}\prod_{l=2}^{i}\frac{a_{l-1}\alpha}{\omega + f_l} + \prod_{l=2}^{m+1}\frac{a_{l-1}\alpha}{\omega + f_l}\sum_{i=m+2}^{m+n}\prod_{l=2}^{i-m}\frac{d_{l-1}\kappa}{\omega + f_{m+l}}\right)$$
$$+ \frac{r_1}{f_1}\left[\sum_{i=m+n+1}^{2m+n} G_{i-(m+n)}(\omega) + \sum_{i=2m+n+1}^{2(m+n)} L_{i-(2m+n)}(\omega)\right],$$

and,

$$F_j(\omega) = \frac{\omega}{f_j}, \text{ for } j = 2, 3, \cdots, 2(m+n)+1,$$

with,

$$G_1(\omega) = \frac{\sigma_1\prod_{l=2}^{i}\frac{a_{l-1}\alpha}{\omega + f_l}}{\omega + f_{m+n+1}}, \quad G_j(\omega) = \frac{\sigma_j}{\omega + f_{m+n+j}} + \frac{b_{j-1}\alpha G_{j-1}(\omega)}{\omega + f_{m+n+j}}, \text{ for } j = 2, 3, \cdots, m,$$
$$L_1(\omega) = \frac{\phi\prod_{l=2}^{m+1}\frac{a_{l-1}\alpha}{\omega + f_l}\prod_{l=2}^{i-m}\frac{d_{l-1}\kappa}{\omega + f_{m+l}}}{f_{2m+n+1}} + \frac{b_m\alpha G_m(\omega)}{f_{2m+n+1}},$$

and,

$$L_j(\omega) = \frac{\phi_j}{\omega + f_{2m+n+j}} + \frac{c_{j-1}\kappa G_{j-1}(\omega)}{\omega + f_{m+n+j}}, \text{ for } j = 2, 3, \cdots, n.$$

Furthermore,

$$M = \begin{pmatrix} A_M & B_M \\ C_M & D_M \end{pmatrix},$$

where A_M is an $(m+n)\times(m+n)$ matrix, B_M is an $(m+n)\times(m+n+1)$ zero matrix, C_M is an $(m+n+1)\times(m+n)$ matrix and D_M is an $(m+n+1)\times(m+n+1)$ matrix, given by

$$A_M = \begin{pmatrix} 0 & 0 & 0 & \cdots & 0 & r_2 & r_2 \cdots & r_2 & r_2 & r_2 \\ \frac{a_1\alpha}{f_2} & 0 & & & & & & & & \\ & \frac{a_2\alpha}{f_3} & 0 & & & & & & & \\ & & \ddots & \ddots & & & & & & \\ & & & \frac{a_{m-1}\alpha}{f_m} & 0 & & & & & \\ & & & & \frac{a_m\alpha}{f_{m+1}} & 0 & & & & \\ & & & & & \frac{d_1\kappa}{f_{m+2}} & 0 & & & \\ & & & & & & \frac{d_2\kappa}{f_{m+3}} & 0 & & \\ & & & & & & & \ddots & \ddots & \\ & & & & & & & & \frac{d_{n-1}\kappa}{f_{m+n}} & 0 \end{pmatrix},$$

$$C_M = \begin{pmatrix} \frac{\sigma_1}{f_{m+n+1}} & & & & & & & & & \\ & \frac{\sigma_2}{f_{m+n+2}} & & & & & & & & \\ & & \ddots & & & & & & & \\ & & & \frac{\sigma_m}{f_{2m+n}} & & & & & & \\ & & & & \frac{\phi_1}{f_{2m+n+1}} & & & & & \\ & & & & & \frac{\phi_2}{f_{2m+n+2}} & & & & \\ & & & & & & \ddots & & & \\ & & & & & & & & \frac{\phi_n}{f_{2(m+n)}} & \\ & & & & & & & & \frac{\gamma_1}{\psi+\mu} & \end{pmatrix},$$

$$D_M = \begin{pmatrix} 0 & & & & & & & & \\ \frac{b_1\alpha}{f_{m+n+2}} & 0 & & & & & & & \\ & \ddots & \ddots & & & & & & \\ & & \frac{b_m\alpha}{f_{2m+n+1}} & 0 & & & & & \\ & & & \frac{c_1\kappa}{f_{2m+n+2}} & 0 & & & & \\ & & & & \ddots & \ddots & & & \\ & & & & & \frac{c_{n-1}\kappa}{f_{2(m+n)}} & 0 & & \\ & & & & & & \frac{\gamma_2}{(\psi+\mu)} & 0 & \end{pmatrix}.$$

It is easy to verify that the equilibrium Ω_1 satisfies $\Omega_1 = M\Omega_1$. The notation $(M\mathbf{Z})_i$ $(i = 1, \ldots, 2(m+n)+1)$ denotes the ith coordinate of the vector $M\mathbf{Z}$, and the matrix M has non-negative entries. If $\mathbf{Z}$ is a solution of (D.5), then it is possible to find a minimal positive real number r such that [28, 29]

$$\|\mathbf{Z}\| \leq r\Omega_1, \tag{D.6}$$

where, $\|\mathbf{Z}\| = (\|Z_1\|, \|Z_2\|, \cdots, \|Z_{2(m+n)+1}\|)$ with lexicographic order, and $\|.\|$ is a norm in $\mathbb{C}$. The main goal is to show that $\mathrm{Re}(\omega) < 0$. Assume, now, that $\mathrm{Re}(\omega) \geq 0$, and consider the following cases.

Case 1: $\omega = 0$.

In this case, (D.4) is a homogeneous linear system in the variables Z_i $(i = 1, \ldots, 2(m+n)+1)$. The determinant of this system is given by

$$\Delta = -A + \left(\frac{S^{**}\mathcal{R}_{cr}}{N^{**}} - 1\right) \prod_{i=1}^{2(m+n+1)} f_i, \tag{D.7}$$

where, A is very long positive expression (not given here). Here, it easy to show that at steady-state $\frac{S^{**}\mathcal{R}_{cr}}{N^{**}} = 1$. Hence, the equation (D.7) becomes

$$\Delta = -A < 0$$

Since the determinant Δ is negative, it follows that the system (D.4) has a unique solution, given by $\mathbf{Z} = 0$ (which corresponds to the DFE (Ω_0)).

Case 2: $\omega \neq 0$.

Recalling that $\text{Re}(\omega) > 0$ (by assumption), it follows then that $|1 + F_i(\omega)| > 1$ for all $i = 1, \ldots, 2(m+n)+1$. Define $F(\omega) = \min_i |1 + F_i|$. Then, $F(\omega) > 1$, and $\dfrac{r}{F(\omega)} < r$. Since r is a minimal positive real number such that $\|\mathbf{Z}\| \leq r\Omega_1$, then

$$\|\mathbf{Z}\| > \frac{r}{F(\omega)}\Omega_1. \tag{D.8}$$

On the other hand, by taking the norm of both sides of the second equation in (D.5), and noting that M is a non-negative matrix, we have,

$$F(\omega)\|Z_2\| \leq |1 + F_2(\omega)| \ \|Z_2\| = \|(MZ)_2\| \leq M\|Z_2\| \leq rM(\Omega_1)_2 = r(\Omega_1)_2 = rE_2^{**}. \tag{D.9}$$

It follows from (D.9) that $\|Z_2\| \leq \dfrac{r}{F(\omega)}I^{**}$, which contradicts (D.8). Hence, Re $(\omega) <$ 0. Thus, all eigenvalues of the characteristic equation associated with the linearized system (D.2) will have negative real part, so that the unique endemic equilibrium, Ω_1, is LAS whenever $\mathcal{R}_{cr} > 1$. □

Appendix E: Proof of Theorem 7.4

Proof. Consider the reduced model (7.21) with (7.22). Let $\mathcal{R}_{cr} > 1$, so that the associated unique endemic equilibrium exists (Lemma 7.4). Further, consider the following non-linear Lyapunov function for the sub-system of the model (7.21), consisting of the equations for S, E_i $(i = 1, \cdots, m)$ and I_j $(j = 1, \cdots, n)$, given by:

$$\mathcal{F} = S - S^{**} - S^{**} \ln\left(\frac{S}{S^{**}}\right) + E_1 - E_1^{**} - E_1^{**} \ln\left(\frac{E_1}{E_1^{**}}\right) + \sum_{i=2}^{m} x_i \left[E_i - E_i^{**} - E_i^{**} \ln\left(\frac{E_i}{E_i^{**}}\right)\right] + \sum_{j=1}^{n} y_i \left[I_j - I_j^{**} - I_j^{**} \ln\left(\frac{I_j}{I_j^{**}}\right)\right],$$

where the coefficients x_i $(i = 1, \cdots, m)$ and y_j $(j = 1, \cdots, n)$ are positive constants to be determined. Thus,

$$\dot{\mathcal{F}} = \dot{S} - \frac{S^{**}}{S}\dot{S} + \dot{E}_1 - \frac{E_1^{**}}{E_1}\dot{E}_1 + \sum_{i=2}^{m} x_i \left(\dot{E}_i - \frac{E_i^{**}}{E_i}\dot{E}_i\right) + \sum_{j=1}^{n} y_j \left(\dot{I}_j - \frac{I_j^{**}}{I_j}\dot{I}_j\right).$$

Substituting the expressions of the derivatives from the system (7.21), using (7.22), gives (note that the relation $\Pi = \beta_1 S^{**} \sum_{j=1}^{n} I_j^{**} + \mu S^{**}$, at endemic steady-state, has been used)

$$
\begin{aligned}
\dot{\mathcal{F}} &= \beta_1 S^{**}\sum_{j=1}^{n} I_j^{**} + \mu S^{**} - \beta_1 S\sum_{j=1}^{n} I_j - \mu S - \beta_1 \frac{S^{**}}{S}\sum_{j=1}^{n} I_j^{**} - \mu\frac{(S^{**})^2}{S} \\
&+ \beta_1 S^{**}\sum_{j=1}^{n} I_j^{**} + \mu S^{**} + \beta_1 S\sum_{j=1}^{n} I_j - f_1 E_1 - \beta_1 S\sum_{j=1}^{n}\frac{I_j E_1^{**}}{E_1} + f_1 E_1^{**} \\
&+ \sum_{i=2}^{m} x_i a_{i-1}\alpha E_{i-1} - x_i f_i E_i - x_i a_{i-1}\alpha\frac{E_{i-1}E_i^{**}}{E_i} + x_i f_i E_i^{**} + y_1 a_m \alpha E_m - y_1 f_{m+1} I_1 \\
&- y_1 a_m \frac{E_m I_1^{**}}{E_m} + y_1 f_{m+1} I_1^{**} + \sum_{j=2}^{n} y_j d_{j-1}\kappa I_{j-1} - y_j f_{m+j} I_j - y_j d_{j-1}\kappa\frac{I_{j-1}I_j^{**}}{I_j} + y_j f_{m+j} I_j^{**},
\end{aligned}
$$

which can simplified to

$$
\begin{aligned}
\dot{\mathcal{F}} &= \mu S^{**}\left(2 - \frac{S^{**}}{S} - \frac{S}{S^{**}}\right) + \beta_1 S^{**}\sum_{j=1}^{n} I_j^{**} - \beta_1\frac{S^{**}}{S}\sum_{j=1}^{n} I_j^{**} + \beta_1 S^{**}\sum_{j=1}^{n} I_j^{**} - \beta_1 S\sum_{j=1}^{n}\frac{I_j E_1^{**}}{E_1} \\
&+ (x_2 a_1\alpha - k_1)E_1 + \sum_{i=2}^{m-1}(x_{i+1}a_i\alpha - x_i f_i)E_i + (y_1 a_m\alpha - x_m f_m)E_m \\
&+ \sum_{j=1}^{n-1}(\beta_1 S^{**} + y_{j+1}d_j\kappa - y_j f_{m+j})I_j + (\beta_1 S^{**} - y_n f_{m+n})I_n \qquad \text{(E.1)} \\
&+ \sum_{i=2}^{m}(x_i f_i E_i^{**} - x_i a_{i-1}\alpha\frac{E_{i-1}E_i^{**}}{E_i}) \\
&- y_1 a_m\frac{E_m I_1^{**}}{I_1} + y_1 f_{m+1} I_1^{**} + \sum_{j=2}^{n}(y_j f_{m+j} I_j^{**} - y_j d_{j-1}\kappa\frac{I_{j-1}I_j^{**}}{I_j}).
\end{aligned}
$$

The coefficients x_i $(i = 2, \cdots, m)$ and y_j $(j = 1, \cdots, n)$ of $\dot{\mathcal{F}}$ are chosen such that

$$
\begin{aligned}
&x_2 a_1\alpha - k_1 = 0, \\
&x_{i+1}a_i\alpha - x_i f_i = 0; \text{ for } i = 3, \cdots, m-1, \\
&y_1 a_m\alpha - x_m f_m = 0, \qquad \text{(E.2)} \\
&\beta_1 S^{**} + y_{j+1}d_j\kappa - y_j f_{m+j} = 0, \\
&\beta_1 S^{**} - y_n f_{m+n} = 0,
\end{aligned}
$$

so that, from (E.2),

$$\begin{aligned} x_i &= \prod_{l=1}^{i-1} \frac{f_l}{a_l \alpha}; \quad i = 2, \cdots, m, \\ y_1 &= \prod_{l=1}^{m} \frac{f_l}{a_l \alpha}; \\ y_n &= \frac{\beta_1 S^{**}}{f_{m+n}}; \end{aligned} \tag{E.3}$$

and,

$$y_{n-j} = \frac{\beta_1 S^{**}}{f_{m+n-j}} + \beta_1 S^{**} \sum_{s=1}^{j} \frac{\prod_{l=s}^{j} d_{n-l} \kappa}{\prod_{l=s-1}^{j} f_{n+m-l}}; \quad j = 1, \cdots, n-2.$$

Using the relations in (E.3) into the equation (E.1) gives

$$
\begin{aligned}
\dot{\mathcal{F}} = {} & \mu S^{**}\left(2 - \frac{S^{**}}{S} - \frac{S}{S^{**}}\right) + 2\beta_1 S^{**}\sum_{j=1}^{n} I_j^{**} - \beta_1 \frac{S^{**}}{S}\sum_{j=1}^{n} I_j^{**} - \beta_1 S \sum_{j=1}^{n} \frac{I_j E_1^{**}}{E_1} \\
& - f_1 \frac{E_1 E_2^{**}}{E_2} + \frac{f_1 f_2}{a_1 \alpha} E_2^{**} + \sum_{i=3}^{m} -\frac{\prod_{l=1}^{i-1} f_l}{\prod_{l=1}^{i-2} a_l \alpha}\frac{E_{i-1}E_i^{**}}{E_i} + \frac{\prod_{l=1}^{i} f_l}{\prod_{l=1}^{i-1} a_l \alpha} E_i^{**} \\
& - \frac{\prod_{l=1}^{m} f_l}{\prod_{l=1}^{m-1} a_l \alpha}\frac{E_m I_1^{**}}{I_1} + \frac{\prod_{l=1}^{m+1} f_l}{\prod_{l=1}^{m} a_l \alpha} I_1^{**} \\
& + \sum_{j=2}^{n-1} -d_{j-1}\kappa \left(\frac{\beta_1 S^{**}}{f_{m+j}} + \beta_1 S^{**} \sum_{s=1}^{n-j} \frac{\prod_{l=s}^{n-j} d_{n-l}\kappa}{\prod_{l=s-1}^{n-j} f_{n+m-l}} \right) \frac{I_{j-1} I_j^{**}}{I_j} \\
& + \sum_{j=2}^{n-1} f_{m+j} \left(\frac{\beta_1 S^{**}}{f_{m+j}} + \beta_1 S^{**} \sum_{s=1}^{n-j} \frac{\prod_{l=s}^{n-j} d_{n-l}\kappa}{\prod_{l=s-1}^{n-j} f_{n+m-l}} \right) I_j^{**} - \frac{\beta_1 S^{**} d_{n-1}\kappa}{f_{m+n}} \frac{I_{n-1} I_n^{**}}{I_n} + \beta_1 S^{**} I_n^{**}.
\end{aligned}
\tag{E.4}
$$

It can be shown from (7.21) that, at endemic steady-state,

$$
\begin{aligned}
f_1 &= \frac{\beta_1 S^{**} \sum_{j=1}^{n} I_j^{**}}{E_1^{**}}, \\
\frac{\prod_{l=1}^{i} f_l}{\prod_{l=1}^{i-1} a_l \alpha} &= \frac{\beta_1 S^{**} \sum_{j=1}^{n} I_j^{**}}{E_i^{**}} \quad i = 2, \cdots, m, \\
\frac{\prod_{l=1}^{m+1} f_l}{\prod_{l=1}^{m} a_l \alpha} &= \frac{\beta_1 S^{**} \sum_{j=1}^{n} I_j^{**}}{I_1^{**}},
\end{aligned}
\tag{E.5}
$$

and,

$$
\frac{d_j \kappa}{f_{m+j+1}} = \frac{I_{j+1}^{**}}{I_j^{**}} \quad j = 1, \cdots, n-1. \tag{E.6}
$$

Using the relations in (E.5) and (E.6) in equation (E.4) gives

$$
\begin{aligned}
\dot{\mathcal{F}} = {} & \mu S^{**} \left(2 - \frac{S^{**}}{S} - \frac{S}{S^{**}} \right) + (m+2) \beta_1 S^{**} \sum_{j=1}^{n} I_j^{**} - \beta_1 \frac{S^{**}}{S} \sum_{j=1}^{n} I_j^{**} - \beta_1 S \sum_{j=1}^{n} \frac{I_j E_1^{**}}{E_1} \\
& - \beta_1 S^{**} \sum_{j=1}^{n} I_j^{**} \left(\sum_{i=1}^{m-1} \frac{E_i E_{i+1}^{**}}{E_{i+1}^{**} E_i} \right) - \beta_1 S^{**} \frac{E_m I_1^{**}}{I_1^{**} E_m} \sum_{j=1}^{n} I_j^{**} \\
& - \beta_1^{**} S^{**} \sum_{j=1}^{n-1} \left(\frac{I_j I_{j+1}^{**}}{I_{j+1}} \sum_{l=j+1}^{n} \frac{I_l^{**}}{I_j^{**}} \right) + \beta_1 S^{**} \sum_{j=2}^{n} \left(\sum_{l=j}^{n} I_l^{**} \right),
\end{aligned}
$$

which can be re-written as

$$\dot{\mathcal{F}} = \mu S^{**}\left(2 - \frac{S^{**}}{S} - \frac{S}{S^{**}}\right) + \beta_1 S^{**}\left[(m+2) - \frac{S^{**}}{S} - \sum_{i=1}^{m-1}\frac{E_i E_{i+1}^{**}}{E_{i+1}^{**}E_i} - \frac{E_m I_1^{**}}{E_m^{**} I_1}\right]$$
$$+ \beta_1 S^{**}\sum_{j=2}^{n} I_j^{**}\left[(m+j+1) - \frac{S^{**}}{S} - \sum_{i=1}^{m-1}\frac{E_i E_{i+1}^{**}}{E_{i+1}^{**}E_i} - \frac{E_m I_1^{**}}{E_m^{**} I_1} - \sum_{l=1}^{j-1}\frac{I_l I_{l+1}^{**}}{I_{l+1} I_l^{**}} - \frac{S I_j E_1^{**}}{S^{**} I_j^{**} E_1}\right]. \tag{E.7}$$

Finally, since the arithmetic mean exceeds the geometric mean, it follows that

$$\begin{aligned} &2 - \frac{S^{**}}{S} - \frac{S}{S^{**}} \leq 0, \\ &(m+2) - \frac{S^{**}}{S} - \sum_{i=1}^{m-1}\frac{E_i E_{i+1}^{**}}{E_{i+1}^{**}E_i} - \frac{E_m I_1^{**}}{E_m^{**} I_1} \leq 0, \end{aligned} \tag{E.8}$$

and,

$$(m+j+1) - \frac{S^{**}}{S} - \sum_{i=1}^{m-1}\frac{E_i E_{i+1}^{**}}{E_{i+1}^{**}E_i} - \frac{E_m I_1^{**}}{E_m^{**} I_1} - \sum_{l=1}^{j-1}\frac{I_l I_{l+1}^{**}}{I_{l+1} I_l^{**}} - \frac{S I_j E_1^{**}}{S^{**} I_j^{**} E_1} \leq 0 \text{ for } j = 2, \cdots, n. \tag{E.9}$$

Further, since all parameters of the model (7.6) are non-negative, it follows from (E.8) and (E.9) , using (E.7), that $\dot{\mathcal{F}} \leq 0$ for $\mathcal{R}_{cr} > 1$. Hence, $\mathcal{F}$ is a Lyapunov function for the sub-system of the model (7.21) consisting of the equations for S, E_i $(i = 1, \cdots, m)$, I_j $(j = 1, \cdots, n)$ of the model (7.21) on $\mathcal{D} \setminus \mathcal{D}_0$. Therefore, by the LaSalle's Invariance Principle (Theorem 2.6),

$$\begin{aligned} &\lim_{t\to\infty} S(t) = S^{**}, \ \lim_{t\to\infty} E_i(t) = E_i^{**}, \text{ for all } i = 1, \cdots, m \\ &\lim_{t\to\infty} I_j(t) = I_j^{**}, \ \text{ for all } j = 1, \cdots, n. \end{aligned} \tag{E.10}$$

It is clear from (E.10) that $\limsup_{t\to\infty} E_1 = E_1^{**}$. Thus, for sufficiently small small $\varpi > 0$,

there exists a constant $n_1 > 0$ such that $\limsup_{t\to\infty} E_1 \le E_1^{**} + \varpi$ for all $t > n_1$. It follows from the $(m+n+2)$th equation of the model (7.21) that, for $t > n_1$,

$$\dot{Q}_1 \le \sigma_1(E_1^{**} + \varpi) - f_{m+n+1}Q_1.$$

Thus, by comparison theorem (Theorem 2.8),

$$Q_1^{\infty} = \limsup_{t\to\infty} Q_1 \le \frac{\sigma_1(E_1^{**} + \varpi)}{f_{m+n+1}},$$

so that, by letting $\varpi \to 0$,

$$Q_1^{\infty} = \limsup_{t\to\infty} Q_1 \le \frac{\sigma_1 E_1^{**}}{f_{m+n+1}}. \tag{E.11}$$

Similarly (by using $\liminf_{t\to\infty} E_1 = E_1^{**}$), it can be shown that

$$Q_{1\infty} = \liminf_{t\to\infty} Q_1 \ge \frac{\sigma_1 E_1^{**}}{f_{m+n+1}}. \tag{E.12}$$

Thus, it follows from (E.11) and (E.12) that

$$Q_{1\infty} \ge \frac{\sigma E_1^{**}}{f_{m+n+1}} \ge Q_1^{\infty}.$$

Hence,

$$\lim_{t\to\infty} Q_1 = \frac{\sigma_1 E_1^{**}}{f_{m+n+1}} = Q_1^{**}. \tag{E.13}$$

Similarly, it can be shown that

$$\begin{aligned}
&\lim_{t\to\infty} Q_i(t) = Q_i^{**}, \text{ for all } i = 2, \cdots, m, \\
&\lim_{t\to\infty} H_j(t) = H_j^{**}, \text{ for all } j = 1, \cdots, n, \\
&\lim_{t\to\infty} R(t) = R^{**}.
\end{aligned} \tag{E.14}$$

Thus, by combining (E.10), (E.13) and (E.14), every solution to the equations of the reduced model, with initial condition in $\mathcal{D} \setminus \mathcal{D}_0$, approaches the unique endemic equilibrium of the reduced model (7.21) with (7.22) as $t \to \infty$ for $\mathcal{R}_{cr} > 1$ and $\psi = 0$. $\square$

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