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Mathematical Models of COVID-19

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Abstract

For more than a year, the COVID-19 pandemic has been a major public health issue, affecting the lives of most people around the world. With both people's health and the economy at great risks, governments rushed to control the spread of the virus. Containment measures were heavily enforced worldwide until a vaccine was developed and distributed. Although researchers today know more about the characteristics of the virus, a lot of work still needs to be done in order to completely remove the disease from the population. However, this is true for most of the infectious diseases in existence, including Influenza, Dengue fever, Ebola, Malaria, and Zika virus. Understanding the transmission process of a disease is usually acquired through biological and chemical studies. In addition, mathematical models and computational simulations offer different approaches to predict the number of infectious cases and identify the transmission patterns of a disease. Information obtained helps provide effective vaccination interventions, quarantine and isolation strategies, and treatment plans to reduce disease transmissions and prevent potential outbreaks. The focus of this paper is to investigate the spread of COVID-19 and its effect on a population through mathematical models. Specifically, we use $SEIR$ and $SEIR$ with vaccine models to formulate the spread of COVID-19, where S, E, I, R, and V are susceptible, exposed, infected, recovered, and vaccinated compartments, respectively. With these two models we calculate a central quantity in epidemiology called the basic reproduction number, $\mathcal{R}_0$. This helps examine the dynamical behavior of the models and how vaccines can help prevent the spread of the virus.

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Contents

Chapter 1

Introduction

The novel coronavirus (COVID-19) was initially identified in late December of 2019 in Wuhan, China [11]. It is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [11]. With little information about this new virus, no known cure or effective therapies, and an incubation period of approximately 14 days, the virus rapidly spread globally [29]. In fact, the long incubation period was not known at first. Also, there were many people that were asymptomatic, unknowingly carrying and spreading the virus even though no symptoms were clearly present. According to Carenzo et al., 40% of positive COVID-19 cases are from asymptomatic yet infectious carriers [9]. In March of 2020, the World Health Organization declared COVID-19 a pandemic [26, 37].

While COVID-19 can be deadly, symptoms, however, vary greatly from person to person [16]. While some may experience mild symptoms such as fever, coughing, and shortness of breath, others may face more severe complications, including damage to the lungs, acute respiratory failure, or sometimes even death [1, 32, 38]. Other symptoms may also include difficulty breathing, fatigue, muscle or body aches, headaches, loss of taste or smell, sore throat, congestion, a runny nose, nausea or vomiting, or diarrhea [16]. In addition, COVID-19 can have serious effects on anyone, but tends to have more serious effects on older people or people with compromised immune systems. For older adults, the seriousness of COVID-19 increases as age increases. The most at-risk age group is 85 years old and older [16]. For other older adults, the pattern is as follows: people in their 50s are more at risk than people in their 40s, people in their 60s are more at risk than people in their 50s, and so on [19].

COVID-19 also has similarities to the severe acute respiratory syndrome (SARS) of 2003 [53]. With SARS there were more than 8,000 cases and 774 deaths [53]. However, within 2 months of the COVID-19 outbreak, there were more than 82,000 cases and more than 2,800 deaths [53]. Explanations for this include that Wuhan, the city that COVID-19 stemmed from, is the biggest city in central China, which allowed for widespread exposure and therefore infections [53]. Another explanation is that COVID-19 spread during the incubation period of the virus, when infectious people were not yet showing symptoms, unlike SARS, where spreading occurred more often after people had already developed symptoms [53]. A review in February of 2020 found that another explanation is that COVID-19 has a higher transmissibility than SARS, as the average reproduction number for COVID-19 was 3.28, higher than the reproduction number of SARS, which was 2.79 [53]. While COVID-19 has similarities to other upper-respiratory illnesses, it is unique in many ways. COVID-19 shares many of the same symptoms of influenza [3]. However, some symptoms of COVID-19 that are not symptoms of the flu or other respiratory viruses include a dry cough, the loss of taste or smell, and blood clots in the veins and arteries of the lungs, heart, legs, and brain [3]. In addition, while young children are a high-risk group for influenza and other upper-respiratory illnesses, they are not a high-risk group for COVID-19, except for the complication of Multisystem Inflammatory Syndrome [3].

At the beginning of the pandemic, the number of hospitalizations increased at an alarming level in multiple regions of the world [30, 48, 8]. In Italy in March of 2020, the government released guidelines

on how to ration hospital care [10]. In the United States, elective surgeries were postponed in an effort to reduce Intensive Care Unit (ICU) overcapacity [48]. According to [48], the cancellation of all elective surgeries allowed for the ICU overcapacity to decrease from 160% to 130%. COVID-19 also severely affected the economy with high unemployment rates and a decline in GDP across the globe [32, 5, 12]

With both asymptomatic and symptomatic infectious carriers with a 14-day incubation period, high transmission rate, and high numbers of fatalities, COVID-19 is deadly and extremely hard to track and contain. To control the spread of the virus, governments worldwide started implementing non-pharmaceutical interventions. These included temporary closures of schools and non-essential businesses, the use of face masks, and social distancing while the world waited for a vaccine that could be used to minimize the spread of the virus [13]. Although the spread of COVID-19 began to slow as a result of these new containment measures, the fight against the virus was far from over. Having a vaccine seems to be the only long-term solution that can stop the virus from devastating people's lives and the global economy further.

The detrimental effects and control measures of COVID-19 can be reduced only after enough people in the population are immune to the disease. This is why the distribution of vaccines is so critical. Vaccines teach the immune system how to fight COVID-19; thus, preventing an exposed individual from developing the infection [21]. This in turn prevents the virus from spreading if an unvaccinated individual comes into contact with the exposed but vaccinated individual, and is a similar but even safer scenario when both individuals that are in contact are vaccinated [14].

Fortunately, by February of 2021, the FDA approved COVID-19 vaccines from three different companies, including Pfizer-BioNTech, Moderna, and Johnson & Johnson [15]. The first approved vaccine was the Pfizer-BioNTech COVID-19 Vaccine, authorized by the FDA on December 11, 2020 [20, 46]. This was the first emergency use authorization (EUA) for a vaccine [46]. The Pfizer vaccine consists of 2 doses administered 21 days apart. It is safe for people ages 16 and older [20]. The efficacy of the vaccine is 95% [20]. The second vaccine authorized by the FDA in another EUA was the Moderna COVID-19 vaccine, authorized on December 18th, 2020 [18, 45]. The Moderna vaccine also includes 2 doses, with doses separated by 28 days, and is for people ages 18 and older [18]. The efficacy of the Moderna vaccine is 94.1% [18]. The third vaccine authorized by the FDA in another EUA was the Janssen (Johnson & Johnson) COVID-19 vaccine, on February 27th, 2021 [17, 44]. This vaccine is a single dose and is safe for people ages 18 and older [17]. The efficacy of the Janssen vaccine is 66.3%, which is underwhelming compared to Pfizer and Moderna vaccines [17].

According to the CDC, individuals are considered fully vaccinated two weeks after receiving the final dose of the vaccine [22]. In addition, after vaccination, restrictions for those vaccinated are slightly lifted [22]. People that are fully vaccinated can gather indoors with other fully vaccinated people without having to wear face masks [22]. Vaccinated people can also gather indoors with one household of unvaccinated people without wearing face masks, unless that household has a member that is at an increased risk of severe illness from COVID-19 [22]. A vaccinated person that comes into contact with someone that has COVID-19 does not need to quarantine or get tested unless the vaccinated person develops symptoms, or does not develop symptoms but lives in a group setting [22]. Vaccines are the answer for keeping people the safest and allowing a return back to normal life.

Researchers from fields such as epidemiology, genetics, and related fields have been working diligently since the disease outbreak to gain a thorough understanding of the virus's mechanism [40, 33, 31]. This helps medical teams understand how the virus spreads biologically, which can lead to the development of viable therapeutic treatments such as vaccines. On the other hand, mathematical models have been shown to be effective methods for imparting knowledge about the nature of infectious diseases. They also contribute insights to help develop optimal controls and facilitate non-pharmaceutical interventions to minimize the spread of a virus [6]. In other words, through epidemiological models we are able to get a better understanding of the disease, how it works, how to contain it, and how it can be cured. In fact, since the outbreak of COVID-19, numerous mathematical studies have been carried out and provided predictions of the spreading of COVID-19 [36]. A summary of various mathematical models used in studies of COVID-19 is shown in Table (1.1)

In this research, a deterministic $SEIR$ model is examined. Here, S, E, I, and R are susceptible,

Models	**References**
SIR	[4, 23, 54, 27]
$SEIR$	[55, 42, 41, 43]
$SIQR$	[25, 39, 47]
$SEIQR$	[52, 56]

Table 1.1: Summary of different mathematical models used in studies of COVID-19

exposed, infected, and recovered compartments, respectively. We also consider an $SEIR$ model with a vaccine compartment. The basic reproduction number of each model is calculated using the next-generation matrix technique. Comparison of the two models show the effect on the population when a vaccine is introduced. In addition, positivity and boundedness of the solutions, equilibrium points and their stability are also inspected.

Chapter 2

The Basic Reproduction Number, $\mathcal{R}_0$

2.1 Definition

The basic reproduction number, denoted as $\mathcal{R}_0$, is defined as the average number of secondary infections caused by a single infectious individual introduced into a completely susceptible population [24, 49]. This number is a central quantity in investigating a disease outbreak. There are two main scenarios that can occur in a population where a disease is present. If the basic reproduction number is less than one, the disease eventually vanishes from the population. If it exceeds one, an epidemic likely occurs [24, 49, 27]. For instance, when $\mathcal{R}_0 = 2$, one infectious person can transmit the disease to two other individuals. Thus, it is important and essential to determine and analyze $\mathcal{R}_0$ of an infectious disease. Mathematically, the basic reproduction number can be obtained using the next-generation matrix method [24, 35, 7]. The mathematical backgrounds required for the method are presented in the next section.

2.2 Mathematical Backgrounds

Definition 2.2.1 (Spectral radius). *[35] The spectral radius of a matrix A is defined as the maximum of the absolute values of the eigenvalues of A:*

$$\rho(A) = sup\{\mid \lambda \mid : \lambda \in \sigma(A)\},$$

where $\sigma(A)$ denotes the set of eigenvalues of A.

Definition 2.2.2 (Nonnegative matrix). *[51] A matrix $A = [a_{ij}]$ is nonnegative if $a_{ij} \geq 0$. The matrix A is a positive matrix if $a_{ij} > 0$.*

Definition 2.2.3 (Irreducible nonnegative matrix). *[34] A nonnegative matrix A is irreducible if it is not the 1×1 zero matrix and it cannot be written as*

$$PAP^{-1} = \begin{bmatrix} A_{11} & A_{12} \\ 0 & A_{22} \end{bmatrix},$$

where A_{11} and A_{22} are nontrivial square block matrices and P is a permutation matrix.

Definition 2.2.4 (Z sign pattern). *[50] A matrix $B = [b_{ij}]$ has the Z sign pattern if $b_{ij} \leq 0$ for all $i \neq j$.*

Definition 2.2.5 (M-matrix). *[35] A matrix A is called an M-matrix if:*

- *A has the Z-pattern, that is, the off-diagonal elements of A are nonpositive.*

- *The inverse of A exists and has nonnegative elements:* $A^{-1} \geq 0$.

Definition 2.2.6 (Singular and nonsingular matrix)**.** *[51] An* $n \times n$ *matrix A is called* ***nonsingular*** *or invertible if there exists an* $n \times n$ *matrix B such that*

$$AB = I_n = BA,$$

where I_n *is the* $n \times n$ *identity matrix. Any matrix B that has the above property is the inverse of A. If A does not have an inverse, then A is called* ***singular****.*

Theorem 2.2.1 (The Perron-Frobenius Theorem)**.** *[34] Let P be an irreducible nonnegative matrix. Then,*

(a) The spectral radius $\rho(P)$ *of P is positive and it is an algebraically simple eigenvalue of P with corresponding left and right positive eigenvector, which are unique up to scalar multiples.*

(b) The spectral radius of P is the unique eigenvalue with a nonnegative eigenvector.

(c) The spectral radius of the matrix P increases (strictly), resp. decreases, if any entry of it increases, resp. decreases.

The proof of Theorem 2.2.1 can be found in [34].

Lemma 2.2.1. *[7] If A has the Z sign pattern, then* $A^{-1} \geq 0$ *if and only if A is a nonsingular M-matrix.*

Lemma 2.2.2. *[7] If F is nonnegative and V is a nonsingular M-matrix, then* $\mathcal{R}_0 = \rho(FV^{-1}) < 1$ *if and only if all eigenvalues of (F-V) have negative real parts.*

Proof: Suppose $F \geq 0$ and V is a nonsingular M-matrix. By Lemma 2.2.1 , $V^{-1} \geq 0$. Thus, $(I - FV^{-1})$ has the Z sign pattern, and by Lemma 2.2.1, $(I - FV^{-1})^{-1} \geq 0$ if and only if $\rho(FV^{-1}) < 1$. From the equalities $(V-F)^{-1} = V^{-1}(I - FV^{-1})^{-1}$ and $V(V-F)^{-1} = I + F(V-F)^{-1}$, it follows that $(V-F)^{-1} \geq 0$ if and only if $(I - FV^{-1})^{-1} \geq 0$. Finally, $(V\text{-}F)$ has the Z sign pattern, so by Lemma 2.2.1, $(V-F)^{-1} \geq 0$ if and only if $(V-F)$ is a nonsingular M-matrix. Since the eigenvalues of a nonsingular M-matrix all have positive real parts, this completes the proof. □

2.3 The Next-Generation Matrix Method

In this section we present the method of the next-generation matrix to calculate the basic reproduction number of ordinary differential equation compartmental models for disease transmission [35, 7, 2]. The method was first proposed by Diekmann et al. in [28] and was later expanded by Driessche et al. in [50]. Here, we provide an outline of the next-generation matrix method.

We divide the compartments of an epidemiological model into two broad categories: infected compartments and noninfected (healthy) compartments. Specifically, a compartment is called an **infected compartment** if the individuals in that compartment are infectious. Compartments where individuals are infected but not infectious (such as latent individuals) are also among the infected compartments. The remaining compartments in which the individuals are not infectious are the **noninfected compartments**. We assume that there are n infected compartments and m noninfected compartments, so the entire ordinary differential equation model has $m + n$ dependent variables. Let x be the vector of dependent variables in the infected compartments, and let y be the vector of variables in the noninfected compartments. We have $x \in R^n$ and $y \in R^m$.

(1) First, we arrange the equations so that the first n components of the ordinary differential equation (ODE) system correspond to the infected compartments. Thus, we write the original ODE system as

$$\begin{aligned} x_i' &= f_i(x, y), \quad i = 1, ..., n, \\ y_j' &= g_j(x, y), \quad j = 1, ..., m. \end{aligned}$$

(2) Second, we partition the right-hand side in the infected compartments in the following way:

$$\begin{aligned} x_i' &= \mathcal{F}_i(x,y) - \mathcal{V}_i(x,y), \quad i = 1, ..., n, \\ y_j' &= g_j(x,y), \quad j = 1, ..., m, \end{aligned} \tag{2.1}$$

where

- $\mathcal{F}_i$ is the rate of appearance of **new** infections in compartment i,
- $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$ represents the difference between the rate of transfer of individuals out of compartment i and the rate of transfer of individuals into compartment i. These include transitional terms, such as births, deaths, disease progression, and recovery.

A visual representation of the partition (2.1) is shown in Fig.(2.1).

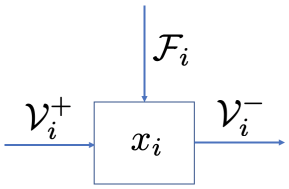

Figure 2.1: Fluxes entering and leaving compartment i

We note that this decomposition in infected and noninfected compartments as well as the decomposition into $\mathcal{F}$ and $\mathcal{V}$ may not be unique. Different decompositions may result in different interpretations of the disease process and may lead to somewhat different expressions of the reproduction number. The decomposition should satisfy the following *properties*:

- $\mathcal{F}_i(0,y) = 0$ and $\mathcal{V}_i(0,y) = 0$ for $y \geq 0$ and $i = 1, ..., n$. The first condition says that all new infections are secondary infections arising from infectious hosts. The second condition says that there is no immigration of susceptible individuals into the disease compartments.
- $\mathcal{F}_i(x,y) \geq 0$ for all $x, y \geq 0$.
- $\mathcal{V}_i(x,y) \leq 0$ whenever $x_i = 0$, for $i = 1, ..., n$. Each component $\mathcal{V}_i$ represents the net outflow of a compartment and must give inflow only (that is, be negative) if the compartment is empty.
- $\sum_{i=1}^{n} \mathcal{V}_i(x,y) \geq 0$ for all $x, y \geq 0$. The total outflow of all infected compartments is positive.

(3) Assume that the disease-free system

$$y' = g(0,y),$$

has a unique disease-free equilibrium $\mathcal{E}^0 = (0, y_0)$ such that all solutions with initial conditions of the form $(0, y)$ approach $(0, y_0)$ as $t \to \infty$. Determine the disease-free equilibrium $\mathcal{E}^0$.

(4) Determine the matrices F and V with components

$$F = \left[\frac{\partial \mathcal{F}_i(0,y_0)}{\partial x_j}\right] \quad \text{and} \quad V = \left[\frac{\partial \mathcal{V}_i(0,y_0)}{\partial x_j}\right].$$

These matrices appear from the linearization of the system (2.1) around the disease-free equilibrium. It can be shown that

$$\frac{\partial \mathcal{F}_i(0,y_0)}{\partial y_j} = \frac{\partial \mathcal{V}_i(0,y_0)}{\partial y_j} = 0,$$

for every pair (i, j). This implies that the linearized equations for the infected compartments x evaluated at the disease-free equilibrium are decoupled from the remaining equations. The linearized system for the infected compartments can be written as

$$x' = (F - V)x,$$

where the F and V matrices are defined above.

(5) The next-generation matrix is defined as FV^{-1} and the basic reproduction number is set to be the dominant eigenvalue of FV^{-1}, or $\mathcal{R}_0 = \rho(FV^{-1})$.

2.3.1 The Main Theorem

Theorem 2.3.1. *[7] Consider the disease transmission model given by (2.1). The disease-free equilibrium of (2.1) is locally asymptotically stable if $\mathcal{R}_0 < 1$, but unstable if $\mathcal{R}_0 > 1$.*

The proof of Theorem 2.3.1 is shown in Appendix 5.1. The above theorem can be summarized by the following widely used theorem to analyze the stability of the disease-free equilibrium [35].

Theorem 2.3.2. *A necessary and sufficient condition for an equilibrium to be locally asymptotically stable is that all eigenvalues of the Jacobian have negative real part.*

2.3.2 Example: An Influenza Model

To illustrate the power of the next-generation matrix introduced in the previous section, we consider the following influenza model. In the model, we assume that there is an incubation period between infection and appearance of symptoms. In addition, a significant fraction of people who are infectious never develop symptoms but go through an asymptomatic period, during which they have some infectivity, and then recover and go to the recovered compartment. And, there is a small number I_0 of initial infections. The model is described by the system of differential equations as [2]

$$\begin{aligned}
\frac{dS}{dt} &= -\beta SI - \beta S\delta A, \\
\frac{dL}{dt} &= \beta SI + \beta S\delta A - \kappa L, \\
\frac{dI}{dt} &= p\kappa L - \alpha I, \\
\frac{dA}{dt} &= (1-p)\kappa L - \eta A, \\
\frac{dR}{dt} &= \alpha I + \eta A,
\end{aligned} \tag{2.2}$$

where S, L, I, A, and R are the susceptible, latent, infected, asymptomatic, and recovered compartments, respectively. The parameters in System (2.2) are detailed in Table (2.1). Next, we use

Parameters	Description
β	transmission rate
δ	infectivity reduced factor
κ	asymptomatic infectious rate
p	fraction of latent members
η	recovery rate of asymptomatic individuals
α	recovery rate of infectious individuals

Table 2.1: Description of parameters of System (2.2)

the next-generation matrix method to determine the basic reproduction number of the model. Since

the next-generation matrix focuses only on compartments containing new infections, we consider the latent, infected, and asymptomatic compartments. The consideration yields the subsystem of differential equations

$$\begin{aligned} \frac{dL}{dt} &= \beta SI + \beta S\delta A - \kappa L, \\ \frac{dI}{dt} &= p\kappa L - \alpha I, \\ \frac{dA}{dt} &= (1-p)\kappa L - \eta A. \end{aligned} \tag{2.3}$$

For each differential equation in System (2.3), we partition the compartments into $\mathcal{F}_i$ and $\mathcal{V}_i$, for $i = 1, 2, 3$, as

$$\begin{aligned} \mathcal{F}_1 &= \beta SI + \beta S\delta A, \\ \mathcal{F}_2 &= 0, \\ \mathcal{F}_3 &= 0, \\ \mathcal{V}_1 &= \kappa L, \\ \mathcal{V}_2 &= -p\kappa L + \alpha I, \\ \mathcal{V}_3 &= -(1-p)\kappa L + \eta A. \end{aligned}$$

The matrices $F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}\right]$ and $V = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}\right]$ at the disease-free equilibrium are

$$F = \begin{bmatrix} \frac{\partial \mathcal{F}_1}{\partial L} & \frac{\partial \mathcal{F}_1}{\partial I} & \frac{\partial \mathcal{F}_1}{\partial A} \\ \frac{\partial \mathcal{F}_2}{\partial L} & \frac{\partial \mathcal{F}_2}{\partial I} & \frac{\partial F_2}{\partial A} \\ \frac{\partial \mathcal{F}_3}{\partial L} & \frac{\partial \mathcal{F}_3}{\partial I} & \frac{\partial \mathcal{F}_3}{\partial A} \end{bmatrix} = \begin{bmatrix} 0 & \beta S^0 & \beta S^0\delta \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} \frac{\partial \mathcal{V}_1}{\partial L} & \frac{\partial \mathcal{V}_1}{\partial I} & \frac{\partial \mathcal{V}_1}{\partial A} \\ \frac{\partial \mathcal{V}_2}{\partial L} & \frac{\partial \mathcal{V}_2}{\partial I} & \frac{\partial \mathcal{V}_2}{\partial A} \\ \frac{\partial \mathcal{V}_3}{\partial L} & \frac{\partial \mathcal{V}_3}{\partial I} & \frac{\partial \mathcal{V}_3}{\partial A} \end{bmatrix} = \begin{bmatrix} \kappa & 0 & 0 \\ -p\kappa & \alpha & 0 \\ -(1-p)\kappa & 0 & \eta \end{bmatrix}.$$

Then, the next-generation matrix FV^{-1} is of the form

$$FV^{-1} = \begin{bmatrix} \frac{\beta S^0 p}{\alpha} + \frac{\beta S^0\delta(1-p)}{\eta} & \frac{\beta S^0}{\eta} & \frac{\beta S^0\delta}{\eta} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

Since FV^{-1} is an upper triangular matrix, the eigenvalues are the entries of the main diagonal of FV^{-1}. That is,

$$\lambda_1 = \frac{\beta S^0 p}{\alpha} + \frac{\beta S^0\delta(1-p)}{\eta}, \qquad \lambda_2 = 0, \qquad \lambda_3 = 0.$$

Thus, by the next-generation matrix method, the basic reproduction number is the dominant eigenvalue of FV^{-1}, or

$$\mathcal{R}_0 = \beta S^0 \frac{p}{\alpha} + \beta S^0 \frac{\delta(1-p)}{\eta}.$$

The reproduction number of the system (2.2) can be explained as follows: a susceptible person becomes infectious with the probability p in which the asymptomatic individual causes $\beta S^0/\alpha$ infections during the infectious period of time $1/\alpha$, or the susceptible person becomes asymptomatic with probability $1-p$, in which the latent member causes $\delta\beta S^0/\eta$ infections during an asymptomatic period of length $1/\eta$.

Chapter 3

Mathematical Models of COVID–19

3.1 $SEIR$ Model

We consider the $SEIR$ model to study the spread and the effects of COVID-19 on a population. Here, S, E, I, and R represent the susceptible, exposed, infected, and recovered compartments, respectively. The model is formulated based on the following assumptions.

3.1.1 Assumptions

(i) The size of the total population remains constant. That is, $N = S(t) + E(t) + I(t) + R(t)$.

(ii) Susceptible individuals are recruited into the S compartment at a constant rate, Λ.

(iii) The transmission rate from an exposed person to a susceptible is β_1 and the transmission rate from an infectious person to a susceptible is β_2. Here, we assume that $\beta_1 < \beta_2$. This means the disease is more likely to spread from an infectious individual than from an exposed individual.

(iv) Individuals in the exposed (E) compartment have a short incubation period. Some become infectious and move to the infected (I) compartment at the rate γ. Whereas, some recover and move to the recovered (R) compartment at the rate σ.

(v) When becoming infectious, individuals can recover from the disease and move to the recovered (R) compartment at the rate κ. In contrast, some perish by the disease at the rate δ.

(vi) Recoveries are assumed to be permanent.

(vii) Natural mortality occurs in all compartments at the rate μ.

(viii) All parameters in the model are positive.

Given the above assumptions, the model can be formulated using the following system of ordinary differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta_1 S(t)E(t) - \beta_2 S(t)I(t) - \mu S(t), \\
\frac{dE}{dt} &= \beta_1 S(t)E(t) + \beta_2 S(t)I(t) - \gamma E(t) - \sigma E(t) - \mu E(t), \\
\frac{dI}{dt} &= \gamma E(t) - \kappa I(t) - \delta I(t) - \mu I(t), \\
\frac{dR}{dt} &= \sigma E(t) + \kappa I(t) - \mu R(t).
\end{aligned} \tag{3.1}$$

A visual representation of System (3.1) is shown in Figure (3.1).

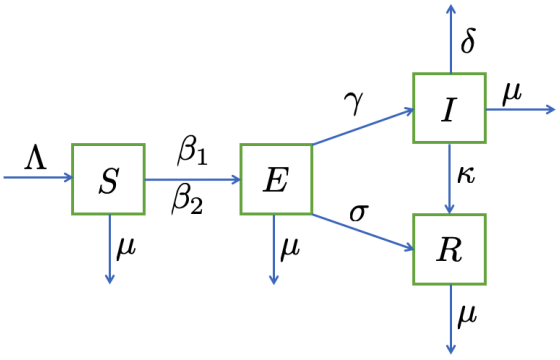

Figure 3.1: The diagram of System (3.1)

In addition, the parameters in the model are summarized in Table (3.1).

Parameters	Description
Λ	recruitment rate
β_1	rate of contraction of susceptible from exposed
β_2	rate of contraction of susceptible from infectious
γ	rate at which an exposed individual becomes infectious
σ	rate at which an exposed person recovers from the disease
κ	rate at which an infectious individual recovers from the disease
δ	disease-induced death rate due to infected class
μ	natural death rate

Table 3.1: Description of parameters of system (3.1)

3.2 Mathematical Model Analysis

In this section we focus on the analysis of the model, including the positivity and boundedness of the solutions, the basic reproduction number, and the different equilibrium points and their stability.

3.2.1 Positivity and Boundedness of Solutions

Theorem 3.2.1. *Given the initial conditions* $\{S(0) \geq 0, E(0) \geq 0, I(0) \geq 0, R(0) \geq 0\}$, *the solution set* $\{S(t), E(t), I(t), R(t)\}$ *is positive whenever the parameters are nonnegative.*

Proof: The proof of the theorem proceeds as follows: for dS/dt,

$$\begin{aligned}\frac{dS}{dt} &= \Lambda - \beta_1 S(t)E(t) - \beta_2 S(t)I(t) - \mu S(t),\\ &= \Lambda - S(t)[\beta_1 E(t) + \beta_2 I(t) + \mu],\\ \frac{dS}{dt} &\geq -S(t)[\beta_1 E(t) + \beta_2 I(t) + \mu].\end{aligned}$$

We denote $\lambda(t) = \beta_1 E(t) + \beta_2 I(t) + \mu$. Then, dS/dt becomes

$$\frac{dS}{dt} \geq -S(t) \cdot \lambda(t).$$

To determine the solution of the inequality we first find the solution of the equality version of the differential equation using a separation of variables method as follows:

$$\begin{aligned}\int \frac{1}{S} dS &= \int -\lambda(t) dt,\\ \ln|S| &= -\int \lambda(t) dt,\\ S &= S(0)\exp\left(-\int_0^t \lambda(u) du\right).\end{aligned}$$

As $S(0) \geq 0$ and the exponential function is always greater than zero, we obtain $S(t) \geq 0$. Following a similar procedure we find that $E(t)$, $I(t)$, and $R(t)$ are always nonnegative. The details of the proofs for the positivity of $E(t)$, $I(t)$, and $R(t)$ are shown in the Appendix 5.2. □

Theorem 3.2.2. *The system of the model has solutions bounded within the invariant region* $\Omega \in \mathbb{R}^4_+$. *That is,*

$$\Omega = \left\{(S, E, I, R) \in \mathbb{R}^4_+ : \frac{\Lambda}{\delta + \mu} \leq N(t) \leq \frac{\Lambda}{\mu}\right\},$$

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

Proof: We assume that $N(t) = S(t) + E(t) + I(t) + R(t)$. Then,

$$\begin{aligned}\frac{dN}{dt} &= \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR}{dt},\\ &= \Lambda - \delta I(t) - \mu S(t) - \mu E(t) - \mu I(t) - \mu R(t),\\ &= \Lambda - \delta I(t) - \mu(S(t) + E(t) + I(t) + R(t)),\\ &= \Lambda - \delta I(t) - \mu N(t).\end{aligned}$$

Since $I(t) \leq N(t)$, or $\delta I(t) \leq \delta N(t)$, then dN/dt is bounded below by $\Lambda - \delta N(t) - \mu N(t)$, or

$$\Lambda - \delta N(t) - \mu N(t) \leq \frac{dN}{dt} = \Lambda - \delta I(t) - \mu N(t).$$

On the other hand, in the case of no infections, $\dfrac{dN}{dt} = \Lambda - \delta I(t) - \mu N(t) \leq \Lambda - \mu N(t)$. Thus,

$$\Lambda - \delta N(t) - \mu N(t) \leq \frac{dN}{dt} \leq \Lambda - \mu N(t). \tag{3.2}$$

Next, we show the boundedness of the solutions from the inequality (3.2). Using the integrating factor method, we obtain the bounds for the solution as

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

As t approaches ∞,

$$\frac{\Lambda}{\delta + \mu} \leq N(t) \leq \frac{\Lambda}{\mu}.$$

Thus, the solutions to the system are bounded within the invariant region Ω. □

3.2.2 Basic Reproduction Number

Following the next-generation matrix technique presented in Section 2.3, we consider the following subsystem

$$\begin{aligned}\frac{dE}{dt} &= \beta_1 S(t)E(t) + \beta_2 S(t)I(t) - \gamma E(t) - \sigma E(t) - \mu E(t),\\ \frac{dI}{dt} &= \gamma E(t) - \kappa I(t) - \delta I(t) - \mu I(t).\end{aligned}$$

The equations can be written in the form of $\frac{dx_i}{dt} = \mathcal{F}_i(x) - \mathcal{V}_i(x)$ for $i = 1, 2$, where $\mathcal{F}_i(x)$ is the rate of appearance of new infections in compartment i, and $\mathcal{V}_i(x)$ is the rate of other transitions between compartment i and other infected compartments. Then,

$$\begin{aligned}\mathcal{F}_1 &= \beta_1 S(t)E(t) + \beta_2 S(t)I(t),\\ \mathcal{F}_2 &= 0,\end{aligned}$$

and

$$\begin{aligned}\mathcal{V}_1 &= \gamma E(t) + \sigma E(t) + \mu E(t),\\ \mathcal{V}_2 &= -\gamma E(t) + \kappa I(t) + \delta I(t) + \mu I(t).\end{aligned}$$

Next, we define the matrices $F = \left[\frac{\partial \mathcal{F}_i(x_0)}{\partial x_j}\right]$ and $V = \left[\frac{\partial \mathcal{F}_i(x_0)}{\partial x_j}\right]$ for $i, j = 1, 2$. Then, the matrices F and V evaluated at the disease-free equilibrium are [7]

$$F = \begin{bmatrix}\frac{\partial \mathcal{F}_1}{\partial E} & \frac{\partial \mathcal{F}_1}{\partial I}\\ \frac{\partial \mathcal{F}_2}{\partial E} & \frac{\partial \mathcal{F}_2}{\partial I}\end{bmatrix} = \begin{bmatrix}\beta_1 S^0 & \beta_2 S^0\\ 0 & 0\end{bmatrix},$$

$$V = \begin{bmatrix}\frac{\partial \mathcal{V}_1}{\partial E} & \frac{\partial \mathcal{V}_1}{\partial I}\\ \frac{\partial \mathcal{V}_2}{\partial E} & \frac{\partial \mathcal{V}_2}{\partial I}\end{bmatrix} = \begin{bmatrix}\gamma + \sigma + \mu & 0\\ -\gamma & \kappa + \delta + \mu\end{bmatrix} = \begin{bmatrix}k_1 & 0\\ -\gamma & k_2\end{bmatrix},$$

$$\begin{aligned}FV^{-1} &= \begin{bmatrix}\beta_1 S^0 & \beta_2 S^0\\ 0 & 0\end{bmatrix} \frac{1}{k_1 k_2}\begin{bmatrix}k_2 & 0\\ \gamma & k_1\end{bmatrix},\\ &= \frac{1}{k_1 k_2}\begin{bmatrix}\beta_1 S^0 & \beta_2 S^0\\ 0 & 0\end{bmatrix}\begin{bmatrix}k_2 & 0\\ \gamma & k_1\end{bmatrix},\\ &= \frac{1}{k_1 k_2}\begin{bmatrix}\beta_1 S^0 k_2 + \beta_2 S^0 \gamma & \beta_2 S^0 k_1\\ 0 & 0\end{bmatrix},\\ &= \begin{bmatrix}\frac{\beta_1}{k_1} S^0 + \frac{\beta_2 \gamma}{k_1 k_2} S^0 & \frac{\beta_2}{k_2} S^0\\ 0 & 0\end{bmatrix},\end{aligned}$$

where $k_1 = \gamma + \sigma + \mu$ and $k_2 = \kappa + \delta + \mu$. Thus, FV^{-1} is the next generation matrix and the basic reproduction number is $\mathcal{R}_0 = \rho\left(FV^{-1}\right)$. Thus, the basic reproduction number is

$$\mathcal{R}_0 = \frac{\beta_1}{k_1} S^0 + \frac{\beta_2 \gamma}{k_1 k_2} S^0,$$

or,

$$\mathcal{R}_0 = \frac{1}{\gamma + \sigma + \mu} \cdot \beta_1 S^0 + \frac{\gamma}{\gamma + \sigma + \mu} \cdot \frac{1}{\kappa + \delta + \mu} \cdot \beta_2 S^0. \tag{3.3}$$

Here, $\beta_1 S^0$ is the contraction rate of the virus of S^0 susceptible individuals from an exposed individual, and $1/(\gamma+\sigma+\mu)$ is the meantime in compartment E. In addition, $\beta_2 S^0$ is the contraction rate of the virus of S^0 susceptibles from an infectious individual, $\gamma/(\gamma + \sigma + \mu)$ is the fraction progressing from compartment E to I, and $1/(\kappa + \delta + \mu)$ is the meantime in compartment I. Thus, the reproduction number, $\mathcal{R}_0$, in Eq.(3.3) is the expected number of secondary infections produced in compartment E by an exposed person or an infectious individual.

3.2.3 Equilibrium Points

Equilibria are points where the variables are constant in time [35]. They can be found by setting each equation in System (3.1) to zero (e.g. $dS/dt = 0$, $dE/dt = 0$, $dI/dt = 0$, $dR/dt = 0$). That is,

$$\begin{aligned} \Lambda - \beta_1 S(t)E(t) - \beta_2 S(t)I(t) - \mu S(t) &= 0, \\ \beta_1 S(t)E(t) + \beta_2 S(t)I(t) - k_1 E(t) &= 0, \\ \gamma E(t) - k_2 I(t) &= 0, \\ \sigma E(t) + \kappa I(t) - \mu R(t) &= 0. \end{aligned} \tag{3.4}$$

There are two types of equilibrium points: disease-free equilibrium and endemic equilibrium. The calculation of each equilibrium is presented as follows.

Disease-free Equilibrium

The disease-free equilibrium (DFE) point is the steady-state solution of the system where no disease is present in the population [35, 7]. That means no individuals are exposed or infected from the disease; thus, no recoveries are necessary. We denote the DFE as $\mathcal{E}^0 = \left(S^0, E^0, I^0, R^0\right)$. For the disease-free equilibrium (DFE), we set

$$I^0 = 0, \qquad E^0 = 0, \qquad R^0 = 0. \tag{3.5}$$

Then, only S^0 needs to be found. Substituting (3.5) into System (3.4) yields

$$\begin{aligned} \Lambda - \beta_1 S^0 E^0 - \beta_2 S^0 I^0 - \mu S^0 &= 0, \\ \Lambda - \mu S^0 &= 0, \\ S^0 &= \frac{\Lambda}{\mu}. \end{aligned}$$

Thus, the DFE is $\mathcal{E}^0 = \left(\dfrac{\Lambda}{\mu}, 0, 0, 0\right)$.

Endemic Equilibrium

The endemic equilibrium point, denoted as $\mathcal{E}^* = (S^*, E^*, I^*, R^*)$, is the steady-state solution where the disease persists in the population [35, 7]. For the endemic equilibrium we consider $I^* \neq 0$, $E^* \neq 0$, and $R^* \neq 0$. The solution of System (3.4) is

$$\begin{aligned} S^* &= \frac{\Lambda}{\beta_1 E^* + \beta_2 I^* + \mu}, \\ E^* &= \frac{\Lambda\beta_1 + \Lambda\beta_2 \dfrac{\gamma}{k_1} - k_1\mu}{k_1\beta_1 + k_1\beta_2 \dfrac{\gamma}{k_2}}, \\ I^* &= \frac{\gamma}{k_2}\left[\frac{\Lambda\beta_1 + \Lambda\beta_2 \dfrac{\gamma}{k_2} - k_1\mu}{k_1\beta_1 + k_1\beta_2 \dfrac{\gamma}{k_2}}\right], \\ R^* &= \frac{1}{\mu}[\sigma E^* + \kappa I^*]. \end{aligned}$$

(See Appendix 5.3 for the details of the derivations of the endemic equilibrium.)

For simplification, the endemic equilibrium point can be written in terms of the basic reproduction number $\mathcal{R}_0$, as shown in Eq. (3.3), as

$$\begin{aligned}
S^* &= \frac{\Lambda}{\mu} \cdot \frac{1}{\mathcal{R}_0}, \\
E^* &= \frac{\Lambda}{k_1}\left(1 - \frac{1}{\mathcal{R}_0}\right), \\
I^* &= \frac{\gamma}{k_2} \cdot \frac{\Lambda}{k_1}\left(1 - \frac{1}{\mathcal{R}_0}\right), \\
R^* &= \frac{\Lambda}{\mu} \cdot \frac{1}{k_1}\left(\sigma + \frac{\kappa\gamma}{k_2}\right)\left(1 - \frac{1}{\mathcal{R}_0}\right).
\end{aligned}$$

This shows that the endemic equilibrium point exists only when $\mathcal{R}_0 > 1$. When $\mathcal{R}_0 < 1$, the equilibrium becomes biologically irrelevant.

3.2.4 Stability Analysis

Theorem 3.2.3. *The disease-free equilibrium* $\mathcal{E}^0 = \left(S^0, 0, 0, 0\right) = \left(\dfrac{\Lambda}{\mu}, 0, 0, 0\right)$ *is locally asymptotically stable if* $\mathcal{R}_0 < 1$ *and is unstable if* $\mathcal{R}_0 > 1$.

Proof: To prove that the disease-free equilibrium is asymptotically stable we need to show that the eigenvalues of the Jacobian matrix, J, of the system (3.1) evaluated at the DFE are all negatives. The eigenvalues can be obtained by solving the characteristic equation $|J - \lambda I| = 0$. That is,

$$\begin{aligned}
|J - \lambda I| &= \begin{bmatrix} -\mu - \lambda & -\beta_1 S^0 & -\beta_2 S^0 & 0 \\ 0 & \beta_1 S^0 - k_1 - \lambda & \beta_2 S^0 & 0 \\ 0 & \gamma & -k_2 - \lambda & 0 \\ 0 & \sigma & \kappa & -\mu - \lambda \end{bmatrix}, \\
&= (-\mu - \lambda) \begin{bmatrix} \beta_1 S^0 - k_1 - \lambda & \beta_2 S^0 & 0 \\ \gamma & -k_2 - \lambda & 0 \\ \sigma & \kappa & -\mu - \lambda \end{bmatrix}, \\
&= (-\mu - \lambda)(-\mu - \lambda) \begin{bmatrix} \beta_1 S^0 - k_1 - \lambda & \beta_2 S^0 \\ \gamma & -k_2 - \lambda \end{bmatrix}, \\
&= (\mu + \lambda)^2 \left[\left(\beta_1 S^0 - k_1 - \lambda\right)\left(-k_2 - \lambda\right) - \beta_2 S^0 \gamma\right] = 0.
\end{aligned}$$

From here, we are able to obtain one eigenvalue, namely, $\lambda = -\mu < 0$. Next, we need to show that the eigenvalues obtained from $\left(\beta_1 S^0 - k_1 - \lambda\right)\left(-k_2 - \lambda\right) - \beta_2 S^0 \gamma = 0$ are also negative.

$$\begin{aligned}
\left(\beta_1 S^0 - k_1 - \lambda\right)\left(-k_2 - \lambda\right) - \beta_2 S^0 \gamma &= 0, \\
\lambda^2 + \lambda k_2 + \lambda k_1 k_2 - \beta_1 S^0 \lambda - \beta_1 S^0 k_2 - \beta_2 S^0 \gamma &= 0, \\
\lambda^2 + \lambda\left(k_1 + k_2 - \beta_1 S^0\right) + k_1 k_2 - \beta_1 S^0 k_2 - \beta_2 S^0 \gamma &= 0.
\end{aligned}$$

Using the quadratic formula we have

$$\lambda = \frac{1}{2}\left[-\left(k_1 + k_2 - \beta_1 S^0\right) \pm \sqrt{\left(k_1 + k_2 - \beta_1 S^0\right)^2 - 4\left(k_1 k_2 - \beta_1 S^0 k_2 - \beta_2 S^0 \gamma\right)}\ \right].$$

To ensure that there are real eigenvalues we need to show that $\Delta \geq 0$. That is,

$$\begin{aligned}
\Delta &= \left(k_1 + k_2 - \beta_1 S^0\right)^2 - 4\left(k_1 k_2 - \beta_1 S^0 k_2 - \beta_2 S^0 \gamma\right), \\
&= (k_1 + k_2)^2 - 2(k_1 + k_2)\beta_1 S^0 + \left(\beta_1 S^0\right)^2 - 4k_1 k_2 + 4\left(\beta_1 S^0 k_2 + \beta_2 S^0 \gamma\right), \\
&= k_1^2 + 2k_1 k_2 + k_2^2 - 2(k_1 + k_2)\beta_1 S^0 + \left(\beta_1 S^0\right)^2 - 4k_1 k_2 + 4\beta_1 S^0 k_2 + 4\beta_2 S^0 \gamma, \\
&= (k_1 - k_2)^2 - 2k_1\beta_1 S^0 + 2\beta_1 S^0 k_2 + \left(\beta_1 S^0\right)^2 + 4\beta_2 S^0 \gamma, \\
&= (k_1 - k_2)^2 - 2(k_1 - k_2)\beta_1 S^0 + \left(\beta_1 S^0\right)^2 + 4\beta_2 S^0 \gamma, \\
&= \left[(k_1 - k_2) - \beta_1 S^0\right]^2 + 4\beta_2 S^0 \gamma > 0.
\end{aligned}$$

Since all the parameters are assumed to be positive, this shows that the eigenvalues are distinct real eigenvalues. We denote

$$\lambda_1 = -\left(k_1 + k_2 - \beta_1 S^0\right) + \sqrt{\Delta},$$

and

$$\lambda_2 = -\left(k_1 + k_2 - \beta_1 S^0\right) - \sqrt{\Delta},$$

where $\Delta = \left(k_1 + k_2 - \beta_1 S^0\right)^2 - 4\left(k_1 k_2 - \beta_1 S^0 k_2 - \beta_2 S^0 \gamma\right)$. Next, we show that λ_1 and λ_2 are negative eigenvalues when $\mathcal{R}_0 < 1$. Suppose that $\lambda_1 < 0$ we have

$$\begin{aligned}
-\left(k_1 + k_2 - \beta_1 S^0\right) + \sqrt{\left(k_1 + k_2 - \beta_1 S^0\right)^2 - 4\left(k_1 k_2 - \beta_1 S^0 k_2 - \beta_2 S^0 \gamma\right)} &< 0, \\
\sqrt{\left(k_1 + k_2 - \beta_1 S^0\right)^2 - 4\left(k_1 k_2 - \beta_1 S^0 k_2 - \beta_2 S^0 \gamma\right)} &< \left(k_1 + k_2 - \beta_1 S^0\right), \\
\left(k_1 + k_2 - \beta_1 S^0\right)^2 - 4\left(k_1 k_2 - \beta_1 S^0 k_2 - \beta_2 S^0 \gamma\right) &< \left(k_1 + k_2 - \beta_1 S^0\right)^2, \\
-4\left(k_1 k_2 - \beta_1 S^0 k_2 - \beta_2 S^0 \gamma\right) &< 0, \\
k_1 k_2 - \beta_1 S^0 k_2 - \beta_2 S^0 \gamma &> 0, \\
1 - \frac{\beta_1 S^0}{k_1} - \frac{\beta_2 S^0 \gamma}{k_1 k_2} &> 0, \\
\mathcal{R}_0 &< 1.
\end{aligned}$$

Using a similar approach we can show that $\lambda_2 < 0$ when $\mathcal{R}_0 < 1$. Then, by Theorem 2.3.1 the DFE $\mathcal{E}^0$ is locally asymptotically stable. On the other hand, if we assume that $\lambda_1 > 0$, then

$$\begin{aligned}
-\left(k_1 + k_2 - \beta_1 S^0\right) + \sqrt{\left(k_1 + k_2 - \beta_1 S^0\right)^2 - 4\left(k_1 k_2 - \beta_1 S^0 k_2 - \beta_2 S^0 \gamma\right)} &> 0, \\
\sqrt{\left(k_1 + k_2 - \beta_1 S^0\right)^2 - 4\left(k_1 k_2 - \beta_1 S^0 k_2 - \beta_2 S^0 \gamma\right)} &> \left(k_1 + k_2 - \beta_1 S^0\right), \\
\left(k_1 + k_2 - \beta_1 S^0\right)^2 - 4\left(k_1 k_2 - \beta_1 S^0 k_2 - \beta_2 S^0 \gamma\right) &> \left(k_1 + k_2 - \beta_1 S^0\right)^2, \\
-4\left(k_1 k_2 - \beta_1 S^0 k_2 - \beta_2 S^0 \gamma\right) &> 0, \\
k_1 k_2 - \beta_1 S^0 k_2 - \beta_2 S^0 \gamma &< 0, \\
1 - \frac{\beta_1 S^0}{k_1} - \frac{\beta_2 S^0 \gamma}{k_1 k_2} &< 0, \\
\mathcal{R}_0 &> 1.
\end{aligned}$$

Then, by Theorem 2.3.1 the DFE is unstable when $\mathcal{R}_0 > 1$. □

3.3 $SEIR$ Model with Vaccine Compartment

Next, we consider a mathematical model where a vaccine compartment is added into the original $SEIR$ model.

3.3.1 Assumptions

To build an $SEIR$ model with a vaccine compartment we use the same assumptions as in Section 3.1.1. In addition, we consider a hypothetical imperfect COVID-19 vaccine. That means the virus can still be transmissible to vaccinated individuals with a reduced rate of $(1-\varepsilon_v)\beta_1$ from an exposed person and $(1-\varepsilon_v)\beta_2$ from an infectious person. Then, the system of the differential equations is presented as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \eta S(t) - \beta_1 S(t)E(t) - \beta_2 S(t)I(t) - \mu S(t),\\
\frac{dV}{dt} &= \eta S(t) - (1-\varepsilon_v)\beta_1 V(t)E(t) - (1-\varepsilon_v)\beta_2 V(t)I(t) - \mu V(t),\\
\frac{dE}{dt} &= \beta_1 S(t)E(t) + \beta_2 S(t)I(t) + (1-\varepsilon_v)\beta_1 V(t)E(t) + (1-\varepsilon_v)\beta_2 V(t)I(t) - \gamma E(t) - \sigma E(t) - \mu E(t),\\
\frac{dI}{dt} &= \gamma E(t) - \kappa I(t) - \delta I(t) - \mu I(t),\\
\frac{dR}{dt} &= \sigma E(t) + \kappa I(t) - \mu R(t).
\end{aligned} \tag{3.6}$$

The diagram of the $SEIR$ with vaccine is shown in Figure (3.2).

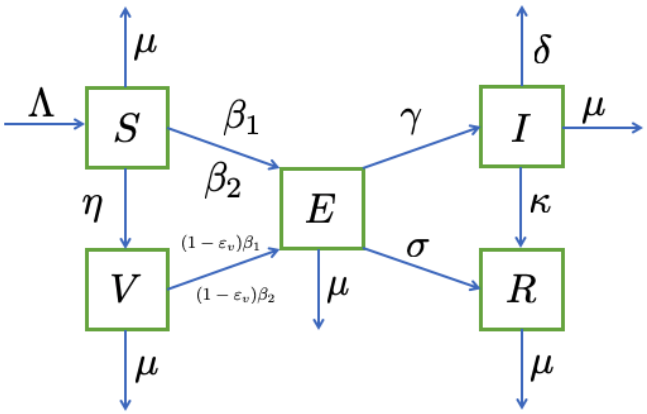

Figure 3.2: The diagram of System (3.6)

A summary of the parameters in System (3.6) is shown in Table (3.2).

3.3.2 Basic Reproduction Number

Similar to the $SEIR$ model, we calculate the basic reproduction number of System (3.6) as follows:

$$\begin{aligned}
\frac{dE}{dt} &= \beta_1 S(t)E(t) + \beta_2 S(t)I(t) + (1-\varepsilon_v)\beta_1 V(t)E(t) + (1-\varepsilon_v)\beta_2 V(t)I(t) - \gamma E(t) - \sigma E(t) - \mu E(t),\\
\frac{dI}{dt} &= \gamma E(t) - \kappa I(t) - \delta I(t) - \mu I(t).
\end{aligned}$$

Parameters	Description
Λ	recruitment rate
β_1	rate of contraction of susceptible from exposed
β_2	rate of contraction of susceptible from infectious
γ	rate at which an exposed individual becomes infectious
σ	rate at which an exposed individual recovers
κ	rate at which an infectious individual recovers
δ	disease-induced death rate
μ	natural death rate
ε_v	vaccine efficacy against acquisition of infection (degree of protection)
η	vaccination rate

Table 3.2: Description of parameters of System (3.6)

Then,

$$\begin{aligned}
&\mathcal{F}_1 = \beta_1 S(t)E(t) + \beta_2 S(t)I(t) + (1-\varepsilon_v)\beta_1 V(t)E(t) + (1-\varepsilon_v)\beta_2 V(t)I(t),\\
&\mathcal{F}_2 = 0,\\
&\mathcal{V}_1 = \gamma E(t) + \sigma E(t) + \mu E(t),\\
&\mathcal{V}_2 = -\gamma E(t) + \kappa I(t) + \delta I(t) + \mu I(t).
\end{aligned}$$

Then the matrices F and V evaluated at the DFE are

$$F = \begin{bmatrix} \dfrac{\partial \mathcal{F}_1}{\partial E} & \dfrac{\partial \mathcal{F}_1}{\partial I} \\ \dfrac{\partial \mathcal{F}_2}{\partial E} & \dfrac{\partial \mathcal{F}_2}{\partial I} \end{bmatrix} = \begin{bmatrix} \beta_1 S_v^0 + (1-\varepsilon_v)\beta_1 V^0 & \beta_2 S_v^0 + (1-\varepsilon_v)\beta_2 V^0 \\ 0 & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} \dfrac{\partial \mathcal{V}_1}{\partial E} & \dfrac{\partial \mathcal{V}_1}{\partial I} \\ \dfrac{\partial \mathcal{V}_2}{\partial E} & \dfrac{\partial \mathcal{V}_2}{\partial I} \end{bmatrix} = \begin{bmatrix} \gamma + \sigma + \mu & 0 \\ -\gamma & \kappa + \delta + \mu \end{bmatrix} = \begin{bmatrix} k_1 & 0 \\ -\gamma & k_2 \end{bmatrix}.$$

Then the basic reproduction number is calculated as

$$\begin{aligned}
FV^{-1} &= \frac{1}{k_1 k_2} \begin{bmatrix} \beta_1 S_v^0 + (1-\varepsilon_v)\beta_1 V^0 & \beta_2 S_v^0 + (1-\varepsilon_v)\beta_2 V^0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} k_2 & 0 \\ \gamma & k_1 \end{bmatrix},\\
&= \frac{1}{k_1 k_2} \begin{bmatrix} (\beta_1 S_v^0 + (1-\varepsilon_v)\beta_1 V^0)k_2 + (\beta_2 S_v^0 + (1-\varepsilon_v)\beta_2 V^0)\gamma & (\beta_2 S_v^0 + (1-\varepsilon_v)\beta_2 V^0)k_1 \\ 0 & 0 \end{bmatrix},\\
&= \begin{bmatrix} \dfrac{(\beta_1 S_v^0 + (1-\varepsilon_v)\beta_1 V^0)k_2 + (\beta_2 S_v^0 + (1-\varepsilon_v)\beta_2 V^0)\gamma}{k_1 k_2} & \dfrac{(\beta_2 S_v^0 + (1-\varepsilon_v)\beta_2 V^0)k_1}{k_1 k_2} \\ 0 & 0 \end{bmatrix}.
\end{aligned}$$

The basic reproduction number is the dominant eigenvalue of the matrix FV^{-1}. Since the matrix FV^{-1} is an upper triangular matrix, the eigenvalues are the entries on the main diagonal. Thus, the basic reproduction number is

$$\mathcal{R}_0^v = \frac{(\beta_1 S_v^0 + (1-\varepsilon_v)\beta_1 V^0)k_2 + (\beta_2 S_v^0 + (1-\varepsilon_v)\beta_2 V^0)\gamma}{k_1 k_2},$$

or,

$$\mathcal{R}_0^v = \mathcal{R}_0^{S_v^0} + \mathcal{R}_0^{V^0}, \tag{3.7}$$

where

$$\mathcal{R}_0^{S_v^0} = \frac{1}{\gamma+\sigma+\mu}\cdot\beta_1 S_v^0 + \frac{\gamma}{\gamma+\sigma+\mu}\cdot\frac{1}{\kappa+\delta+\mu}\cdot\beta_2 S_v^0,$$
$$\mathcal{R}_0^{V^0} = \frac{1}{\gamma+\sigma+\mu}\cdot(1-\varepsilon_v)\beta_1 V^0 + \frac{\gamma}{\gamma+\sigma+\mu}\cdot\frac{1}{\kappa+\mu+\delta}\cdot(1-\varepsilon_v)\beta_2 V^0.$$

Here, $\beta_1 S_v^0$ is the rate of contraction of the virus of S_v^0 susceptible individuals from exposed individuals, $(1-\varepsilon_v)\beta_1 V^0$ is the rate of contraction of the virus of V^0 vaccinated individuals from exposed individuals, and $\frac{1}{\gamma+\sigma+\mu}$ is the meantime in compartment E. Also, $\beta_2 S_v^0$ is the rate of contraction of the virus of S_v^0 susceptible individuals from infectious individuals, $(1-\varepsilon_v)\beta_2 V^0$ is the rate of contraction of the virus of V^0 vaccinated individuals from infectious individuals, $\frac{\gamma}{\gamma+\sigma+\mu}$ is the progression from compartment E to compartment I, and $\frac{1}{\kappa+\delta+\mu}$ is the meantime in compartment I. Thus, the reproduction number $\mathcal{R}_0^v$ in Eq. (3.6) is the expected number of secondary infections produced in compartment E by an exposed or infectious individual.

3.3.3 Disease-free Equilibrium of the Vaccine Model

The basic reproduction number of the vaccine model is estimated based on the disease-free equilibrium (DFE), denoted as $\mathcal{E}_v^0 = (S_v^0, V^0, E_v^0, I_v^0, R_v^0)$. To determine the solutions we set each equation of System (3.6) equal to zero. In other words,

$$\begin{aligned}
\Lambda - \eta S(t) - \beta_1 S(t)E(t) - \beta_2 S(t)I(t) - \mu S(t) &= 0,\\
\eta S(t) - (1-\varepsilon_v)\beta_1 V(t)E(t) - (1-\varepsilon_v)\beta_2 V(t)I(t) - \mu V(t) &= 0,\\
\beta_1 S(t)E(t) + \beta_2 S(t)I(t) + (1-\varepsilon_v)\beta_1 V(t)E(t) + (1-\varepsilon_v)\beta_2 V(t)I(t) - \gamma E(t) - \sigma E(t) - \mu E(t) &= 0,\\
\gamma E(t) - \kappa I(t) - \delta I(t) - \mu I(t) &= 0,\\
\sigma E(t) + \kappa I(t) - \mu R(t) &= 0.
\end{aligned}$$

Since there is no disease present in the population, we set $E_v^0 = 0$, $I_v^0 = 0$, and $R_v^0 = 0$. This yields

$$S_v^0 = \frac{\Lambda}{\eta+\mu},$$
$$V^0 = \frac{\Lambda}{\eta+\mu}\cdot\frac{\eta}{\mu}.$$

Thus, the DFE point is $\mathcal{E}_v^0 = \left(\frac{\Lambda}{\eta+\mu}, \frac{\Lambda\cdot\eta}{\mu(\eta+\mu)}, 0, 0, 0\right)$.

Chapter 4

Discussion and Conclusion

COVID-19 was first identified in December 2019. Since then it has had detrimental impacts on many factors of life globally. Many lives were lost and the economy plummeted. The implementation of government control measures helped to slow the spread of the virus, but the real breakthrough was in the development of multiple vaccines. The aim of the research is to obtain a theoretical result on the impact of a vaccine in slowing the spread of the virus through epidemiology. In fact, we use an $SEIR$ deterministic compartment model to analyze the spread of the virus. Additionally, a vaccine compartment is added into the $SEIR$ model (e.g. $SEIR$ with vaccine model) with the hypothesis that the vaccine is imperfect to see how a vaccine would change the dynamics of the whole system.

We see improvement in lowering the number of cases of COVID-19 when people are vaccinated. In fact, it is clear that the susceptible individuals of the $SEIR$ model, $S^0 = \dfrac{\Lambda}{\mu}$, are reduced to $S_v^0 = \dfrac{\Lambda}{\eta + \mu}$. In other words, susceptibles that are vaccinated are assumed to move to the vaccine compartment. Although vaccinated individuals are still able to contract the virus, they occur at reduced rates of $(1-\varepsilon_v)\beta_1$ and $(1-\varepsilon_v)\beta_2$. This shows it is less likely for the vaccinated individuals to be infected. Thus, it helps lower the number of cases moving from the S compartment to the E compartment and potentially becoming infectious.

To further see the effect of vaccines we calculate the basic reproduction number for each model using the next-generation matrix technique. The basic reproduction number of the $SEIR$ model ($\mathcal{R}_0$) and the $SEIR$ with vaccine model ($\mathcal{R}_0^v$) are shown in Eq. (3.3) and Eq. (3.7), respectively. It is important to obtain the basic reproduction number since it represents the number of individuals the virus can spread to in a susceptible population from one infectious individual.

There are some similarities between the forms of the two basic reproduction numbers. Both reproduction numbers have the same infection rates of a susceptible individual contracting the virus from an exposed individual and of a susceptible individual contracting the virus from an infectious individual. They also contain the same meantimes in compartments E and I, and the same rates of progression from compartment E to compartment I.

The differences occur in the application of these rates and meantimes to the different compartments in each model, seen in the differences between $\mathcal{R}_0$ with $\mathcal{R}_0^{S_v^0}$ and $\mathcal{R}_0^{V^0}$, the latters whose sum represents $\mathcal{R}_0^v$. The main difference between $\mathcal{R}_0$ and $\mathcal{R}_0^{V^0}$ is that $\mathcal{R}_0^{V^0}$ represents the implementation of the vaccine, with the rates and meantimes being applied to the vaccine compartment of the model. While $\mathcal{R}_0^{S_v^0}$ is more similar to $\mathcal{R}_0$ because the rates and meantimes are applied to the susceptible compartments of each model, the differences lie in the susceptible compartments themselves. S_v^0 is comprised of S^0 with the addition of η, the vaccination rate, in the denominator. This makes S_v^0 smaller than S^0, and combined with a similar situation in V^0, explains why $\mathcal{R}_0^{V^0}$ is smaller than $\mathcal{R}_0$. Since the rate of infection decreases with the vaccine, the reproduction number also decreases. Thus, with the availability of vaccines, fewer individuals will get the virus from one infectious individual.

The implementation of a vaccine reduces the number of infections and minimizes fatalities. Thus, the more people who are vaccinated, the lower the number of infections and potential deaths. Al-

though lockdowns and other interventions such as social distancing and face masks were shown to help reduce COVID-19 infections, the addition of a vaccine reduced infections and deaths even more.

In an imperfect vaccine scenario like the one presented in this paper, the vaccine efficacy (ε_v) is not 100%. This is a realistic model reflecting the vaccines that are available today. For example, in America, the vaccines available include Pfizer, with 95% efficacy, Moderna, with 94.1% efficacy, and Johnson & Johnson, with 66.3% efficacy. In an expansion of our work, we can implement the different percentages into the model to compare the reproduction numbers. However, in a perfect vaccine scenario, the efficacy of a perfect vaccine is 100%. That means once an individual is vaccinated, they are immune to the disease, and thus cannot contract the disease from an exposed or infectious individual. The preliminary results show that the disease-free equilibrium points for both cases of the imperfect vaccine and perfect vaccine are the same. The endemic equilibrium points are different. However, they are rather lengthy and tedious to analyze, and are beyond the scope of the report.

Throughout our research we have looked at many theorems and epidemiological models in an effort to get the best models and methods for understanding COVID-19 infections. For the possible continuation of this research, we have planned what our future work might look like. This includes work on the sensitivity analysis as well as the optimal control for each model presented in the prior sections. Since the effect of the virus is different for different age groups, we would also want to create a mathematical model with age-structure. For instance, we would consider different age-dependent compartments, such as a juvenile compartment (from ages 0 - 17), adult compartment (from ages 18 - 64), and elderly compartment (from ages 65-onward). Another extension we might consider is analyzing the minimum number of people that need to be vaccinated in a given population with other containment methods to keep $\mathcal{R}_0^v < 1$.

Chapter 5

Appendix

5.1 The Proof of Theorem 2.3.1

Proof: Let F and V be defined as above, and let J_{21} and J_{22} be the matrices of partial derivatives of g with respect to x and y evaluated at the disease-free equilibrium. The Jacobian matrix for the linearization of the system about the disease-free equilibrium has the block structure

$$J = \begin{bmatrix} F - V & 0 \\ J_{21} & J_{22} \end{bmatrix}.$$

The disease-free equilibrium is locally asymptotically stable if the eigenvalues of the Jacobian matrix all have negative real parts. Since the eigenvalues of J are those of $(F - V)$ and J_{22}, and the latter all have negative real parts by assumption, the disease-free equilibrium is locally asymptotically stable if all eigenvalues of $(F - V)$ have negative real parts. By the assumptions on $\mathcal{F}$ and $\mathcal{V}$, F is nonnegative and V is a nonsingular M-matrix. Hence, by Lemma 2.2.2 all eigenvalues of $(F - V)$ have negative real parts if and only if $\rho(FV^{-1}) < 1$. It follows that the disease-free equilibrium is locally asymptotically stable if $\mathcal{R}_0 = \rho(FV^{-1}) < 1$.

Instability for $\mathcal{R}_0 > 1$ can be established by a continuity argument. If $\mathcal{R}_0 \leq 1$ then for any $\varepsilon > 0, ((1+\varepsilon)I - FV^{-1})$ is a nonsingular M-matrix and by Lemma 2.2.1, $((1+\varepsilon)I - FV^{-1})^{-1} \geq 0$. By Lemma 2.2.2, all eigenvalues of $((1+\varepsilon)V - F)$ have positive real parts. Since $\varepsilon > 0$ is arbitrary, and eigenvalues are continuous functions of the entries of the matrix, it follows that all eigenvalues of $(V - F)$ have nonnegative real parts. To reverse the argument, suppose all the eigenvalues of $(V - F)$ have nonnegative real parts. For any positive ε, $(V + \varepsilon I - F)$ is a nonsingular M-matrix, and by Lemma 2.2.2, $\rho(F(V + \varepsilon I)^{-1}) < 1$. Again, since $\varepsilon > 0$ is arbitrary, it follows that $\rho(FV^{-1}) \leq 1$. Thus, $(F - V)$ has at least one eigenvalue with positive real part if and only if $\rho(FV^{-1}) > 1$, and the disease-free equilibrium is unstable whenever $\mathcal{R}_0 > 1$. □

Further discussions of the theorem can be found in [35, 6, 7].

5.2 The Proof of Theorem 3.2.1 for $E(t)$, $I(t)$, and $R(t)$

Proof: Here, we show the detailed proof of the positivity of the solutions, $E(t)$, $I(t)$, and $R(t)$. That is, consider

$$\begin{aligned} \frac{dE}{dt} &= \beta_1 S(t)E(t) + \beta_2 S(t)I(t) - \gamma E(t) - \sigma E(t) - \mu E(t), \\ &= \beta_2 S(t)I(t) + E(t)[\beta_1 S(t) - \gamma - \sigma - \mu], \\ \frac{dE}{dt} &\geq E(t)[\beta_1 S(t) - \gamma - \sigma - \mu]. \end{aligned}$$

In addition, we denote $\lambda_E(t) = \beta_1 S(t) - \gamma - \sigma - \mu$. Then, the inequality becomes

$$\frac{dE}{dt} \geq E(t) \cdot \lambda(t).$$

To obtain the solution of the inequality we can first consider the differential equation $\frac{dE}{dt} = E(t) \cdot \lambda_E(t)$. Using a Separation of Variables method we can obtain the solution of $E(t)$ as

$$\begin{aligned}
\int \frac{1}{E} dE &= \int \lambda_E(t) dt, \\
\ln |E| &= \int \lambda_E(t) dt = \int \lambda_E(t) dt, \\
E(t) &= E(0) \exp\left(\int_0^t \lambda_E(u) du \right) > 0.
\end{aligned}$$

This shows that $E(t)$ is a positive solution. Next, we show that $I(t)$ is also a positive solution. That is, consider

$$\begin{aligned}
\frac{dI}{dt} &= \gamma E(t) - \kappa I(t) - \delta I(t) - \mu I(t), \\
&= \gamma E(t) - I(t) \left(\kappa + \delta + \mu \right), \\
\frac{dI}{dt} &\geq -I(t) \left(\kappa + \delta + \mu \right).
\end{aligned}$$

We denote $\lambda_I = \kappa + \delta + \mu$. The differential equation becomes

$$\frac{dI}{dt} \geq -I(t) \lambda_I.$$

Consider the equality $\frac{dI}{dt} = -I(t) \cdot \lambda_I$ by Separation of Variables

$$\begin{aligned}
\int \frac{1}{I} dI &= \int -\lambda_I dt, \\
\ln |I| &= -\int \lambda_I dt, \\
I(t) &= I(0) \exp\left(\int_0^t \lambda_I du \right) \geq 0.
\end{aligned}$$

Finally, for $R(t)$ we consider

$$\begin{aligned}
\frac{dR}{dt} &= \sigma E(t) + \kappa I(t) - \mu R(t), \\
\frac{dR}{dt} &\geq -\mu R(t).
\end{aligned}$$

Denote $\lambda_R = \mu$, then the differential equation becomes

$$\frac{dR}{dt} \geq -R(t) \lambda_R.$$

Consider the equality $\frac{dR}{dt} = -R(t)_R$. By Separation of Variables,

$$\begin{aligned}
\int \frac{1}{R} dR &= -\int \lambda_R dt, \\
\ln |R| &= -\int \lambda_R dt, \\
R &= R(0) \exp\left(-\int_0^t \lambda_R du \right) \geq 0.
\end{aligned}$$

□

5.3 Endemic Equilibrium of $SEIR$ Model

First, we solve $dS/dt = 0$ as

$$\begin{aligned}
\Lambda - \beta_1 S^* E^* - \beta_2 S^* I^* - \mu S^* &= 0, \\
\Lambda &= \beta_1 S^* E^* + \beta_2 S^* I^* + \mu S^*, \\
\Lambda &= S^*[\beta_1 E^* + \beta_2 I^* + \mu], \\
S^* &= \frac{\Lambda}{\beta_1 E^* + \beta_2 I^* + \mu}. \qquad (5.1)
\end{aligned}$$

Next, we solve for $dE/dt = 0$ as

$$\begin{aligned}
\beta_1 S^* E^* + \beta_2 S^* I^* - k_1 E^* &= 0, \\
S^*(\beta_1 E^* + \beta_2 I^*) - k_1 E^* &= 0, \\
S &= \frac{k_1 E^*}{\beta_1 E^* + \beta_2 I^*}, \qquad (5.2)
\end{aligned}$$

where $k_1 = \gamma + \sigma + \mu$. Setting Eq. (5.1) and Eq. (5.2) equal to one another yields

$$\begin{aligned}
\frac{k_1 E^*}{\beta_1 E^* + \beta_2 I^*} &= \frac{\Lambda}{\beta_1 E^* + \beta_2 I^* + \mu}, \\
k_1 E^*(\beta_1 E^* + \beta_2 I^* + \mu) &= \Lambda(\beta_1 E^* + \beta_2 I^*), \\
k_1\beta_1 E^{*2} + k_1\beta_2 E^* I^* + k_1\mu E^* &= \Lambda\beta_1 E^* + \Lambda\beta_2 I^*, \\
k_1\beta_1 E^{*2} + k_1\beta_2 E^* I^* + k_1\mu E^* - \Lambda\beta_1 E^* - \Lambda\beta_2 I^* &= 0. \qquad (5.3)
\end{aligned}$$

But, from $dI/dt = 0$ we obtain $\frac{\gamma}{k_2} E^* = I^*$, where $k_2 = \kappa + \delta + \mu$. Then, substituting $\frac{\gamma}{k_2} E^* = I^*$ into Eq. (5.4) yields

$$\left(\kappa_1\beta_1 + k_1\beta_2\frac{\gamma}{k_2}\right) E^{*2} + \left(k_1\mu - \Lambda\beta_1 - \Lambda\beta_2\frac{\gamma}{k_2}\right) E^* = 0.$$

The equation yields a disease-free equilibrium point $E^0 = 0$ and

$$E^* = \frac{\Lambda\beta_1 + \Lambda\beta_2\frac{\gamma}{k_1} - k_1\mu}{k_1\beta_1 + k_1\beta_2\frac{\gamma}{k_2}}.$$

To easily analyze the endemic equilibrium we rewrite E^* in terms of the basic reproduction number, $\mathcal{R}_0$, as follows.

$$\begin{aligned}
E^* &= \frac{\mu\left(\frac{\Lambda}{\mu}\left(\frac{\beta_1}{k_1} + \frac{\beta_2\gamma}{k_1 k_2}\right) - 1\right)}{k_1\left(\frac{\beta_1}{k_1} + \frac{\beta_2\gamma}{k_1 k_2}\right)}, \\
&= \frac{\Lambda\left(\frac{\Lambda}{\mu}\left(\frac{\beta_1}{k_1} + \frac{\beta_2\gamma}{k_1 k_2}\right) - 1\right)}{k_1\frac{\Lambda}{\mu}\left(\frac{\beta_1}{k_1} + \frac{\beta_2\gamma}{k_1 k_2}\right)}, \\
&= \frac{\Lambda\left(\mathcal{R}_0 - 1\right)}{k_1\mathcal{R}_0}, \\
&= \frac{\Lambda}{k_1}\left(1 - \frac{1}{\mathcal{R}_0}\right), \\
E^* &= \frac{\Lambda}{\gamma + \sigma + \mu}\left(1 - \frac{1}{\mathcal{R}_0}\right). \qquad (5.4)
\end{aligned}$$

Next, we substitute E^* into $\frac{\gamma}{k_2}E^* = I^*$ and obtain

$$I^* = \frac{\gamma}{\kappa+\delta+\mu} \cdot \frac{\Lambda}{\gamma+\sigma+\mu}\left(1 - \frac{1}{R_0}\right). \tag{5.5}$$

To find R^* we solve for $dR/dt = 0$ and get

$$R^* = \frac{1}{\mu}\left(\sigma E^* + \kappa I^*\right).$$

Substituting E^* and I^* from Eq. (5.4) and Eq. (5.5) into S^* of Eq. (5.2) and R^*, we arrive at

$$\begin{aligned} S^* &= \frac{\Lambda}{\mu} \cdot \frac{1}{\mathcal{R}_0}, \\ R^* &= \frac{\Lambda}{\mu} \cdot \frac{1}{\gamma+\sigma+\mu}\left(\sigma + \frac{\kappa\gamma}{\kappa+\delta+\mu}\right)\left(1 - \frac{1}{R_0}\right). \end{aligned}$$

5.4 Endemic Equilibrium of $SEIR$ Model with Vaccine Compartment

We use Mathematica to obtain the endemic equilibria of System (3.6). There are two endemic equilibria and they are shown below.

It is obvious that the points are complicated and tedious to analyze. We hope this is part of the future work that we can look more closely into.

```
{S → ((beta2 gamma + beta1 k2) ((-1 + epsilon) (eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda) + epsilon k1 k2 mu) +
      √((beta2 gamma + beta1 k2)^2 ((-1 + epsilon)^2 (eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda)^2 +
            2 (-1 + epsilon) epsilon k1 k2 (eta k1 k2 - (beta2 gamma + beta1 k2) Lambda) mu + epsilon^2 k1^2 k2^2 mu^2))) /
   (2 epsilon (beta2 gamma + beta1 k2)^2 mu), V → ((beta2 gamma + beta1 k2)
      ((-1 + epsilon) (eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda) - epsilon k1 k2 mu) +
      √((beta2 gamma + beta1 k2)^2 ((-1 + epsilon)^2 (eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda)^2 +
            2 (-1 + epsilon) epsilon k1 k2 (eta k1 k2 - (beta2 gamma + beta1 k2) Lambda) mu + epsilon^2 k1^2 k2^2 mu^2))) /
   (2 (-1 + epsilon) epsilon (beta2 gamma + beta1 k2)^2 mu), En →
   ((beta2 gamma + beta1 k2) ((-1 + epsilon) (-eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda) - (-2 + epsilon) k1 k2 mu) -
      √((beta2 gamma + beta1 k2)^2 ((-1 + epsilon)^2 (eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda)^2 +
            2 (-1 + epsilon) epsilon k1 k2 (eta k1 k2 - (beta2 gamma + beta1 k2) Lambda) mu + epsilon^2 k1^2 k2^2 mu^2))) /
   (2 (-1 + epsilon) k1 (beta2 gamma + beta1 k2)^2), In → (gamma ((beta2 gamma + beta1 k2)
         ((-1 + epsilon) (-eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda) - (-2 + epsilon) k1 k2 mu) -
        √((beta2 gamma + beta1 k2)^2 ((-1 + epsilon)^2 (eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda)^2 +
              2 (-1 + epsilon) epsilon k1 k2 (eta k1 k2 - (beta2 gamma + beta1 k2) Lambda) mu + epsilon^2 k1^2 k2^2 mu^2)))) /
   (2 (-1 + epsilon) k1 k2 (beta2 gamma + beta1 k2)^2), R →
   -(((((beta2 gamma + beta1 k2) ((-1 + epsilon) (eta k1 k2 - (beta2 gamma + beta1 k2) Lambda) + (-2 + epsilon) k1 k2 mu) +
            √((beta2 gamma + beta1 k2)^2 ((-1 + epsilon)^2 (eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda)^2 + 2
                  (-1 + epsilon) epsilon k1 k2 (eta k1 k2 - (beta2 gamma + beta1 k2) Lambda) mu + epsilon^2 k1^2 k2^2 mu^2))))
         (gamma kappa + k2 sigma)) / (2 (-1 + epsilon) k1 k2 (beta2 gamma + beta1 k2)^2 mu))},
{S → ((beta2 gamma + beta1 k2) ((-1 + epsilon) (eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda) + epsilon k1 k2 mu) -
      √((beta2 gamma + beta1 k2)^2 ((-1 + epsilon)^2 (eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda)^2 +
            2 (-1 + epsilon) epsilon k1 k2 (eta k1 k2 - (beta2 gamma + beta1 k2) Lambda) mu + epsilon^2 k1^2 k2^2 mu^2))) /
   (2 epsilon (beta2 gamma + beta1 k2)^2 mu), V → ((beta2 gamma + beta1 k2)
      ((-1 + epsilon) (eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda) - epsilon k1 k2 mu) -
      √((beta2 gamma + beta1 k2)^2 ((-1 + epsilon)^2 (eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda)^2 +
            2 (-1 + epsilon) epsilon k1 k2 (eta k1 k2 - (beta2 gamma + beta1 k2) Lambda) mu + epsilon^2 k1^2 k2^2 mu^2))) /
   (2 (-1 + epsilon) epsilon (beta2 gamma + beta1 k2)^2 mu), En →
   ((beta2 gamma + beta1 k2) ((-1 + epsilon) (-eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda) - (-2 + epsilon) k1 k2 mu) +
      √((beta2 gamma + beta1 k2)^2 ((-1 + epsilon)^2 (eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda)^2 +
            2 (-1 + epsilon) epsilon k1 k2 (eta k1 k2 - (beta2 gamma + beta1 k2) Lambda) mu + epsilon^2 k1^2 k2^2 mu^2))) /
   (2 (-1 + epsilon) k1 (beta2 gamma + beta1 k2)^2), In → (gamma ((beta2 gamma + beta1 k2)
         ((-1 + epsilon) (-eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda) - (-2 + epsilon) k1 k2 mu) +
        √((beta2 gamma + beta1 k2)^2 ((-1 + epsilon)^2 (eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda)^2 +
              2 (-1 + epsilon) epsilon k1 k2 (eta k1 k2 - (beta2 gamma + beta1 k2) Lambda) mu + epsilon^2 k1^2 k2^2 mu^2)))) /
   (2 (-1 + epsilon) k1 k2 (beta2 gamma + beta1 k2)^2), R → (((beta2 gamma + beta1 k2)
         ((-1 + epsilon) (-eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda) - (-2 + epsilon) k1 k2 mu) +
        √((beta2 gamma + beta1 k2)^2 ((-1 + epsilon)^2 (eta k1 k2 + beta2 gamma Lambda + beta1 k2 Lambda)^2 +
              2 (-1 + epsilon) epsilon k1 k2 (eta k1 k2 - (beta2 gamma + beta1 k2) Lambda) mu + epsilon^2 k1^2 k2^2 mu^2)))
      (gamma kappa + k2 sigma)) / (2 (-1 + epsilon) k1 k2 (beta2 gamma + beta1 k2)^2 mu)}}
```

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