MATHEMATICAL ANALYSIS OF A VACCINATED EPIDEMIC MODEL OF INFLUENZA

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Abstract

Influenza is a serious disease caused by an influenza virus. This disease is spreading so widely that it is difficult to control. Vaccination is a common method to protect this disease. The Susceptible-Vaccinated-Exposed-Infectious-Recovered ($SVEIR$) model is used to predict the number of infected population and the duration of an outbreak when it occurs. Both disease-free and endemic equilibriums of the model are derived to study the effect of vaccination on the number of infectious population. In this research, the threshold value of the model which is called the basic reproductive number is derived. The stability analysis of the model shows that the disease-free equilibrium is locally asymptotically stable if the basic reproductive number is less than unity by using Next Generation Method. It is also shown that the disease can be eradicated from the population if the vaccination coverage level exceeds a certain threshold value. On the other hand, the disease will persist within the population if the coverage level of vaccination is below this critical value. These results are verified by the numerical simulations. Numerical results show the number of infectious proportion when the vaccination rates are varied. The critical value of vaccination rate is 0.00715. It is found that sufficient vaccination rate can be eradicated the disease.

Keywords : Basic Reproductive Number / Disease-Free Equilibrium / Endemic Equilibrium / Stability

หัวข้อวิทยานิพนธ์	การวิเคราะห์ทางคณิตศาสตร์ของตัวแบบการแพร่ระบาดของโรคไข้หวัดใหญ่ที่มีการฉีดวัคซีน
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บทคัดย่อ

โรคไข้หวัดใหญ่เป็นโรคติดต่อที่เกิดจากเชื้อไวรัส Influenza โรคนี้มีการระบาดอย่างกว้างขวางทำให้ยากแก่การควบคุม การฉีดวัคซีนเป็นทางเลือกหนึ่งที่ได้รับความนิยมในการป้องกันการเกิดโรคไข้หวัดใหญ่ ตัวแบบเชิงคณิตศาสตร์ กลุ่มเสี่ยงต่อการติดเชื้อ กลุ่มที่ได้รับวัคซีน กลุ่มฟักตัวของเชื้อ กลุ่มที่ติดเชื้อ กลุ่มที่หายจากการเป็นโรค (*SVEIR*) ใช้พยากรณ์จำนวนประชากรกลุ่มที่ติดเชื้อ และช่วงเวลาของการระบาดของโรค วิเคราะห์จุดสมดุลของแบบจำลองทั้งจุดที่ไม่มีการระบาดของโรคและจุดที่มีการระบาดของโรคเพื่อศึกษาผลการฉีดวัคซีนต่อจำนวนผู้ติดเชื้อ ในงานวิจัยชิ้นนี้ได้คำนวณค่าวิกฤตของแบบจำลองซึ่งเรียกว่า ค่าระดับการติดเชื้อพื้นฐาน การวิเคราะห์เสถียรภาพของตัวแบบจำลองแสดงให้เห็นว่า จุดสมดุลที่อิสระจากโรคมีเสถียรภาพเชิงตำแหน่งตามแนวเส้นกำกับถ้าระดับการติดเชื้อพื้นฐานมีค่าน้อยกว่าหนึ่งโดยใช้วิธี Next Generation Method แสดงให้เห็นว่าโรคสามารถถูกกำจัดจากกลุ่มประชากร ถ้ามีอัตราการฉีดวัคซีนมากกว่าค่าวิกฤตของอัตราการฉีดวัคซีน ในทางกลับกันโรคยังคงถูกพบในกลุ่มประชากร ถ้าหากค่าอัตราการฉีดวัคซีนต่ำกว่าค่าวิกฤตของอัตราการฉีดวัคซีน ผลลัพธ์นี้ได้รับการยืนยันด้วยการจำลองเชิงตัวเลข โดยผลเชิงตัวเลขได้แสดงให้เห็นจำนวนประชากรกลุ่มติดเชื้อเมื่อมีการเปลี่ยนแปลงอัตราการฉีดวัคซีน และคำนวณค่าวิกฤตของอัตราการฉีดวัคซีนมีค่าเป็น 0.00715 ซึ่งเพียงพอที่จะส่งผลทำให้ประชากรกลุ่มติดเชื้อหายไปจากระบบ

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LIST OF SYMBOLS

Symbols	Description
β	Contact rate
$\beta_{_E}$	Ability to cause infection by exposed individuals
$\beta_{_I}$	Ability to cause infection by infectious individuals
$\beta_{_V}$	Ability to cause infection by vaccination individuals
σ	Rate of latency
γ	Rate of clinically ill
δ	Rate of duration of immunity loss
μ	Natural mortality rate
r	Birth rate
κ	Recovery rate of latens
α	Flu induced mortality rate
θ	Rate of susceptible
ϕ	Rate of vaccination
R_{VAC}	The basic reproductive number

CHAPTER 1 INTRODUCTION

1.1 Introduction

Influenza is a contagious disease, caused by an Influenza virus. It is transmitted between the human contact from the contaminated objects and the air that contains the virus. A lot of people around the world have a die caused from the disease. The important cause of influenza virus is it has spreading widely. Sometimes it spreads into worldwide then the disease can not stop. Basically, every winter, there are a lot of the patients from this disease more than other diseases. The cause of virus has now spread widely is that the capacity of virus can change to other strain. When the virus is changed its strain to another strain, there is an effect on the human who never receive this virus. In particular, they cannot protect the new breed of virus. Thus, when the virus has changed to one that is often followed by an outbreak because no immunity to the new virus. So there are many strains of influenza virus. However the level of outbreak now are increase more than before. Mathematical models is useful to understand the disease dynamics and the implications of various preventive and control strategies [1].

Vaccination is the preparation which can improves the immunity to influenza disease. It is a common method to control disease .The coverage vaccination is important factor to prevent human from the disease. Most of vaccination programs are specific for each individual.There are many studies to identify the mass vaccination and the efficacy of vaccination which need to control the disease [2].

Mathematical models have been used to determine the ability an imperfect vaccine to control other infectious diseases. There are several published mathematical models suggested for the transmission dynamics of influenza [3, 4]. Such as, Samsuzzoha, et al. constructed a system of ODE which is called an influenza epidemic model and analyze the basic reproductive number and the effect of all parameters by using the sensitivity analysis to the basic reproductive number.

Alexander, et al.[5] constructed a deterministic mathematical model to study the transmission dynamic of influenza. The model is analyzed qualitatively to determine criteria for control of an influenza epidemic and is used to compute the threshold vaccination rate necessary for community-wide control of vaccination. Lui et al. [6] studied two $SVIR$ models which are established to describe continuous vaccination strategy and puse vaccination strategy. It shown that both systems exhibit stric threshold dynamics which depend on the reproduction number. Mathematical results suggest that vaccination is helpful for disease control by decreasing the reproduction number.

Samsuzzoha, et al.[3] presented the impact of vaccination as well as diffusion on the transmission dynamics of influenza. Sensitivity analysis of the reproduction number

based on parameters are investigated.

Kuniya [7] studied the global stability of a multi-group *SVIR* epidemic model is investigated. The heterogeneity of population and the effect of immunity are induced by vaccination. The method of Lyaponov is used to prove the globally asymptotically stable.

Samsuzzoha, et al. [4] studied the sensitivity analysis based on mathematical as well as statistical technique and determined the important of the epidemic model parameters. It is shown that the reproduction number is the most sensitive to the transmission rate of the disease.

1.2 Objective

The objective of this research is to analyze the stability of SVEIR influenza epidemic model with vaccination by samsuzzoha, et al. [4].

1.3 Scope

To study the mathematical model of influenza with vaccination and the effect of reproduction number using specific estimated input parameters values.

In Chapter 2, epidemic models with vaccination are reviewed and background mathematics used in later chapters are given. Chapter 3, the basic reproduction number of the model 2.1 is derived. The local stability is analyzed to verify that the equilibrium of the model are locally asymptotically stable under the condition of the reproductive number and the vaccination coverage level exceeds a certain threshold value. Chapter 4, we discuss the numerical solutions of the model 2.1 to describe the effect of vaccination. Finally, discussion and conclusions of this thesis are given.

CHAPTER 2 LITERATURE REVIEWS AND BASIC MATHEMATICS

2.1 Literature Reviews

Alexander, et al.[5] constructed a deterministic mathematical model $SVIR$ to study the transmission dynamic of influenza. The model is divided the population N into four subpopulations: susceptible S, vaccinated V, infected I and recovered R. The model is analyzed qualitatively to determine criteria for control of an influenza epidemic and is used to compute the threshold vaccination rate necessary for community-wide control of influenza by using two specific populations of similar size, an office and a personal care home. The linear stability analysis showed that the model has a disease-free which is locally asymtotically stable when the basic reproductive number (R_0) is less than unity and unstable otherwise. In this research the persistence of the disease depends on the initial size of the subpopulation. However, the estimated parameters in the model and indeed for any infection where immunity acquired by natural infection does not wane faster than by vaccination. The model showed that the spread of influenza can be controlled if the combined effect of the vaccine efficacy and vaccination rate reached a threshold determined by the duration of infectiousness and the rate of contact between infected and susceptible individuals.

Lui, et al. [6] studied two $SVIR$ models which are established to describe continuous vaccination strategy and pulse vaccination strategy. This research is shown that both models exhibit strict threshold dynamic which depend on the basic reproductive number (R_0). If this number is below unity, the disease can be eradicated. On the other hand if it is above the unity, the disease is endemic in the sense of global asymptotical stability of the a positive equilibrium for continuous vaccination strategy and disease parameters. This research determined a control system for the optimality and its existence, and the optimal control are derived. Mathematical results suggest that vaccination is helpful for disease control by decreasing the reproduction number (R_0). The results verified by a numerical solution of the optimality system consisting of the original state system, the adjoint system and their boundary condition.

Samsuzzoha, et al. [3] presented the impact of vaccination as well as diffusion on the transmission dynamics of influenza. The model based on $SVEIR$ model. The population is divided into five sub-population, which are susceptible (S), vaccinated (V), exposed (E), infective (I) and recovered (R).

$$
\begin{aligned}
\frac{dS}{dt} &= -\beta\beta_{_E}\frac{ES}{N} - \beta\beta_{_I}\frac{IS}{N} - \phi S - \mu S + \delta R + \theta V + rN, \\
\frac{dV}{dt} &= -\beta\beta_{_E}\beta_{_V}\frac{EV}{N} - \beta\beta_{_I}\beta_{_V}\frac{IV}{N} - \mu V - \theta V + \phi S, \\
\frac{dE}{dt} &= \beta\beta_{_E}\frac{ES}{N} + \beta\beta_{_I}\frac{IS}{N} + \beta\beta_{_E}\beta_{_V}\frac{EV}{N} + \beta\beta_{_I}\beta_{_V}\frac{IV}{N} - (\mu+\kappa+\sigma)E, \quad (2.1) \\
\frac{dI}{dt} &= \sigma E - (\mu+\alpha+\gamma)I, \\
\frac{dR}{dt} &= \kappa E + \gamma I - \mu R - \delta R.
\end{aligned}
$$

and

$$
\frac{dN}{dt} = rN + \mu N - \alpha I.
$$

The total population size is denoted by $N = S + V + E + I + R$. The system has been solved by using the operator splitting method with three different initial conditions to study the effect of the rate of vaccination and vaccine efficiency. Contact parameter, the conclusion may be summarized. Measure of vaccination efficacy is essential before implementation of mass vaccination program. An increase of vaccination rate decreases reproduction number R_{VAC}, thus resulting in less severity of outbreak of disease. Contact parameter, β, is very sensitive to spread of disease. Its value must not exceed the bifurcation point to make the system unstable. Diffusion in the system can help to stabilize the system, thus reducing the chances of outbreak of disease beyond control. Initial distribution of popupation definitely plays an important role in the spread of disease. Sensitivity analysis of the reproduction number based on parameters are investigated.

Kuniya [7] investigeted the global stability of a multi-group *SVIR* epidemic model by consider the heterogeneity of population and the effect of immunity are induced by vaccination. The basic reproductive number is derived. R_0 played the role of a threshold for the long-time behavior of the model. That is, the disease-free equilibrium is globally asymtotically stable when $R_0 \leq 1$ and endemic equilibrium E^* existed uniquely and is globally asymtotically stable if $R_0 > 1$. The method of Lyaponov is used to prove the globally asymptotically stable.

Recently, Samsuzzoha, et al. [4] studied the sensitivity analysis based on mathematical and well as statistical techniques are determined the importance of the epidemic model parameters.

$$
\begin{aligned}
\frac{dS}{dt} &= -\beta\beta_{_E}ES - \beta\beta_{_I}IS + \alpha IS - \phi S - rS + \delta R + \theta V + r, \\
\frac{dV}{dt} &= -\beta\beta_{_E}\beta_{_V}EV - \beta\beta_{_I}\beta_{_V}IV - rV + \alpha IV - rV - \theta V + \phi S, \\
\frac{dE}{dt} &= \beta\beta_{_E}ES + \beta\beta_{_I}IS + \beta\beta_{_E}\beta_{_V}EV + \beta\beta_{_I}\beta_{_V}IV + \alpha IE - (r+\kappa+\sigma)E, \\
\frac{dI}{dt} &= \sigma E - (r+\alpha+\gamma)I + \alpha I^2, \\
\frac{dR}{dt} &= \kappa E + \gamma I - rR - \delta R + \alpha IR.
\end{aligned} \tag{2.2}
$$

and

$$1 = S + V + E + I + R.$$

It was shown that the reproduction number is the most sensitive to the transmission rate of the disease. There are six parameters out of the 11 input parameters play a prominent role in determining the magnitude of the basic reproductive number. It was also shown that the control of transmission rate and recovery rate of clinically ill were crucial to stop the spreading of influenza epidemics.

In this thesis, the reproductive number of the model (2.2) is derived and the stability of the disease-free and endemic equilibriums are analyzed and will be discussed in Chapter 3.

2.2 Basic Mathematics

In this section, some theories and basic mathematics are reviewed, and will be used in Chapter 3.

2.2.1 Linear Stability Analysis

Linear stability of the systems of ordinary differential equations arised in interacting population models and reaction kinetics system is determined by the roots of the characteristic polynomial. The stability analysis are concerned with involving linear systems in the vector form

$$\frac{d\mathbf{x}}{dt} = A\mathbf{x}, \tag{2.3}$$

where A is an $n \times n$ matrix and $\mathbf{x} = (x_1, x_2, \ldots, x_n)^T$, T denotes transpose. Solutions of (2.3) are obtained by setting

$$\mathbf{x} = \mathbf{v}e^{\lambda t}, \tag{2.4}$$

where $\mathbf{v}$ is a constant vector (eigenvector corresponding to eigenvalue λ) and λ is the eigenvalue which is a root of the *characteristic polynomial*

$$|A - \lambda I| = 0, \tag{2.5}$$

where I is the identity matrix. The solution of (2.3) is **stable** if all roots λ of the characteristic polynomial lie on the left-hand complex plane, that is the real part of λ, $\mathrm{Re}(\lambda)$, is less than zero for all roots λ [8].

The stability of linear system (2.3) is given in the following definitions and theorem. (see more detail in [11]).

Definition 2.1. Stable Critical Point [11] Let $\mathbf{x}^* \equiv 0$ be an equilibrium (critical) point of (2.3), and let $\mathbf{x} = \mathbf{x}(t)$ denote the solution which satisfies the initial condition $\mathbf{x}(0) = \mathbf{x}_0$ where $\mathbf{x}_0 \neq \mathbf{x}^*$. The equilibrium $\mathbf{x}^*$ is a **stable critical point** if given any radius $\rho > 0$, there is a corresponding radius $r > 0$, such that if initial position $\mathbf{x_0}$ satisfies $|\mathbf{x_0} - \mathbf{x}^*| < r$, then the corresponding solution $\mathbf{x}(t)$ satisfies $|\mathbf{x(t)} - \mathbf{x}^*| < \rho$ for all $t > 0$. In addition, if $\lim_{t\to\infty} \mathbf{x}(t) = \mathbf{x}^*$ wherever $|\mathbf{x_0} - \mathbf{x}^*| < r$, then $\mathbf{x}*$ is an **asymptotically stable critical point**.

Definition 2.2. Unstable Critical Point [11] Let $\mathbf{x}^*$ be an equilibrium (critical) point of (2.3), and let $\mathbf{x} = \mathbf{x}(t)$ denote the solution which satisfies the initial condition $\mathbf{x}(0) = \mathbf{x}_0$ where $\mathbf{x}_0 \neq \mathbf{x}^*$. The equilibrium $\mathbf{x}^*$ is a **unstable critical point** in this case: There is a disk of radius $\rho > 0$ with the property that, for any $r > 0$, there is an initial position $\mathbf{x_0}$ satisfies $|\mathbf{x_0} - \mathbf{x}^*| < r$, yet the corresponding solution $\mathbf{x}(t)$ satisfies $|\mathbf{x(t)} - \mathbf{x}^*| \geq \rho$ for at least one $t > 0$.

Theorem 2.1. [11] Let $\mathbf{x}^*$ be a critical point of $\dfrac{d\mathbf{x}}{dt} = A\mathbf{x}$. Then

(i) if A has all eigenvalues with negative real part, then $\mathbf{x}^*$ is a locally asymptotically stable (LAS) critical point.

(ii) if A has an eigenvalue with positive real part, then $\mathbf{x}^*$ is an unstable critical point.

2.2.2 Linearization of Nonlinear System

In this section, the linearization of system described by a nonlinear differential equation is performed. The procedure is based on the Taylor series expansion and on knowledge of the behaviour solution of linear systems. The main idea is to approximate a nonlinear system by a linearized system (around the equilibrium point), which is known that the behaviour of the solutions of the linear system will be the same as the nonlinear one.

Consider the general nonlinear system given by

$$\frac{d\mathbf{x}}{dt} = \mathbf{F(x)} \tag{2.6}$$

where

$$\mathbf{x} = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{bmatrix} \qquad \text{and} \qquad \mathbf{F(x)} = \begin{bmatrix} F_1(x_1, x_2, \ldots, x_n) \\ F_2(x_1, x_2, \ldots, x_n) \\ \vdots \\ F_n(x_1, x_2, \ldots, x_n) \end{bmatrix}.$$

Supposed that $\mathbf{x}^* = (x_1, x_2, \ldots, x_n)^T$ is an equilibrium point which is obtained by setting $\frac{d\mathbf{x}}{dt} = \mathbf{0}$ where $\mathbf{0}$ is and $n \times 1$ zero matrix. Linearization (2.6) about $\mathbf{x}*$ by setting $\mathbf{z} = \mathbf{x} - \mathbf{x}^*$, where $\mathbf{z} = (z_1, z_2, \ldots, z_n)^T$ represents a small quantity. Using Taylor series expansion on the right-hand side of (2.6), it yields that

$$\begin{aligned}
\frac{dz_1}{dt} &= F_1(x_1^*, x_2^*, \ldots, x_n^*) + z_1\frac{\partial F_1}{\partial x_1} + z_2\frac{\partial F_1}{\partial x_2} + \cdots + z_n\frac{\partial F_1}{\partial x_n} \\
&\quad +\text{higher order term}, \\
\frac{dz_2}{dt} &= F_2(x_1^*, x_2^*, \ldots, x_n^*) + z_1\frac{\partial F_2}{\partial x_1} + z_2\frac{\partial F_2}{\partial x_2} + \cdots + z_n\frac{\partial F_2}{\partial x_n} \\
&\quad +\text{higher order term}, \\
&\vdots \\
\frac{dz_n}{dt} &= F_n(x_1^*, x_2^*, \ldots, x_n^*) + z_1\frac{\partial F_n}{\partial x_1} + z_2\frac{\partial F_n}{\partial x_2} + \cdots + z_n\frac{\partial F_n}{\partial x_n} \\
&\quad +\text{higher order term},
\end{aligned} \tag{2.7}$$

where all partial derivatives are evaluated at $\mathbf{x}^*$. Canceling higher order terms (which contain very small quantities), the matrix form of (2.8) is given by

$$\frac{d}{dt}\begin{bmatrix} z_1 \\ z_2 \\ \vdots \\ z_n \end{bmatrix} \approx \begin{bmatrix} F_1(x_1^*, x_2^*, \ldots, x_n^*) \\ F_2(x_1^*, x_2^*, \ldots, x_n^*) \\ \vdots \\ F_n(x_1^*, x_2^*, \ldots, x_n^*) \end{bmatrix} + \begin{bmatrix} \frac{\partial F_1}{\partial x_1} & \frac{\partial F_1}{\partial x_2} & \cdots & \frac{\partial F_1}{\partial x_n} \\ \frac{\partial F_2}{\partial x_1} & \frac{\partial F_2}{\partial x_2} & \cdots & \frac{\partial F_2}{\partial x_n} \\ \vdots & & & \\ \frac{\partial F_n}{\partial x_1} & \frac{\partial F_n}{\partial x_2} & \cdots & \frac{\partial F_n}{\partial x_n} \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \\ \vdots \\ z_n \end{bmatrix},$$

or

$$\frac{d\mathbf{z}}{dt} \approx \mathbf{F}(\mathbf{x}^*) + J(\mathbf{x}^*)\mathbf{z},$$

where $J(\mathbf{x}^*)$ is called the Jacobian matrix of $\mathbf{F}$ at $\mathbf{x}^*$. Since $\mathbf{F}(\mathbf{x}^*) = \mathbf{0}$, the linearized system can be represented as

$$\frac{d\mathbf{z}}{dt} \approx J(\mathbf{x}^*)\mathbf{z}. \tag{2.8}$$

The stability of nonlinear system (2.6) may be analyzed in a neighborhood of the equilibrium point $\mathbf{x}^*$ by studying the linearized system (2.8).

2.2.3 Next generation method

The next generation method is used to establish the local asymptotic stability of the disease-free equilibrium (DFE) for epidemiological models which can be grouped into n homogeneous compartments. The method was first introduced by Diekmann, et al [9], and refined for epidemiological models by P. van den Driessche and Watmough [10]. The formulation is reproduced below.

First of all, let $\mathbf{x} = (x_1, x_2, \ldots, x_n)^T$, with each $x_i \geq 0$, be the number of individuals in each compartment of the model. Define $\mathbf{X_s} = \{\mathbf{x} \geq \mathbf{0} | x_i = 0, i = 1, 2, \ldots, m\}$

with $m < n$ be the set of disease-free states of the model. It is important to distinguish new infections from all other changes in population. Let $\mathcal{F}_i(\mathbf{x})$ be the rate of appearance of new infections in compartment i, $\mathcal{V}_i^+(\mathbf{x})$ be the rate of transfer of individuals into compartment i by all other means, and $\mathcal{V}_i^-(\mathbf{x})$ be the rate of transfer of individuals out of compartment i. It is assumed that each function is at least twice continuously differentiable in each variable. Suppose that the disease transmission model, with non-negative initial conditions, can be written in the term of the following system:

$$\frac{dx_i}{dt} = f_i(\mathbf{x}) = \mathcal{F}_i(\mathbf{x}) - \mathcal{V}_i(\mathbf{x}), \quad i = 1, 2, \ldots, n, \tag{2.9}$$

where $\mathcal{V}_i(\mathbf{x}) = \mathcal{V}_i{}^-(\mathbf{x}) - \mathcal{V}_i{}^+(\mathbf{x})$ and the functions satisfy assumptions A(1)−A(5) described below.

A(1) if $\mathbf{x} \geq \mathbf{0}$, then $\mathcal{F}_i(\mathbf{x}), \mathcal{V}_i{}^+(\mathbf{x}), \mathcal{V}_i{}^-(\mathbf{x}) \geq 0$ for $i = 1, 2, \ldots, m$.

A(2) if $x_i = 0$, then $\mathcal{V}_i{}^-(\mathbf{x}) = 0$. In particular, if $\mathbf{x} \in \mathbf{X_s}$ then $\mathcal{V}_i{}^-(\mathbf{x}) = 0$ for $i = 1, 2, \ldots, m$.

A(3) $\mathcal{F}_i(\mathbf{x}) = 0$ if $i > m$.

A(4) if $\mathbf{x} \in \mathbf{X_s}$, then $\mathcal{F}_i(\mathbf{x}) = 0$ and $\mathcal{V}_i{}^+(\mathbf{x}) = 0$ for $i = 1, 2, \ldots, m$.

A(5) if $\mathcal{F}_i(\mathbf{x})$ is set to be zero, then all eigenvalues of $Df(\mathbf{x}_0)$ have negative real parts.

Here, $\mathcal{F}_i(\mathbf{x})$ represents the rate of appearance of new infections in compartment i,
$\mathcal{V}_i{}^-(\mathbf{x})$ represents the rate of transfer of individuals out in the compartment i,
$\mathcal{V}_i{}^+(\mathbf{x})$ represents the rate of transfer of individuals into in compartment i,
$\mathbf{x}_0$ denotes the disease-free equilibrium, $Df(\mathbf{x}_0)$ is derivative $\dfrac{\partial f_i}{\partial x_j}$ evaluated at $\mathbf{x}_0$.

The following lemma is obtained to partition the matrix $Df(\mathbf{x}_0)$ by above conditions.

Lemma 2.1 ([10])**.** If $\mathbf{x}_0$ is a disease-free eqiolibrium of (2.9) and f_i satisfies A(1)−A(5), then the derivatives $D\mathcal{F}(\mathbf{x}_0)$ and $D\mathcal{V}(\mathbf{x}_0)$ are partitioned as

$$D\mathcal{F}(x_0) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix}, \quad D\mathcal{V}(x_0) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix},$$

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

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(x_0) \right] \quad \text{and} \quad V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(x_0) \right] \quad \text{with} \quad 1 \leq i, j \leq m.$$

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

Finally, the following stability result follows.

Definition 2.3. Let $\lambda_1, \lambda_2, \ldots, \lambda_s$ be the eigenvalues of square matrix A. Then its spectral radius denoted by $\rho(A)$, that is defined as $\rho(A) = \max_i(|\lambda_i|)$.

Theorem 2.2. [10]. Consider the disease transmission model given by (2.9) with $f(x)$ satisfying conditions $\mathrm{A}(1) - \mathrm{A}(5)$. If x_0 is a DFE of the model, then x_0 is locally asymptotically stable if $\mathcal{R}_0 < 1$, but unstable if $\mathcal{R}_0 > 1$, where $\mathcal{R}_0$ is defined by $\mathcal{R}_0 = \rho\big(FV^{-1}\big)$ and ρ is the spectral radius (dominate eigenvalue is magnitude).

2.2.4 Center manifold theorem

Theorem 2.3. [12] Consider the following general system of ordinary differential equation with a parameter ϕ

$$\frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}, \text{and} f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}) \tag{2.10}$$

Without loss of generality, it is assumed that 0 is an equilibrium for system (2.10) for all values of the parameter ϕ, (that is $f(0, \phi) \equiv 0$ for all ϕ).

Assume

(A1) : $\mathrm{A} = D_x\ f(0,0) = (\frac{\partial f_i}{\partial x_j}, (0,0))$ is the linearized matrix of system (2.10) around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts;

(A2) : Matrix A has a nonnegative right eigenvector ω and a left eigenvector υ corresponding to the zero eigenvalue.

Let f_k be the k^{th} component of f and

$$\begin{aligned} \tilde{a} &= \sum_{k,i,j=1}^{n} \upsilon_k \omega_i \omega_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\ \tilde{b} &= \sum_{k,i=1}^{n} \upsilon_k \omega_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0) \end{aligned}$$

The local dynamics of system 2.10 are totally round 0 determinate by $\hat{a}$ and $\hat{b}$.

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

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

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

iv. $\hat{a} < 0, \hat{b} > 0$. When ϕ changes from negative to positive , 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable. Particularly, if $\hat{a} > 0$ and $\hat{b} > 0$, then a backward bifurcation occurs at $\phi = 0$.

CHAPTER 3 ANALYSIS OF A VACCINATED EPIDEMIC MODEL OF INFLUENZA

This chapter is organized as follows. The model is displayed in section 3.1. The model with vaccination which illustrated by Samsuzzoha, et al. [4] is divided into five population groups : susceptible (S), vaccinated (V), exposed (E), Infectious (I) and recovered (R). In section 3.2, the effect of vaccine studied via mathematical analysis of model including stability of equilibria of the model has been provided.

3.1 Model Formulation

A vaccinated epidemic model of influenza is based on monitoring the dynamics of the sub-population (susceptible;$S(t)$, vaccinated;$V(t)$, exposed(latent); $E(t)$, infectious; $I(t)$, recovered; $R(t)$ at time t. Thus the total population in the system is given by $N = S(t) + V(t) + E(t) + I(t) + R(t)$.

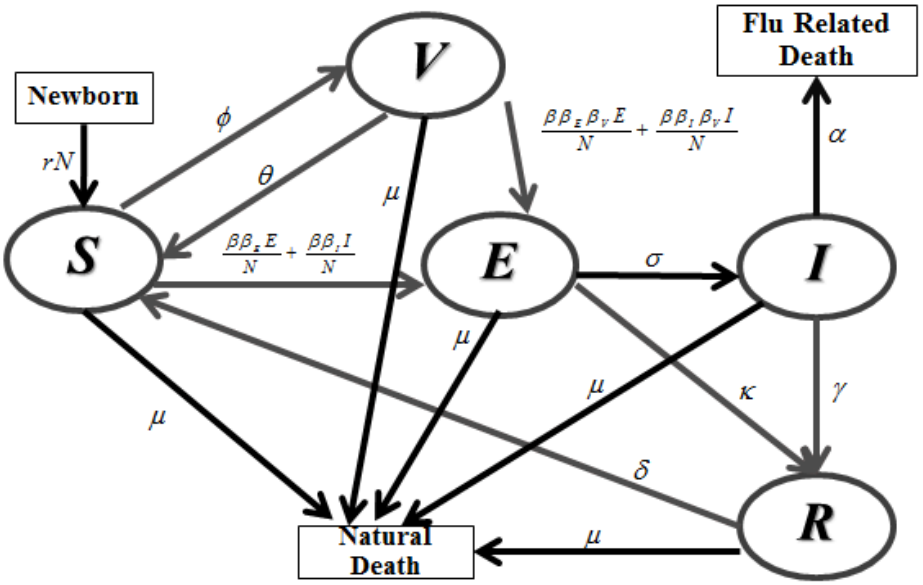

Figure 3.1: The flow diagram of *SVEIR* model

The susceptible population is increased by new born and vaccinated population who loss immunity because of earlier infection and vaccination. The susceptible population is reduced through vaccination (moving to V), infection (moving to I) and by natural death.

The vaccinated population is increased by vaccination of susceptible. Since the vaccine does not confer immunity to all vaccine recipients the the vaccinated population is reduced through susceptible (moving to S), vaccinated individuals may become exposed (moving to E) and by natural death.

The exposed population is increased by vaccinated who remain susceptible even after being vaccination, by susceptible who are not vaccinated (moving to E). The exposed population is reduced by the recover (moving to R), natural death and infected (moving to I).

The infected population is increased by exposed individuals become to infected. The infected population is reduced by natural death, flu related death and recover (moving to R).

The recovered population is increased by recovered individuals from infected and exposed. The recovered population is reduced by natural death and loss immunity (moving to S).

A flow diagram of these processes is shown in Figure 3.1. The details of transmissions between the populations can be transformed to the following non-linear differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= -\beta\beta_{_E}\frac{ES}{N} - \beta\beta_{_I}\frac{IS}{N} - \phi S - \mu S + \delta R + \theta V + rN, \\
\frac{dV}{dt} &= -\beta\beta_{_E}\beta_{_V}\frac{EV}{N} - \beta\beta_{_I}\beta_{_V}\frac{IV}{N} - \mu V - \theta V + \phi S, \\
\frac{dE}{dt} &= \beta\beta_{_E}\frac{ES}{N} + \beta\beta_{_I}\frac{IS}{N} + \beta\beta_{_E}\beta_{_V}\frac{EV}{N} + \beta\beta_{_I}\beta_{_V}\frac{IV}{N} - (\mu+\kappa+\sigma)E, \\
\frac{dI}{dt} &= \sigma E - (\mu+\alpha+\gamma)I, \\
\frac{dR}{dt} &= \kappa E + \gamma I - \mu R - \delta R.
\end{aligned} \tag{3.1}$$

and

$$N = S + V + E + I + R. \tag{3.2}$$

The total population is defined by the derivative of N with depends on t is

$$\frac{dN}{dt} = rN - \mu N - \alpha I. \tag{3.3}$$

To reduce the model (3.2) in terms of the dimensionless proportions of susceptible, vaccinated, exposed, infectious and recovered populations, let

$$s = \frac{S}{N}, v = \frac{V}{N}, e = \frac{E}{N}, i = \frac{I}{N}, r_1 = \frac{R}{N}. \tag{3.4}$$

After calculating and replacing s by S, v by V, e by E, i by I and r_1 by R, systems 3.2-3.3 can be written as

$$\begin{aligned}
\frac{dS}{dt} &= -\beta\beta_{_E}ES - \beta\beta_{_I}IS + \alpha IS - \phi S - rS + \delta R + \theta V + r,\\
\frac{dV}{dt} &= -\beta\beta_{_E}\beta_{_V}EV - \beta\beta_{_I}\beta_{_V}IV - rV + \alpha IV - rV - \theta V + \phi S,\\
\frac{dE}{dt} &= \beta\beta_{_E}ES + \beta\beta_{_I}IS + \beta\beta_{_E}\beta_{_V}EV + \beta\beta_{_I}\beta_{_V}IV + \alpha IE - (r+\kappa+\sigma)E,\\
\frac{dI}{dt} &= \sigma E - (r+\alpha+\gamma)I + \alpha I^2,\\
\frac{dR}{dt} &= \kappa E + \gamma I - rR - \delta R + \alpha IR.
\end{aligned} \tag{3.5}$$

and

$$1 = S + V + E + I + R.$$

Table 3.1: Description and parameter values of the models (3.5)

Parameters	Descriptions	Values	References
β	Contact rate	0.514 day^{-1}	[4]
β_E	Ability to cause infection by exposed individuals	0.250	[4]
β_I	Ability to cause infection by infectious individuals	1.000	[4]
β_V	Ability to cause infection by vaccination individuals	0.1	[4]
σ	Rate of latency	0.5 day^{-1}	[4]
γ	Rate of clinically ill	0.2 day^{-1}	[4]
δ	Rate of duration of immunity loss	1/365 day^{-1}	[4]
μ	Natural mortality rate	5.5×10^{-8} day^{-1}	[4]
r	Birth rate	7.14×10^{-5} day^{-1}	[4]
κ	Recovery rate of latents	1.857×10^{-4} day^{-1}	[4]
α	Flu induced mortality rate	9.3×10^{-6} day^{-1}	[4]
θ	Rate of susceptible	1/365 day^{-1}	[4]
ϕ	Rate of vaccination	Varied	[4]

3.2 Analysis of the Model

The equilibrium points will be explored in the case of disease-free and endemic. In each points, the locally of its associated equilibrium is investigated to understand the effect of vaccine for disease transmission.

3.2.1 Disease-Free Equilibrium

In the absence of infection (that is $E = I = 0$), the model (3.2) has a unique disease-free equilibrium (DFE), P_0, obtained by setting the derivatives in (3.2) of zero. The disease-free equilibrium of the system (3.2) is given by

$$P^0 = (\frac{S^0}{N}, \frac{V^0}{N}, \frac{E^0}{N}, \frac{I^0}{N}, \frac{R^0}{N}) = (\frac{r(\mu+\theta)}{\mu(\mu+\theta+\phi)}, \frac{r\phi}{\mu(\mu+\theta+\phi)}, 0, 0, 0). \tag{3.6}$$

The basic reproductive number of (3.2) can be established using the next generation matrix operator method. Using the notation in Lemma 2.1 and Theorem 2.2, the $\mathcal{F}$ and $\mathcal{V}$ (for the transition term) are given by

$$\mathcal{F} = \begin{pmatrix} \frac{\beta\beta_E ES}{N} + \frac{\beta\beta_I IS}{N} + \frac{\beta\beta_E\beta_V EV}{N} + \frac{\beta\beta_I\beta_V IV}{N} \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

and

$$\mathcal{V} = \begin{pmatrix} (\mu+\kappa+\sigma)E \\ -\sigma E + (\mu+\alpha+\gamma)I \\ -\kappa E - \gamma I + \mu R + \delta R \\ \frac{\beta\beta_E ES}{N} + \frac{\beta\beta_I IS}{N} + \phi S + \mu S - \delta R - \theta V - rN \\ \frac{\beta\beta_E\beta_V EV}{N} + \frac{\beta\beta_I\beta_V IV}{N} + \mu V + \theta V - \phi S \end{pmatrix}$$

The linear stability of P^0 can be established using the next generation operator method on the system (3.2). Using the notation in Lemma 2.1 and Theorem 2.2, the matrices F for the new infection terms and V for the transition terms are given, respectively, by

$$D\mathcal{F}(P_0) = F = \begin{pmatrix} \frac{r\beta\beta_E(\mu+\theta+\beta_V\phi)}{\mu(\mu+\theta+\phi)} & \frac{r\beta\beta_I(\mu+\theta+\phi)}{\mu(\mu+\theta+\phi)} \\ 0 & 0 \end{pmatrix}$$

and

$$D\mathcal{V}(P_0) = V = \begin{pmatrix} \mu+\kappa+\sigma & 0 \\ -\sigma & \mu+\alpha+\gamma. \end{pmatrix}.$$

Hence, the basic reproductive number for model 3.2 is given by $R_{VAC} = \rho(FV^{-1})$, where ρ is the spectral radius.

$$R_{VAC} = \frac{r\beta(\mu\beta_E + \alpha\beta_E + \gamma\beta_E + \sigma\beta_I)(\mu+\theta+\beta_V\phi)}{\mu(\mu+\alpha+\gamma)(\mu+\kappa+\sigma)(\mu+\theta+\beta_V\phi).} \tag{3.7}$$

Hence, using Theorem 2.2, the following result is established.

Theorem 3.1. The DFE, P^0 , of the model (3.2) is locally asymptotically stable (LAS) if $R_{VAC} < 1$, and unstable if $R_{VAC} > 1$

The basic reproductive number [10], denoted as R_{VAC} , represents the expected number of secondary cases produced in a completely susceptible population, by a typical infective individual. If $R_{VAC} < 1$, when infected individuals, its entire period of infectivity will produce less than one infected individuals on average. Thus, disease will be wiped out of population. On the contrary, if $R_{VAC} > 1$, then infected individuals in its entire infective period having contact with susceptible individuals will produce more than one infected individuals on average, which will then lead to the disease invading the susceptible population.

3.2.2 Endemic Equilibrium

In order to find equilibrium of the model (3.2) (that is, equilibria where at least one of infected components of the model (3.2) is non-zero), the following steps are taken. Let $P^* = (\tilde{S}*, \tilde{V}^*, \tilde{E}^*, \tilde{I}^*, \tilde{R}^*) = (\frac{S^*}{N}, \frac{V^*}{N}, \frac{E^*}{N}, \frac{I^*}{N}, \frac{R^*}{N})$ represents any arbitrary endemic equilibrium of the model (3.2). Further, let

$$G = \beta\beta_E\tilde{E}^* + \beta\beta_I\tilde{I}^*. \tag{3.8}$$

Solving the equations in (2.2) at the steady state gives

$$\begin{aligned}
\tilde{S}^* &= \frac{\theta\tilde{V}^* + r + \delta\tilde{R}^*}{G^* + \mu + \phi}, \\
\tilde{V}^* &= \frac{\phi\tilde{S}^*}{G^*\beta_V + \mu + \theta}, \\
\tilde{E}^* &= \frac{G^*(\tilde{S}^* + \beta_V\tilde{V}^*)}{\mu + \kappa + \sigma}, \\
\tilde{I}^* &= \frac{\sigma\tilde{E}^*}{\mu + \alpha + \gamma}, \\
\tilde{R}^* &= \frac{\tilde{E}^*(\kappa\mu + \kappa\alpha + \kappa\gamma + \gamma\sigma)}{(\mu + \delta)(\mu + \alpha + \gamma)}.
\end{aligned} \tag{3.9}$$

where

$$\tilde{S}^* = \frac{S^*}{N}, \tilde{V}^* = \frac{V^*}{N}, \tilde{E}^* = \frac{E^*}{N}, \tilde{I}^* = \frac{I^*}{N}, \tilde{R}^* = \frac{R^*}{N}. \tag{3.10}$$

Substituting (3.8) into (3.9) and simplifying, it can be shown that the non-zero equilibrium of the model satisfy the following quadratic (in term of G)

$$G^*(a_0{G^*}^2 + b_0G^* + c_0) = 0. \tag{3.11}$$

Clearly, $G^* = 0$ corresponds to the diseases-free equilibrium P^0 given in (3.2.1). For $G^* \neq 0$ the positive equilibrium of the model (2.2) can be obtained by solving (3.12)

$$a_0{G^*}^2 + b_0G^* + c_0 = 0. \tag{3.12}$$

where

$a_0 = \beta_V(\delta\kappa k_4 + \delta\gamma\sigma - k_3k_4k_5)$,
$b_0 = \beta_V\phi\delta\kappa k_4 - k_3k_4k_5k_2 - k_3k_4k_5k_1\beta_V + \phi\delta\sigma\gamma\beta_V + \delta\kappa k_4k_2 + r\beta_V\beta\beta_E k_5k_4 +$
$rk_5\beta\beta_V\beta_I\sigma + \delta\gamma\sigma k_2$,
$c_0 = \dfrac{\mu k_5k_3k_4(k_2+\phi)}{(r\beta(k_2\beta_V\phi)(\beta_E k_4 + \beta_I\sigma))^2}[1 - R_{VAC}]$.

and

$$k_1 = \mu + \phi, k_2 = \mu + \theta, k_3 = \mu + \kappa + \sigma, k_4 = \mu + \alpha + \gamma, k_5 = \mu + \delta. \tag{3.13}$$

From solving (3.12)for G^* and substituting the result into (3.8). Thus, the positive endemic equilibrium of the model (3.2) are obtained by solving for G^* from the quadratic (3.12) and substituting the results (positive values of G) into the expression in (3.9).

Theorem 3.2. The vaccinated epidemic model has :
(i) a unique endemic equilibrium if $c_0 < 0 \Longleftrightarrow R_{VAC} > 1$,
(ii) a unique endemic equilibrium if $b_0 < 0$ and $c_0 = 0$ or $b_0^2 - 4a_0c_0 = 0$,
(iii) no endemic equilibrium otherwise.

3.2.3 Local Stability of Endemic Equilibrium

Theorem 3.3. If $R_{VAC} > 1$, then the unique endemic equilibrium P^* is locally asymptotically stable.

Proof. To apply Theorem 2.3 in Chapter 2, let let $S = x_1, V = x_2, E = x_3, I = x_4 and R = x_5$. The system (3.2) can be written in the form as follow:

$$\begin{aligned}
\frac{dx_1}{dt} &= -\beta\beta_{_E}x_3x_1 - \beta\beta_{_I}x_4x_1 + \alpha x_4x_1 - \phi x_1 - rx_1 + \delta x_5 + \theta x_2 + r,\\
\frac{dx_2}{dt} &= -\beta\beta_{_E}\beta_{_V}x_3x_2 - \beta\beta_{_I}\beta_{_V}x_4x_2 + \alpha x_4x_2 - rx_2 - \theta x_2 + \phi x_1,\\
\frac{dx_3}{dt} &= \beta\beta_{_E}x_3x_1 + \beta\beta_{_I}x_4x_1 + \beta\beta_{_E}\beta_{_V}x_3x_2 + \beta\beta_{_I}\beta_{_V}x_4x_2 + \alpha x_4x_3\\
&- (r+\kappa+\sigma)x_3,\\
\frac{dx_4}{dt} &= \sigma x_3 - (r+\alpha+\gamma)x_4 + \alpha x_4^2,\\
\frac{dx_5}{dt} &= \kappa x_3 + \gamma x_4 - rx_5 - \delta x_5 + \alpha x_4x_5.
\end{aligned} \tag{3.14}$$

It is found that the model (3.2) has the disease-free, P^0, and reproductive number,R_{VAC} which are identical to (3.6) and (5.3) , when $\mu = r$, respectively, in Section 3.2.1. Choosing $\beta = \beta^*$ as a bifurcation parameter and solving for $\beta = \beta^*$ from R_{VAC} gives

$$\beta = \beta^* = \frac{(r+\alpha+\gamma)(r+\kappa+\sigma)(r+\theta+\sigma)}{(r\beta_E + \alpha\beta_E + \gamma\beta_E + \sigma\beta_I)(r+\theta+\beta_V\phi)} \tag{3.15}$$

The Jacobian of the system evacuated at disease-free, P^0 when $\beta = \beta^*$ is given by

$$J(P^0,\beta^*) = \begin{pmatrix} -k_1 & \theta & -\frac{\beta_1 k_2}{(k_2+\phi)} & -\frac{\beta_2 k_2}{(k_2+\phi)} & \delta \\ \phi & -k_2 & -\frac{\beta_1\beta_V\phi}{(k_2+\phi)} & -\frac{\beta_2\beta_V\phi}{(k_2+\phi)} & 0 \\ 0 & 0 & \frac{\beta_1(k_2+\beta_V\phi)}{(k_4+\phi)} - k_3 & \frac{\beta_2(k_2+\beta_V\phi)}{(k_4+\phi)} & 0 \\ 0 & 0 & \sigma & -k_4 & 0 \\ 0 & 0 & \kappa & \gamma & -k_5 \end{pmatrix} \tag{3.16}$$

where

$$\beta_1 = \beta\beta_E, \beta_2 = \beta\beta_I, k_1 = r+\phi, k_2 = r+\theta,$$

$$k_3 = r+\kappa+\sigma, k_4 = r+\alpha+\gamma, k_5 = r+\delta.$$

It can be verified that the eigenvalues of (3.14) has a simple zero eigenvalue and the other negative eigenvalues. Hence, the DFE, P^0 is a nonhyperbolic equilibrium when $\beta = \beta^*$. The assumption (A1) of the Theorem (2.3) is then verified.

Further, the $J(P^0,\beta^*)$ eigenvectors are computed as follows.
Let $w = [w_1, w_2, w_3, w_4, w_5]^T$ and $v = [v_1, v_2, v_3, v_4, v_5]^T$ be a right and a left eigenvector of $J(P^0,\beta^*)$ respectively. It follows that the components of w are given by

$$\begin{aligned} w_1 &= w_4\frac{k_5{k_4}^2 - k_4k_7 - {k_4}^2k_6 - k_6\theta\phi + \beta_V k_5\theta\phi}{\theta\phi - \phi k_4 - rk_4}, \\ w_2 &= w_4\phi\frac{-rk_6 + k_4k_5 - k_7 - k_4k_6 - \phi k_6 + \beta_V\phi k_5 + r\beta_V k_5}{\theta\phi - \phi k_4 - rk_4}, \\ w_3 &= w_4\frac{k_2}{\sigma}, \\ w_4 &> 0, \\ w_5 &= w_4\frac{\kappa k_2 + \gamma\sigma}{\sigma(r+\delta)}. \end{aligned} \tag{3.17}$$

Similarly, the components of V are given by,

$$\begin{aligned} v_1 = 0, v_2 &= 0, v_3 = \frac{v_4k_2}{k_3\beta_I k_4 + k_3\beta_I\beta_V\phi}, \\ v_4 &> 0, v_5 = 0. \end{aligned} \tag{3.18}$$

where

$$\begin{aligned} k_1 &= r+\kappa+\sigma, k_2 = r+\alpha+\delta, k_3 = \frac{k_1k_2}{k_2\beta_E + \sigma\beta_I(k_4+\beta_V\phi)}, k_4 = r+\theta, \\ k_5 &= \frac{k_3(k_2\beta_E+\sigma\beta_I)}{\sigma}, k_6 = \frac{\alpha}{k_4+\phi}, k_7 = \frac{\delta(\kappa(r+\alpha+\gamma)+\gamma\sigma)}{\sigma(r+\delta)}, k_8 = k_2\beta_E + \sigma\beta_I. \end{aligned}$$

To compute the coefficients $\hat{a}$ and $\hat{b}$ (defined in Theorem 2.3):

$$\tilde{a} = \sum_{k,i,j=1}^{n} \upsilon_k \omega_i \omega_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \tag{3.19}$$

$$\tilde{b} = \sum_{k,i=1}^{n} \upsilon_k \omega_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*}(0,0) \tag{3.20}$$

the associated non-zero second-order partial derivatives of all functions on the right-hand sides of system (3.14) are evaluated at DFE and are given by

$$\begin{aligned}
\frac{\partial^2 f_1}{\partial x_1 \partial x_3} &= -\beta^* \beta_E, \frac{\partial^2 f_4}{\partial x_1 \partial x_4} = -\beta^* \beta_I + \alpha, \\
\frac{\partial^2 f_2}{\partial x_2 \partial x_3} &= -\beta^* \beta_E \beta_V, \frac{\partial^2 f_2}{\partial x_2 \partial x_4} = -\beta^* \beta_E \beta_V + \alpha, \\
\frac{\partial^2 f_3}{\partial x_1 \partial x_3} &= \beta^* \beta_E, \frac{\partial^2 f_3}{\partial x_1 \partial x_4} = \beta^* \beta_I, \\
\frac{\partial^2 f_3}{\partial x_2 \partial x_3} &= \beta^* \beta_E \beta_V, \frac{\partial^2 f_3}{\partial x_2 \partial x_4} = \beta^* \beta_I \beta_V, \\
\frac{\partial^2 f_3}{\partial x_3 \partial x_4} &= \alpha, \frac{\partial^2 f_4}{\partial {x_4}^2} = 2\alpha, \\
\frac{\partial^2 f_5}{\partial x_4 \partial x_5} &= \alpha, \frac{\partial^2 f_1}{\partial \beta^* \partial x_3} = -\frac{\beta_E(r+\theta)}{r+\theta+\phi}, \\
\frac{\partial^2 f_1}{\partial x_4 \partial \beta^*} &= -\frac{\beta_I(r+\theta)}{r+\theta+\phi}, \frac{\partial^2 f_2}{\partial x_3 \partial \beta^*} = -\frac{\beta_E \beta_V \phi}{r+\theta+\phi}, \\
\frac{\partial^2 f_2}{\partial x_4 \partial \beta^*} &= -\frac{\beta_I \beta_V \phi}{r+\theta+\phi}, \frac{\partial^2 f_3}{\partial x_3 \partial \beta^*} = \frac{\beta_E(r+\theta)}{r+\theta+\phi} + \frac{\beta_E \beta_V \phi}{r+\theta+\phi}, \\
\frac{\partial^2 f_3}{\partial x_4 \partial \beta^*} &= \frac{\beta_I(r+\theta)}{r+\theta+\phi} + \frac{\beta_I \beta_V \phi}{r+\theta+\phi}.
\end{aligned}$$

Thus, it follows from the above expressions that

$$\begin{aligned}
\tilde{a} &= \frac{2k_8 v_4 {w_4}^2 \beta^*}{k_1 r \beta_I \sigma \beta k_8 (k_4+\phi)}[r(\alpha k_2 k_8 + \sigma\alpha\beta_I k_1)(k_4+\phi) + Q_1 Q_2 + \phi\beta_V Q_1 Q_3 \\
&\quad -\{Q_1 Q_4\}] \\
\tilde{b} &= \frac{5 v_4 k_2 w_4 (k_4+\phi\beta_V)(k_2\beta_E + \sigma\beta I)}{k_1(k_4+\phi)}[\frac{\beta_E k_2 + \sigma\beta_I}{\sigma k_2 \beta_I}]
\end{aligned} \tag{3.21}$$

where Q_1=$\beta^* k_8 k_2 \beta_E + \beta_I \sigma \beta k_8$.
Q_2=$k_4 k_7 + {k_4}^2 k_6 + k_6 \theta \phi$.
Q_3=$r k_6 + k_7 + k_4 k_6 + \phi k_6$.
Q_4=${k_4}^2 k_5 + \theta\phi\beta_V k_5) + \phi\beta_V Q_1(k_5 k_4 + \phi\beta_V k_5 + r\beta_V k_5)$.

The coefficient $\tilde{a}$ is negative if $Q_1 Q_4 > r(\alpha k_2 k_8 + \sigma\alpha\beta_I k_1)(k_4+\phi) + Q_1 Q_2 + \phi\beta_V Q_1 Q_3)$ and $\tilde{b}$ is positive so that, according to Theorem (2.3), the unique endemic equilibrium point, P^*, is locally asymptotically stable whenever $R_{VAC} > 1$ and $\beta > \beta^*$

with β close to β^*. This completes the proof.

In particular, by, theory of center manifold is confirmed that the unique endemic equilibrium is locally asymptotically stable when $R_{VAC} > 1$.

3.2.4 The Optimal Vaccine Coverage Level

The epidemiological implication of Lemma (2.1) is that if model parameters can be selected (either via vaccination or other control measures) such that the basic reproductive number, R_{VAC} is less than unity, then the disease will be eradicated from the community. The effect of vaccinated rate, ϕ , on R_{VAC} is investigated by using sensitivity analysis (i.e., differentiating R_{VAC} partially with respect to control parameter ϕ). It is found that

$$\frac{\partial R_{VAC}}{\partial \phi} = -\frac{(1-\beta_V)(\mu+\theta)R_0}{(\mu+\theta+\phi)^2} \tag{3.22}$$

where R_0 is the basic reproductive number of infection for the vaccination-free model ($\phi = 0$).

$$R_0 = \frac{r\beta(\mu\beta_E + \alpha\beta_E + \gamma\beta_E + \sigma\beta_I)}{\mu(\mu+\alpha+\gamma)(\mu+\kappa+\sigma)}. \tag{3.23}$$

from which it follows that R_{VAC} is decreasing function of ϕ . It is clear that vaccination is critically important in making R_{VAC} less than unity. This implies that vaccination to susceptible populations will reduce number of infections down. From the definition of R_{VAC} in 3.7, it can be seen that if

$$\phi_c = \frac{(\mu+\theta)(R_0-1)}{1-\beta_V R_0} \tag{3.24}$$

then $R_{VAC} = 1$. Since R_{VAC} is a decreasing function of ϕ, it follows that if $\phi > \phi_c$ then $R_{VAC} < 1$. Thus, the condition for disease eradication is satisfied if $\phi > \phi_c$ and ϕ_c is called the optimal vaccine coverage level needed for disease eradication.

3.2.5 The effect of the rate of recovery (γ) latency(κ) and vaccination-induced immunity loss (θ) on (R_{VAC})

By differentiating R_{VAC} partially with respect to control parameters γ, κ and θ respectively, yield

$$\frac{\partial R_{VAC}}{\partial \gamma} = -\frac{(r\beta\sigma\beta_I)(\mu+\theta+\beta_V\phi)}{\mu(\mu+\theta+\phi)(\mu+\kappa+\sigma)(\mu+\alpha+\gamma)^2} < 0, \tag{3.25}$$

$$\frac{\partial R_{VAC}}{\partial \kappa} = -\frac{r\beta(\mu\beta_E + \alpha\beta_E + \gamma\beta_E + \sigma\beta_I)(\mu+\theta+\beta_V\phi)}{\mu(\mu+\alpha+\gamma)(\mu+\theta+\phi)(\mu+\kappa+\sigma)^2} < 0, \tag{3.26}$$

$$\frac{\partial R_{VAC}}{\partial \theta} = \frac{R_0(1-\beta_V)}{(\mu+\theta+\phi)^2} > 0, \tag{3.27}$$

Clearly, R_{VAC} is decreasing function of γ and κ , see (3.25) and (3.26), respectively. Whereas R_{VAC} is increasing function of θ , see (3.27).

CHAPTER 4 NUMERICAL EXPERIMENTS

The dynamic of the model (3.5) is illustrated in this chapter. All the numerical results were performed on a desktop computer with 4.00 GHz core i3 processer and 4 GB Ram. The software uses MATHLAB R2010a running under window 8. This chapter is organized as follows. The dynamic behavior of the model, the system (3.2) is integrated numerically by using fourth order Rungge-Kutta method with the parameter values in Table 4.1 ,where $N = 1,000,000$ and various value of ϕ . The initial conditions [4] are $S(0) = 0.799, V(0) = 0.197, E(0) = 0, I(0) = 0, R(0) = 0$.

Table 4.1: Description and parameter values of the models (3.2)

Parameters	**Descriptions**	**Values**	**References**
β	Contact rate	0.514 day^{-1}	[4]
β_E	Ability to cause infection by exposed individuals	0.250	[4]
β_I	Ability to cause infection by infectious individuals	1.000	[4]
β_V	Ability to cause infection by vaccination individuals	0.1	[4]
σ	Rate of latency	0.5 day^{-1}	[4]
γ	Rate of clinically ill	0.2 day^{-1}	[4]
δ	Rate of duration of immunity loss	1/365 day^{-1}	[4]
μ	Natural mortality rate	5.5×10^{-8} day^{-1}	[4]
r	Birth rate	7.140×10^{-5} day^{-1}	[4]
κ	Recovery rate of latents	1.857×10^{-4} day^{-1}	[4]
α	Flu induced mortality rate	9.3×10^{-6} day^{-1}	[4]
θ	Rate of susceptible	1/365 day^{-1}	[4]
ϕ	Rate of vaccination	Varied	[4]

With parametervalues in Table 4.1 , the threshold vaccination coverage or critical vaccination parameter is $\phi_c = 0.00715$. Table **??** depicts the variables of the model at steady-state as a function of ϕ and R_{VAC} . It is clear from this table that when the vaccination coverage level (ϕ) increases, the value of R_{VAC} decreases. The result verify that the endemic equilibrium, $P^* = (\tilde{S}^*, \tilde{V}^*, \tilde{E}^*, \tilde{I}^*, \tilde{R}^*)$ (that is the number of exposed ($\tilde{E}^*$) and infectious ($\tilde{I}^*$) individuals are not zero) is stable if the vaccination coverage level (ϕ)is below the threshold (ϕ_c) . Thus, the disease will persist in the population since R_{VAC} is greater than unity. The profiles of infected populations for $\phi = 0, 0.003, 0.005$. are depicted in Figure. 4.1 . The result show, as increases, the number of infectious individual decreases and the duration of outbreak is delayed before convergence to the corresponding endemic equilibrium as shown in Table **??**. However, when ϕ is increased to values greater than ϕ_c , such as $\phi = 0.0072$ Table **??** confirms that the disease-free equilibrium (P^0) is stable (since R_{VAC} is less than unity in this case) and the infected population (the sum of exposed and infected individuals) vanishes in time. This leads to the eradication of

the disease from the community. These simulation results are in line with Theorem 2.2 in Chapter 2.

The effect of the recovery rate of latent(κ), the recovery rate of infectious(γ), and vaccination-induced immunity loss rate (θ) are investigated using the parameter values in Table 4.1,$\phi = 0.001$ and vary the parameters κ , γ and θ , respectively. The results are tabulated in Table 4.3-4.5. Tables 4.3 and **??** show that the number of infectious individuals decrease as κ and γ increase. Table 4.5 also shows that increasing the duration of the loss of immunity induced by vaccination increase the number of of infectious individuals because it reduces the threshold vaccination coverage (ϕ_c) which is critically important for the success of public health strategies for controlling an epidemic.

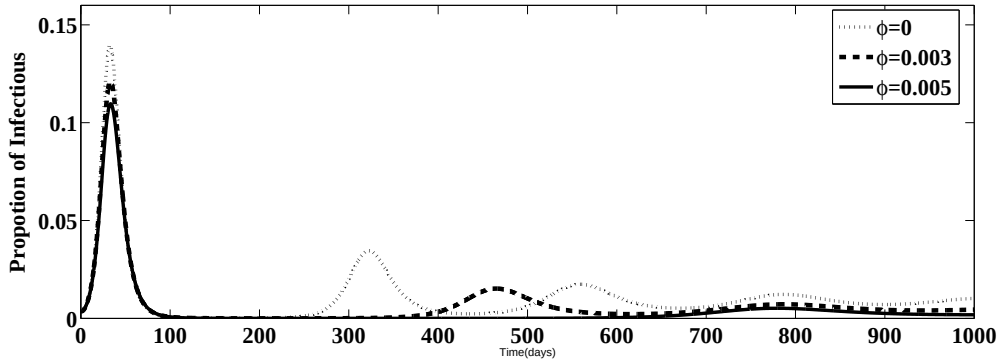

Figure 4.1: Profile of the proportion of infectious individuals using $\phi = 0, 0.003, 0.005$.

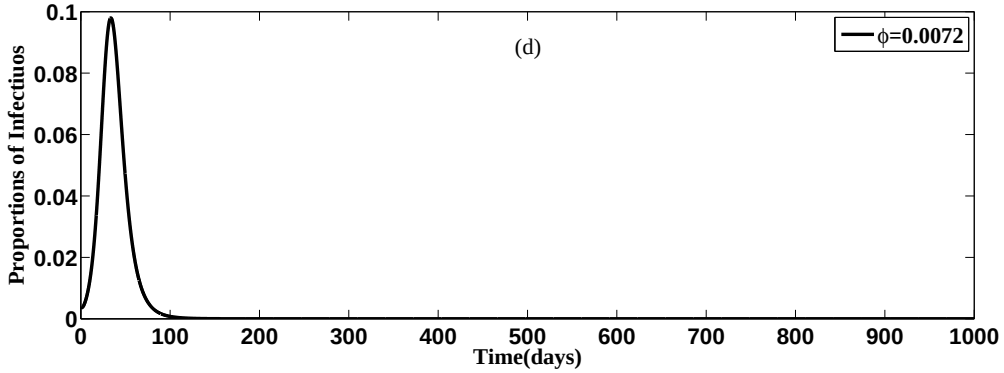

Figure 4.2: Profile of the proportion of infectious individuals using $\phi = 0.0072$.

Table 4.2: Effect of vaccination coverage(ϕ) on R_{VAC} And S^*, V^*, E^*, I^*, R^* at steady state

ϕ	R_{VAC}	S^*	V^*	E^*	I^*	R^*
0	2.82	354,045	0	3,562	8,900	633,493
0.003	1.51	322,759	312,855	2,009	5021	357,356
0.005	1.19	302,812	512,349	1,019	2,546	181,274
0.007	1.01	283,657	703,902	68	171	12,202
0.0071	1.00	282,718	713,261	22	55	3,944
0.0072	0.99	280,800	719,200	0	0	0

Table 4.3: Effect of recovery rate of latents(κ)on R_{VAC} And S^*, V^*, E^*, I^*, R^* at steady state

κ	R_{VAC}	S^*	V^*	E^*	I^*	R^*
0	2.15	343,316	105,952	3,037	7,591	540,104
0.1	1.79	411,447	132,370	2,103	5,256	448,824
0.3	1.34	547,613	186,154	924	2,310	262,999
0.5	1.07	683,706	240,667	210	526	74,891
0.55	1.02	717,723	254,368	74	185	27,650
0.6	0.98	737,610	262,390	0	0	0

Table 4.4: Effect of recovery rate of infectious(γ)on R_{VAC} And S^*, V^*, E^*, I^*, R^* at steady state

γ	R_{VAC}	S^*	V^*	E^*	I^*	R^*
0.1	4.11	180,939	45,862	4,206	21,017	747,976
0.2	2.15	343,444	106,001	3,035	7,586	539,934
0.3	1.50	491,523	163,890	1,908	3,180	339,499
0.4	1.17	627,159	217,960	859	1,074	152,948
0.45	1.06	690,806	243,529	364	405	64,896
0.5	0.98	737,610	262,390	0	0	0

Table 4.5: Effect of rate of vaccination-induced immunity(θ)on R_{VAC} And S^*, V^*, E^*, I^*, R^* at steady state

θ	R_{VAC}	S^*	V^*	E^*	I^*	R^*
0.0001	0.65	146,320	853,680	0	0	0
0.0002	0.82	213,465	786,535	0	0	0
0.0003	0.97	270,818	729,182	0	0	0
0.00035	1.03	297,987	560,569	779	1,948	138,717
0.0004	1.10	306,101	479,436	1,182	2,955	210,326

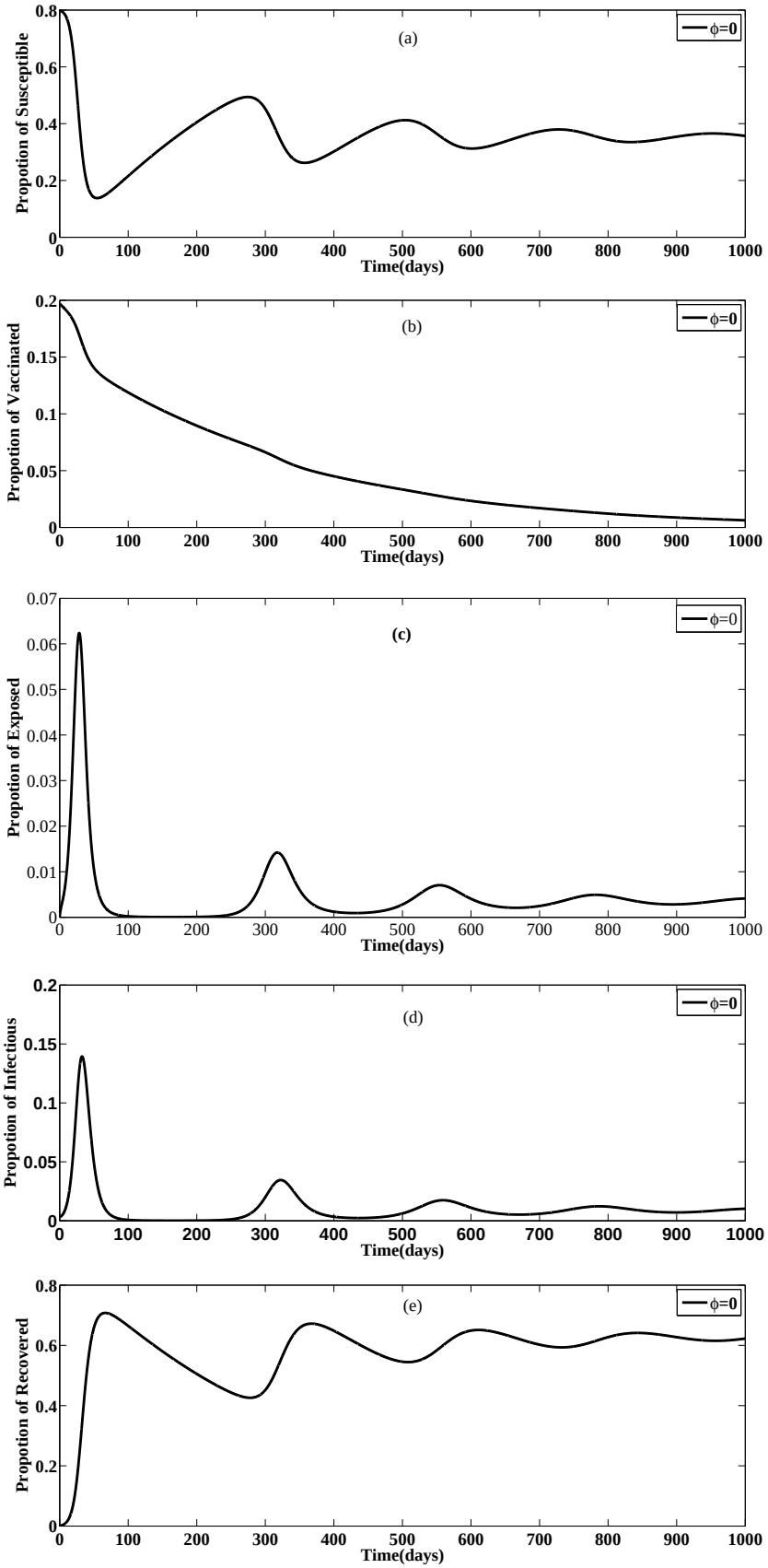

Figure 4.3: Profile of the proportion of susceptible, vaccinated, exposed, infectious, recovered individuals using $\phi = 0$.

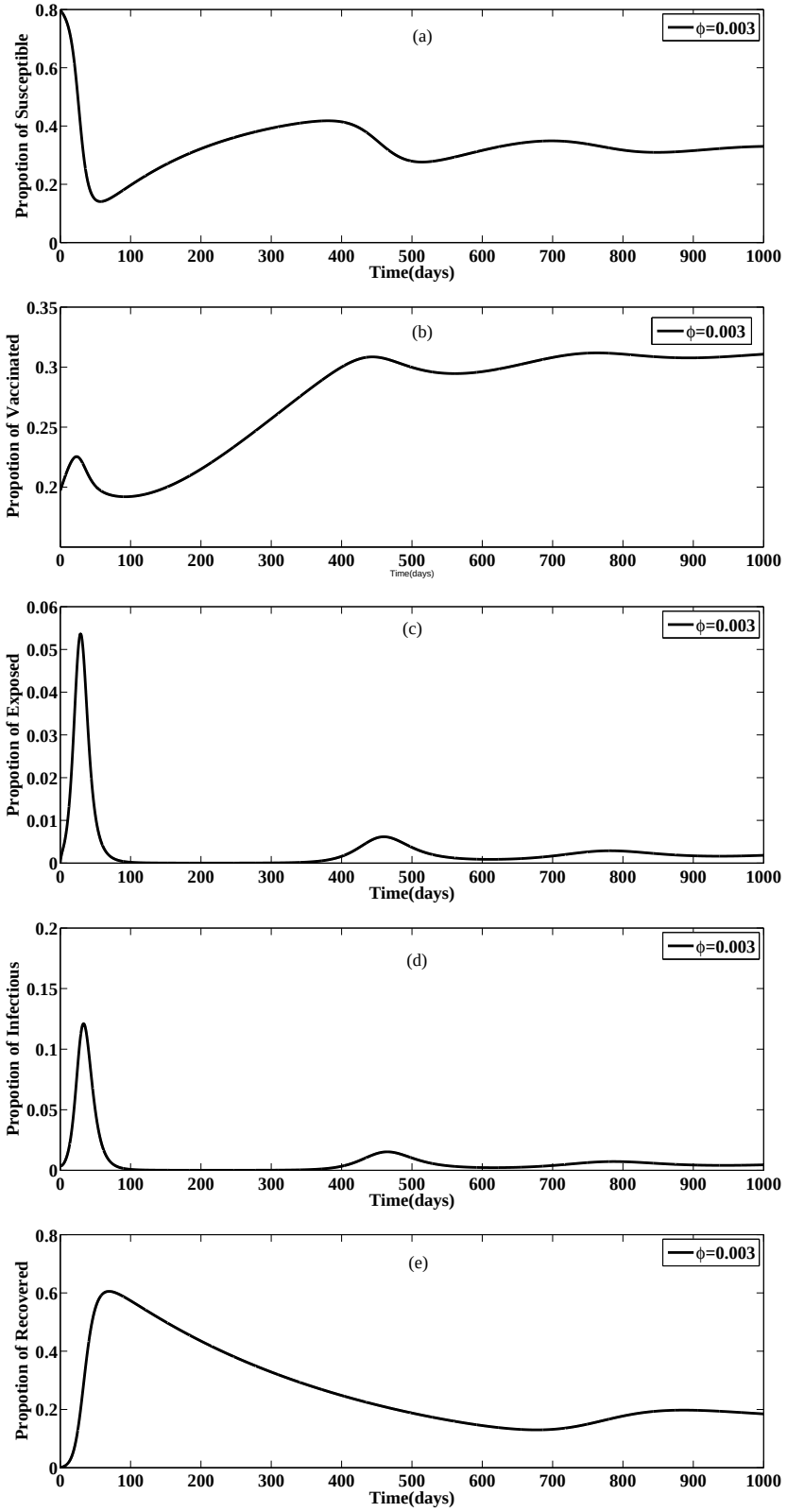

Figure 4.4: Profile of the proportion of susceptible, vaccinated, exposed, infectious, recovered individuals using $\phi = 0.003$.

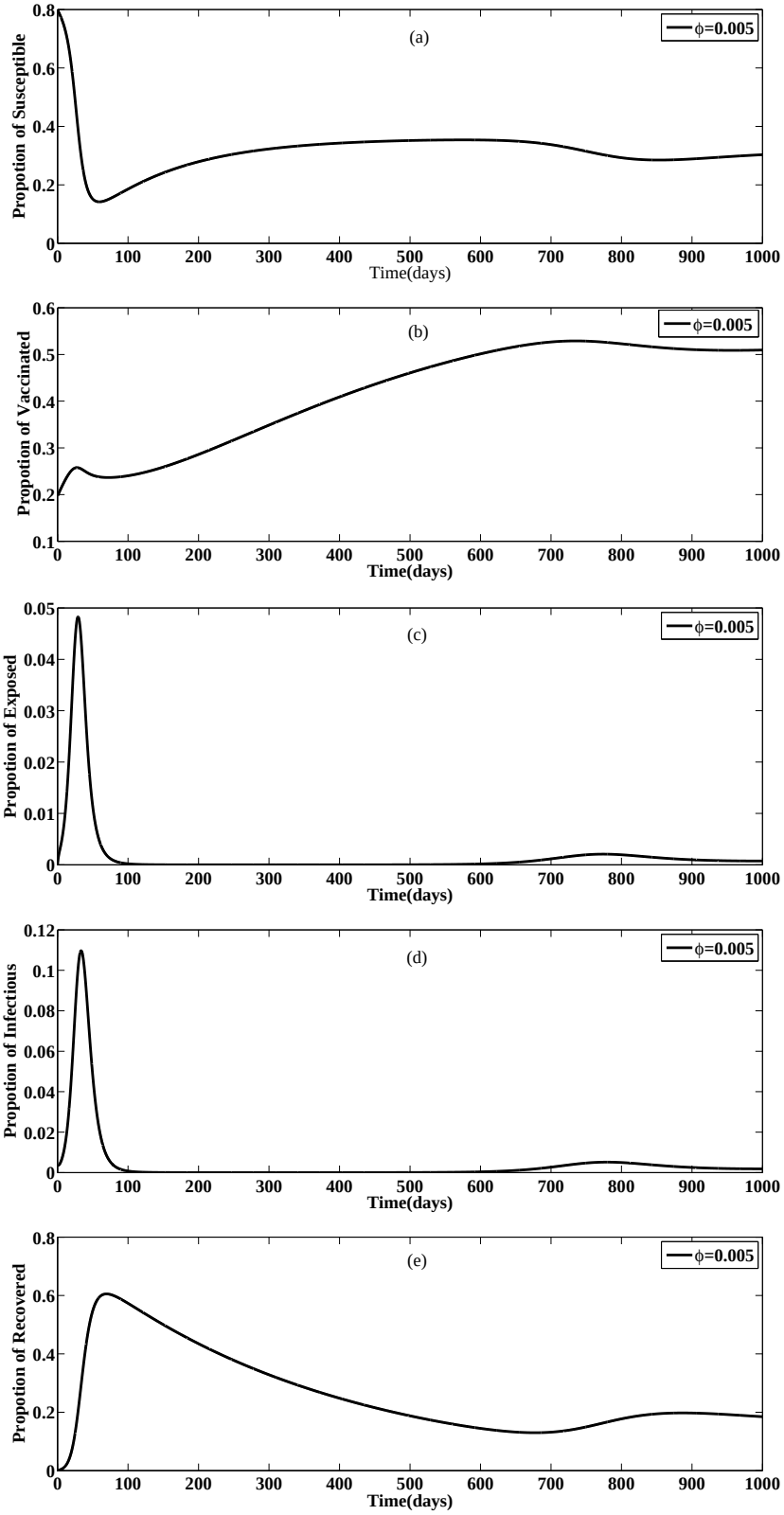

Figure 4.5: Profile of the propotion of susceptible, vaccinated, exposed, infectious, recovered individuals using $\phi = 0.005$.

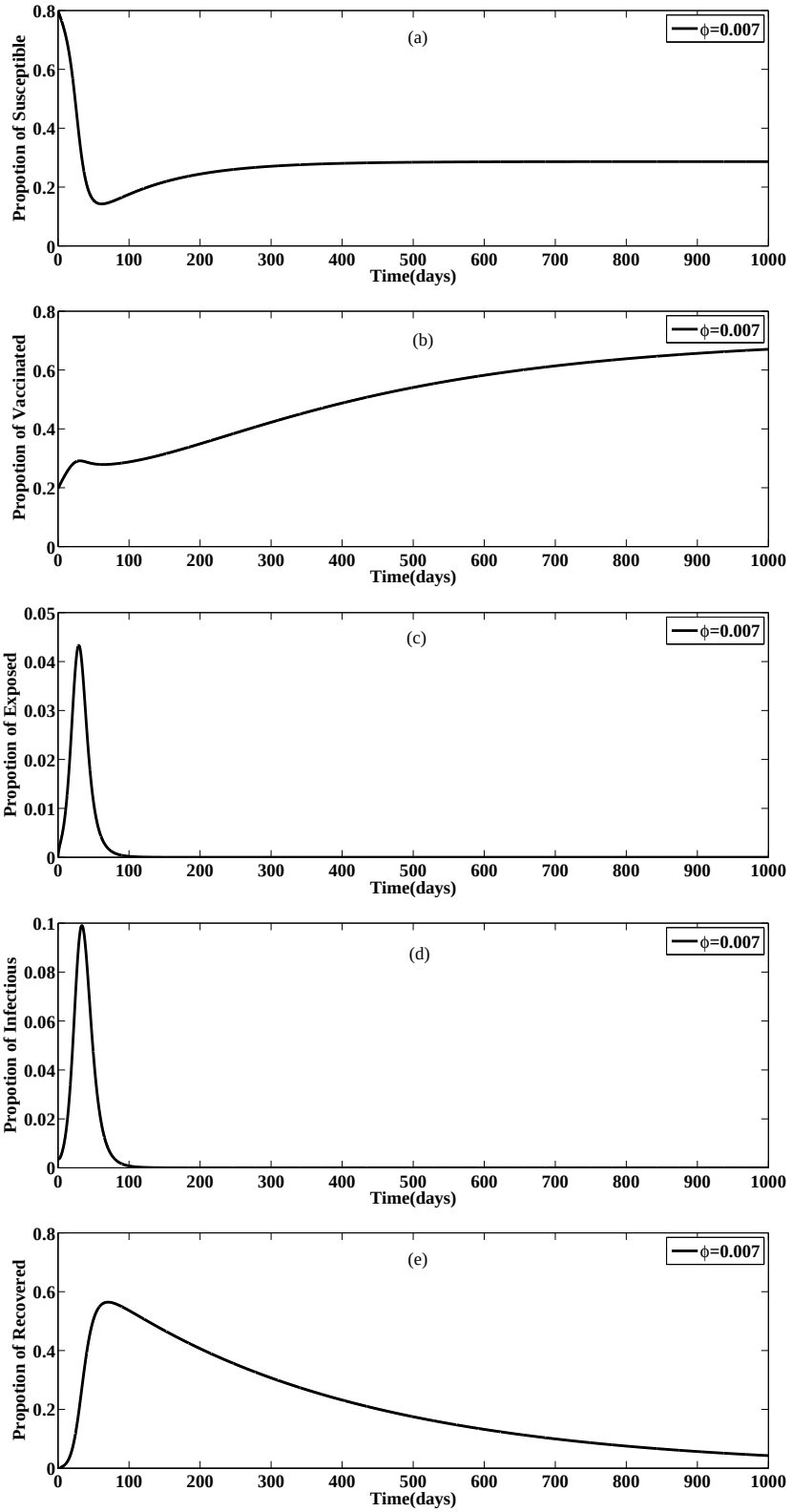

Figure 4.6: Profile of the propotion of susceptible, vaccinated, exposed, infectious, recovered individuals using $\phi = 0.007$.

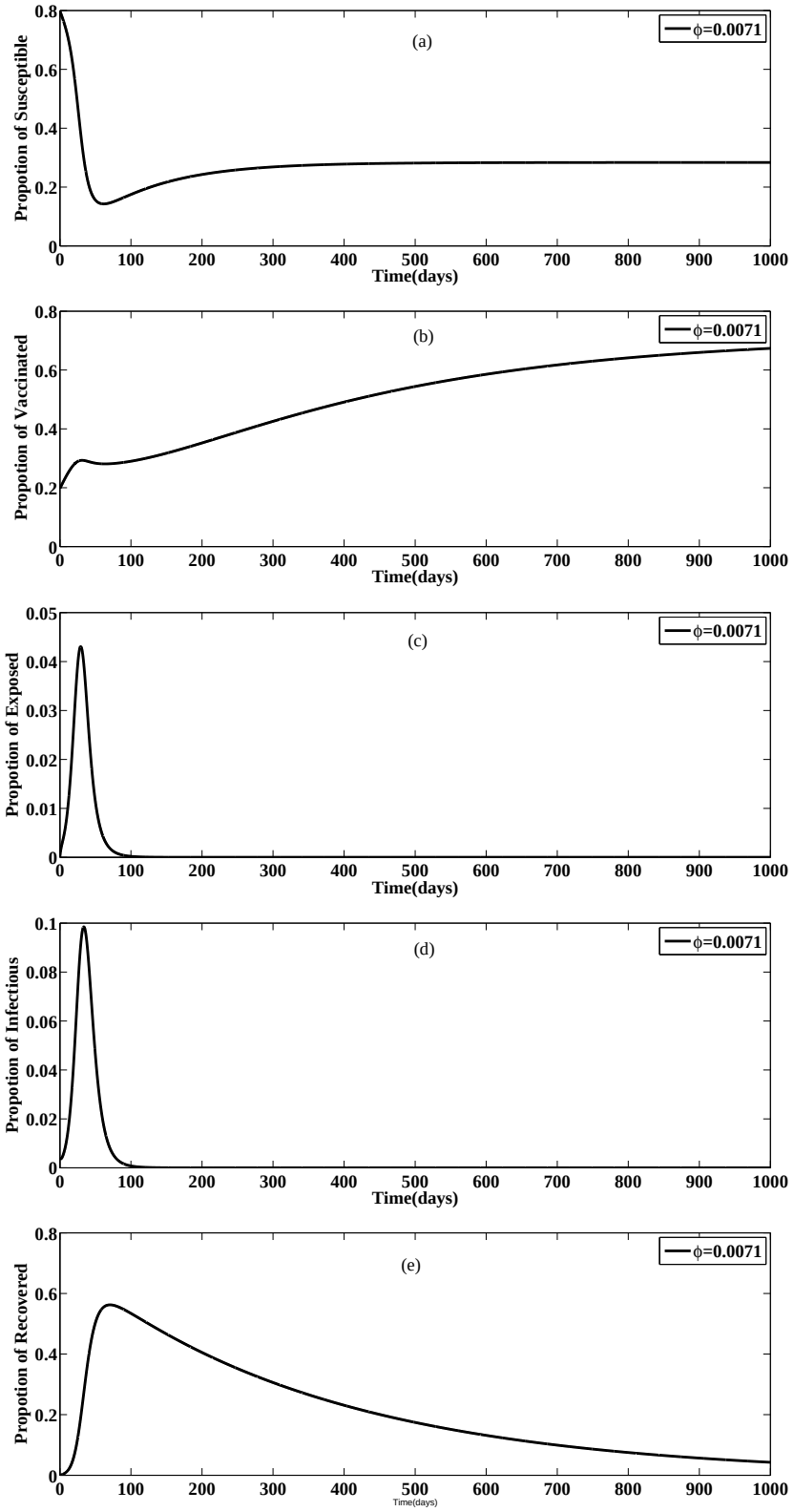

Figure 4.7: Profile of the propotion of susceptible, vaccinated, exposed, infectious, recovered individuals using $\phi = 0.0071$.

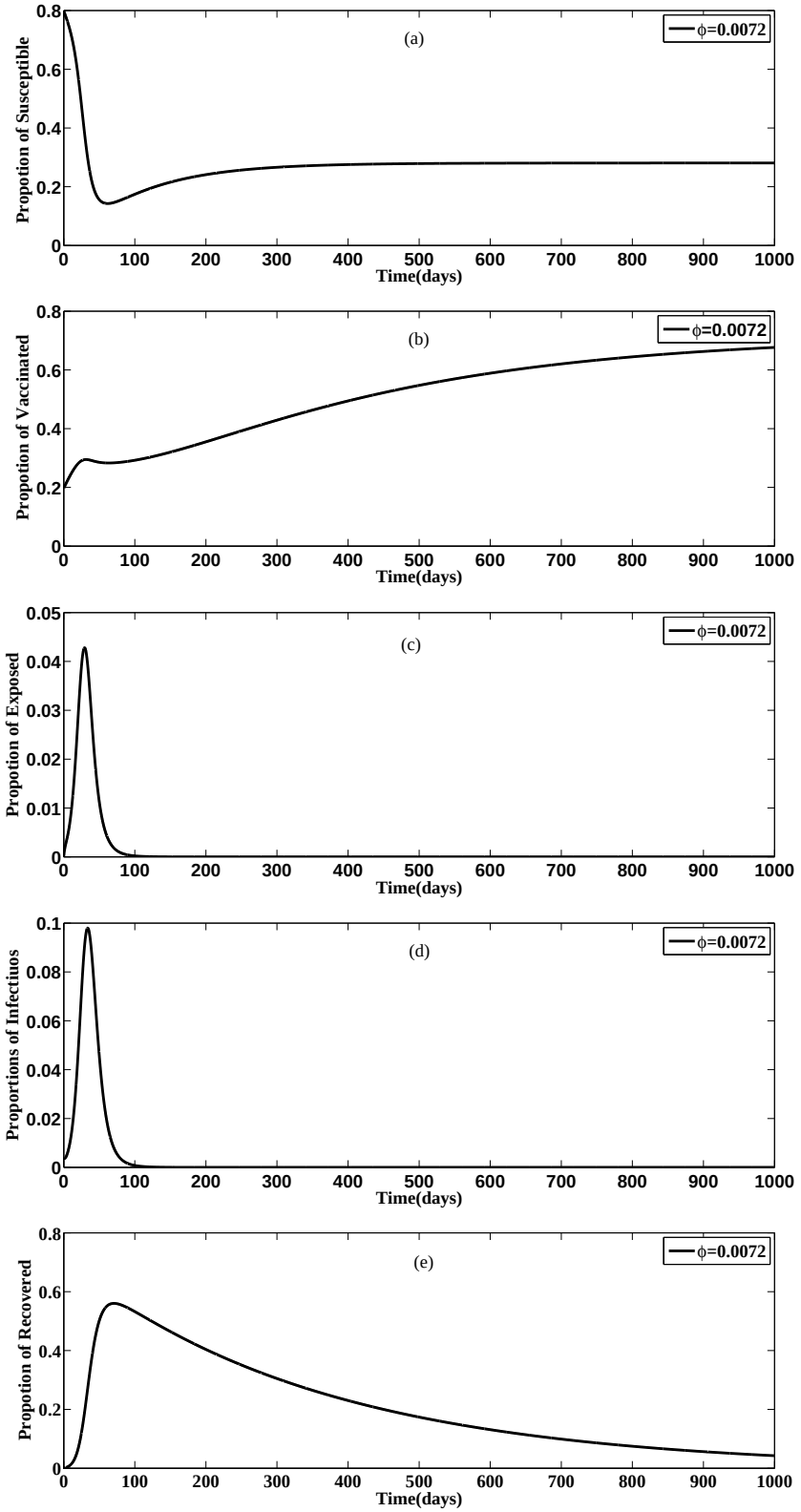

Figure 4.8: Profile of the propotion of susceptible, vaccinated, exposed, infectious, recovered individuals using $\phi = 0.0072$.

CHAPTER 5 DISCUSSIONS AND CONCLUSIONS

5.1 Conclusion

In this thesis using an influenza model with vaccination presented in [3] analyzed stability of disease-free equilibrium and endemic equilibrium.

$$\begin{aligned}
\frac{dS}{dt} &= -\beta\beta_{_E}\frac{ES}{N} - \beta\beta_{_I}\frac{IS}{N} - \phi S - \mu S + \delta R + \theta V + rN, \\
\frac{dV}{dt} &= -\beta\beta_{_E}\beta_{_V}\frac{EV}{N} - \beta\beta_{_I}\beta_{_V}\frac{IV}{N} - \mu V - \theta V + \phi S, \\
\frac{dE}{dt} &= \beta\beta_{_E}\frac{ES}{N} + \beta\beta_{_I}\frac{IS}{N} + \beta\beta_{_E}\beta_{_V}\frac{EV}{N} + \beta\beta_{_I}\beta_{_V}\frac{IV}{N} - (\mu+\kappa+\sigma)E, \\
\frac{dI}{dt} &= \sigma E - (\mu+\alpha+\gamma)I, \\
\frac{dR}{dt} &= \kappa E + \gamma I - \mu R - \delta R.
\end{aligned} \tag{5.1}$$

The total population is defined by the derivative of N with respect to t is

$$N = S + V + E + I + R, \frac{dN}{dt} = rN - \mu N - \alpha I. \tag{5.2}$$

The basic reproductive number of the model is derived by using next generation method.

$$R_{VAC} = \frac{r\beta(\mu\beta_E + \alpha\beta_E + \gamma\beta_E + \sigma\beta_I)(\mu + \theta + \beta_V\phi)}{\mu(\mu+\alpha+\gamma)(\mu+\kappa+\sigma)(\mu+\theta+\phi).} \tag{5.3}$$

This number (5.3) is the threshold condition for the existence of the endemic state. Stability analysis of the model (3.2) shows that the disease-free equilibrium (P^0) is locally asymptotically stable, that is no endemic equilibrium (P^*), if the basic reproductive number is less than unity $R_{VAC} < 1$ and unstable when $R_{VAC} > 1$

On the other hand, by theory of center manifold, there is non-existence endemic equilibrium when $R_{VAC} < 1$. This theory is confirmed that the unique endemic equilibrium is locally asymptotically stable when $R_{VAC} > 1$. The model is analyzed to gain insight into their dynamical features and used to monitor transmission dynamics in a population. The study shows the following :

The vaccination coverage level, ϕ_c is defined and is given by

$$\phi_c = \frac{(\mu+\theta)(R_0 - 1)}{(1 - \beta_V R_0)} \tag{5.4}$$

where

$$R_0 = \frac{\beta(\mu\beta_E + \alpha\beta_E + \gamma\beta_E + \sigma\beta_E)}{(\mu+\alpha+\gamma)(\mu+\kappa+\sigma)}$$

is the reproductive number of infection for the vaccination-free model ($\phi = 0$).

From the parameters in Table 4.1, The optimal vaccine coverage level is 0.00715. The reproductive number R_{VAC} is less than one provided the vaccination coverage level exceeds a certain threshold ϕ_c. This result predicts in Table **??**. Meanwhile, the endemic equilibrium is stable if the vaccination coverage level (ϕ) is less than ϕ_c, see Table **??** and Figure 4.1 Meanwhile, the endemic equilibrium is stable if the vaccination coverage level (ϕ) is less than 0.00715 , see Table **??** and Figure 4.2.

The relative importance parameters in the transmission are tabulated in Tables **??**-4.5 These results $\phi, \theta, \kappa, \gamma$ are the sensitive parameters for S^*, V^*, E^*, I^*, R^*. The results also show that the use of vaccines that offer life-long protection is a crucial public health objective for disease control or eradication. This is especially critical in countries where finances play a critical role in the number of people who receive vaccines.

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APPENDICES

Appendix A To reduce the model (3.2) in terms of the dimensionless proportions of susceptible, vaccinated, exposed, infectious and recovered populations,
let

$$s = \frac{S}{N}, v = \frac{V}{N}, e = \frac{E}{N}, i = \frac{I}{N}, r_1 = \frac{R}{N}.$$

To calculate derivative of s, v, e, i and r_1 with time t.

$$\begin{aligned}
\frac{ds}{dt} &= \frac{d\frac{S}{N}}{dt} \\
&= \frac{1}{N}[\frac{dS}{t} - s\frac{dN}{dt}] \\
&= -\beta\beta_{_E} es - \beta\beta_{_I} is + \alpha is - \phi s - rs + \delta r_1 + \theta v + r \\
\frac{dv}{dt} &= \frac{d\frac{V}{N}}{dt} \\
&= \frac{1}{N}[\frac{dV}{t} - v\frac{dN}{dt}] \\
&= -\beta\beta_{_E}\beta_{_V} ev - \beta\beta_{_I}\beta_{_V} iv - \alpha iv - \theta v + \phi s \\
\frac{de}{dt} &= \frac{d\frac{E}{N}}{dt} \\
&= \frac{1}{N}[\frac{dE}{t} - e\frac{dN}{dt}] \\
&= \beta\beta_{_E} es + \beta\beta_{_I} is + \beta\beta_{_E}\beta_{_V} ev + \beta\beta_{_I}\beta_{_V} iv - (r + \kappa + \sigma)e \\
\frac{di}{dt} &= \frac{d\frac{I}{N}}{dt} \\
&= \frac{1}{N}[\frac{dI}{t} - i\frac{dN}{dt}] \\
&= \sigma e - (r + \alpha + \gamma)i + \alpha i^2 \\
\frac{dr_1}{dt} &= \frac{d\frac{R}{N}}{dt} \\
&= \frac{1}{N}[\frac{dR}{t} - r_1\frac{dN}{dt}] \\
&= \kappa e + \gamma i - rr_1 - \delta r + \alpha i r_1
\end{aligned}$$

After replacing s by S, v by V, e by E, i by I and r_1 by R, systems (3.2) - (3.3) can be written as

$$
\begin{aligned}
\frac{dS}{dt} &= -\beta\beta_{_E}ES - \beta\beta_{_I}IS + \alpha IS - \phi S - rS + \delta R + \theta V + r, \\
\frac{dV}{dt} &= -\beta\beta_{_E}\beta_{_V}EV - \beta\beta_{_I}\beta_{_V}IV - rV + \alpha IV - rV - \theta V + \phi S, \\
\frac{dE}{dt} &= \beta\beta_{_E}ES + \beta\beta_{_I}IS + \beta\beta_{_E}\beta_{_V}EV + \beta\beta_{_I}\beta_{_V}IV + \alpha IE - (r+\kappa+\sigma)E, \\
\frac{dI}{dt} &= \sigma E - (r+\alpha+\gamma)I + \alpha I^2, \\
\frac{dR}{dt} &= \kappa E + \gamma I - rR - \delta R + \alpha IR.
\end{aligned} \tag{5.5}
$$

and

$$1 = S + V + E + I + R.$$

BIOGRAPHY

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High school	Queen's College, 2008
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