SENSITIVITY ANALYSIS IN COVID-19 EPIDEMIC MODEL

A THESIS SUBMITTED TO THE INSTITUTE OF GRADUATE STUDIES

OF

NEAR EAST UNIVERSITY

By

SARKHEL AKBAR MAHMOOD MAHMOOD

In Partial Fulfillment of the Requirements for the Degree of Master of Science in Mathematics

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Approval of Director of Instıtute of Graduate Studies

Prof. Dr. K. Hüsnü Can BAŞER

We certify this thesis is satisfactory for the award of the degree of Masters of Science in Mathematics

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I declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

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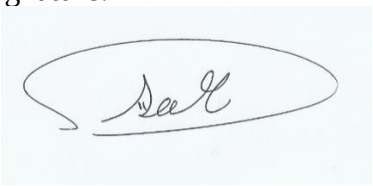

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To my parents…

ABSTRACT

This thesis studied the sensitivity analysis of COVID-19 epidemics models of two epidemics models, with and without vaccination model to see the effect of each parameter on the basic reproduction number.

The first vaccination-free model utilizes the SIR scheme. The second model with vaccination uses the SVIR model. With the assumption that the population is fixed, the average birth and death ratio for the susceptible class are included in the model with all births. However, in the second model, it is assumed that there is no double infection for the disease.

Both models are represented mathematically by the set of nonlinear first-order ordinary differential equations. The boundedness and persistence of both models' solutions are investigated. The local stability condition of all possible equilibrium points is established, the global stability condition for some of the possible equilibrium points, and the basic reproduction number for both models discussed. Finally, a numerical solution of both models are solved to study the dynamic behavior, with the sensitivity of each parameter in basic reproduction number to show the influence of each parameter on the model with the help of code (ode45) solver in Matlab program.

Keywords: epidemic model; influenza; vaccination; basic reproduction number; stability; sensitivity analysis

ÖZET

Bu tez, aşılama ve aşılama olmadan oluşturulan iki epidemik Covid-19 modelinin modellerinin duyarlılık analizini incelemiştir. Amaç, her parametrenin temel üreme sayısı üzerindeki etkisini görmektir.

Aşısız modelde SIR modeli oluşturulmuştur. Aşılamanın olduğu ikinci modelde SVIR modeli oluşrturulmuştur. Nüfusun sabit olduğu varsayımı duyarlı sınıf için ortalama doğum ve doğal ölüm oranı modele dahil edilmiştir. Ancak ikinci modelde hastalığın 2. kez tekrarlanmadığı varsayılmıştır.

Her iki model de doğrusal olmayan birinci dereceden adi diferansiyel denklemler seti ile matematiksel olarak temsil edilmiştir. Her iki modelin çözümlerinin sınırlılığı ve kalıcılığı araştırılmıştır. Tüm olası denge noktalarının yerel kararlılık koşulu belirlenip, bazı olası denge noktaları için küresel kararlılık koşulu ve her iki model için de temel üreme sayısı çözümlenmiştir. Son olarak, her parametrenin model üzerindeki etkisini göstermek için temel üreme oranındaki her parametrenin hassasiyeti ile dinamik davranışı incelemek adına her iki modelin sayısal bir çözümü bulunmuştur. Bu çözümlemede Matlab programında kod (ode45) kullanılmıştır.

Anahtar Kelimeler: salgın modeli; grip; aşılama; temel üreme sayısı; istikrar; duyarlılık analizi.

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CHAPTER 1
INTRODUCTION

Throughout the world, infectious diseases burden populations and cultures. In every population, as the occurrence of an infectious disease continues to escalate, individuals tend to search at the most appropriate ways to combat the epidemic or calculate the number of pathogens. In the battle against sickness, scientists have produced enormous strides. Infectious diseases, however, remain an important source of mortality. In epidemiology, in order to monitor associated health issues, one attempts to study the enhancement of well-being and circumstances in a given population. Utilizing assumptions and theories about the associated pathways, this study applies mathematics to explain complicated disease dynamics.

1.1 Background of Influenza

In this section, we give some backgrounds of influenza, vaccination, and coronaviruses.

1.1.1 Influenza Viruses

Influenza viruses belong to the clan Orthomyxoviridae and have a single-stranded segmented RNA genome. The influenza viruses are distributing into types A, B, and C based on their core proteins. Type A influenza viruses are the most malignant human pathogens among the three influenza types and cause acute disease. Moreover, they can be subdivided according to their envelope glycoproteins with hemagglutinin (HA) or neuraminidase (NA) into eleven serotypes based on H and N. These serotypes are H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, H7N9 (RHilleman, 2002; Alan J. Hay, 2001). The influenza B virus almost exclusively infects humans and is less common than influenza A. Only human beings are influenced by the last form (C), and it could seldom be Distinguished since it triggers no outbreaks from the flu virus (Webster, 1992). The creepiest part is that subgroups of influenza A and influenza B viruses could be identified by genealogy. A modern genealogy of influenza

occurs in two best strategies; antigenic drift and antigenic change. Antigenic drift emerges, which occurs, by incremental shifts in the virus. There is a new genealogy, which could then be unique to the recipient antibodies.

In addition, a drastic alteration in the influenza virus is an antigenic move that results in a new strain that has seldom become observed previously. Influenza A undergoes both alterations, whereas B undertakes just antigenic drift. That has never been seen before (N L Michael, M Vahey, D S Burke, R R Redfield, 1992).

1.1.2 Vaccination

Vaccine, suspension of scattered microorganisms or lymphocytes have been destroyed or diminished, or of antibodies or toxins that have been provided to deter diseases including Covid-19. By activating the immune system to fight the agent, a vaccine may provide effective immunity against a particular harmful variable. If it once again reaches the person, the time a vaccine, the antibody-producing cells, labeled B cells (or B lymphocytes), stay sensitized and planned to react to the variable. A vaccination could also grant passive immunity by having antibodies or lymphocytes already produced by an animal or human donor. Vaccines, delivered by injection, are popular but others are given orally or even nasally. Those passages of the gut or nasal lining seem to induce a stronger effect from antibodies, and therefore the most powerful route of administration (Brunson, 2008).

1.1.3 Coronavirus (CoV-2) Pandemic, COVID-19

The 2019 (COVID-19) spread-unfolding coronavirus disease pandemic has devastated life worldwide. In Wuhan, China, the novel coronavirus (CoV-2, later renamed SARS-CoV-2) arose from an undisclosed origin (Qun Li, M.Med., Xuhua Guan, 2020). Unlike past epidemics of coronaviruses, (El Zowalaty ME, Järhult JD, 2020). An as-yet-unconfirmed animal source, this extremely infectious zoonotic virus (McCloskey B, Zumla A, 2020). It

progressed from a moderate acute respiratory illness associated with local flu to a pandemic that endangered the existences of millions within several months. In many nations, COVID-19 created huge challenges for global public health and halted several healthcare programs. They rapidly moved from china to all over the world for just two months (Anderson M, Mckee M, 2020). As it circulated via social interaction, to reduce the distribution percentage, billions were pushed into quarantine. The shutdown was important because, as with past pandemics, including SARS and MARS, researchers needed time to create a vaccine or successful treatment. No pressing approach is definitely in the near future for COVID-19 (CDC, 2020).

For the rapidly increasing number of affected individuals, let alone emerging or poorly developed countries, the first-world healthcare system has struggled to deliver medical services (D, 2020). In most situations, nations insensitive to leadership and officialism are struggling to control the outbreak. The active exchange of any single individual on planet, in the context of exercise, solitude, quarantine, social distancing, enhancing personal cleanliness, and employing personal protective instruments including masks, gloves, and hand sanitizers, has turned strict for the first time in global history to collect COVID-19, deter desirable exhausted health professionals, and allow scholars way to do (Fraser C, Riley S, Anderson RM, Ferguson NM, 2004). Thousands of millions have lost Their freedom, jobs, career, leisure, and education. Nevertheless, due to shifting awareness, perceptions, and procedures, securing willing involvement in COVID-19 prohibitions policies has faced numerous countries (KAP). Therefore, the resolution and effectiveness of anti-contagion interventions depend on the macro-and micro-level perception of KAP in the regions involved and within each community.

1.2 Epidemic Prevention

In this part, some background of the epidemic, epidemic model, and classification of the epidemic model are given.

1.2.1 History of The Epidemic

The record of outbreaks dates back decades, and their related human morbidity and mortality was a problem for many millennia (WHO, 2005). It has been reported that 25 million Europeans perished from the Bubonic plague throughout the 14th century, comprising 30-60 percent of the whole populace. Approximately half of the Aztec population reportedly died from smallpox during the year 1520, and around 150 years afterward, 68,000 deaths occurred from the plague outbreak in London. Another 2.5 million are believed to have been killed since World War 1 by Typhus in Russia. It is believed that about 20 million deaths were reported from worldwide influenza outbreaks during that time. (R. Anderson, R. May R, 1991). The importance of clinical study has long been recognized in the area of epidemiology (J.A.P. Heesterbeek, M.G. Roberts, 2015). In specific, with the 'germ theory of disease' growth. This definition explains that microorganisms (pathogens) trigger certain illnesses, and the circumstances they develop are considered infectious diseases. Mathematical simulation of epidemiology has a long tradition as well. (R. Anderson, R. May R, 1991). Numerous mathematical epidemiology developments led to general information available, improved understanding of disease spreading advances in medicine and computer programming (J.A.P. Heesterbeek, M.G. Roberts, 2015). Countries consequently started to take advantage of recognizing disease outbreaks to global surveillance systems (P. Yan, H. Chen, D. Zeng, 2008). Over the years, protocols and incentive vaccine systems have been developed to discourage or monitor widespread transmission (J.S. Nguyen-Van-Tama, A.W. Hampson, 2003). To improve vaccination rates in different communities (T. Jefferson, C. Di Pietrantonj, L.A. Al-Ansary, E. Ferroni, S. Thorning, R.E. Thomas, 2010). In the middle of such advances in the epidemiological sector, due to the ongoing occurrences of specific influenza viruses impacting diverse populations, there is still space for significant development to understand disease transmission better (C.R. Simpson, N. Lone, J. McMenamin, R. Gunson, C. Robertson, L.D. Ritchie, A.Sheikh, 2015). Influenza diseases have severe health issues, like physical disease or death, pose a risk to individuals with poor immune systems (Cassar, 1965). These consequences result in a substantial workload on the health and wellbeing states. (J.F.

Bishop, M.P. Murnane, R. Owen, 2009). This demonstrates the central role and growing influence of mathematical modeling in epidemiology in forecasting and projecting societies' future state and, most notably, in quantifying the variability in these expectations (Keeling, 2009). This, in essence, advises public health decision about the risk of an epidemic of an infectious illness, how the epidemic can occur, and how it could be managed (Woolhouse, 2011).

1.2.2 Epidemiology Study

Epidemiology is the study of how many times diseases occur in diverse groups of people and why. Epidemiological information is used to plan and assess strategies to prevent illness and evidence from managing patients whom the disease has already developed (D.Coggon, 2003).

1.2.3 Epidemic Models

Under the presumption that the observational population can be separated into many subsets, named compartments, and pandemics' mathematical models are developed. Kermack and McKendrick described the simplest compartmental models in 1927 (C.R. Simpson, N. Lone, J. McMenamin, R. Gunson, C. Robertson, L.D. Ritchie, 2015). In its modern formulation, the Kermack-McKendrick Model (M.I. Meltzer, N.J. Cox, K. Fukuda,, 1999). The overall flow between the multiple compartments is based on reasonably basic assumptions. It uses a delay time and a generalized mode of dissemination to model the transmission of infectious diseases. The SIR and SEIR models explain nonlinear transmission. The impact of immunity from re-infection is included in these models. This indicates that there is a flow of persons from the vulnerable class "S" via the exposed "E" to the infected " I." Upon exposure, individuals join the group "R," meaning that they are excluded from the community of concern through demise or through immunity. This model underlies several theories. The population is believed to be huge and closed, for example. Natural births and deaths during diseases are therefore not taken into account. The lack of a delay cycle (individuals remain infectious as soon as they become infected). lifelong immunity following regeneration and homogeneous mixture are other

simplifications (L. Temime, G. Hejblum, M. Setbon, A.J. Valleron , 2008).

1.2.4 Classifications of Epidemic Model

When research models, the categories of models it is so helpful to identify. It is easy to show some of their fundamental principles to the individual model if classified into different categories (Daniel Lawson and Glenn Marion, 2015). the model that represents a situation where uncertainty is present is said a stochastic model. In other words, the model that has some random operation. The name stochastic comes from the Greek word stokhazesthai, meaning to aim or guess. In the real world, uncertainty is a part of everyday life, so that a stochastic model could represent anything. Deterministic is the opposite of random. They can be used to find some future event accurately, without the involvement of randomness. If some object is deterministic, you have all of the data necessary to predict the outcome with certainty (stephanie, 2013).

1.3 Type of Model

This section gives information about the model, scientific model, mathematic model, and SIR model with the next-generation matrix's basic reproduction number.

1.3.1 Scientific Model

When you hear the word 'model,' what is the first thing that comes to mind? Maybe the beautiful girls on the stage dressing in very nice clothes. So, what is a model? Unfortunately, a model is a bit more abstract, which is the seed scientific model. A scientific model represents a particular phenomenon in the world using something else to describe it, making it easier to know. A scientific model could be anything, a graph or a physical model, or complex mathematics set that. Whatever it is, the aim is to make the particular thing you are modelling easier to understand. We can use it to prophesy. When we do that, we can forecast what will

happen in the next step-for example, predicting what will happen when a complex generation of the epidemic virus becomes? It gets simple to make a fully careful model of all viruses come before (Wood, 2017).

1.3.2 Mathematical Modelling

Models create assumptions about the goal of the planet. We transform such values into the vocabulary of mathematics in mathematical modeling. This has multiple benefits.

1) Mathematics is a very specific language. This encourages one to articulate thoughts and describe fundamental assumptions.
2) Mathematics is a simplified vocabulary of manipulation techniques with well-defined concepts.
3) It can be used at any time for all outcomes that are proven by mathematics.
4) Computers may be configured for computational simulations to conduct (Daniel Lawson and Glenn Marion, 2015).

1.3.3 The SIR Model

Mathematical models are easily showing how infection across the population over time. In general, the endemic model is based on dividing the population into different categories. Mathematical models are the impersonation of infection spreads in the inhabitance throw time. Each is containing individuals that are identical in terms of their status concerning the disease in question. In the SIR model, the three rooms are:

1) Susceptible (S): The class of individuals who are susceptible to infection; this can include all population, especially the people, have weak immune.
2) Infected (I): In this class, the level of a deadhead is sufficiently large within the host, and there is the possibility of transmitting the infection to other people.
3) Recovered or Resistant (R): This class contains all people who have been infected

and recovered.

The total population size is considered constant, i.e., $N = S + I + R$ (Rodrigues, 2016).

$$\frac{dS}{dt} = -\alpha SI$$

$$\frac{dI}{dt} = \alpha SI - \lambda I \qquad (1.1)$$

$$\frac{dR}{dt} = \lambda I$$

Here α is the rate of infection and λ is the rate of removal.

1.3.4 The Basic Reproductive Number, R_0

The next-generation matrix G in which the ij^{th} G is the expected number of secondary infections of type 1 caused by a single infection individual of type j assuming that the population of type 1 is completely susceptible. Furthermore, the basic reproduction number is defined as the dominant eigenvalue of the new generation matrix G:

$$G = FV^{-1}, F = \left[\frac{\partial f_{i(x0)}}{\partial x_j}\right], V = \left[\frac{\partial v_{i(x0)}}{\partial x_j}\right]$$

where,

f_i are new infection,

v_i are transferred infection from one compartment to another,

x_0 is the disease-free equilibrium state.

The specific reproduction number, R_0, is described as the predicted number of secondary instances in a fully susceptible population created by a single (typical) infection. It is a prophecy that R_0 should be remembered. It is a dimensionless number and it is not a proportion that will have time, e_{-1}. Some journalists wrongly name R_0 as the "basic

reproductive ratio." To assist us to quantify it, we can utilize the fact that "R_0" is a dimensionless number."

$$R_0 \propto \left(\frac{infection}{contact}\right) \times \left(\frac{contact}{time}\right) \times \left(\frac{time}{infection}\right).$$

More specifically: $R_0 = ICT,$

where I is the transmissibility (i.e., probability of infection given to contact between a susceptible and infected individual), C is the average rate of contact between susceptible and infected individuals, and T is the duration of infectiousness (Jones, 2007).

1.4 Mathematical Tool

The mathematical instruments, concepts, and theorems utilized analytically in this study are discussed in this section.

1.4.1 Local Stability Analysis

Considering the preceding system, which contains of n n-dimensional first-order independent differential equations

$$\left.\begin{aligned} \frac{dx_1}{dt} &= F_1(x_1, x_2, \dots, x_n); \\ \frac{dx_2}{dt} &= F_2(x_1, x_2, \dots, x_n); \\ &\vdots \\ \frac{dx_n}{dt} &= F_n(x_1, x_2, \dots, x_n); \end{aligned}\right\} \Longrightarrow x' = F(x), \qquad (1.2)$$

where $x = (x_1, x_2, \dots, x_n) \in R^n$ and $F = (F_1, F_2, \dots, F_n)^T \in R^n$. The non-linear functions $F_i = i = 1,2, \dots, n$ are continuously differentiable functions defined on $U \subseteq R$.

Moreover, before explaining the linearization procedure for equation, some basic definitions needed to study the system's stability (1.2) are presented.

1.4.1.1 Definition

A point $x^* = (x_1^*, x_2^*, \dots, x_n^*)$ is supposed to be the equilibrium point (or a steady fixed point) of the system (1.2) if it satisfies the subsequent equations $F_i(x^*) = 0;\ \forall\ i = 1,2, \dots, n$.

1.4.1.2 Definition

An equilibrium point x^* of the system (1.2) is said to be stable if for any $\varepsilon < 0$, there exist $\delta = \delta(\varepsilon) > 0$ such that if $\|x(0) - x^*\| < \delta$, then $\|\vartheta(t, x(0) - x^*\| < \varepsilon$ for all $t \geq 0$. Here $\vartheta(t, x(0))$ represents the solution of system (1.2) at a time t that started of $x(0)$. If besides, $\|\vartheta(t, x(0) - x^*\| \longrightarrow 0$ as $t \to 0$ for all $\|x(0) - x^*\|$ sufficiently small, then the equilibrium point x^* is said it to be asymptotically stable. The equilibrium point that is not stable is said to be unstable.

1.4.1.3 Definition

An equilibrium point x^* The system (1.2) is globally asymptotically stable if it is asymptotically stable for any initial point $(0) \in R$.

1.4.1.4 Definition

Let x^* Be an equilibrium point of the system (1.2). then x^* is called a hyperbolic equilibrium point if some of the eigenvalue of $J = dF(x^*)$ has zero areal part. Otherwise, it is a non-hyperbolic equilibrium point.

Note that according to the above argument, the following classification of an equilibrium point x^* Of the system (1.2) can be made.

(A) A saddle Point: A hyperbolic equilibrium point of a vector field given by Eq. (1.2) termed a saddle point if some, but not all, of the eigenvalues of $J = dF(x^*)$, have positive real parts, and the rest of the eigenvalues have genuine negative parts.

(B) A stable Node (sink): If all the eigenvalues of $J = dF\ (x^*)$ have negative real parts, then the hyperbolic equilibrium point, is called a stable node or sink.

(C) Unstable Node (source): If all the eigenvalues of $J = dF\ (x^*)$ have positive real parts, then the hyperbolic equilibrium point, is called an unstable node or source.

(D) Center: if all the eigenvalues of $J = dF\ (x^*)$ are purely imaginary and non-zero, then the non-hyperbolic equilibrium point is called a center (Henry, 1994).

1.4.2 Lyapunov Method

The mechanism of Lyapunov is an effective tool for evaluating the equilibrium of the stability or unitability of nonlinear systems. In addition, zero and infinite dimensions' work; the fundamental concept of this technique is as follows.

Suppose that a vector field (1) exists with an equilibrium point x, then determining whether x is stable, it is sufficient to find a neighborhood N of X for which the orbits starting in N remain in N for all positive time. This condition would be satisfied if it can be shown that the vector field is either tangent to the boundary of N or pointing inward towards X. This situation should also remain true even as N is shrunk down onto X. Notice that the Lyapunov process understands how this condition is illustrated. The general theorem for the stabilization of an equilibrium point thus describes these principles in the following theorem (PARKS, A. M. Lyapunov's stability theory—100 years on, 1992).

Theorem 1.1 (Lyapunov Stability Theorem).

Let X be an equilibrium point of system (1) and let $L: N \rightarrow R$ be a C real-valued function defined on some neighborhoods N of X ($N \subseteq R^n$) such that:

1. $L(x) = 0$ and $L(x) > 0$ for all $x \in N$, $x \neq X$ (that means L is a positive definite function).
2. $\frac{d}{dt} L(x) > 0$ in $N - \{X\}$, then X is stable.
3. $\frac{d}{dt}(x) < 0$ in $N - \{X\}$, then X is asymptotically stable.

Note that the function L provided above is recognized as the function Lyapunov (weak function Lyapunov) if and only if the assumptions (1) and (2) hold. On the other hand, the Lyapunov function (strong Lyapunov function) is strictly understood if and only if conditions (1) and (3) have it. Besides, when it is possible to choose N to be all of R_n, then X is said to be worldwide asymptotically constant if conditions (1) and (3) hold (PARKS, 1992).

1.4.2.1 Definition

A scaler function $V(x)$ in any domain D, is a Lyapunov function for nay dynamic system $x = F(x)$ if its continuous and there exist a $\delta > 0$ such that for any $x \in D$,

1. $V(x)$ has a positive defined function about x,
2. $V(x)$ has continuous partial derivative,
3. $V(x)$ is a negative semi-defined.

1.4.2.2 Definition

Let

$$x^{\cdot} = f(x), \ f(0) = 0. \qquad (1.3)$$

A set $M \subseteq R^n$ is said to be

- an invariant set concerning (1.3) if $x(0) \in M \Longrightarrow x(t) \in M, \bigvee t \in R$.
- a positively invariant set concerning if: $x(0) \in M \Longrightarrow x(t) \in M, \bigvee t \geq 0$.

Theorem 1.2 (LaSalle's Theorem).

Let $\Omega \subset D \subset R^n$ be a compact, positively invariant set for the system dynamics (1.3). Let $V:$ $D \rightarrow R$ be a continuously differentiable function such that $V\big(x(t)\big) \leq 0$ in Ω. Let $E \subset \Omega$ be the set of all points in Ω where $V(x) = 0$. Let $M \subset E$ be the largest invariant set in E. Then any solution starts in the Ω approaches M as $t \rightarrow \infty$, that is

$$\lim_{t\to\infty}(\inf\|x(t) - z\|) = 0, \text{ where } \inf\|x(t) - z\| = dist\ (x(t), M).$$

1.4.3 Jacobian Matrix

Generally, any $f: R^m \rightarrow R^n$ is defined by n coordinate functions $f_1, f_2, \ldots, f_n$ and we write

$$f = \begin{pmatrix} \mathrm{f}_1\ (x_1, \ldots x_m) \\ \mathrm{f}_2\ (x_1, \ldots x_m) \\ \vdots \\ \mathrm{f}_\mathrm{n}\ (x_1, \ldots x_m) \end{pmatrix}. \qquad (1.4)$$

Then, our first issue is how we interpret the derivative of several variables as a vector-valued function. Recall that if $f: R^2 \rightarrow R$, then we can form the directional product, i.e.,

$$D_u f = u_1 \frac{\partial f}{\partial x} + u_2 \frac{\partial f}{\partial y} = \nabla f \times u,$$

where $u = (u_1, u_2)$ is a unit vector. Thus, knowledge of the gradient of (f) provides all directional derivatives details. It is rational, thus, to presume

$$\nabla_\mathrm{p} f = \left(\frac{\partial f}{\partial x}\ (\mathrm{p}), \frac{\partial f}{\partial y}\ (\mathrm{p})\right)$$

is the derivative of $(f)\ at\ (p)$. (The story is more complicated than this, but when we say f is differentiable, we mean ∇f represents the derivative, to be discussed a little later). More generally, if $f: R^m \rightarrow R$, then we take the derivative at (p) to be the row vector

$$\left(\frac{\partial f}{\partial x1}\ (\mathrm{p}), \frac{\partial f}{\partial x2}\ (\mathrm{p}), \ldots, \frac{\partial f}{\partial xm}\ (\mathrm{p})\right) = \nabla_{\mathrm{p}} f.$$

Now take $f: R^m \rightarrow R^n$ where f is as in equation (1.4), then the natural candidate for the derivative of $f\ at\ p$ is

$$Jpf = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \ldots & \frac{\partial f_1}{\partial x_m} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \ldots & \frac{\partial f_2}{\partial x_m} \\ \vdots & & & \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \ldots & \frac{\partial f_n}{\partial x_m} \end{pmatrix}, \qquad (1.5)$$

where the partial derivatives are evaluated $at\ p$. This $n \times m$ matrix is termed the Jacobian matrix of (f). Writing the function f as a column assists us get the Jacobian matrix rows and columns the right way. Note the Jacobian is generally the determinant of this matrix when the matrix is square, i.e., when $m = n$ (Tisdell, 2011).

Theorem 1.3 (Stability of Nonlinear Systems).

Consider the system

$$x'(t) = f(x, y), \quad y'(t) = g(x, y),$$

where f, g is differentiable with continuous partial derivatives, and they both disappear at the point (x_0, y_0). Let J denote the Jacobian matrix at that point, namely

$$J = \begin{pmatrix} f_x(x_0, y_0) & f_y(x_0, y_0) \\ g_x(x_0, y_0) & g_y(x_0, y_0) \end{pmatrix}.$$

If all eigenvalues of (J) have a negative real part, then (x_0, y_0) is asymptotically stable. And if some eigenvalue of (J) has a positive real part, then (x_0, y_0) is unstable.

Remark 1.1

This theorem provides no conclusions in the case that some eigenvalue of J has zero real part. Should that case arise, stability can be determined either by finding a Lyapunov function for the system or else by explicitly solving the method.

1.5 Sensitivity Analysis

(H.S.rodrigues, monteiro,torres, 2013), the normalized forward sensitivity index of R_0 that depended differentiable on parameter P is defined by

$$Y_P^{R_0} = \frac{\partial R_0}{\partial P} \times \frac{P}{R_0}.$$

For mathematical models, sensitivity analysis is highly significant. The variance of a model's outputs induced by differences in the inputs is analyzed by sensitivity analysis. Sensitivity analysis basically defines the parameters, and initial conditions (inputs) influence the model's quantities of interest (outputs) the most (Francesca,Keith,Jim, 2016). The first explanation for this study's significance is that it shows the researcher which parameters merit the most numerical consideration. As a small difference in that parameter can result in significant quantitative changes to the volume of interest and yield qualitatively different outcomes, a highly sensitive parameter should be meticulously planned. Qualitative changes to an amount of interest fall under the scope of bifurcation theory and will not be explored in great detail here (M. Teresa. Monteiro,Delfim , 2013).

An insensitive parameter, on the other hand, does not take as much work to measure. A slight difference in the parameter would not cause a significant amount of concern to shift. In model

analysis, the most sensitive parameters are often the most well-established, since they do not alter much from one time to the next. The second explanation for sensitivity analysis is more pronounced if this is the case (Keith, Jim f.,Jim w., 2016). That is, sensitivity analysis highlights which parameters should be attacked in management strategies. One purpose of mathematical modeling is to decide what a system's current result could be, and to figure out how to adjust any detrimental results if appropriate. Adjusting the most sensitive parameters' values would be the most powerful technique for modifying the effects of the model. The model will then implement any applicable real-world scenarios that will change the most sensitive parameter values to obtain the most control over the outcome (Edmundas,Zenonas,Titas, 2007)

CHAPTER 2

SENSITIVITY ANALYSIS WITHOUT VACCINATION

We have analyzed an outbreak model of (Covid-19) with one strain liner in this chapter. The model contains two equilibrium points; disease-free equilibrium point and endemic equilibrium point.

Using the Jacobian matrix, we found eigenvalues to show the global asymptotically stability for both the equilibrium points. The basic reproduction number, R_0, is found by applying the next generation matrix to demonstrate that the outbreak dies out if it is less than one, and if it is more than one, an outbreak happens.

In final, to support the analytic results, the numerical simulation was carried out, and the sensitivity analysis was used to show each parameter's effect on the pandemic.

2.1 Model without Vaccine for Covid-19

We considered a framework for (Covid-19) in this section, (Figure 2.1). The population $N(t)$ is divided into three compartments, which are $S(t)$, $I(t)$, and $R(t)$ that denotes the population of susceptible, infected, and recovered individuals, respectively.

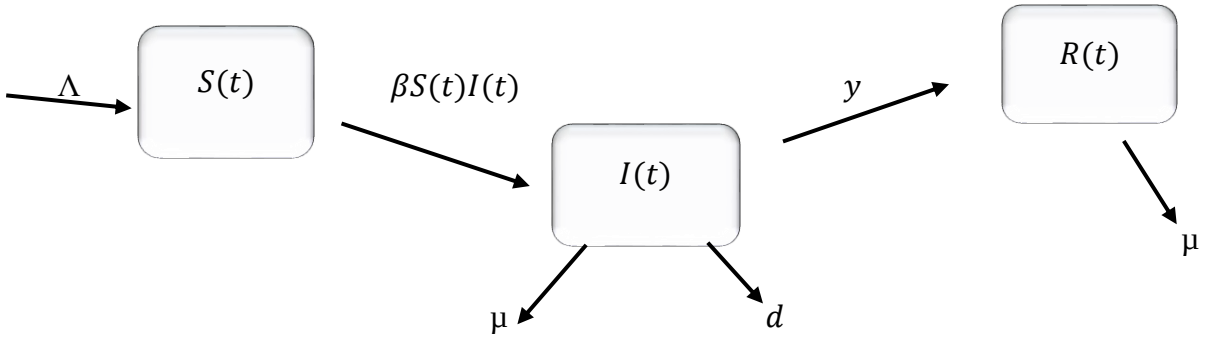

Figure 2.1: Transfer diagram of the model.

With using Figure (2.1) and with the following assumptions,

1. The population is fixed,
2. The natural birth and death rate are included in the model,
3. All birth is for susceptible class only,

the system of ordinary differential equations is obtained. Parameters are explained in Table 2.1.

$$\frac{dS(t)}{dt} = \Lambda - (\beta I(t) + \mu)S(t),$$

$$\frac{dI(t)}{dt} = \beta I(t)S(t) - (\mu + y + d)I(t), \qquad (2.1)$$

$$\frac{dR(t)}{dt} = \mu I(t) - d R(t).$$

Table 2.1: Describes the variable and the parameter of the model (2.2).

Parameters	**Descriptions**
Λ	The recruitment rate of individual
B	The transmission coefficient of susceptible to the infection compartment
d	The death rate from the disease
$\frac{1}{\mu}$	Average time of life expanding
$\frac{1}{y}$	Average infection period

2.2 Mathematical Analysis

Since $N = \mathrm{S} + \mathrm{I} + \mathrm{R}$,

$$\begin{aligned} N'(t) &= \frac{dS}{dt} + \frac{d\mathrm{I}}{dt} + \frac{dR}{dt} \\ &= \Lambda - (\beta\,\mathrm{I}(t) + \mu)\mathrm{S}(t) + \beta\,\mathrm{I}(t)\mathrm{S}(t) - (\mu + \mathrm{y} + \mathrm{d})\mathrm{I}(t) \\ &+ \mathrm{y}\,\mathrm{I}(t) - \mu\mathrm{R}(t) - \mu\mathrm{S}(t) - (\mu + \mathrm{d})\mathrm{I}(t) - \mu\mathrm{R}(t) \\ &\leq \Lambda - \mu\mathrm{N}(t), \end{aligned}$$

then,

$$\frac{dN}{dt} = \Lambda - \mu\mathrm{N}.$$

Hence, the general solution is obtained as

$$N(t) = \frac{\Lambda}{\mu} + \mathrm{c}\,\mathrm{e} - \mu\,\mathrm{t},$$

thus,

$$\lim_{t\to\infty} sup\,(S + I + R) \leq \frac{\Lambda}{\mu}.$$

The feasible region for (2.1) is,

$$\pi = \{(S + I + R): S + I + R \leq \Lambda, S(t) > 0, I(t) \geq 0, R(t) \geq 0\},$$

Therefore, in the system (2.1), instead of $R(t)$, it can be written, $N(t) - S(t) - I(t)$. Then it is enough to study with the following system,

$$\begin{aligned} \frac{dS(t)}{dt} &= \Lambda - (\beta\, I(t) + \mu)S(t), \\ \frac{dI(t)}{dt} &= \beta\, I(t)S(t) - (\mu + y + d)I(t). \end{aligned} \qquad (2.3)$$

2.2.1 Equilibria Point

To detect the equilibrium points of the system (2.3), each equation is equalized to zero as follows:

$$\Lambda - (\beta\, I(t) + \mu)\, S(t) = 0, \tag{2.4}$$

$$\beta\, I(t)\, S(t) - (\mu + y + d)\, I(t) = 0. \tag{2.5}$$

Then, we have two biologically equilibrium points;

For disease free equilibrium point, $I(t) = 0$,

$$\Lambda - \mu\, S(t) = 0 \implies S(t) = \frac{\Lambda}{\mu}.$$

for endemic equilibrium point $I(t) \neq 0$,

$$\Lambda - (\beta\, I(t) + \mu) S(t) = 0 \implies S(t) = \frac{\Lambda}{\beta\, I(t) + \mu}. \tag{2.6}$$

If put (2.5) in (2.6) we get,

$$\beta\, I(t) \frac{\Lambda}{\beta\, I(t) + \mu} - (\mu + y + d)\, I(t) = 0,$$

$$\left[\beta \frac{\Lambda}{\beta\, I(t) + \mu} - (\mu + y + d)\right] I(t) = 0.$$

$$I(t) = 0 \qquad \text{or} \qquad \beta \frac{\Lambda}{\beta\, I(t) + \mu} - (\mu + y + d) = 0.$$

Since,

$$I(t) \neq 0 \implies \frac{\beta\Lambda}{\beta\, I(t) + \mu} - (\mu + y + d) = 0,$$

$$(\beta\, I(t) + \mu)(\mu + y + d) = \beta\Lambda,$$

$$I(t) = \frac{\Lambda}{\mu + y + d} - \frac{\mu}{\beta}.$$

By using the above calculations, the below two equilibrium points have been acquired:

i) disease-free equilibria point $E_0 = (S_0, I_0) = \left(\frac{\Lambda}{\mu}, 0\right)$

ii) the endemic equilibrium point $E_1 = (S^*, I^*) = \left(\frac{\mu + y + d}{\beta}, \frac{\Lambda}{\mu + y + d} - \frac{\mu}{\beta}\right)$.

Since E_0 is always positive for the equilibrium point (biologically), we only need to show endemic equilibrium is greater than or equal to zero. The first coordinate of the endemic equilibrium,

$$S^* = \frac{\mu + y + d}{\beta}$$

which is always positive. For the existence of the second coordinate, I^* must be greater than zero, that means

$$I^* = \frac{\Lambda}{\mu + y + d} - \frac{\mu}{\beta} > 0.$$

Therefore,

$$\frac{\Lambda}{\mu + y + d} \geq \frac{\mu}{\beta}.$$

Hence the endemic equilibria exist if,

$$\frac{\Lambda\beta}{\mu(\mu + y + d)} \geq 1.$$

2.2.2 Basic Reproduction Number

This can be described as the number of secondary infections in a fully susceptible population induced by an infected person. Here, we utilize matrix approach of the next generation to test it.

Let

$$\mathrm{F} = \begin{bmatrix} 0 \\ \beta\, \mathrm{S(t)I(t)} \end{bmatrix}, V = \begin{bmatrix} -\Lambda + (\beta\, \mathrm{I(t)} + \mu)\, \mathrm{S(t)} \\ (\mu + \mathrm{y} + \mathrm{d})\, \mathrm{I(t)} \end{bmatrix}$$

$$\partial \mathrm{F} = \begin{bmatrix} 0 & 0 \\ \beta\, \mathrm{I(t)} & \beta\, \mathrm{S(t)} \end{bmatrix}, \quad \partial \mathrm{V} = \begin{bmatrix} \beta\, \mathrm{I(t)} + \mu & \beta\, \mathrm{S(t)} \\ 0 & \mu + \mathrm{y} + \mathrm{d} \end{bmatrix}$$

$$\partial \mathrm{F}(E_0) = \begin{bmatrix} 0 & 0 \\ 0 & \beta \frac{\Lambda}{\mu} \end{bmatrix}, \ \partial \mathrm{V}(E_0) = \begin{bmatrix} d\mu & \beta \frac{\Lambda}{\mu} \\ 0 & \mu + \mathrm{y} + \mathrm{d} \end{bmatrix}$$

$$V^{-1} = \frac{1}{\det V} \times adj\, V$$

$$\mathrm{V}^{-1} = \frac{1}{\mathrm{d}(\,\mu + \mathrm{d})} \begin{bmatrix} \mu + \mathrm{y} + \mathrm{d} & -\beta \frac{\Lambda}{\mu} \\ 0 & \mathrm{d} \end{bmatrix} = \begin{bmatrix} \frac{1}{d\mu} & \frac{-\beta\Lambda}{\mu(\,\mu + \mathrm{y} + \mathrm{d})} \\ 0 & \frac{1}{\mu + \mathrm{y} + \mathrm{d}} \end{bmatrix}$$

the basic reproduction number is the spectrum of the $FV^{-1}, G = FV^{-1}$.

$$G = F\, V^{-1} = \begin{bmatrix} 0 & 0 \\ 0 & \beta \frac{\Lambda}{\mu} \end{bmatrix} \begin{bmatrix} \frac{1}{d} & \frac{-\beta\Lambda}{\mu^2(\mu + \mathrm{d})} \\ 0 & \frac{1}{\mu + \mathrm{y} + \mathrm{d}} \end{bmatrix} = \begin{bmatrix} 0 & 0 \\ 0 & \frac{\beta\Lambda}{\mu(\mu + \mathrm{y} + \mathrm{d})} \end{bmatrix}$$

The Jacobian matrix of (G) will be

$$R_{01} = \frac{\beta\Lambda}{\mu(\mu + \mathrm{y} + \mathrm{d})}. \qquad (2.7)$$

2.3 Stable Analysis

Theorem 2.1. The disease-free equilibrium E_0 is locally asymptotically stable.

Proof. Evaluating (2.2) in the Jacobian matrix, we get,

$$J(S,I) = \begin{bmatrix} -\beta\, I(t) - \mu & -\beta\, S(t) \\ \beta\, I(t) & \beta\, S(t) - (\mu + y + d) \end{bmatrix}. \qquad (2.8)$$

Evaluating the disease-free equilibria point E_0 in (2.4) Jacobian matrix we get,

$$J\left(\frac{\Lambda}{\mu}, 0\right) = \begin{bmatrix} -\mu & -\beta\, \frac{\Lambda}{\mu} \\ 0 & \beta\, \frac{\Lambda}{\mu} - (\mu + y + d) \end{bmatrix}.$$

By using the previous Jacobian matrix, the eigenvalues obtained as $\lambda_1 = -\mu$ and $\lambda_2 = \frac{\beta\Lambda}{\mu} - (\mu + y + d)$.

Since $\lambda_1 < 0$, to show that the stability of the disease-free equilibrium E_0, we need to show

$\lambda_2 < 0$,

$\lambda_2 = \frac{\beta\Lambda}{\mu} - (\mu + y + d) = (\mu + y + d)\left(\frac{\beta\Lambda}{\mu(\mu+y+d)} - 1\right) = (\mu + y + d)\,(R_{01} - 1)$.

Since $\lambda_2 < 0$, if $R_{01} < 1$, then both eigenvalues are negative, so the disease-free equilibrium point is locally asymptotically stable.

Furthermore, the global stability condition of $E_0 = \left(\frac{\Lambda}{\mu}, 0\right)$ is established in the Theorem 2.2.

Theorem 2.2. If $R_0 \leq 1$, then the system's disease-free equilibrium point is worldwide asymptotically stable on Ʊ.

Proof. To establish the global stability of disease equilibrium point, we build the below Lyapunov function W: Ʊ $\rightarrow$ R. Then the time derivative of W is

$W'(S,I) = \beta\, I(t)S(t) - (\mu + y + d)I(t)$,

$W'(S,I) = (\mu + y + d)I(t)[R_{01} - 1]$.

Thus, $W'(S,I) \leq 0$ for $R_{01} \leq 1$, further $W'(S,I) = 0$ and if $R_{01} = 1$, then $W'(S, I) = 0$. Hence, by the LaSalle invariance principle, the diseases free equilibrium point is globally asymptotically stable.

Theorem 2.3. The endemic equilibrium E_1 is locally asymptotically stable.

Proof. Evaluating the endemic equilibria point E_1 in (2.4) Jacobian matrix we get,

$$J\left(\frac{\mu+y+d}{\beta}, \frac{\Lambda}{\mu+y+d} - \frac{\mu}{\beta}\right) = \begin{bmatrix} \frac{-\Lambda\beta}{\mu+y+d} & -(\mu+y+d) \\ \frac{\Lambda\beta}{\mu+y+d} - \mu & 0 \end{bmatrix}.$$

By using the previous Jacobian matrix, the eigenvalues obtained from the characteristic equation of the endemic equilibria point

$$\lambda^2 + R_{01}\lambda + d(\mu+y+d)(R_{01}-1) = 0.$$

The root of the above equation or the eigenvalue is,

$$\lambda_{1,2} = \frac{1}{2}\left[-R_{01} \pm \sqrt{R_0^2 - 4d(\mu+y+d)(R_0-1)}\right].$$

Since $4d(\mu+y+d)(R_{01}-1)$ it is positive. The volume under the square root is getting $R_{01}^2 < 4d(\mu+y+d)(R_{01}-1)$ then the eigenvalues are complex with a negative real part. If $R_{01}^2 > 4d(\mu+y+d)(R_{01}-1)$ then the volume under the square root must be smaller than R_0 . We both assume that the endemic equilibrium point is asymptotically stable since the real part of both eigenvalues is negative with one condition, which is under the square root must be smaller than R_{01}.
Furthermore, the global stability condition of $E_0 = (\frac{\mu+y+d}{\beta}, \frac{\Lambda}{\mu+y+d} - \frac{\mu}{\beta})$ is established in the Theorem 2.4.

Theorem 2.4. The endemic equilibrium point $E^*(S^*, I^*)$ is the system is globally asymptotically stable on $\mho$.

Proof. We construct a Lyapunov function

$$L: \mho+ \rightarrow R,$$

where

$$\mho+ = \{S(t), I(t) \in \mho, S(t) > 0, \quad I(t) > 0\}.$$

They are given, where $W1$ and $W2$ are positive constant,

$$L(S,I) = W1\left[(S-S^*)In\left(\frac{S}{S^*}\right)\right] + W2\left[(I-I^*)In\left(\frac{I}{I^*}\right)\right].$$

Then, the time derivative is given by,

$$\frac{dL}{dt} = W_1(S-S^*)\left(\frac{\Lambda}{S} - \beta I - \mu\right) + W_2(I-I^*)(\beta S - (\mu + y + d)),$$

consider the equilibrium point we get $\beta S^* = \mu + y + d$, $\mu = \frac{\Lambda}{S} - \beta I^*$, and

$$\frac{dL}{dt} = \beta(S-S^*)(I-I^*)(W1-W2).$$

For $W1$ and $W2$, if we put the same price, $\frac{dL}{dt} \leq 0$ also if $S = S^*$ and $I = I^*$, $\frac{dL}{dt} = 0$. Hence, by the LaSalle invariance principle, the endemic equilibrium point is globally asymptotically stable.

2.4 Numerical Simulations

The simulation was conducted for the initial state utilizing following value $(S,I) = (471,7)$; the final time was $t = 100$ days. Solved numerically by using the (ode45) solvers in Matlab in a table, and the parameter is given in Table 2.2.

Table 2.2: The value of the parameters in the system (2.2).

Parameters	**Values**
Λ	200
B	0.005
d	0.02
μ	0.002
y	0.69

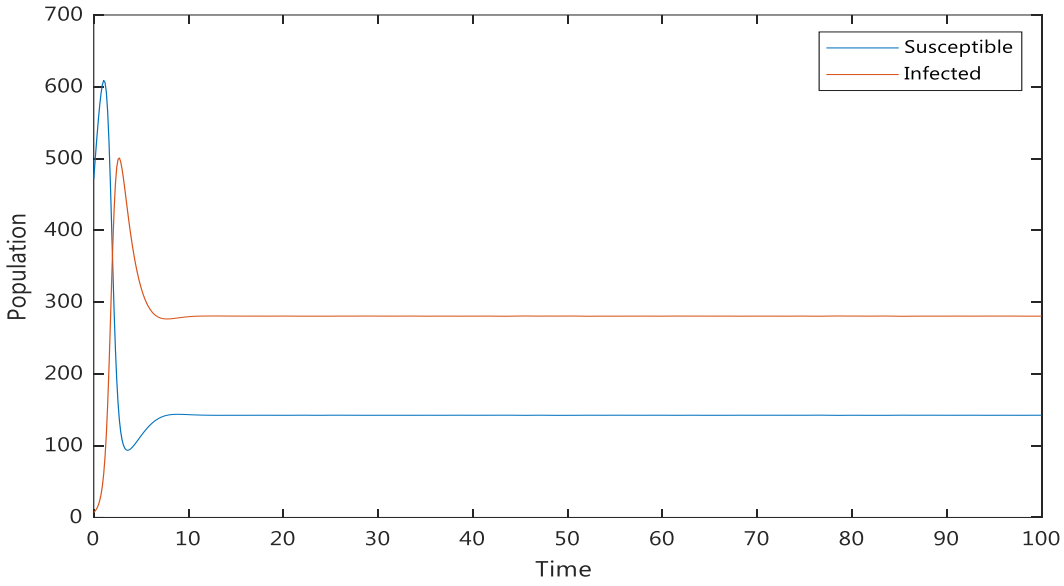

Figure 2.2: State variable of the system (2.1) with initial condition and parameter in Table 2.2.

2.5 Sensitivity Analysis

Give the free formula (2.3) for R_0; a theoretical expression for the sensitivity of R_0 can be conveniently obtained with regard to each parameter in Table 2.1. The values of the parameters obtained are listed in Table 2.2, which displays the sensitivity indices in the last row of the table for the baseline parameter value in Table 2.2.

Take sensitivity for parameter β,

$$Y_{\beta}^{R_0} = \frac{\partial R_0}{\partial \beta} \times \frac{\beta}{R_0} \rightarrow \frac{\Lambda}{\mu(\mu+y+d)} \times \frac{\beta\mu(\mu+y+d)}{\Lambda\beta} = 1.$$

Take sensitivity for parameter Λ,

$$Y_{\Lambda}^{R_0} = \frac{\partial R_0}{\partial \Lambda} \times \frac{\Lambda}{R_0} \rightarrow \frac{\beta}{\mu(\mu+y+d)} \times \frac{\Lambda\mu(\mu+y+d)}{\Lambda\beta} = 1.$$

Take sensitivity for parameter d,

$$Y_{d}^{R_0} = \frac{\partial R_0}{\partial d} \times \frac{d}{R_0} \rightarrow \frac{-\beta \Lambda \mu}{[\mu(\mu+y+d)]^2} \times \frac{d\mu(\mu+y+d)}{\Lambda\beta} = \frac{-d}{\mu+y+d} =$$

$$-0.0280898.$$

Take sensitivity for parameter μ,

$$Y_{\mu}^{R_0} = \frac{\partial R_0}{\partial \mu} \times \frac{\mu}{R_0} \rightarrow \frac{-\beta \Lambda (2\mu+y+d)}{[\mu(\mu+y+d)]^2} \times \frac{\mu^2(\mu+y+d)}{\Lambda\beta} = \frac{-(2\mu+y+d)}{\mu+y+d} =$$

$$-1.00228089.$$

Take sensitivity for parameter y,

$$Y_{y}^{R_0} = \frac{\partial R_0}{\partial y} \times \frac{y}{R_0} \rightarrow \frac{-\beta \Lambda \mu}{[\mu(\mu+y+d)]^2} \times \frac{y\mu(\mu+y+d)}{\Lambda\beta} = \frac{-y}{\mu+y+d} =$$

$$-0.9691011.$$

By using the above calculations, we obtained Table 2.3 as follows.

Table 2.3: Sensitivity indices.

Parameters	**Values**
Λ	1
β	1
d	-0.0280898
μ	-1.0022808
y	-0.9691011

The sensitivity indices are positive and the remaining are negative. Since all indices are the other parameter's function, the sensitivity indices will change with different parameter values.

The most sensitivity parameter for R_0 is the β (Transmission coefficient of $(S)\ to\ (I), \Lambda$ (Recruitment of individual) have the positive sensitivity parameter, $Y_{\Lambda,\beta}^{R_0} = +1$

(see Figure 2.3 and Figure 2.4), which has increased the sensitivity index, then the reproduction number has the same.

The parameter (d, y, μ) has a negative sensitivity index (see figure 2.4,2.5,2.6). Then the average of expanding and rare disease, where those are increasing by 10%, the basic reproduction number is decreasing by 10%.

The most effective variables are Λ and y while the least effectives are μ and d.

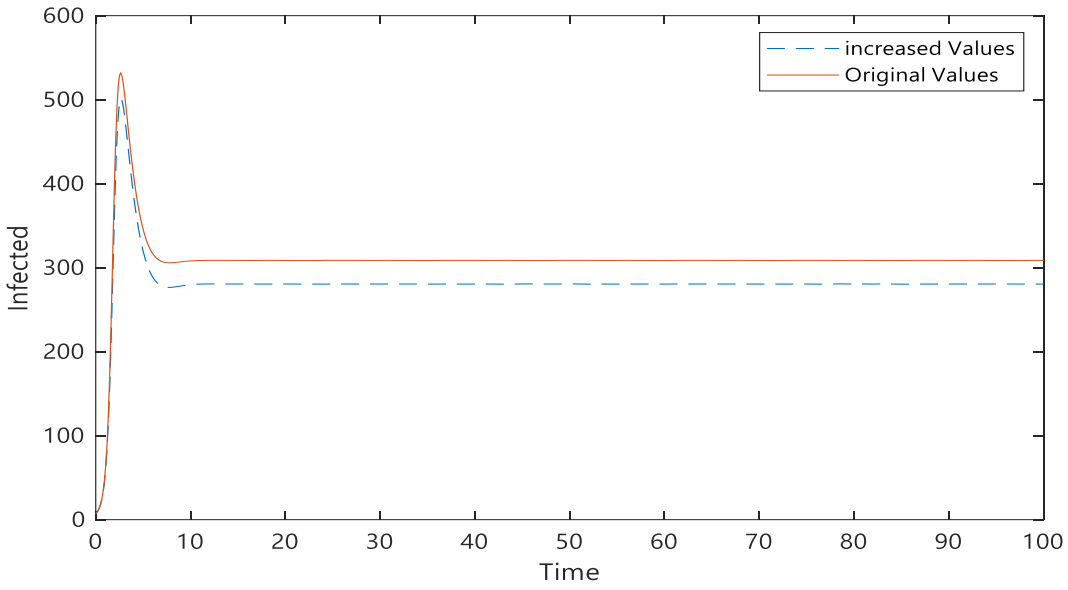

Figure 2.3: Effect on I of the variation of $\Lambda, ;\ \boldsymbol{\Lambda = 220}, \beta = 0.005, d = 0.02, y = 0.69, \mu = 0.002, (S, I) = (471,7)$.

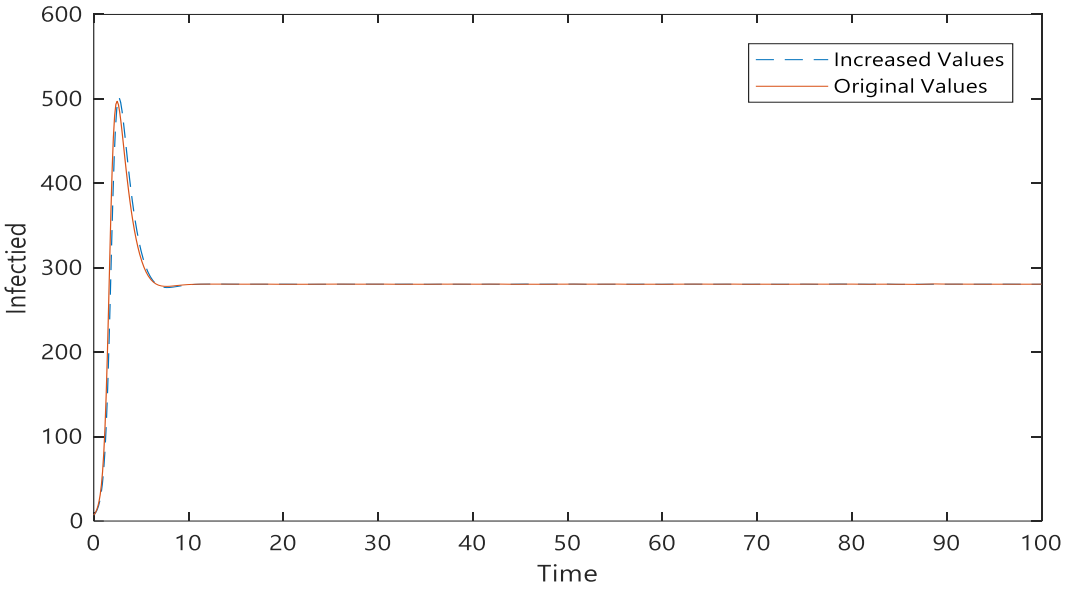

Figure 2.4: Effect on I of the variation of β; $\Lambda = 220, \boldsymbol{\beta} = \mathbf{0.0055}, d = 0.02, y = 0.69, \mu = 0.002, (S, I) = (471,7)$.

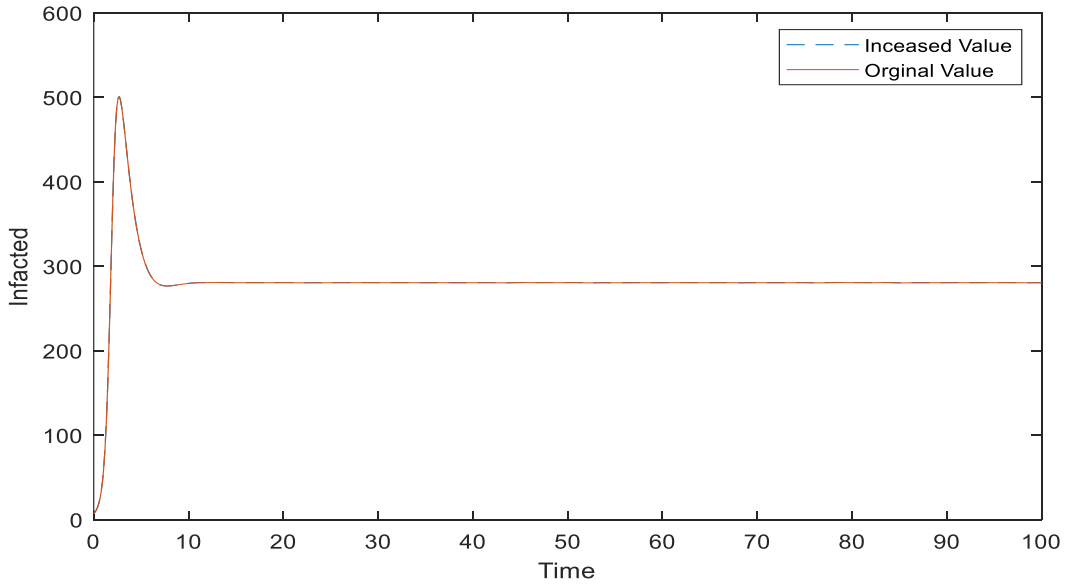

Figure 2.5: Effect on I of the variation of μ; $\Lambda = 200, \beta = 0.005, d = 0.02, y = 0.69, \mu = \mathbf{0.0022}, (S, I) = (471,7)$.

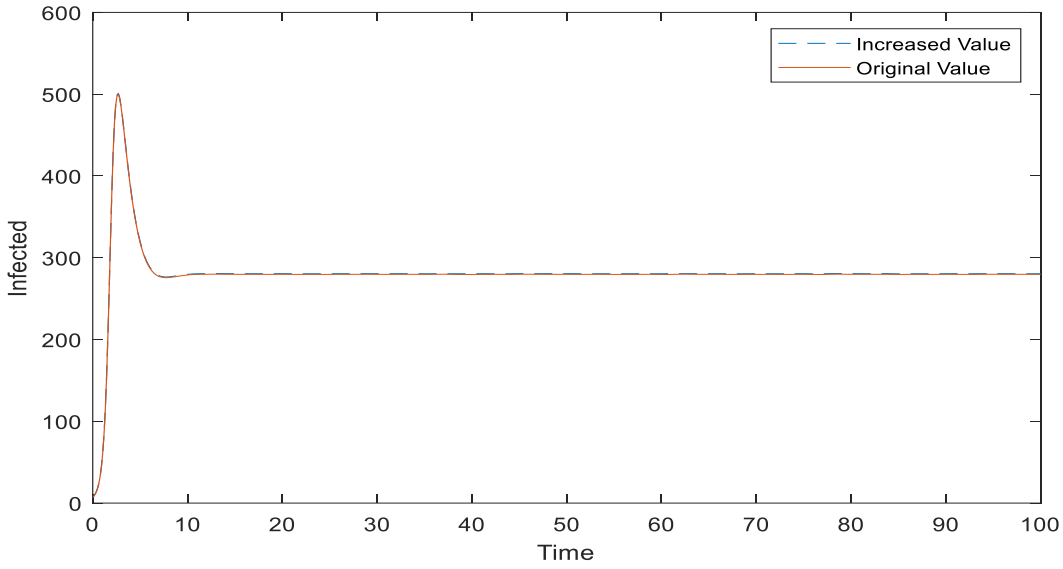

Figure 2.6: Effect on I of the variation of d; $\Lambda = 200, \beta = 0.005, \boldsymbol{d = 0.022}, y = 0.69, \mu = 0.002, (S, I) = (471,7)$.

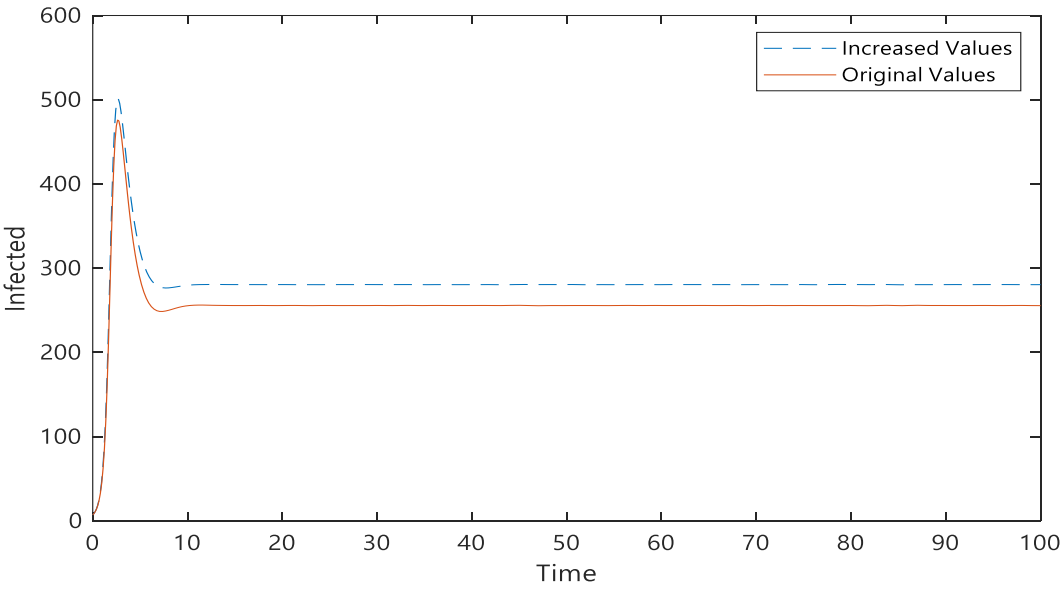

Figure 2.7: Effect on I of the variation of y; $\Lambda = 200, \beta = 0.005, d = 0.02, \boldsymbol{y = 0.759}, \mu = 0.002, (S, I) = (471,7)$.

CHAPTER 3

SENSITIVITY ANALYSIS WITH VACCINATION

We researched an outbreak model of (Covid-19) for one strain liner in this chapter. The model contains two equilibrium points; disease-free equilibrium point and endemic equilibrium point with vaccination influence.

The Jacobian matrix eigenvalue is used to show the global asymptotically stability for both of the equilibrium point. Basic reproduction number, R_0, is found, and we have to prove that the outbreak dies out if there is less than one, and if there is more than one epidemic.

In final, we showed that the numerical simulation was carried out to support the logical result. Furthermore, the reproduction number's sensitivity is used to show the effect of each parameter on the model.

3.1 Model with Vaccine for Covid-19

We considered a framework for Covid-19 in this section, (Figure 3.1). The population $N(t)$ is divided into four compartments, which are $S(t)$, $\mathrm{V(t)}$, $I(t)$, and $R(t)$ that denotes the population of susceptible, vaccinated, infected, and recovered individuals, respectively.

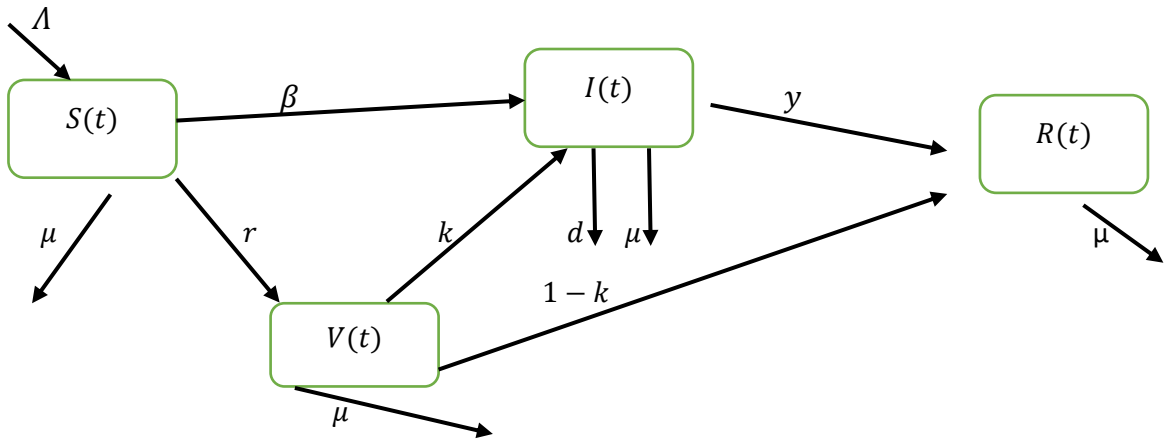

Figure 3.1: Transfer diagram of a model with vaccination.

With using Figure 3.1 and with the following assumptions,

1. The population is fixed,
2. The natural birth and death rate are included in the model,
3. All birth is for susceptible class only,
4. There is no double infection,

we obtained the following system of ordinary differential equation,

$$\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda - (\beta I(t) + r + \mu) S(t), \\
\frac{dV(t)}{dt} &= r S(t) - k I(t)V(t) - (\mu + 1 - k)V(t), \\
\frac{dI(t)}{dt} &= [\beta S(t) + kV(t)]I(t) - (\mu + y + d)I(t), \\
\frac{dR(t)}{dt} &= (1 - k) V(t) + y I(t) - \mu R(t).
\end{aligned} \tag{3.1}$$

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

Parameters	**Description**
Λ	The recruitment rate of individual
B	The transmission coefficient of susceptible to the infection compartment
d	The death rate from the disease
$\frac{1}{\mu}$	Average time of life expanding
$\frac{1}{y}$	Average infection period
r	Rate of vaccination
k	The transmission coefficient of vaccination V to I
$1-k$	The transmission coefficient of vaccination V to R

3.2 Mathematical Analysis

Since,

$$N = S + V + I + R,$$

$$\frac{dN}{dt} = \frac{dS(t)}{dt} + \frac{dV(t)}{dt} + \frac{dI(t)}{dt} + \frac{dR(t)}{dt}.$$

Then,

$$\begin{aligned}\frac{dN}{dt} = {} & \Lambda - (\beta I(t) + r + \mu)S(t) \\ & + [\beta S(t) + kV(t)]I(t) - (\mu + y + d)I(t) + r S \\ & - k I(t)V(t) - (\mu + 1 - k)v(t) + (1 - k)V(t) + y I(t) \\ & - \mu R(t) \leq \Lambda - \mu N.\end{aligned}$$

Therefore,

$$\frac{dN}{dt} = \Lambda - \mu N.$$

Hence, the general solution is obtained as

$$N(t) = \frac{\Lambda}{\mu} + c\, e - \mu\, t.$$

Thus,

$$\lim_{t \to \infty} sup\, N(t) \leq \frac{\Lambda}{\mu}.$$

The feasible region for (3.1) is,

$$\begin{aligned}\pi = \{(S + I + V + R) : {} & S + I + V + R \leq \Lambda, S(t) > 0, V(t) \geq 0, I(t) \\ & \geq 0, R(t) \geq 0\}.\end{aligned}$$

Therefore, in the system (3.1) instead of $R(t)$ it can be written, $N(t) - S(t) - V(t) - I(t)$. So, it is enough to study with the following system,

$$\frac{dS(t)}{dt} = \Lambda - (\beta\, I(t) + r + \mu)S(t),$$
$$\frac{dV(t)}{dt} = r\, S(t) - k\, I(t)V(t) - (\mu + 1 - k)V(t), \quad (3.2)$$
$$\frac{dI(t)}{dt} = [\beta S(t) + kV(t)]\, I(t) - (\mu + y + d)\, I(t).$$

3.2.1 Equilibria Point

To detect the equilibrium point of the system (3.2), each equation is equalized to zero,

$$\Lambda - (\beta\, I(t) + r + \mu)\, S(t) = 0, \quad (3.3)$$
$$r\, S(t) - k\, I(t)\, V(t) - (\mu + 1 - k)\, V(t) = 0, \quad (3.4)$$
$$[\beta S(t) + kV(t)]\, I(t) - (\mu + y + d)\, I(t) = 0. \quad (3.5)$$

Then, biologically we have two equilibrium points, where $\boldsymbol{\alpha} = \mu + \boldsymbol{y} + \boldsymbol{d}$, $\boldsymbol{\delta} = \mu + \boldsymbol{r}$.

For disease free equilibrium point, $I(t) = 0$.

Putting it in equation (3.3) we get,

$$S(t) = \frac{\Lambda}{\mu + r}. \quad (3.6)$$

Putting it in equation (3.3) we get,

$$r\, S(t) - (\mu + 1 - k)\, V(t) = 0.$$

Hence,

$$V(t) = \frac{r\ s(t)}{\mu + 1 - k}. \quad (3.7)$$

Putting equation (3.6) in equation (3.7), we get,

$$V(t) = \frac{\Lambda r}{(\mu + r)\mu + 1 - k}.$$

For endemic equilibrium point $I(t) \neq 0$, we putted it in equation (3.3) and we get,

$$S(t) = \frac{\Lambda}{\beta\, I(t) + \mu + r}. \quad (3.8)$$

Put in equation (3.4) we get,

$$r\,S(t) - [k\,I(t) - (\mu + 1 - k)]\,V(t) = 0.$$

Hence,

$$V(t) = \frac{r\,S(t)}{k\,I(t) - (\mu + 1 - k)}. \tag{3.9}$$

Put in equation (3.5) we get,

$$([\beta\,S(t) + k\,V(t)] - (y + \mu + d))\,I(t) = 0.$$

So, this means either $I(t) = 0$ or $\left([\beta\,S(t) + k\,V(t)] - (y + \mu + d)\right) = 0$.

But we say $I(t) \neq 0$ so,

$$[\beta\,S(t) + k\,V(t)] - (y + \mu + d) = 0, \quad \text{and}$$

$$V(t) = \frac{(y + \mu + d) - \beta\,S(t)}{k} \tag{3.10}$$

Equalizing to (3.8), (3.9) and putting equation (3.6) we get,

$$\frac{\frac{r\Lambda}{\beta\,I(t) + (\mu + r)}}{k\,I(t) - (\mu + 1 - k)} = \frac{(y + \mu + d) - \frac{\beta\Lambda}{\beta\,I(t) + (\mu + r)}}{k}$$

and,

$$\frac{r\Lambda k}{\beta\,I(t) + (\mu + r)} = (y + \mu + d)k\,I(t) - (y + \mu + d)(\mu + 1 - k) - \frac{(y + \mu + d)\beta\Lambda\,k\,I(t) - (\mu + 1 - k)\beta\Lambda}{\beta\,I(t) + (\mu + r)},$$

$$\beta\alpha k\,(I^*)^2 + \left[\alpha\left(k\delta + \beta(\mu + 1 - k)\right) - \beta\Lambda k\right]I^* + \delta(\mu + 1 - k)\alpha - r\Lambda k - \beta\Lambda(\mu + 1 - k) = 0.$$

By using the above calculations, we obtained the followings:

i) Disease-free equilibria point,

$$E_0 = (S_0, V_0, I_0) = \left(\frac{\Lambda}{\mu + r}, \frac{\Lambda r}{(\mu + r)\mu + 1 - k}, 0\right).$$

ii) The endemic equilibrium point

$$E_1 = (S^*, V^*, I^*) = \left(\frac{\Lambda}{\beta I^* + \delta}, \frac{(y + \mu + d) - \beta S(t)}{k}, I^*\right).$$

where I^* is the solution of the following equation,

$$\beta\boldsymbol{\alpha}\, k\, (I^*)^2 + \left[\boldsymbol{\alpha}\left(k\delta + \beta(\mu + 1 - k)\right) - \beta\Lambda k\right]I^* + \delta(\mu + 1 - k)\alpha - r\Lambda k - \beta\Lambda(\mu + 1 - k) = 0.$$

Since E_1 is always positive for the equilibrium point (biologically), we only need to show endemic equilibrium is greater than or equal to zero. The first coordinate of the endemic equilibrium,

$$S^* = \frac{\Lambda}{\beta I^* + \delta}$$

is always positive. For the existence of the second coordinate, I^* must be greater than zero, that means,

$$V^* = \frac{(y + \mu + d) - \beta S(t)}{k}.$$

Hence, exist if $k \geq 0$.

When I^* given by,

$$\beta\boldsymbol{\alpha}\, k\, (I^*)^2 + \left[\boldsymbol{\alpha}\left(k\delta + \beta(\mu + 1 - k)\right) - \beta\Lambda k\right]I^* + \delta\alpha(\mu + 1 - k) - r\Lambda k - \beta\Lambda(\mu + 1 - k) = 0.$$

The solution of I^* can be found with the following formula,

$$I^* = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

here,

$$a = \beta\boldsymbol{\alpha}\, k,$$
$$b = [\boldsymbol{\alpha}(k\delta + \beta(\mu + 1 - k)) - \beta\Lambda k],$$
$$c = \delta(\mu + 1 - k)\alpha - r\Lambda k - \beta\Lambda(\mu + 1 - k).$$

I^* exist if $4ac \leq 0$. Since, $a = \beta\boldsymbol{\alpha}\, k \geq 0$ we only need to satisfy $c \leq 0$,

$$\Longrightarrow c = \delta(\mu + 1 - k)\alpha - r\Lambda k - \beta\Lambda(\mu + 1 - k) \leq 0,$$
$$\Longrightarrow \delta(\mu + 1 - k)\alpha \leq r\Lambda k + \beta\Lambda(\mu + 1 - k),$$
$$\Longrightarrow 1 \leq \frac{\Lambda}{\alpha\delta}\left[\beta + \frac{rk}{\mu + 1 - k}\right].$$

Therefore, I^* exist when,

$1 \leq \frac{\Lambda}{\alpha\delta}\left[\beta + \frac{rk}{\mu + 1 - k}\right]$, $\boldsymbol{\alpha}\big(k\delta + \beta(\mu + 1 - k)\big) > \beta\Lambda k$ and $-b > \sqrt{b^2 - 4ac}$.

3.2.2 Basic Reproduction Number

A fully susceptible population can be described as the number of secondary infections triggered by an infected person. Here, we use the matrix approach of the next generation to test it. Where (F_i) is represents the rate of appearance of new infections into the compartment F_i, V_i represent the rate of transfer output of the i^{th} compartment the rate transfer input of the i^{th} compartment. Where $\boldsymbol{\alpha} = \mu + \boldsymbol{y} + \boldsymbol{d}$, $\boldsymbol{\delta} = \mu + \boldsymbol{r}$.

Let

$$F = \begin{bmatrix} 0 \\ r\,S(t) \\ [\beta S(t) + kV(t)]\,I(t) \end{bmatrix}, V = \begin{bmatrix} -\Lambda + (\beta\, I(t) + \delta)\, S(t) \\ k\, I(t)V(t) + (\mu + 1 - k)\, v(t) \\ \alpha\, I(t) \end{bmatrix}.$$

$$\partial \mathrm{F} = \begin{bmatrix} 0 & 0 & 0 \\ r & 0 & 0 \\ \beta \mathrm{I}(\mathrm{t}) & \mathrm{kI}(\mathrm{t}) & \beta \mathrm{S}(\mathrm{t}) + \mathrm{kV}(\mathrm{t}) \end{bmatrix},$$

$$\partial \mathrm{V} = \begin{bmatrix} \beta \mathrm{I}(\mathrm{t}) + \delta & 0 & \beta \mathrm{S}(\mathrm{t}) \\ 0 & \mathrm{k}\,\mathrm{I}(\mathrm{t}) + (\mu + 1 - \mathrm{k}) & \mathrm{k}\,\mathrm{V}(\mathrm{t}) \\ 0 & 0 & \alpha \end{bmatrix},$$

put free equilibrium point $\left(\frac{\Lambda}{\delta}, \frac{\Lambda \mathrm{r}}{\delta(\mu + 1 - \mathrm{k})}, 0\right)$ in matrix we get,

$$\partial \mathrm{F}\,(\mathrm{E}_0) = \begin{bmatrix} 0 & 0 & 0 \\ r & 0 & 0 \\ 0 & 0 & \beta \frac{\Lambda}{\delta} + \mathrm{k} \frac{\Lambda \mathrm{r}}{\delta\, \alpha} \end{bmatrix},$$

$$\partial \mathrm{V}(\mathrm{E}_0) = \begin{bmatrix} \delta & 0 & \beta \frac{\Lambda}{\delta} \\ 0 & (\mu + 1 - \mathrm{k}) & \mathrm{k} \frac{\Lambda \mathrm{r}}{\delta\, \alpha} \\ 0 & 0 & \alpha \end{bmatrix}.$$

The basic reproduction number is the spectrum of the FV^{-1}. Let $G = FV^{-1}$ and,

$$V^{-1} = \frac{1}{\det V} \times adj\, V$$

take the determinant to $\partial \mathrm{V}(\mathrm{E0})$ we get,

$$det\, V = \delta \begin{bmatrix} \mu + 1 - k & k \frac{r\Lambda}{\lambda(\mu + 1 - k)} \\ 0 & \alpha \end{bmatrix} - 0 \begin{bmatrix} 0 & \beta \frac{\Lambda}{\mu} \\ 0 & \alpha \end{bmatrix} + \beta \frac{\Lambda}{\mu} \begin{bmatrix} 0 & \mu + 1 - k \\ 0 & 0 \end{bmatrix}$$

then,

$$det\, V = \delta\, \alpha\, (\mu + 1 - k), \qquad (3.11)$$

$$adj\ V(E_0) = \begin{bmatrix} +\begin{bmatrix} \mu + 1 - k & k\frac{r\Lambda}{\delta(\mu + 1 - k)} \\ 0 & \alpha \end{bmatrix} & -\begin{bmatrix} 0 & k\frac{r\Lambda}{\delta(\mu + 1 - k)} \\ 0 & \alpha \end{bmatrix} & +\begin{bmatrix} 0 & \mu + 1 - k \\ 0 & 0 \end{bmatrix} \\ -\begin{bmatrix} 0 & \beta\frac{\Lambda}{\mu} \\ 0 & \alpha \end{bmatrix} & +\begin{bmatrix} \lambda & \beta\frac{\Lambda}{\delta} \\ 0 & \alpha \end{bmatrix} & -\begin{bmatrix} \delta & 0 \\ 0 & 0 \end{bmatrix} \\ +\begin{bmatrix} 0 & \beta\frac{\Lambda}{\mu} \\ \mu + 1 - k & k\frac{r\Lambda}{\delta(\mu + 1 - k)} \end{bmatrix} & -\begin{bmatrix} \delta & \beta\frac{\Lambda}{\mu} \\ 0 & k\frac{r\Lambda}{\delta(\mu + 1 - k)} \end{bmatrix} & +\begin{bmatrix} \delta & 0 \\ 0 & \mu + 1 - k \end{bmatrix} \end{bmatrix}$$

$$adj\ V(E_0) = \begin{bmatrix} \alpha(\mu + 1 - k) & 0 & -(\mu + 1 - k)\beta\frac{\Lambda}{\mu} \\ 0 & \delta\alpha & -k\frac{r\Lambda}{(\mu + 1 - k)} \\ 0 & 0 & \delta(\mu + 1 - k) \end{bmatrix},$$

$$V^{-1}(E_0) = \begin{bmatrix} \frac{1}{\delta} & 0 & \beta\frac{\Lambda}{\delta\alpha\mu} \\ 0 & \frac{1}{(\mu + 1 - k)} & -k\frac{r\Lambda}{\delta\alpha(\mu + 1 - k)^3} \\ 0 & 0 & \frac{1}{\alpha} \end{bmatrix}.$$

Then,

$$R_{02} = F\,V^{-1}$$

$$= \begin{bmatrix} 0 & 0 & 0 \\ r & 0 & 0 \\ 0 & 0 & \beta\frac{\Lambda}{\delta} + k\frac{r\Lambda}{\delta(\mu + 1 - k)} \end{bmatrix} \times \begin{bmatrix} \frac{1}{\delta} & 0 & \beta\frac{\Lambda}{\delta\alpha\mu} \\ 0 & \frac{1}{(\mu + 1 - k)} & -k\frac{r\Lambda}{\delta\alpha(\mu + 1 - k)^3} \\ 0 & 0 & \frac{1}{\alpha} \end{bmatrix}$$

$$R_{02} = \frac{\Lambda}{\alpha\delta}\left[\beta + \frac{rk}{\mu + 1 - k}\right].$$

3.3 Stable Analysis

Theorem 3.1. The disease-free equilibrium E_0 is locally asymptotically stable.

Proof. Evaluating the Jacobian matrix, we get,

$$J(S,V,I) = \begin{bmatrix} -\beta I(t) - \delta & 0 & -\beta S(t) \\ r & -kI(t) - (\mu + 1 - k) & -kV(t) \\ \beta I(t) & kI(t) & \beta S(t) + kV(t) - \alpha \end{bmatrix}. \quad (3.4)$$

Evaluating the disease-free equilibria point E_0 in (3.4) Jacobian matrix we get,

$$J\left(\frac{\Lambda}{\delta}, \frac{\Lambda r}{\delta(\mu + 1 - k)}, 0\right) = \begin{bmatrix} -\delta & 0 & \frac{-\beta\Lambda}{\delta} \\ r & -(\mu + 1 - k) & -k\,\frac{\Lambda r}{\delta(\mu + 1 - k)} \\ 0 & 0 & \frac{\beta\Lambda}{\delta} + k\,\frac{\Lambda r}{\delta(\mu + 1 - k)} - \alpha \end{bmatrix}$$

Solving the matrix, those Eigenvalues we arrive,

$$(-\delta - \lambda)\left[(-(\mu + 1 - k) - \lambda)\left(\frac{\beta\Lambda}{\delta} + k\,\frac{\Lambda r}{\delta(\mu + 1 - k)} - \alpha - \lambda\right)\right] = 0.$$

Further solving and simplifying the previous equation, we get,

$$\lambda_1 = -\delta,\ \lambda_2 = -(\mu + 1 - k),\ \lambda_3 = \frac{\beta\Lambda}{\delta} + k\,\frac{\Lambda r}{\delta(\mu + 1 - k)} - \alpha,$$

then $E_0 = \left(\frac{\Lambda}{\delta}, \frac{\Lambda r}{\delta(\mu + 1 - k)}, 0\right)$, is locally asymptotically stable if,

$$R_{02} < 1,$$

furthermore, the global stability condition of $E_0 = \left(\frac{\Lambda}{\delta}, \frac{\Lambda r}{\delta(\mu + 1 - k)}, 0\right)$ is established in the Theorem 3.2.

Theorem 3.2. The global stability of the disease-free equilibrium point of the system is globally asymptotically stable on $\cup$.

Proof. To find the global stability of the disease-free equilibrium point, we construct the following Lyapunov function,

$$W: \text{ʊ} \rightarrow R, W(S, V, I) = S(t) + I(t).$$

Then,

$$W'(S, V, I) = S'(t) + I'^{(t)},$$

$$W'(S, V, I) = \left[\frac{r\Lambda k}{\delta(\mu+1-k)} - (\mu + y + d)\right] I(t),$$

$$W'(S, V, I) = \left[\alpha(R_{02} - 1) - \frac{\beta\Lambda}{\delta}\right] I(t),$$

Thus, if $R_{02} < 1$ then, $W'(S, V, I) = 0$. Hence, if $R_{02} = 1$ then, $W'(S, V, I) \leq 0$ so by LaSalle invariance principle, the disease-free equilibrium point is globally asymptotically stable.

Theorem 3.3. The disease-free equilibrium E_0 is locally asymptotically stable.

Proof. Evaluating the endemic equilibria point E_1 in (3.4) Jacobian matrix we get,

$$J\left(\frac{\Lambda}{\beta I^* + \delta}, \frac{(y + \mu + d) - \beta S(t)}{k}, I^*\right)$$

$$= \begin{bmatrix} -\beta I^* - \delta & 0 & -\beta \dfrac{\Lambda}{\beta I^* + \delta} \\ r & -kI^* - (\mu + 1 - k) & \beta \dfrac{\Lambda}{\beta I^* + \delta} - \alpha \\ \beta I^* & kI^* & 0 \end{bmatrix}$$

$$-\beta I(t) - \delta - \lambda[(-kI(t) - \text{þ} - \lambda)(\beta S(t) + kV(t) - \alpha - \lambda) +$$
$$k^2 V(t) I(t)] - \beta S(t)[rkI(t) + \beta I(t)(kI(t) + \text{þ} + \lambda)] = 0,$$

$$\Longrightarrow [k\beta^2 S(t) I(t)^2 - \beta k\, \alpha I(t)^2 - \beta k \lambda I(t)^2 + \text{þ}\beta^2 I(t) S(t) +$$
$$\text{þ} kV(t)\, \beta I(t) - \text{þ}\, \alpha\, \beta I(t) - \beta I(t) \text{þ}\lambda + \lambda \beta^2 S(t) I(t) + \lambda\, k\beta V(t) I(t) -$$

$\beta\lambda\ \alpha\mathrm{I}(\mathrm{t}) - \beta I(t)\lambda^2] + [\delta\beta k\mathrm{S}(\mathrm{t})\mathrm{I}(\mathrm{t}) - \delta k\ \alpha\mathrm{I}(\mathrm{t}) - \delta k\lambda\mathrm{I}(\mathrm{t}) + \delta\text{þ}\beta\mathrm{S}(\mathrm{t}) + \delta\text{þ}\mathrm{kV}(\mathrm{t}) - \delta\text{þ}\ \alpha - \delta\text{þ}\lambda + \delta\lambda\beta\mathrm{S}(\mathrm{t}) + \delta\lambda\ \mathrm{kV}(\mathrm{t}) - \delta\lambda\ \alpha - \delta\lambda^2] + [\lambda\beta k\mathrm{S}(\mathrm{t})\mathrm{I}(\mathrm{t}) - \lambda k\ \alpha\mathrm{I}(\mathrm{t}) - k\lambda^2\mathrm{I}(\mathrm{t}) + \lambda\text{þ}\beta\mathrm{S}(\mathrm{t}) + \lambda\text{þ}\mathrm{kV}(\mathrm{t}) - \lambda\text{þ}\ \alpha - \text{þ}\lambda^2 + \lambda^2\beta\mathrm{S}(\mathrm{t}) + \lambda^2\ \mathrm{kV}(\mathrm{t}) - \lambda^2\ \alpha - \lambda^3] + [-rkI(t)\beta S(t) - \beta^2 kI(t)^2 S(t) - \text{þ}\beta^2 I(t)S(t) - \lambda\beta^2 I(t)S(t))]=0,$

$\Longrightarrow -\lambda^3 + \lambda^2[-\beta I(t) - \delta - \text{þ} - kI(t) + \beta S(t) + \ kV(t) - \ \alpha] + \lambda[-\ \beta kI(t)^2 - \ \beta I(t)\text{þ} + \ k\beta V(t)I(t) - \beta\ \alpha I(t) - \delta kI(t) - \delta\text{þ} + \delta\beta S(t) + \delta kV(t) - \delta\alpha + \beta kS(t)I(t) - k\ \alpha I(t) + \text{þ}\beta S(t) + \text{þ}kV(t) - \text{þ}\ \alpha] + [-\ \beta k\ \alpha I(t)^2 + \text{þ}kV(t)\ \beta I(t) - \text{þ}\ \alpha\ \beta I(t) + \delta\beta kS(t)I(t) - \delta k\ \alpha I(t) + \delta\text{þ}\beta S(t) + \delta\text{þ}kV(t) - \delta\text{þ}\ \alpha - rkI(t)\beta S(t)]=0.$

So, from above calculation, we get,

$\Longrightarrow a\lambda^3 + b\lambda^2 + c\lambda + d,$

then,

$a = -1 < 0,$

$b = -\beta I^*(t) - \delta - \text{þ} - kI^*(t) + \beta S^*(t) + \alpha - \beta S^*(t) - \ \alpha,$
$\Longrightarrow -(\beta + k)I(t) - \delta - \text{þ} < 0,$

$c = -\ \beta k\mathrm{I}^*(\mathrm{t})^2 - \ \beta I^*(t)\text{þ} + \ \beta I^*(t)\big(\alpha - \beta\mathrm{S}^*(\mathrm{t})\big) - \beta\ \alpha\mathrm{I}^*(\mathrm{t}) - \delta k\mathrm{I}^*(\mathrm{t}) - \delta\text{þ} + \delta\beta\mathrm{S}^*(\mathrm{t}) + \delta\big(\alpha - \beta\mathrm{S}^*(\mathrm{t})\big) - \delta\alpha + \beta k\mathrm{S}^*(\mathrm{t})\mathrm{I}^*(\mathrm{t}) - k\ \alpha\mathrm{I}^*(\mathrm{t}) + \text{þ}\beta\mathrm{S}^*(\mathrm{t}) + \text{þ}\big(\alpha - \beta\mathrm{S}^*(\mathrm{t})\big) - \text{þ}\ \alpha,$
$\Longrightarrow -\ \beta k\mathrm{I}^*(\mathrm{t}) - \ \beta\text{þ} - \beta^2\mathrm{S}^*(\mathrm{t}) - \delta k - k^2V^*(\mathrm{t}) < 0,$

$$d = -\beta k\,\alpha I^*(t)^2 \text{þ}\,\beta I^*(t)\big(\alpha - \beta S^*(t)\big) - \text{þ}\,\alpha\,\beta I^*(t) + \delta\beta k S^*(t) I^*(t)$$
$$- \delta k\,\alpha I^*(t) + \delta\text{þ}\beta S^*(t) + \delta\text{þ}\big(\alpha - \beta S^*(t)\big) - \delta\text{þ}\,\alpha$$
$$- rkI^*(t)\beta S^*(t),$$
$$\Longrightarrow -\alpha\beta k\, I^*(t) - \text{þ}\beta^2 S^*(t) - rk\beta S^*(t) - \delta k^2 V^*(t) < 0,$$

hence,

$a, b, c, d < 0$ we get all confliction is negative, hence we get all λ is negative, so the endemic equilibrium point is locally stable.

Theorem 3.4. the epidemic equilibrium point of the system is globally asymptotically stable on ʊ.

Proof. To found the global stability of the epidemic equilibrium point, we construct the following Lyapunov function

L: $ʊ_+ \rightarrow$ R,

where

$$ʊ+ = \{S(t), I(t) \in ʊ, S(t) > 0, V(t) > 0\; I(t) > 0\}$$

given, where W_3, W_2 *and* W_3 positive constant,

$$L(S, I, V) = W1\left[S - S^*\, In\left(\frac{S}{S^*}\right)\right] + W2\left[I - I^*\, In\left(\frac{I}{I^*}\right)\right]$$
$$+ W_3\left[V - V^*\, In\left(\frac{V}{V^*}\right)\right]$$

then, the time derivative is given by,

$$\frac{dL}{dt} = W_1(S - S^*)\left[\frac{\Lambda}{S} - \beta\text{I} - \delta\right] + W_2(I - I^*)[(\beta\text{S} + \text{kV}) - (\mu + \text{y} + \text{d})]$$
$$+ W_3(V - V^*)\left[\frac{rS}{V} - kI - (\mu + 1 - k)\right]$$

consider the equilibrium point we get,

$$\delta = \frac{\Lambda}{S^*} - \beta I^*, (\mu + y + d) = kv^* + \beta S^*$$

$$\frac{dL}{dt} = -W_1 \frac{\Lambda(S - S^*)}{S^* S} - W \beta(S - S^*)(I + I^*) + W_2(I - I^*)\beta(S - S^*) - kW_2(I - I^*)(V^* - V)$$

$$\frac{dL}{dt} = -W_1 \frac{\Lambda(S-S^*)}{S^* S} + \beta(W_2 - W_1)(I - I^*)(S - S^*) - kW_2(I - I^*)(V^* - V)$$

Now if $W_1 = W_2 = W_3$, then

$$\frac{dL}{dt} = -W_1 \frac{\Lambda(S-S^*)}{S^* S} - kW_2(I - I^*)(V^* - V) \leq 0 \quad \text{and if } S = S^*, V^* = V, \text{ then}$$

$$\frac{dL}{dt} = 0 .$$

Hence, by using the LaSalle invariance principle, the endemic equilibrium point is globally asymptotically stable.

3.4 Numerical Simulations

For the initial state, simulation was performed utilizing the below value (S, I, V) = (471, 7, 118), the final time was $t = 100$ days. Solved numerically by using the (ode45) solvers in Matlab in a table, and the parameter is given by Table 3.2.

Table 3.2: The value of the parameters in the system (3.2).

Parameters	Values
Λ	200
B	0.005
d	0.02
μ	0.002

y	0.69
r	0.2
k	0.00001

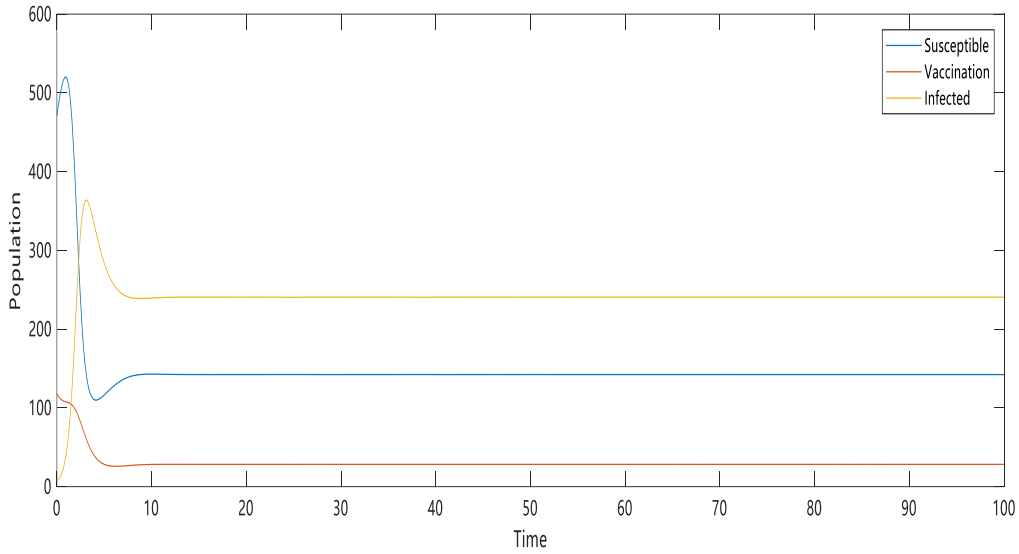

Figure 3.2: State variable of the system (3.1) with initial condition and parameter in Table 3.2.

3.5 Sensitivity Analysis

Give the free formula (3.3) for R_0, one can easily derive an analytical expression for the sensitivity of R_0 concerning each parameter. The obtained values are described in Table 3.1, which presents the sensitivity indices for the baseline parameter value in the last row of Table 3.2.

$$R_0 = \frac{\Lambda}{\alpha\delta}\left[\beta + \frac{rk}{\mu + 1 - k}\right].$$

Take sensitivity for parameter β,

$$Y_{\beta}^{R_0} = \frac{\partial R_0}{\partial \beta} \times \frac{\beta}{R_0} \rightarrow \frac{\Lambda}{\alpha\delta} \times \frac{\beta}{\frac{\Lambda}{\alpha\delta}\ [\beta + \frac{rk}{\mu + 1 - k}]} = \frac{\beta}{\beta + \frac{rk}{\mu + 1 - k}} = 0.9996009.$$

Take sensitivity for parameter Λ,

$$Y_{\Lambda}^{R_0} = \frac{\partial R_0}{\partial \Lambda} \times \frac{\Lambda}{R_0} \rightarrow \left[\beta \frac{1}{\alpha\delta} + \frac{rk}{\alpha\delta(\mu + 1 - k)}\right] \times \frac{\Lambda}{\frac{\Lambda}{\alpha\delta}\ \left[\beta + \frac{rk}{\mu + 1 - k}\right]} =$$

$$\frac{\beta}{\beta + \frac{rk}{\mu + 1 - k}} + \frac{rk}{(\mu + 1 - k)\beta + kr} = 1.$$

Take sensitivity for parameter d,

$$Y_{\mathrm{d}}^{R_0} = \frac{\partial R_0}{\partial \mathrm{d}} \times \frac{\mathrm{d}}{R_0} \rightarrow \left[\frac{-\Lambda\beta\delta}{(\alpha\delta)^2} + \frac{-\Lambda rk\delta(\mu + 1 - k)}{(\alpha\delta(\mu + 1 - k))^2}\right] \times \frac{\mathrm{d}}{\frac{\Lambda}{\alpha\delta}\ \left[\beta + \frac{rk}{\mu + 1 - k}\right]} =$$

$$\left[\frac{-\Lambda\beta\delta}{(\alpha\delta)^2} \times \frac{\mathrm{d}}{\frac{\Lambda}{\alpha\delta}\ \left[\beta + \frac{rk}{\mu + 1 - k}\right]} + \frac{-\Lambda rk\delta(\mu + 1 - k)}{(\alpha\delta(\mu + 1 - k))^2} \times \frac{\mathrm{d}}{\frac{\Lambda}{\alpha\delta}\ \left[\beta + \frac{rk}{\mu + 1 - k}\right]}\right] =$$

$$\left[\frac{-\beta\mathrm{d}}{\alpha\left[\beta + \frac{rk}{\mu + 1 - k}\right]} + \frac{-rk\mathrm{d}}{\alpha\left[(\mu + 1 - k)\beta + rk\right]}\right] = -0.0280898.$$

Take sensitivity for parameter μ,

$$Y_{\mu}^{R_0} = \frac{\partial R_0}{\partial \mu} \times \frac{\mu}{R_0} \rightarrow \left[\frac{-\beta\Lambda(2\mu + y + d + r)}{[\mu(\mu + y + d)]^2} + \frac{-\Lambda rk\mathrm{Q}}{(\alpha\delta(\mu + 1 - k))^2}\right] \times \frac{\mu}{\frac{\Lambda}{\alpha\delta}\ \left[\beta + \frac{rk}{\mu + 1 - k}\right]} =$$

$$\left[\frac{-\beta\Lambda(2\mu + y + d + r)}{[\alpha\delta]^2} \times \frac{\mu}{\frac{\Lambda}{\alpha\delta}\ \left[\beta + \frac{rk}{\mu + 1 - k}\right]} + \frac{-\Lambda rk\mathrm{Q}}{(\alpha\delta(\mu + 1 - k))^2} \times \frac{\mu}{\frac{\Lambda}{\alpha\delta}\ \left[\beta + \frac{rk}{\mu + 1 - k}\right]}\right] =$$

$$\left[\frac{-\beta\mu(2\mu + y + d + r)}{\alpha\delta\ \left[\beta + \frac{rk}{\mu + 1 - k}\right]} + \frac{-rk\mu\mathrm{Q}}{\alpha\delta(\mu + 1 - k)\ \ [(\mu + 1 - k)\beta + rk]}\right] = -0.0127107.$$

Take sensitivity for parameter y,

$$Y_{\mathrm{y}}^{R_0} = \frac{\partial R_0}{\partial \mathrm{y}} \times \frac{\mathrm{y}}{R_0} \rightarrow \left[\frac{-\Lambda\beta\delta}{(\alpha\delta)^2} + \frac{-\Lambda rk\delta(\mu+1-k)}{\left(\alpha\delta(\mu+1-k)\right)^2}\right] \times \frac{\mathrm{d}}{\frac{\Lambda}{\alpha\delta}\left[\beta+\frac{rk}{\mu+1-k}\right]} =$$

$$\left[\frac{-\Lambda\beta\delta}{(\alpha\delta)^2} \times \frac{\mathrm{y}}{\frac{\Lambda}{\alpha\delta}\left[\beta+\frac{rk}{\mu+1-k}\right]} + \frac{-\Lambda rk\delta(\mu+1-k)}{\left(\alpha\delta(\mu+1-k)\right)^2} \times \frac{\mathrm{y}}{\frac{\Lambda}{\alpha\delta}\left[\beta+\frac{rk}{\mu+1-k}\right]}\right] =$$

$$\left[\frac{-\beta\mathrm{y}}{\alpha\left[\beta+\frac{rk}{\mu+1-k}\right]} + \frac{-rk\mathrm{y}}{\alpha\left[(\mu+1-k)\beta+rk\right]}\right] = 0.9691011.$$

Take sensitivity for parameter r,

$$Y_{\mathrm{r}}^{R_0} = \frac{\partial R_0}{\partial \mathrm{r}} \times \frac{\mathrm{r}}{R_0} \rightarrow \left[\frac{-\Lambda\beta\alpha}{(\alpha\delta)^2} + \frac{-\Lambda\alpha k(\mu+1-k)(\delta-r)}{\left(\alpha\delta(\mu+1-k)\right)^2}\right] \times \frac{\mathrm{r}}{\frac{\Lambda}{\alpha\delta}\left[\beta+\frac{rk}{\mu+1-k}\right]} =$$

$$\left[\frac{-\Lambda\beta\alpha}{(\alpha\delta)^2} \times \frac{\mathrm{r}}{\frac{\Lambda}{\alpha\delta}\left[\beta+\frac{rk}{\mu+1-k}\right]} + \frac{\Lambda\alpha k(\mu+1-k)(\delta-r)}{\left(\alpha\delta(\mu+1-k)\right)^2} \times \frac{\mathrm{r}}{\frac{\Lambda}{\alpha\delta}\left[\beta+\frac{rk}{\mu+1-k}\right]}\right] =$$

$$\left[\frac{-\beta\mathrm{r}}{\delta\left[\beta+\frac{rk}{\mu+1-k}\right]} + \frac{rk(\delta-r)}{\delta\left[(\mu+1-k)\beta+rk\right]}\right] = -0.9896999.$$

Take sensitivity for parameter k,

$$Y_{\mathrm{k}}^{R_0} = \frac{\partial R_0}{\partial \mathrm{k}} \times \frac{\mathrm{k}}{R_0} \rightarrow \left[\frac{-\Lambda\beta\alpha}{(\alpha\delta)^2} + \frac{-\Lambda\alpha k(\mu+1-k)(\delta-r)}{\left(\alpha\delta(\mu+1-k)\right)^2}\right] \times \frac{\mathrm{k}}{\frac{\Lambda}{\alpha\delta}\left[\beta+\frac{rk}{\mu+1-k}\right]} =$$

$$\left[\frac{-\Lambda\beta\alpha}{(\alpha\delta)^2} \times \frac{\mathrm{k}}{\frac{\Lambda}{\alpha\delta}\left[\beta+\frac{rk}{\mu+1-k}\right]} + \frac{\Lambda\alpha k(\mu+1-k)(\delta-r)}{\left(\alpha\delta(\mu+1-k)\right)^2} \times \frac{\mathrm{k}}{\frac{\Lambda}{\alpha\delta}\left[\beta+\frac{rk}{\mu+1-k}\right]}\right] =$$

$$\left[\frac{-\beta\mathrm{y}}{\delta\left[\beta+\frac{rk}{\mu+1-k}\right]} + \frac{rk(\delta-r)}{\delta\left[(\mu+1-k)\beta+rk\right]}\right] = 0.00039905.$$

By using the above calculations, we obtained Table 3.3.

Table 3.3: Sensitivity indices.

Parameters	Values
Λ	1
B	0.9996009
d	-0.0280898
μ	-0.0127107
y	-0.9691011
r	-0.9896999
k	0.00039905

The sensitivity indices are positive and the remaining are negative. Since all indices are the other parameter's function, the sensitivity indices will change with different parameter values.

The most sensitivity parameter for (R_0) is the Λ (Recruitment of individual) have the positive sensitivity parameter, $Y_{\Lambda}^{R_0} = +1$ see Figure (3.3,3.4,3.9), with the parameter β(Transmission coefficient of $(S)\ to\ (I)$), and parameter k(transmission coefficient of vaccinated individuals V to I). which has increased the sensitivity index, then the reproduction number has the same.

The parameter (d, y, μ, r) has a negative sensitivity index (see Figure 3.5, Figure 3.6, Figure 3.7, Figure 3.8). Then, the average of expanding and rare disease, where they are increasing by 10%, the basic reproduction number is decreasing by 10%.

The most effective variables are Λ and y; the least effectives are μ and k.

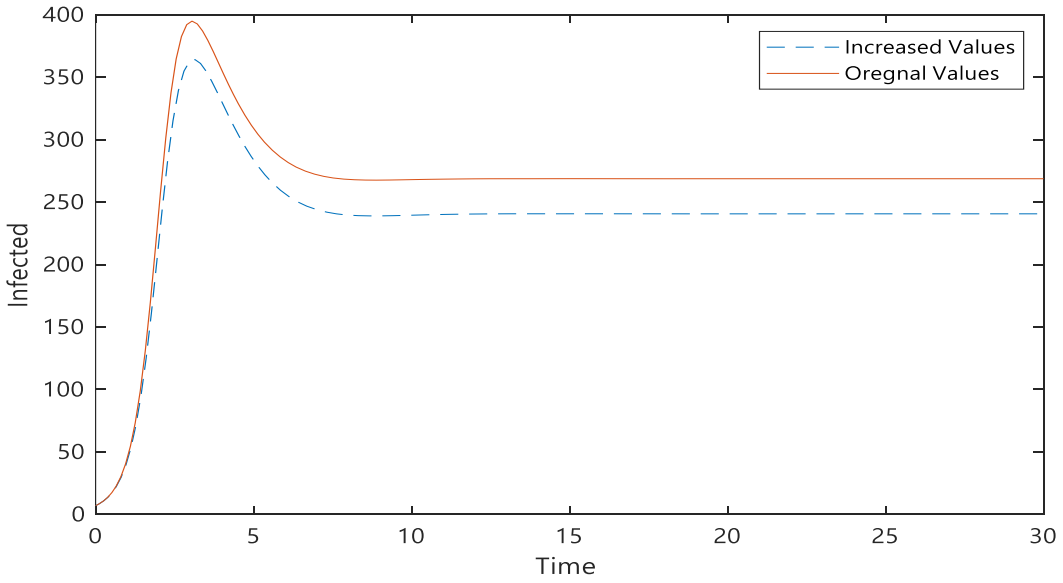

Figure 3.3: Effect on I of the variation of Λ; $\boldsymbol{\Lambda = 220}, \beta = 0.005, d = 0.02, y = 0.69, \mu = 0.002, r = 0.2, k = 0.00001, (S, I, V) = (471, 7, 118)$.

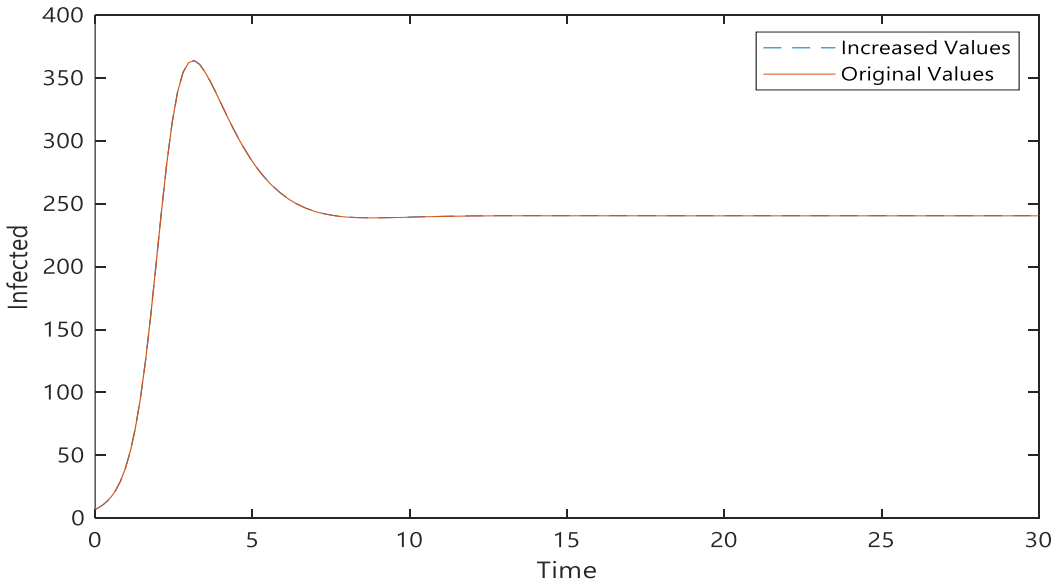

Figure 3.4: Effect on I of the variation of β; $\Lambda = 200, \boldsymbol{\beta = 0.0055}, d = 0.02, y = 0.69, \mu = 0.002, r = 0.2, k = 0.00001\ (S, I, V) = (471, 7, 118)$.

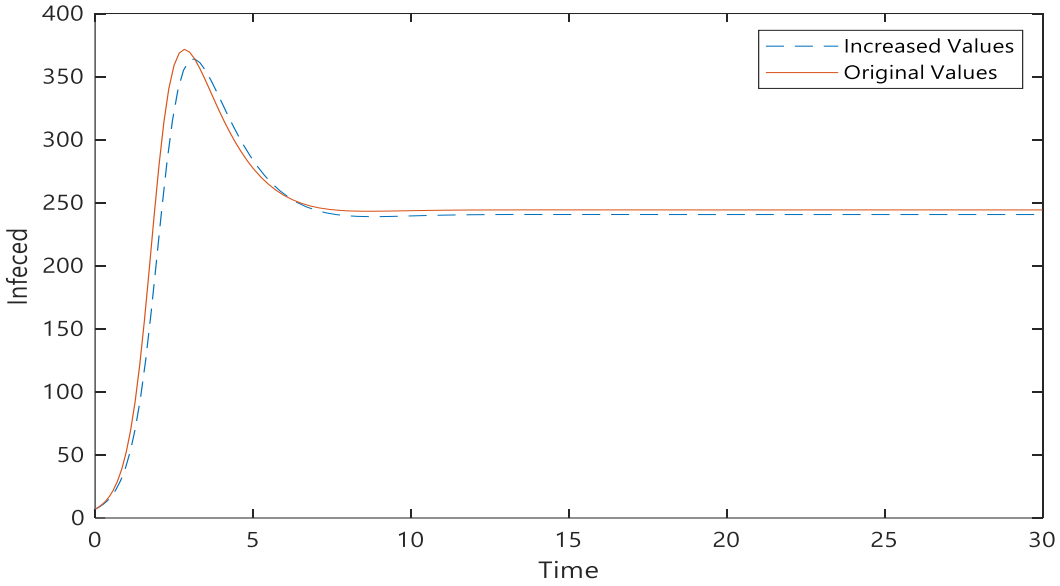

Figure 3.5: Effect on I of the variation of μ; $\Lambda = 200, \beta = 0.005, d = 0.02, y = 0.69, \mu = \mathbf{0.0022}, r = 0.2, k = 0.00001$ $(S, I, V) = (471, 7, 118)$.

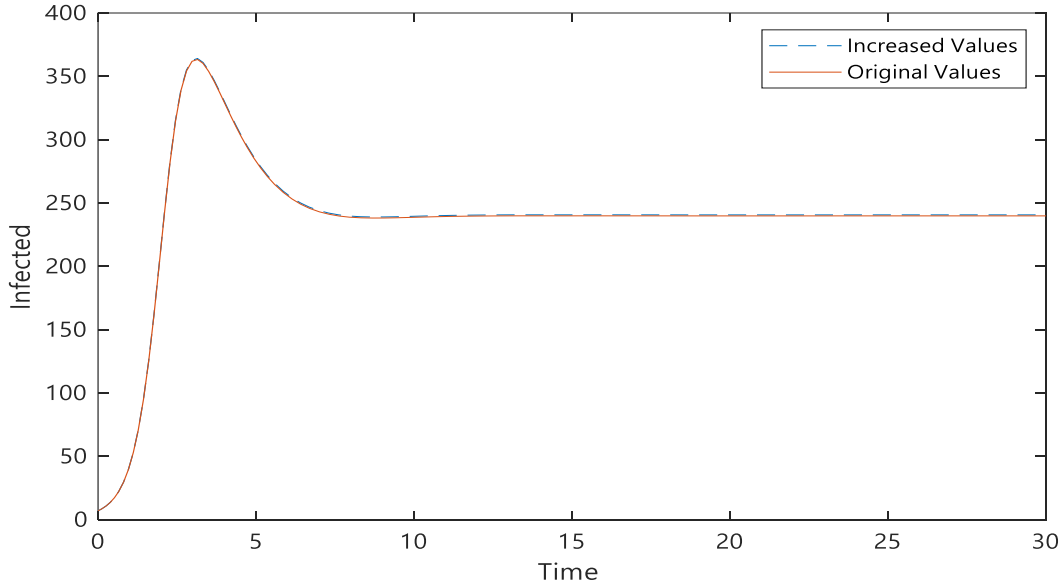

Figure 3.6: Effect on I of the variation of d; $\Lambda = 200, \beta = 0.005, \boldsymbol{d} = \mathbf{0.022}, y = 0.69, \mu = 0.002, r = 0.2, k = 0.00001$ $(S, I, V) = (471, 7, 118)$.

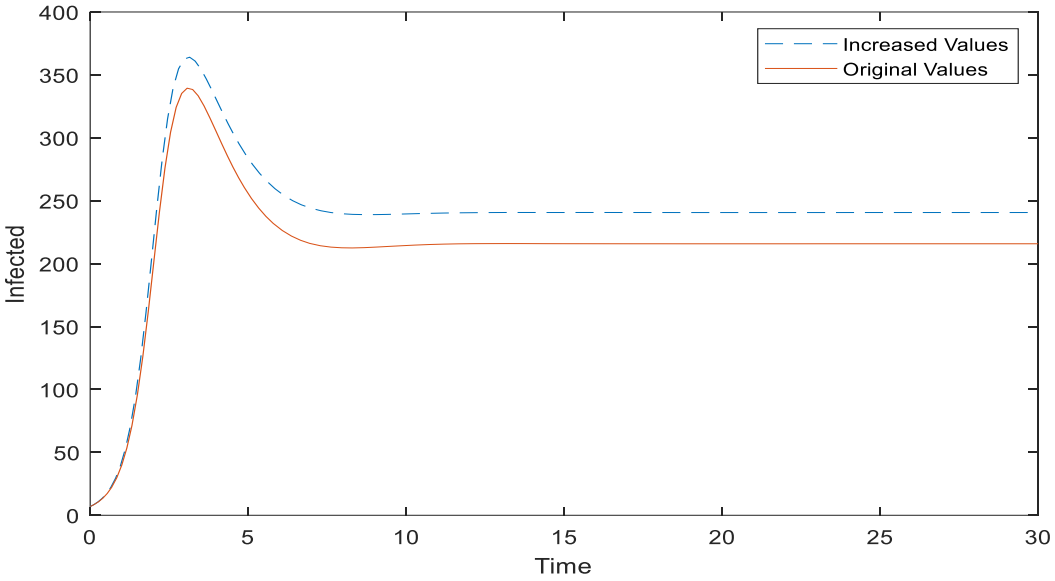

Figure 3.7: Effect on I of the variation of y; $\Lambda = 200, \beta = 0.005, d = 0.02, \boldsymbol{y} = \boldsymbol{0.759}, \mu = 0.002, r = 0.2, k = 0.00001$ $(S,\ I,\ V) = (471, 7, 118)$.

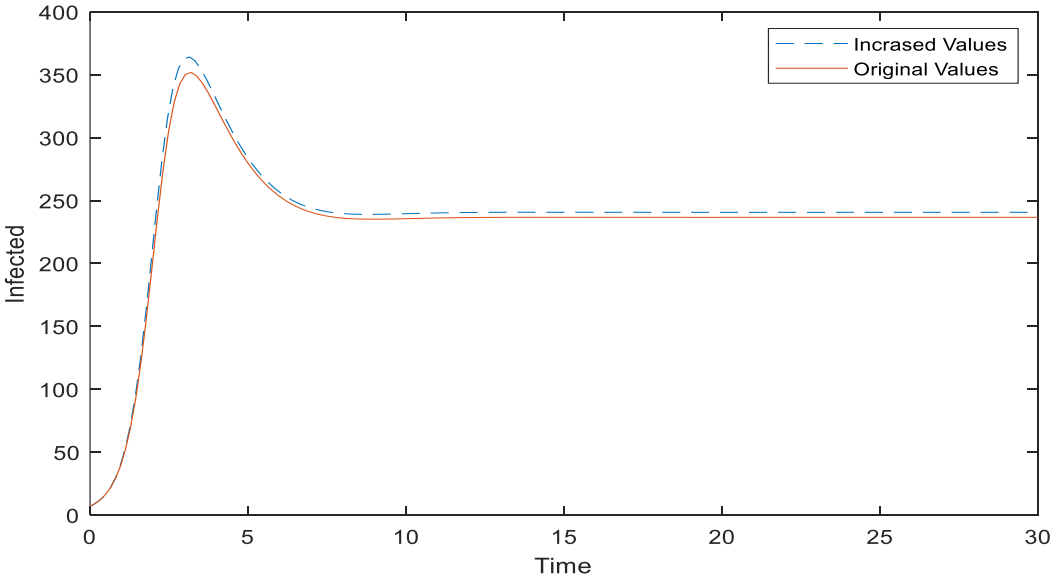

Figure 3.8: Effect on I of the variation of r; $\Lambda = 200, \beta = 0.005, d = 0.02, y = 0.69, \mu = 0.002, \boldsymbol{r} = \boldsymbol{0.22}, k = 0.00001$ $r(S,\ I,\ V) = (471, 7, 118)$.

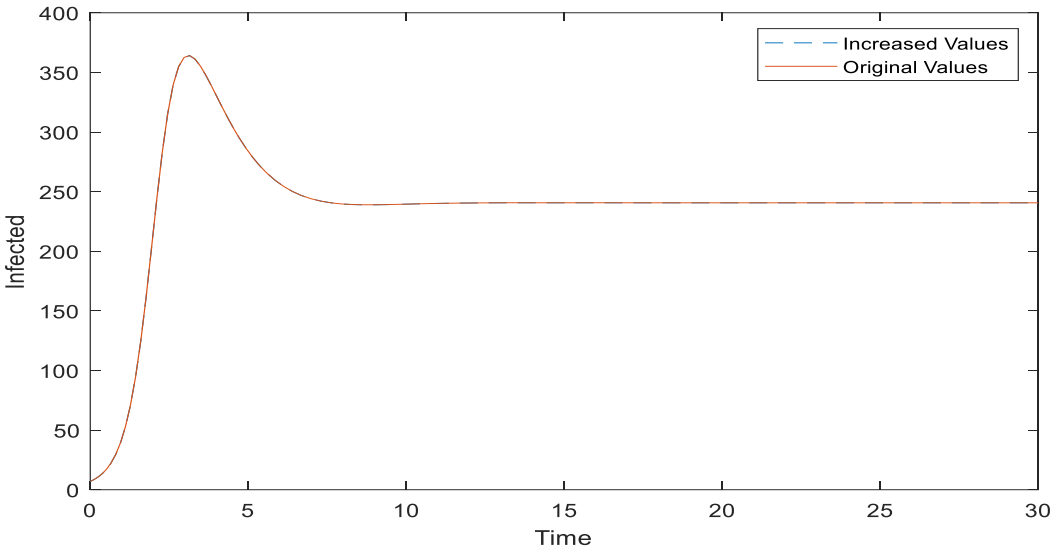

Figure 3.9: Effect on I of the variation of k; $\Lambda = 200, \beta = 0.005, d = 0.02, y = 0.69, \mu = 0.002, r = 0.2, \boldsymbol{k = 0.000011}$ $(S, I, V) = (471, 7, 118$

CHAPTER 4

RESULTS AND CONCLUSION

In this thesis, two models of epidemics; SIR, and SVIR models constructed of Covid-19. In the models, the effect of disease on inhabitants is discussed where the model has vaccination, and they do not have the vaccination.

In chapter 2, firstly, we constructed the model with and without vaccination showed in Figure 2.1, and the two-equilibrium points are discovered which are the free and endemic equilibrium points. We noted that the disease-free equilibrium point exists when the $R_{01} < 1$, which inference that the disease will disappear in the population over some time. The endemic equilibrium point exists when $R_{01} > 1$. Further, it is observed that the endemic and free-disease equilibrium point cannot exist together.

For the basic reproduction numbers of the model, we used the matrix approach of the next generation to test it as $\mathrm{R}_{01} = \frac{\beta\Lambda}{\mu(\mu+y+d)}$. From this basic reproduction number, it can be seen that for the control of the disease, only way is to contract the transmission coefficient of the susceptible to the infection.

We used Jacobian matrix for stability analysis to show that each equilibrium points; disease-free and endemic equilibrium points are locally asymptotically stable. Furthermore, using the Lyapunov function and the LaSalle invariance principle to show that global stability.

At the end of the chapter, the sensitivity study of the basic reproduction ratio is taken R_{01}, located the relative importance of the parameters of the model as the epidemic is spreading. This knowledge helps one discern the robustness of the measurement stations, values of parameters and the effect of each parameter on the particular number of reproductions and, subsequently, diseases. Furthermore, we see in Figure 2.4 the sensitivity they did not has the Mentioned influence on the infection the disease, in order in the other hand in Figure 2.3 show as the Mentioned change when we increase the recruitment of individual the infection

increased to, but when increased the average infection period the infection decreasing which is seen in figure (2.7).

Chapter three constructs the model with vaccination shown in Figure (3.1) same chapter two, we have an equilibrium point endemic and disease-free equilibrium point.

We use the next generation matrix to find the basic reproduction matrix method to evaluate it as a $R_{02} = \frac{\Lambda}{\alpha\delta}\ [\beta + \frac{rk}{\mu+1-k}]$, from this basic reproduction number, we can see to control the disease by increasing the rate of vaccination.

We are using a jacobian matrix for stability analysis to show that each equilibrium disease-free and endemic equilibrium point are locales asymptotically stable. And using the Lyapunov function and the LaSalle invariance principle to show that global stability

At the end of the chapter, we take the sensitivity analysis of the basic reproduction ratio R_{02}, To define the relative value of the parameters of the model in transmitting the disease. This knowledge helps one to discern the robustness of model projections about parameter values and the effect of each parameter on the particular number of reproductions and the frequency of outbreaks subsequently, we see in Figure (3.5,3.6,3.9) the sensitivity they did not has the Mentioned influence on the infection the disease, in order on the other hand in figure (3.3,3.7) show as the big change when increasing 10%.

Comparison between chapter two and chapter three, we see that in figure (2.2) and figure (3.2), the effect of vaccination %20 of the population can be seen. Where there is no vaccine on the population the number of infected people is around 300 000 and when %20 of the population vaccinated infected people will be around 50 000. It is shown that created for the covid-19 outbreak reduces the number of case of an infected individual. However, it can be seen that it would not be sufficient to control the epidemic, and if we looked to the death rate change in both models, we see in the first model death rate is greater than the death rate in model with vaccination.

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APPENDICES

YAKIN DOĞU ÜNİVERSİTESİ

APPENDIX 1

ETHICAL APROVAL DOCUMENT

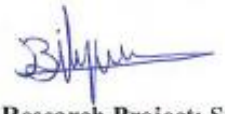
Date: 04/02/2021

To the **Graduate School of Applied Sciences**

The research project titled "Sensitivity Analysis in Covid-19 Epidemic Model" has been evaluated. Since the researcher(s) will not collect primary data from humans, animals, plants or earth, this project does not need to go through the ethics committee.

Title: Assist.Prof.Dr.

Name Surname: Bilgen Kaymakamzade

Signature: 

Role in the Research Project: Supervisor

APPENDIX 2

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