A DELAYED VACCINATION MODEL FOR ROTAVIRUS

BY

ADONGO FLORENCE AKINYI

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Declaration

This thesis is my own work and has not been presented for a degree award in any other institution.

Adongo Florence Akinyi

MSC/MAT/00170/2014

Signature:.....Date:.....

This thesis/project has been submitted for examination with my approval as the university supervisor.

Dr. Lawrence Omondi Onyango

Department of Mathematics

Egerton University

Signature:.....Date:.....

Dr. Job Otieno Bonyo

Department of Pure and Applied Mathematics

Maseno University

Signature:.....Date:.....

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Dedication

This work is dedicated to my husband John ouko, my two sons Tonny and Gift and my Mother Karren Adongo. Through your prayers, this research has become possible.

Abstract

Rotavirus is the most common cause of severe gastroenteritis infection in infants and young children, occurring even with very high standard of hygiene. The disease spreads by contact with infected faeces and might also be transmitted through faecally-contaminated: food, water and respiratory droplets. Rota teq and Rotarix are the two licensed oral vaccine intervention for rotavirus. However, it takes time for the development of vaccine-induced immunity to complete, hence the need to investigate the impact of this time delay τ on the dynamics of rotavirus. The objectives of the study were: to formulate a mathematical model for rotavirus incorporating time delay in vaccination; to perform stability analysis of the model formulated and to simulate the long term effect of time delay. A mathematical model based on a system of delay differential equation for rotavirus incorporating time delay in the effects of vaccination was formulated. The disease free equilibrium has been proved to be both locally and globally stable. The endemic equilibria is proved to be locally stable whenever $\tau = 0$ and undergoes a Hopf bifurcation if $\tau > 0$. From the analytical and simulation results, we observe a decrease in rotavirus infection as result of using vaccine with high efficacy rates and a shorter delay time. Hence we recommend vaccine with high efficacy rates and a shorter delay time should be introduced in order to effectively control rotavirus infections. The fundings of this study can be adopted by policy makers and health practitioners in planning and allocation of resources towards vaccination strategies for control of rotavirus infection.

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CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Rotavirus is the most common cause of severe gastroenteritis infection in infants and young children, leading to half of all hospitalized cases in children under five years of age. It gets its name from the fact that under microscope, the virus resembles a wheel [29]. Seven species of rotavirus, referred to as A, B, C, D, E, F and G have been identified. Human beings are primarily infected by species A, B and C but most commonly A. Rotavirus spreads by contact with infected faeces and might also be transmitted through faecally-contaminated: food, water and respiratory droplets. The incubation period is about two days. Its symptoms, which may last for eight days include fever, nausea, vomiting, abdominal cramps and frequently watery diarrhoea. The diagnosis of rotavirus infection is commonly made clinically, although a rapid antigen stool test is available.

Children between 6 to 24 months of age can be infected with rotavirus several times during their lives, and infection can occur despite very high standards of hygiene [44] .

After a single natural infection, 38% of children are protected against any subsequent rotavirus infection, 77% are protected against rotavirus diarrhoea and 87% are protected against severe diarrhoea. Re-infection can occur at any age [44]. However, with each infection immunity develops and this makes subsequent infections less severe [29].

In the United States, rotavirus infection affects approximately 2.7 million children under five years of age resulting in the hospitalization of 55000 children every year. Over 600,000 children die annually worldwide because of rotavirus infections [37]. In Kenya, 8,000 children die each year due to rotavirus infections [28].

When diarrhoea occurs, essential fluids and salts are lost from the body and must be quickly replaced. Oral Rehydration Treatment (ORT) which is the administering of fluid through the mouth, is used to prevent and/or contain the dehydration that is a result of diarrhoea in combination with continued feeding. This treatment method requires intensive education so that it can be properly administered [33, 44]. This intensive education program is one of the main reasons why vaccination is being seriously considered over ORT.

Vaccination is the administration of antigenic material (vaccine) into the body to stimulate an individual's immune system to develop adaptive immunity to a pathogen [42]. Rotavirus vaccine is a vaccine used to protect against rotavirus infections. The vaccine contains a weakened strain of rotavirus. This helps the body to build up immunity to fight off the disease in the event of an infection. There are two types of rotavirus vaccines namely Rota teq (pentavalent human bovine reassortant) and Rotarix (Glaxosmithkline human monvalent) currently licensed for use. Rota teq requires 3 doses and should be given at the ages of 2 months, 4 months and 6 months respectively. Rotarix only requires

two doses at 2 months and 4 months. The Canadian Paediatric Society recommends that all babies between 6 weeks and 32 weeks(8 months) of age be vaccinated against rotavirus [42]. The American Academy of Paediatrics recommends that the rotavirus vaccine be included as part of routine immunizations given to infants.

Studies [4, 33] have shown that rotavirus vaccine can prevent about 74% of rotavirus infections. More importantly, it can prevent approximately 98% of severe infections and 96% of hospitalizations from rotavirus. For example in a hospital in Massachusetts, USA, over a period two years the number of reported cases of rotavirus infections dropped from 65% to 3% as a result of vaccination [4, 33, 44].

Through analysis and simulation, Onyango et.al [29] proved that vaccination is a very effective way of controlling rotavirus infection and the study recommends that all newborns be vaccinated if possible in order to effectively control rotavirus infection. Five mathematical models were fitted to rotavirus gastroenteritis (RVGE) data from England and Wales, as well as evaluate outcomes for short and long term vaccination effects [41]. The models predicted that during initial year after vaccine introduction, the incidence of severe RVGE would be reduced by 1.8-2.9 times more than expected from direct effects of the vaccine alone ($28-50\%$ at 90% coverage). Over a 5 year period following vaccine introduction, severe RVGE would be reduced only by 1.1-1.7 times more than expected from direct the effects ($54-90\%$ at90% coverage). The models predicted short term reductions in the incidence of RVGE that exceeded estimates of the direct effects consistent with observations from the United States and other countries. Some of the models predicted that the short term indirect benefits may be offset by a partial shifting of the burden of RVGE to older unvaccinated individuals. The model predictions

reflect uncertainties about age variation in the risk and reporting of RVGE, while the duration of natural and vaccine-induced immunity could not be clearly explained [41]. The models mentioned above, based on the framework of Ordinary Differential Equations are at best approximations with the assumption that future state of the system or model is independent of the past and is determined entirely by the present. Processes such as the development of immunity upon the administration of vaccine take time to complete. Therefore, it is imperative to incorporate such process times or history into mathematical models of vaccination. These process times are referred to as time delays or delays. Models incorporating such delays are known as Delay Differential Equations models. Time delays can greatly affect the dynamics of a system. For example, from the model in [21] for small time delay the unique endemic equilibrium is locally stable but as the time delay increases the endemic equilibrium destabilizes and stable limit cycles arise by Hopf bifurcation.

Mathematical modeling is the art of using mathematical concepts, reasoning, and language to explain, explore, and predict the behavior of a system. Mathematical models can take different forms, including but not limited to dynamical systems, statistical models or game theoretic models . The most persisting feature of our world and state we meet in our daily lives is change. Any move, therefore, to comprehend some facets of actuality includes understanding changes that take place over time. Indeed, the ultimate objective of mathematical modeling is to predict change and possibly make suggestions that will effectively enable one to handle such a change [30].

A dynamical system is a set of equations expressing the rate of change of in terms of the variables and time. Symbolically, if $(x_1, \cdots, x_n)$ are variables, then a dynamical

system is a set of equations of the form

$$\begin{aligned} x_1' =& f_1(x_1, \cdots, x_n) \\ &\vdots \\ x_n' =& f_n(x_1, \cdots, x_n). \end{aligned} \tag{1.1}$$

A non-autonomous dynamical system is an equation of the form

$$x' = F(t, x), \text{ where } F : \mathbb{R}^{n+1} \to \mathbb{R}^n. \tag{1.2}$$

A discrete dynamical system takes the form

$$x[k+1] = F_k(x[k]), \quad \text{where} \quad F_k : \mathbb{R}^n \to \mathbb{R}^n \quad \forall k \in \mathbb{Z}, \tag{1.3}$$

and an autonomous discrete dynamical system takes the form of

$$x[k+1] = F(x[k])$$

where F is a function from $\mathbb{R}^n \to \mathbb{R}^n$ and $\mathbb{Z}$ is a discrete time variable. The trajectories of (1.3) include a sequence of points $\{x_n\}$ that is contained by iterating the map f. If $f^n = f \circ f \circ \cdots \circ f$ denotes the $n-$ folds composition of f, then $x_n = f^n(x_0)$. If f is invertible, then orbit occur forward and backward in time ($n \in \mathbb{Z}$) while if f is not invertible, then the orbits exist only forward in time [34]. In summary, we define a dynamical system as a set of equations which express the rates of change of a set of variables with time. The word "system" in the phrase "dynamical system " refers to the set of equations explicitly giving the rates of change of all state variables.

An epidemiological model may be defined as a mathematical formulation that represents the epidemiology of a disease transmission and its associated processes. It gives a clear definition of how a disease spreads among groups of human beings and animals.

It provides an insight into how a disease can be controlled, the duration or extent of an outbreak and a prediction for both short and long term behaviors of an outbreak. The usefulness of an epidemic model lie on its ability to study "what if" scenarios and provide decision-makers with an inferable knowledge of the effects of disease incursions and impact of disease control measures. The processes involved in formulating an epidemiological model may be defined as shown in Figure 1.1.

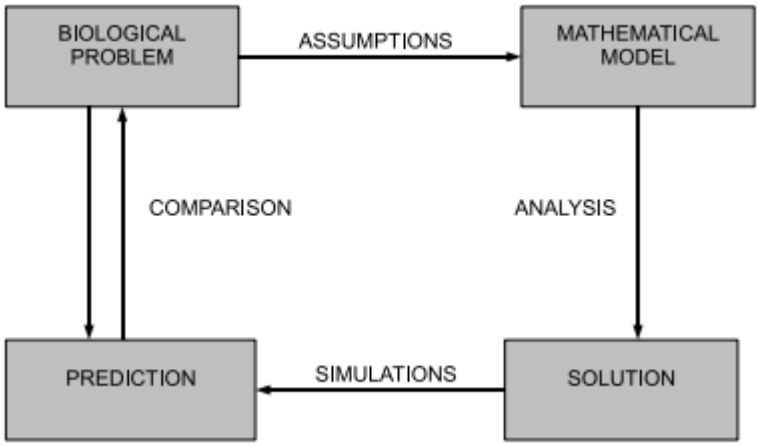

Figure 1.1: Description of the processes of an epidemiological model formulation, see [11].

Epidemic modeling contribute to better disease control through:

- reflective analysis of the outbreaks and assessment of different control measures;
- investigation of different strategies in hypothetical outbreaks;
- exploration of the resource requirements of different strategies in hypothetical epidemics;
- risk assessment to identify priority areas, those that might be at greater risk to better target preparedness and surveillance activities;

- underpinning economic impacts studies;
- provision of realistic schemes for training exercises and communication principles of epidemiology and disease control;
- provision of tactical support during epidemic through analysis and hypothesis testing.

Models can be used retrospectively or prospectively, see [23, p. 355-381]. Retrospective use involves fitting mathematical equations to epidemiological data and interpreting these data quantitatively. Prospective models can either be predictive or explanatory.

1.2 Preliminaries

In this section, certain definitions, theorems and results are used in the development of the subsequent sections in this thesis. For the following definitions, see (p. 5-14) [40].

Definition 1.2.1 (Equilibrium)**.** Consider a general autonomous vector field

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n \tag{1.4}$$

An equilibrium solution of (1.4) is a point $\bar{x} \in \mathbb{R}^n$ such that $f(\bar{x}) = 0$. For nonautonomous vector field $\dot{x} = f(x,t)$, the equilibrium point is given as $f(\bar{x},t) = 0$.

Definition 1.2.2 (Stability)**.** A point $\bar{x}(t)$ is said to be stable if, given $\epsilon > 0$, there exists a $\delta = \delta(\epsilon) > 0$ such that, for any other solution $y(t)$ of (1.4) satisfying $|\bar{x}(t_0) - y(t_0)| < \delta$ (where $|\cdot|$ is a norm on $\mathbb{R}^n$), then $|\bar{x}(t) - y(t)| < \epsilon$ for $t > t_0$, $t_0 \in \mathbb{R}$.

Definition 1.2.3 (Asymptotic stability)**.** A point $\bar{x}(t)$ is said to asymptotically stable if it is stable and for any solution, $y(t)$, of (1.4), there is a constant $b > 0$ such that, if $|\bar{x}(t_0) - y(t)| < b$, then

$$\lim_{t\to\infty} |\bar{x}(t) - y(t)| = 0.$$

Theorem 1.2.4 (Fundamental theorem of algebra)**.** *Consider a polynomial with real coefficients of the form:*

$$p(\lambda) = a_0\lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n, \quad a_i \in \mathbb{R},\ a_0 \neq 0. \tag{1.5}$$

Equation (1.5) *has exactly n real or complex roots,* $\lambda_1, \lambda_2, \cdots, \lambda_n$*, where repetition of roots is possible, that is,* $\lambda_i = \lambda_j$ *for some i and j., [?, 40].*

Theorem 1.2.5 (Descartes' rule of signs)**.** *This rule is used to determine the number of real zeros of a polynomial function. It tells us that the number of positive real zeros in a polynomial function f(x) is the same or less than by an even numbers as the numbers of changes in the sign of the coefficients. The number of negative real zeroes of the f(x) is the same as the number of changes in sign of the coefficients of the terms of f(-x) or less than this by an even number, [19].*

Consider the sequence of coefficients of (1.5)*:*

$$a_n, a_{n-1}, \cdots, a_1, a_0.$$

Let k be the total number of sign changes from one coefficient to the next in the sequence, then the number of positive real roots of the polynomial is either equal to k or k minus a positive even integer. (Note: if $k = 1$*, then there is exactly one positive real root.)*

Theorem 1.2.6 (Routh-Hurwitz criterion)**.** *This criterion state that a negative trace and a positive determinant guarantees that eigenvalues of jacobian matrix will have negative real parts [40]. Given the polynomial,* $p(\lambda) = \lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n$*, where the coefficients* a_i *are real constants,* $i = 1, 2, \cdots, n$*, define the* n *Hurwitz matrices using coefficients* a_i *of the characteristic polynomial:*

$$H_1 = (a_1),\ \ H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix}\ \ H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix}\ \ \textit{and}\ \ H_n = \begin{pmatrix} a_1 & 1 & 0 & \cdots & 0 \\ a_3 & a_2 & a_1 & \cdots & 0 \\ a_5 & a_4 & a_3 & \cdots & 0 \\ \vdots & \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & 0 & \cdots & a_n \end{pmatrix},$$

where $a_j = 0$ *if* $j > n$*. All roots of the polynomial* $p(\lambda)$ *are negative or have negative real part if and only if the determinant of Hurwitz matrices are positive: det* $H_j > 0, \quad j = 1, 2, \cdots, n$*. When* $n = 2$*, the creteria simplify to det* $H_1 = (a_1) > 0$ *and det* $H_2 = \begin{pmatrix} a_1 & 0 \\ 0 & a_2 \end{pmatrix} = a_1a_2 > 0$ *or* $a_1 > 0$ *and* $a_2 > 0$*. The Routh-Hurwitz criteria for polynomials of degree* $n = 2, 3, 4, 5$ *are summarized below:*

$$n = 2: \ a_1 > 0 \ \textit{and} \ a_2 > 0;$$

$$n = 3: \ a_1 > 0, a_3 > 0 \ \textit{and} \ a_1a_2 > a_3;$$

$$n = 4: \ a_1 > 0, a_3 > 0, a_4 > 0 \ \textit{and} \ a_1a_2a_3 > a_3^2 + a_1^2a_4;$$

$$n = 5: \ a_i > 0, \ i = 1, 2, 3, 4, 5, \quad a_1a_2a_3 > a_3^2 + a_1^2a_4, \quad \textit{and}$$

$$(a_1a_4 - a_5)(a_1a_2a_3 - a_3^2 - a_1^2a_4) > a_5(a_1a_2 - a_3)^2 + a_1a_5^2.$$

Definition 1.2.7 (Positive definite functions)**.** A real-valued, continuously differentiable function V is positive definite on a neighborhood of the origin ,D, if and for every non-zero . A function $V : D \to \mathbb{R}$ is positive semi definite if and only if:

(i) $0 \in D$ and $V(0) = 0$;

(ii) $V(x) \geq 0, \quad \forall x \quad \text{in} \quad D - \{0\}$.

V is a positive definite function if item (i) holds and $V(x) > 0 \quad \forall x \quad \text{in} \quad D - \{0\}$. The function $V : D \to \mathbb{R}$ is negative definite or negative semi definite in D if $-V$ is positive definite or positive semidefinite respectively. If $V(x)$ is a quadratic function, that is $V(x) : \mathbb{R}^n \to \mathbb{R} = x^T Q x, \quad Q \in \mathbb{R}^{n \times n}, \quad Q = Q^T$. Since $Q = Q^T$, its eigenvalues, $\lambda_i, \ i = 1, \cdots, n$ are all real,[**?**]. Thus,

$$V(\cdot) \ \text{is positive definite} \iff \lambda_i > 0, \quad \forall_i = 1, \cdots, n;$$

$$V(\cdot) \ \text{is positive semidefinite} \iff \lambda_i \geq 0, \quad \forall_i = 1, \cdots, n;$$

$$V(\cdot) \ \text{is negative definite} \iff \lambda_i < 0, \quad \forall_i = 1, \cdots, n;$$

$$V(\cdot) \ \text{is negative semidefinite} \iff \lambda_i \leq 0, \quad \forall_i = 1, \cdots, n.$$

Time Delays

The inclusion of time delay terms in differential equations is a concept of modeling systems of differential equation that is gaining prominence. The delays or lags can represent gestation times, incubation periods, transport delays, or can simply lump complicated biological processes together, accounting only for the time required for these processes to occur. Such models have the advantage of combining a simple, intuitive derivation with a wide variety of possible behavior regimes for a single system. On the negative side, these models hide much of the detailed workings of complex biological systems, and it is sometimes precisely these details which are of interest. Delay models are becoming more common, appearing in many branches of biological modeling. They have been used

for describing several aspects of infectious disease dynamics: primary infection [39], drug therapy [32] and immune response [6], to name a few.

- **Basic Properties of Delay Differential Equations**

  While similar in appearance to ordinary differential equations, delay differential equations have several features which make their analysis more complicated. Let us examine an example of the form

  $$\dot{x} = f(x(t), x(t-\tau)) \tag{1.6}$$

  To start with, an initial value problem needs more information than a general problem for a system without delays. For an ordinary differential system, a unique solution is determined by an initial point in Euclidean space at an initial time t_0. For a delay differential system, one requires information on the entire interval $[t_0, t_0+\epsilon]$. Clearly, to know the rate of change at t_0, one needs $x(t_0)$ and $x(t_0+\epsilon)$, and for $\dot{x}(t_0+\epsilon)$, one needs to know $x(t_0+\epsilon)$ and $x(t_0+\epsilon\tau)$. So, in order for the initial value problem to make sense, one needs to give an initial function or initial history, the value of $x(t)$ for the interval $[\tau, 0]$. Each such initial function determines a unique solution to the delay differential equation. If we require that initial functions be continuous, then the space of solutions has the same dimensionality as $C([t_0+\epsilon\tau, t_0], \mathbb{R})$.

1.3 Statement of the problem

It is a common practice in many resource-limited settings that vaccination is done intensely when there is an outbreak. However, it takes time for the development of vaccine-

induced immunity to complete. It is therefore desirable to investigate the impact of the time delay on the effectiveness of rotavirus vaccine and consequently its effects on the dynamics of rotavirus.

1.4 Objectives of the study

The main objective of this study was to develop and analyse a mathematical model incorporating time delay on the effectiveness of vaccination impacts on rotavirus infection. The specific objectives of the study were:

(i) To formulate a mathematical model for rotavirus incorporating time delay in vaccination.

(ii) To prove the existence of both disease free and endemic equilibria.

(iii) To perform stability analysis of the model formulated.

(iv) To simulate the long term effect of time delay in vaccination.

1.5 Significance of the study

It has been observed that rotavirus is the most common cause of severe gastroenteritis among children under the age of five years. Mathematical models have been used to underscore the important role vaccination plays in the reduction of rotavirus incidence. By highlighting the effect of delay in vaccination on the transmission dynamics of rotavirus,

the findings of this study will help policy makers and health practitioners in planning and allocation of resources towards vaccination strategies.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

The critical analysis of relevant literature begins with a review of the development of mathematical epidemiology. This is followed by a general review of compartmental mathematical models applied to infectious diseases at a population level. Models which are relevant to this study are explored. The chapter is concluded by outlining the original chapters of this study, giving their relationship with the previous work, innovations and contributions to the field of research.

2.2 Development of mathematical epidemiology

The development of mathematical epidemiology dates back to late nineteenth century and early twentieth century by public-health physicians and biological scientists such

as En'ko [9], Hamer, see (p.733-739) [12], Browlee [17], Sir Ross [35], McKendrick and Kermack [20, 43]. In 1889, En'ko developed a chain binomial model for the spread of an infection in a susceptible population. The first models of mathematical epidemiology were developed by Ross and Kermack and Mckendrick. Ross used his model to show that malaria is spread through mosquito bites [35]. He further observed from his model that malaria could possibly be controlled by reducing the population of mosquitoes. Ross model was probably the one that gave birth to the threshold concept which has been vital in epidemiology ever since. All mathematical models, including those with a high degree of heterogeneity show this 'threshold' behavior. In epidemiological terms, this threshold is stated as: *If the average number of secondary infections caused by a single infective introduced in a wholly susceptible population is below unity, a disease will die out, while if it exceeds unity, an epidemic will occur.* this threshold was later called a basic reproduction number, denoted as R_0 [13, 27].

Kermack and McKendrick greatly extended the concept of basic reproduction number in their work on general compartmental model, both for diseases in which recovery result into permanent immunity and for diseases in which there is possibility of re-infection [20, 43]. Another important extension of the epidemiology model was done by Dietz and Schenzle [8] and later on by Bailey [26]. Bailey incorporated an exposed (latent) period in his model. This is the period in which the infected members of the population do not infect others. Hamer developed a model with mass-action incidence [12]. This was a representation of the rate of transmission from infective to susceptible individuals. This law assumes that the average number of contacts needed to cause an infection per unit individual in unit time is proportional to population density.

Continuing from the tradition of Ross, mathematical models that focused on specific diseases have been developed; see [10, 46] among others. These models have included basic ideas of importance, for example vaccination, relation between ages, herd immunity and even treatments. Due to continued outbreaks of new infectious diseases, more new models are still being developed to take care of these challenges. Recently, HIV models [22] and Ebola models [1] have been developed among others. These studies [1, 22] have also developed two other models, that is rotavirus model and co-infection of malaria and rotavirus model. These two models will greatly help in understanding the behavior of rotavirus infection.

2.3 Mathematical models of infectious diseases

Infectious diseases remain a leading cause of deaths worldwide with HIV, tuberculosis, cancer, malaria and recently Ebola being the leading. New pathogens continue to emerge as shown by the outbreak of SARS in 2003, swine flu in 2009 and MERS CoV in 2013. Mathematical models are being used to explore the transmissions of these infections and to analyze the potential impact of control measures being applied. The first mathematical model was formulated by Bernoulli in 1760 [7]. He used his model to analyze the effectiveness of vaccinating healthy people against smallpox. In 1906, Hammer formulated and evaluated a discrete time model which he used to explain why measles epidemic continue to recur in a population [12]. In 1911, Ross developed a differential equation model for malaria as a host-vector disease [35]. In 1927, Kermack and Mckendrick ex-

tended Ross' work and formulated the first compartmental model (SIR), which consists of system of three coupled nonlinear ordinary differential equations [24]. This model was simply presented as

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma I$$
$$\frac{dR}{dt} = \gamma I,$$

where t is time, $S(t)$ is susceptible people, $I(t)$ are infected people and $R(t)$ are those who have recovered. The parameters β is the transmission probability and γ is death/recovery rate. In 1984, Aron and Schwartz formulated a SEIR model [16]. They used this model to investigate the role of seasonality in driving cycles in recurrent epidemics by numerically analyzing the susceptible/exposed/infected/ recovered (SEIR) population. This type of model is generally given as

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dE}{dt} = \beta SI - \kappa E$$
$$\frac{dI}{dt} = \kappa E - \gamma I$$
$$\frac{dR}{dt} = \gamma I,$$

where β, κ and γ are positive constants.

2.4 Mathematical models of rotavirus

Before the introduction of rotavirus vaccine, rotavirus disease was a common and serial health problem for children below 5 years. According to WHO estimates of 2013, about 215,000 children aged below 5 years die each year from vaccine preventable rotavirus infections; with the vast majority of these children living in low income countries. In the

United States, before the vaccine was introduced, almost all children had at least one rotavirus infection before their 5th birthday. More than 400,000 young children had to see a doctor for illness caused by rotavirus, more than 200,000 had to go to be admitted to the emergency wards, 55,000-70,000 had to be hospitalised while 20-60 died [44]. In 2014, it was estimated that 27% of all under-five diarrhoeal disease hospitalizations in Kenya were caused by rotavirus [33].

The public health impact of rotavirus vaccination has been demonstrated in several countries and states. In the USA, a measurable decrease was seen in the number of rotavirus gastroenteritis hospitalizations accompanied by a suggested herd-effect protecting old non-vaccinated children. In Mexico, a decline of up to 50% in diarrheal deaths in children below 5 years of age was attributed directly to the use of the vaccine. Studies have shown that rotavirus vaccine can prevent about 74% of rotavirus infections. More importantly, it can prevent approximately 98% of severe infection and 96% of hospitalizations from rotavirus. For example in a hospital in Massachusetts over a period of two years, the number of reported cases of rotavirus infections dropped from 65% to 3% as result of vaccination [4, 33, 44]. Clinical trials in Africa found that rotavirus vaccines reduced severe rotavirus disease by more than 60% during the first year of life when children are at greatest risk of severe rotavirus disease. WHO reiterates that the use of rotavirus vaccines should be part of comprehensive strategy to control diarrheal disease with the scaling up of both prevention (promotion of early and exclusive breastfeeding, hand washing with soap, treated water and improved sanitation) and treatment packages (lo osmolarity, ORS and Zink) [33, 44]. WHO recommends that rotavirus vaccines should

be included in all National immunization programs and considered a priority particularly in countries in South East Asia and Sub-Saharan Africa [44]. Since the introduction of the rotavirus vaccine, hospitalizations and emergency visits for rotavirus infections have dropped drastically [4]. Vaccination is the best way to prevent severe rotavirus disease and the deadly dehydrating diarrhea that it causes.

Studies in Kenya and other African countries [4, 33, 44] show that rotavirus vaccines are safe, effective against severe rotavirus disease and are cost-effective. The vaccine was introduced in Kenya's national immunization program with Global Alliance for Vaccines and Immunization (GAVI) support. In Kazakhstan, a middle income country, the cost effectiveness analysis of rotavirus vaccination spanning 20 years by using a synthesis of dynamic transmission models accounted for the herd protection was performed and found that vaccination program with 90% coverage would prevent 880 rotavirus deaths and save an average of 54,784 life years for children below 5 years. Indirect protection accounting for 40% and 60% reduction in severe and mild rotavirus gastroenteritis respectively. Vaccination reduces productivity losses because of lower mortality rates and less work absenteeism among parents [3].

A mathematical model of a rotavirus infection incorporating vaccination has been developed and comprehensively analyzed [29]. Through the analysis and simulation, it has been shown that both the disease-free and endemic equilibria are globally asymptotically stable. Real data fitted to the model shows that it can be used to predict the nature of rotavirus infection in a population. Simulation shows that vaccination is a very effective way of controlling rotavirus infection. It was recommended that all newborns be vaccinated if possible in order to effectively control rotavirus infection. The model did not

predict what will happen between the time the vaccine is administered and the time it becomes effective.

A model of indirect effects of rotavirus vaccination was developed to project the impact of a vaccination programme on the incidence of rotavirus infection and disease for five countries in the European Union [41]. With vaccination coverage rates of 70%, 90% and 95%, the model predicted that in addition to the direct effect of vaccination herd protection induced a reduction in rotavirus-related gastroenteritis incidence of 25%, 22%,and 20% respectively. It was observed that from countries that have introduced rotavirus vaccination, there may be indirect protection for unvaccinated individuals but it is unclear whether these benefits will extend to long term. The direct and indirect benefits of vaccination can only be realized once vaccine protection for vaccinated individual becomes effective.

Five mathematical models were fitted to rotavirus gastroenteritis (RVGE) data from England and Wales, as well as evaluate outcomes for short and long term vaccination effects [41]. The models predicted that during initial year after vaccine introduction, the incidence of severe RVGE would be reduced 1.8-2.9 times more than expected from direct effects of the vaccine alone ($28 - 50\%$ at 90% coverage). Over a 5 year period following vaccine introduction, severe RVGE would be reduced only by 1.1-1.7 times more than expected from direct effects($54 - 90\%$ at90% coverage). The models predicted short term reductions in the incidence of RVGE that exceeded estimates of the direct effects consistent with observations from the the United States and other countries. Some of the models predicted that the short term indirect benefits may be offset by a partial shifting of the burden of RVGE to older unvaccinated individuals. From this study is it clear

that the reduction in the incidences of RVGE, due to vaccination, is higher over shorter time periods than over longer periods. Therefore vaccination should be done as often as possible to maximize the benefit of both direct and indirect protection.

The number of rotavirus infections tend to be highest under cool dry conditions in the tropics. In the United States, seasonal rotavirus activity occurs in sequential manner, beginning first in the Southwest from October through December and ending in the Northeast in April or May. In Kenya rotavirus peak incidences were observed in the January-March periods, when weather is dry, hot and with low relative humidity [25]. It is recommended that vaccination is to be carried out before these periods for it to be effective. The dynamics of rotavirus infections were studied using a simple mathematical model that included the impact of breastfeeding, seasonality and the possibility of control via vaccination [36]. The study conducted which the dynamic of a regular after birth vaccine [6 weeks and 32 weeks(8 months)of age] for the child was more effective in controlling rotavirus disease than a neonatal vaccine.

A SEIRS epidemic disease model with two profitless delays and nonlinear incidence are proposed and the dynamic of the model under pulse vaccination are analyzed [45]. In this model, the latent period of the disease is defined as the time delay. A long latent period of the disease or a long immunity period of the recovery is sufficient condition for the global attractivity of infection eradication periodic solution. On the contrary, a longer time delay in vaccination may lead to instability.

A model of Hopf bifurcation in epidemic with a time delay in vaccination was analyzed [21]. Introduction of a time delay is a destabilizing process in the sense that increasing the time delay could cause the population to fluctuate. Hopf bifurcation was used to help find

the existence of a possible region of instability in the neighborhood of a non-zero endemic equilibrium where the population will survive undergoing regular fluctuations. Using the time delay as a bifurcation parameter necessary and sufficient conditions for Hopf bifurcation were examined to occur. For small time delay the unique endemic equilibrium is locally stable but as the time delay increases the endemic equilibrium destabilizes and stable limit cycles arise by Hopf bifurcation. Hopf bifurcation may occur if the death rate from the disease is high compared with the recovery rate so that the chance of an infected person dying from the disease exceeds 50%. For rotavirus, the death rate is lower than the recovery rate, it would therefore be necessary to determine the effect of varying the time delay.

A model of HIV-1 infection with two time delays was mathematically analyzed and comparison with patient data done [18]. One of the time delay represent the time needed for infected cells to produce virion after viral entry (intracellular delay) and the other denotes the time needed for the adaptive immune response to emerge to control viral replication (immune delay). Through the analysis positivity and boundedness of the solutions, local stability of the infection free and infected steady states and uniform persistence of the system were proved. The model was used to estimate parameter values which were fitted to viral load data from 10 patients during primary HIV-1 infection. The delay model provided better fits to patient data (achieving a smaller error between data and modeling prediction) as compared to models without delay. Rotavirus infection has vaccines unlike HIV-1 infection. It is important to investigate effect of delay in vaccination because this affects the time required for immune system to respond to a viral invasion.

CHAPTER 3

METHODOLOGY

3.1 Model description and formulation.

A mathematical model based on a system of delay differential equation for rotavirus incorporating time delay in the effects of vaccination was formulated. The total human population size under study, N(t), at any time t is subdivided into distinct classes such as susceptible S(population capable of becoming infected), Infected I(infectious with rotavirus), vaccinated V(vaccinated population) and recovered R(comprise of those who have been removed from the scene of infection by such means as infection acquired immunity and death). The total population $N(t) = S(t) + V(t) + I(t) + R(t)$. Assume that the mass action incidence transmission is defined by βSI, where β is the effective contact rate for disease transmission and the initial conditions are such that the variables S, V, I, R remain non-negative for all time $t \geq 0$. Since the incubation period is two days [29], we assume that the probability of survival till the infectious state for the individuals exposed to rotavirus is unity and therefore exclude the exposure stage. The individuals infected

with rotavirus include both symptomatic and asymptomatic cases because they are capable of infecting others [41]. It is possible children can develop some level of immunity to rotavirus from maternal antibody due to breastfeeding but this immunity does not last for long hence we consider the effect of vaccination at birth and vaccination of susceptibles [29]. The human population is not assume to be constant, since birth, immigration, emigration and death occur. Assumed a constant recruitment ρ out of which $(1-\rho)\Lambda$ is into susceptible class and $\rho\Lambda$ is into the vaccinated class. Susceptibles are vaccinated at the rate γ and the vaccine efficacy which has been shown to wane is assumed to take place at the rate ω [2]. The parameter $0 \leq 1-\epsilon < 1$ models the decrease in the risk of infection as a result of vaccination. Disease mortality takes place at the rate δ and recovery from infection takes place at the rate κ, it is therefore natural that after a single natural infection immunity is developed, subsequent infections are less severe [29]. The population decreases due to natural deaths at a rate μ. Most vaccines take time in the body to become effective (time delay denoted by τ), this is because immunity has to be developed to protect the body against infection. These parameter values are summarized in Table 3.1 below.

Table 3.1: Parameter values

Parameter	**Symbol**
Recruitment rate into susceptible	$(1-\rho)\Lambda$
Recruitment rate into vaccination	$\rho\Lambda$
Vaccination rate of susceptible	γ
Vaccine efficacy waning rate	ω
Expected decrease in the risk of infection	ϵ
Rate of flow into the removed class	κ
Transmission rate	β
Natural death rate of human	μ
Rotavirus induced deaths	δ
Rate of vaccination	ρ
Delay time in completion of vaccination immunity	τ
Recruitment rate of humans	Λ

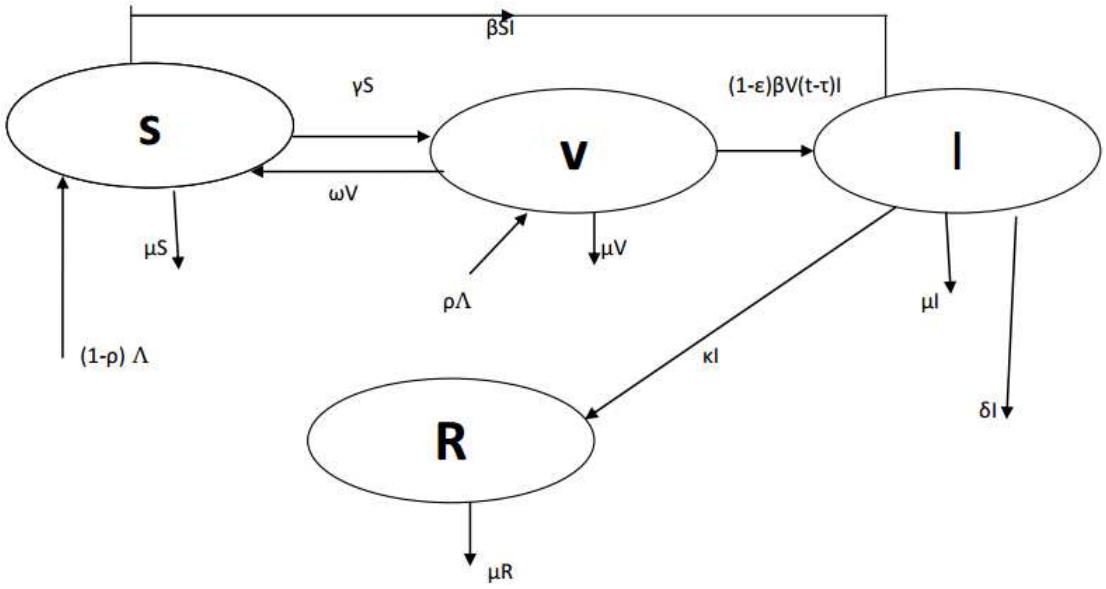

Figure 3.1: Model Flow Chart

The model is therefore given by the following set of delay differential equations.

$$\begin{aligned}
\frac{dS}{dt} &= (1-\rho)\Lambda - \beta SI - \gamma S + \omega V - \mu S, \\
\frac{dV}{dt} &= \rho\Lambda + \gamma S - (1-\epsilon)\beta V(t-\tau)I - (\omega+\mu)V, \\
\frac{dI}{dt} &= \beta SI + (1-\epsilon)\beta V(t-\tau)I - (\delta+\kappa+\mu)I, \\
\frac{dR}{dt} &= \kappa I - \mu R
\end{aligned} \tag{3.1}$$

We set the initial conditions for system (3.1) as

$$S = S(0) > 0,\ V = V(0) \geq 0,\ I = I(O) \geq 0,\ R = R(0) \geq 0,\ t = 0$$

3.2 Model analysis

The formulated model was analysed by proving positivity and boundedness of the solutions of the system, deriving the basic reproduction number, establishing the existence of both the disease free and endemic equilibrium points and finally proving whether these equilibrium points are both locally and globally stable or there exists a bifurcation point at any time. Equilibrium point is a constant solution to a differential equation that does not change with time. The equilibrium points of the system were obtained by setting the right hand side of the differential equations to zero and solving each variable. These points are also referred to as steady state solutions. The existence of the equilibrium points (disease free and endemic) of the model is determined with respect to basic reproduction number, which is derived using the next generation matrix approach.

3.2.1 Positivity and boundedness of solutions

Model (3.1) describes human population and we therefore show that the associated state variables are non-negative for all time, $t \geq 0$. Using the first equation of the system (3.1), that is

$$\frac{dS}{dt} = (1-\rho)\Lambda - \beta SI - \gamma S + \omega V - \mu S,$$

which can be rearranged as

$$\frac{dS}{dt} = (1-\rho)\Lambda + \omega V - (\beta I + \gamma + \mu)S,$$

and therefore we can conclude that

$$\frac{dS}{dt} \geq -(\beta I + \gamma + \mu)S. \tag{3.2}$$

Separating the variables yields

$$\frac{dS}{S} \geq -(\beta I + \gamma + \mu)dt \tag{3.3}$$

By integrating the differential inequality (3.3), that is,

$$\int_{S_0}^{S} \frac{dS_1}{S_1} \geq \int_{t_0}^{t} -(\beta I + \gamma + \mu)dt_1,$$

we obtain

$$\ln S_1 \mid_{S_0}^{S} \geq -(\beta I + \gamma + \mu)t_1 \mid_{t0}^{t} \tag{3.4}$$

Applying the initial condition at $t = 0, S = S(0)$ on (3.4) we get

$$S(t) \geq S(0)e^{-(\beta I+\gamma+\mu)(t-t(0))} \geq 0. \tag{3.5}$$

For I(t):

$$\frac{dI}{dt} = \beta SI + (1-\epsilon)\beta V(t-\tau)I - (\delta + \kappa + \mu)I \tag{3.6}$$

Factoring out I

$$\frac{dI}{dt} = [\beta S + (1-\epsilon)\beta V(t-\tau) - (\delta + \kappa + \mu)]I. \tag{3.7}$$

we conclude that

$$\frac{dI}{dt} \geq -(\delta + \kappa + \mu)I. \tag{3.8}$$

Separating the variables yields,

$$\frac{dI}{I} \geq -(\delta + \kappa + \mu)dt. \tag{3.9}$$

Integrating the differential equation (3.9)

$$\int_{I_0}^{I} \frac{dI_1}{I_1} \geq \int_{t_0}^{t} -(\delta + \kappa + \mu)dt_1,$$

gives

$$\ln I_1 \mid_{I_0}^{I} \geq -(\delta + \kappa + \mu) t_1 \mid_{t_0}^{t} . \tag{3.10}$$

Applying the initial condition $t = 0, I = I(0)$ on (3.10), we get

$$I(t) \geq I(0) e^{-(\delta+\kappa+\mu)(t-t(0))} \geq 0. \tag{3.11}$$

From the solutions [inequalities ((3.5) and (3.11))] all $S(t)$, $V(t)$, $I(t)$ and $R(t)$ are non negative for $t \geq 0$.

To show that all feasible solutions are uniformly bounded.

We sum up the four equations of the system (3.1).

Since $N = S + V + I + R$, we have

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dV}{dt} + \frac{dI}{dt} + \frac{dR}{dt}, \tag{3.12}$$

which on substitution of corresponding value from system (3.1) and simplify

$$\frac{dN}{dt} = \Lambda - \delta I - (\mu S + \mu V + \mu I + \mu R). \tag{3.13}$$

Thus

$$\frac{dN}{dt} = \Lambda - \delta I - \mu(S + V + I + R) \tag{3.14}$$

and therefore

$$\frac{dN}{dt} = \Lambda - \mu N - \delta I. \tag{3.15}$$

It therefore follows that

$$\frac{dN}{dt} \leq \Lambda - \mu N,$$

which implies that

$$\frac{dN}{dt} + \mu N \leq \Lambda \tag{3.16}$$

and solving c (3.16) by the intergrating factor/separation of variables we get

$$N(t) \leq \frac{\Lambda}{\mu} + N(0)e^{-\mu t} \tag{3.17}$$

From inquality (3.17), it can be clearly seen that

$$0 \leq N(t) \leq \frac{\Lambda}{\mu} + N(0)e^{-\mu t} \tag{3.18}$$

where $N(0)$ is the initial population.

Thus as $t \to \infty$, we have

$$0 \leq N(t) \leq \frac{\Lambda}{\mu} \tag{3.19}$$

Which shows that the solutions of system (3.1) are bounded.

3.2.2 The Disease Free Equilibrium, $E^0(S^0, V^0, I^0)$

Since the first three equations of system (3.1) do not contain terms in R, therefore we rewrite system (3.1) as:

$$\begin{aligned}
\frac{dS}{dt} &= (1-\rho)\Lambda - \beta SI - \gamma S + \omega V - \mu S, \\
\frac{dV}{dt} &= \rho\Lambda + \gamma S - (1-\epsilon)\beta V(t-\tau)I - (\omega+\mu)V, \\
\frac{dI}{dt} &= \beta SI + (1-\epsilon)\beta V(t-\tau)I - (\delta+\kappa+\mu)I,
\end{aligned} \tag{3.20}$$

To determine the disease free equilibrium, which is a state at which no rotavirus infection is present in the population, we equate the right hand side of the system (3.20) to zero and solve for the variables S^0 and V^0 since $I^0 = 0$

This gives

$$\begin{aligned}(1-\rho)\Lambda - \beta S^0 I^0 - \gamma S^0 + \omega V^0 - \mu S^0 &= 0 \\ \rho\Lambda + \gamma S^0 - (1-\epsilon)\beta V^0(t-\tau)I^0 - (\omega+\mu)V^0 &= 0 \\ \beta S^0 I^0 + (1-\epsilon)\beta V^0(t-\tau)I^0 - (\delta+\kappa+\mu)I^0, &= 0 \end{aligned} \tag{3.21}$$

Solving for S^0 and V^0 when I^0 and τ are both zero, from the first equation of the system (3.21), we get

$$S^0 = \frac{(1-\rho)\Lambda + \omega V^0}{\gamma + \mu}, \tag{3.22}$$

and from the second equation of the system (3.21), we obtain

$$S^0 = \frac{(\omega+\mu)V^0 - \rho\Lambda}{\gamma}. \tag{3.23}$$

Equating equations (3.22) and (3.23) and solving for V^0, we get

$$V^0 = \frac{(\gamma+\mu\rho)\Lambda}{\mu(\mu+\omega+\gamma)} > 0. \tag{3.24}$$

Substituting equation (3.24) into equation (3.23) and solving for S^0, we get

$$S^0 = \frac{\omega\Lambda + (1-\rho)\mu\Lambda}{\mu(\omega+\gamma+\mu)} > 0. \tag{3.25}$$

Using equations (3.24) and (3.25), the disease free equilibrium E^0, of model (3.20) is then given as

$$E^0(S^0, V^0, I^0,) = \left(\frac{\omega\Lambda + (1-\rho)\mu\Lambda}{\mu(\omega+\gamma+\mu)}, \frac{(\gamma+\mu\rho)\Lambda}{\mu(\mu+\omega+\gamma)}, 0\right). \tag{3.26}$$

3.2.3 Existence of Endemic equilibrium (EE) point

In epidemiology, an infection is said to have attained its endemic equilibrium when that infection is constantly maintained at a baseline level in a geographical area without external inputs, such as medication, vaccination among others. In order to prove the existence

of endemic equilibrium, we first calculate the basic reproduction number of system (3.20) and use it to test the positivity of I^* which leads to the positivity of S^* and V^*. This shown in Theorem 3.2.1 below.

The Basic Reproduction Number

The basic reproduction number, denoted as R_0, is defined as the average number of secondary infections caused by a single infectious individual during their entire infectious lifetime in a fully susceptible population [15]. We define the vaccine reproduction number, R_v, of the model as the number of secondary rotavirus infections caused by a single rotavirus infected individual in the presence of vaccination. When no such intervention is employed, then the basic reproduction number is denoted by R_0. When the basic reproduction number is greater than one, it means that an infectious individual is causing, on average, more than one new infections and thus the disease invades and persists in the population. The constant R_v is determined by the method of next generation operator approach.

The reproduction

$$R_v = r(\mathcal{F}\mathcal{V}^{-1})$$

is the spectral radius of the matrix (the largest absolute value of its eigenvalues) $(\mathcal{F}\mathcal{V}^{-1})$ where $\mathcal{F}$ is the Jacobian of f_j such that f_j is the rate of new infections in compartment j and $\mathcal{V}$ is the Jacobian of v_j is the rate of transfer of individuals in and out of compartments by means other than infection. From the model infection class is I.

f= $\left(\beta SI + (1-\epsilon)\beta V(t-\tau)I\right)$

$$\mathrm{F}=\left(\beta S+(1-\epsilon)\beta V\right)$$
$$\mathrm{v}=\left((\mu+\kappa+\delta)I\right)$$
$$\mathrm{V}=\left(\kappa+\mu+\delta\right)$$
$$\mathrm{V}^{-1}=\left(\tfrac{1}{\kappa+\mu+\delta}\right)to$$
$$\mathrm{FV}^{-1}=\left(\tfrac{\beta}{\kappa+\mu+\delta}[S+(1-\epsilon)V]\right) \quad (3.27)$$

Substitute S and V at DFE from equation (3.26) to get

$$R_v = \frac{\beta}{(\kappa+\delta+\mu}\left[(\frac{\omega\Lambda+(1-\rho)\mu\Lambda}{\mu(\omega+\gamma+\mu)}+(1-\epsilon)\frac{(\gamma+\mu\rho)\Lambda}{\mu(\mu+\omega+\gamma)}\right]$$

Rearranging we get

$$R_v=\frac{\beta}{\mu(\kappa+\delta+\mu}\left[\frac{\omega\Lambda+(1-\rho)\mu\Lambda+(1-\epsilon)(\rho\mu+\gamma)\Lambda}{(\gamma+\omega+\mu)}\right]. \quad (3.28)$$

In the absence of vaccination,

$$\rho=\omega=\gamma=0,$$

and the basic reproduction number becomes,

$$R_0=\frac{\beta\Lambda}{\mu(\kappa+\delta+\mu)} \quad (3.29)$$

Theorem 3.2.1. *An endemic equilibrium $E^*(S^*,V^*,I^*)$ exists provided that $R_v>1$*

Proof. At an endemic equilibrium state, equation (3.20) becomes

$$\begin{aligned}(1-\rho)\Lambda-\beta S^*I^*-\gamma S^*+\omega V^*-\mu S^* &= 0\\ \rho\Lambda+\gamma S^*-(1-\epsilon)\beta V^*I^*-(\omega+\mu)V^* &= 0\\ \beta S^*I^*+(1-\epsilon)\beta V^*I^*-(\delta+\kappa+\mu)I^* &= 0. \quad (3.30)\end{aligned}$$

Solving for S^* from the first equation of system (3.30), we obtain

$$S^* = \frac{(1-\rho)\Lambda + \omega V^*}{\beta I^* + \gamma + \mu}, \tag{3.31}$$

Solving for V^* from the second equation of system (3.30), we obtain

$$V^* = \frac{\rho\Lambda + \gamma S^*}{(1-\epsilon)\beta\ I^* + \omega + \mu}. \tag{3.32}$$

From the third equation of (3.30), we obtain

$$S^* = \frac{(\delta + \kappa + \mu) - (1-\epsilon)\beta V^*}{\beta}. \tag{3.33}$$

Equating equation (3.31) to equation (3.33) and solving for V^*, we obtain

$$V^* = \frac{(\delta + \kappa + \mu)(\beta I^* + \gamma + \mu) - \beta(1-\rho)\Lambda}{\beta[\omega + (1-\epsilon)(\beta I^* + \gamma + \mu)]}. \tag{3.34}$$

Substituting (3.33) into (3.32) and simplifying, we get

$$V^* = \frac{\beta\rho\Lambda + \gamma(\delta + \kappa + \mu)}{\beta(1-\epsilon)(\beta I^* + \omega + \mu + \gamma)} \tag{3.35}$$

To obtain I^*, we equate equations (3.34) and (3.35) to obtain

$$\mu\rho\beta\Lambda - (1-\epsilon)\mu\rho\beta\Lambda - (1-\epsilon)\gamma\beta\Lambda + (1-\epsilon)\gamma\beta(\delta + \kappa + \mu)$$

$$I^* + \gamma\mu(\delta + \kappa + \mu) - (1-\epsilon)\beta^2\Lambda I^* + (1-\epsilon)\beta^2(\delta + \kappa + \mu)I^{*2}$$

$$+(1-\epsilon)\mu\beta(\delta + \kappa + \mu)I^* - \omega\beta\Lambda + \omega\beta\beta(\delta + \kappa + \mu)16$$

$$I^* + \mu\omega(\delta + \kappa + \mu) - \mu\beta\Lambda + \mu\beta(\delta + \kappa + \mu)I^* + \mu^2(\delta + \kappa + \mu) = 0,$$

which can be expressed as

$$AI^{*2} + BI^* + C = 0, \tag{3.36}$$

where

$$A = (1-\epsilon)\beta^2(\delta + \kappa + \mu)$$

$$
\begin{aligned}
B &= [\gamma(1-\epsilon)\beta(\delta+\kappa+\mu) - (1-\epsilon)\beta^2\Lambda + (1-\epsilon)\mu\beta(\delta+\kappa+\mu) \\
&\quad +\omega\beta(\delta+\kappa+\mu) + \mu\beta(\delta+\kappa+\mu)]
\end{aligned}
$$

$$
\begin{aligned}
C &= [\mu\rho\beta\Lambda - (1-\epsilon)\mu\rho\beta\Lambda + \gamma\mu(\delta+\kappa+\mu) \\
&\quad -\omega\beta\Lambda + \mu\omega(\delta+\kappa+\mu) - \mu\beta\Lambda + \mu^2(\delta+\kappa+\mu)]
\end{aligned}
$$

To determine the sign of C we express it as

$$
C = \mu[\beta\rho\Lambda + (\delta+\kappa+\mu)(\gamma+\omega+\mu)] - \beta\Lambda[1-\epsilon)\mu\rho + (1-\epsilon)\gamma + \omega + \mu]. \tag{3.37}
$$

Since $R_v = \frac{\beta}{\mu(\delta+\kappa+\mu}\left[\frac{\mu(1-\rho)\Lambda+\omega\Lambda+(1-\epsilon)\Lambda(\rho\mu+\gamma}{(\gamma+\mu+\omega}\right] > 1$, it can be easily seen that $\beta\Lambda[\mu+\omega+(1-\epsilon)\mu\rho+(1-\epsilon)\gamma] > \mu[\beta\rho\Lambda+(\delta+\kappa+\mu)(\gamma+\omega+\mu)]$. From equation (3.37), it can be concluded that $C < 0$ when $R_v > 1$. This proves that $C < 0$, when $R_v > 1$. We therefore see that, the only possible signs of equation (3.36) are $(+,-,-)$ and $(+,+,-)$ and by Descartes Rule of sign change [14], it shows that there is only one positive root of I^*, that is, $I^* > 0$. We therefore conclude that the model has a positive endemic equilibrium. □

3.2.4 The Local Stability of Disease Free Equilibrium (D.F.E)

Theorem 3.2.2. *The disease free equilibrium of model* (3.20) *is locally asymptotically stable provided that* $R_v < 1$ *and unstable when* $R_v > 1$ *for any time delay* $\tau \geq 0$.

Proof. We prove the local stability of the disease free equilibrium of model (3.20) by

evaluating its Jacobian matrix as given below

$$J_{E^0} = \begin{pmatrix} -(\beta I^0 + \gamma + \mu) & \omega & -\beta S^0 \\ \gamma & -(1-\epsilon)\beta I^0 - (\omega + \mu) & -(1-\epsilon)\beta V^0 \\ \beta I^0 & (1-\epsilon)\beta I^0 & \beta S^0 + (1-\epsilon)\beta V^0 - (\delta + \kappa + \mu) \end{pmatrix} \tag{3.38}$$

Substituting the values of S^0, V^0, I^0 into equation (3.38) at the disease free equilibrium, we get;

$$J_{E^0} = \begin{pmatrix} -(\gamma + \mu) & \omega & -\beta \left[\frac{\omega\Lambda + (1-\rho)\mu\Lambda}{\mu(\gamma+\omega+\mu)}\right] \\ \gamma & -(\omega + \mu) & -\beta(1-\epsilon)\left[\frac{\Lambda(\rho\mu+\gamma)}{\mu(\gamma+\omega+\mu)}\right] \\ 0 & 0 & \beta\left[\frac{\omega\Lambda+(1-\rho)\mu\Lambda}{\mu(\gamma+\omega+\mu)}\right] + \beta(1-\epsilon)\left[\frac{\Lambda(\rho\mu+\gamma)}{\mu(\gamma+\omega+\mu)}\right] - (\delta+\kappa+\mu) \end{pmatrix} \tag{3.39}$$

Equation (3.39) can be simplified as

$$J_{E^0} = \begin{pmatrix} -(\gamma + \mu) & \omega & -\beta \left[\frac{\omega\Lambda + (1-\rho)\mu\Lambda}{\mu(\gamma+\omega+\mu)}\right] \\ \gamma & -(\omega + \mu) & -\beta(1-\epsilon)\left[\frac{\Lambda(\rho\mu+\gamma)}{\mu(\gamma+\omega+\mu)}\right] \\ 0 & 0 & \frac{\beta}{\mu}\left[\frac{\omega\lambda+\mu(1-\rho)\Lambda+(1-\epsilon)(\mu\rho+\gamma)\Lambda}{\mu+\omega+\gamma}\right] - (\delta+\kappa+\mu) \end{pmatrix} \tag{3.40}$$

By using R_v, we can rewrite equation (3.40) as

$$J_{E^0} = \begin{pmatrix} -(\gamma + \mu) & \omega & -\beta[\frac{\omega\Lambda + (1-\rho)\mu\Lambda}{\mu(\gamma+\omega+\mu)}] \\ \gamma & -(\omega + \mu) & -\beta(1-\epsilon)\left[\frac{\Lambda(\rho\mu+\gamma)}{\mu(\gamma+\omega+\mu)}\right] \\ 0 & 0 & (\delta+\kappa+\mu)(R_v - 1) \end{pmatrix} \tag{3.41}$$

This Jacobian matrix has a distinct eigenvalue given by $(\delta + \kappa + \mu)(R_v - 1)$, which is negative if and only if $R_v < 1$. To determine the nature of other eigenvalues, equation (3.41) is reduced to a 2×2 given as

$$\begin{pmatrix} -(\gamma + \mu) & \omega \\ \gamma & -(\omega + \mu) \end{pmatrix} \tag{3.42}$$

We determine local stability by examining the trace and determinant of the block matrix (3.42). The trace of the matrix (3.42) is $-(\gamma + \omega + 2\mu)$, which is negative and its determinant is given by $\mu(\mu + \omega + \gamma)$ which is positive. It can be clearly seen that the Routh-Hurwitz condition holds [31]. We therefore conclude that the disease free equilibrium is locally asymptotically stable. □

This means that if there is a small perturbation on the system, the system will still return to the disease free equilibrium.

3.2.5 The Global Stability of Disease Free Equilibrium

The disease free equilibrium of model (3.20) is globally asymptotically stable if $R_v \leq 1$. We use the technique by Castillo Chavez [5]. We write system (3.20) in the form; $\frac{dX}{dt}=H(X,Z)$

$\frac{dZ}{dt}=G(X,Z)$, $G(X,0)=0$ where $X \in \mathbb{R}^2$ denotes uninfected compartments (S,V) and $Z \in \mathbb{R}^1$ denotes infected compartment (I). The disease free equilibrium is now denoted as $E_1^0 = (X^0, 0)$, $X^0 = \left(\frac{\omega\Lambda+(1-\rho)\mu\Lambda}{\mu(\omega+\gamma+\mu)}, \frac{(\gamma+\mu\rho)\Lambda}{\mu(\mu+\omega+\gamma)}\right)$

The technique stipulates that the following conditions H1 and H2 must be met to guarantee global asymptotically stability:

H1: For $\frac{dX}{dt}=H(X,0)$, X^0 is globally asymptotically stable.

H2: $G(X,Z) = PZ - \widehat{G}(X,Z), \widehat{G}(X,Z) \geq 0$ for $(X,Z) \in \Omega$,

where X^0 is the disease free equilibrium, $P = D_z G(X,0)$ is an M-matrix (the off-diagonal element of $|P|$ are non-negative) and Ω is the region where the model (3.20) is biologically feasible.

Theorem 3.2.3. *The disease free equilibrium E^0 of system* (3.20) *is globally stable if $R_v < 1$ and unstable whenever $R_v > 1$, provided that the conditions H1 and H2 above are satisfied.*

Proof. From system (3.20), and taking note that $X = (S, V)$ and $Z = I$, we get

$$H(X, 0) = \begin{pmatrix} (1-\rho)\Lambda - (\gamma + \mu)S + \omega V \\ \\ \rho\Lambda + \gamma S - (\omega + \mu)V \end{pmatrix}$$

and rearranging condition H2 we get

$$G(X, Z) = PZ - \widehat{G}(X, Z).$$

Differentiating the right hand side of equation 3 of system (3.20) with respect to I, we obtain

$$P = \beta S + (1-\epsilon)\beta V(t-\tau) - (\delta + \kappa + \mu).$$

Therefore

$$PZ = \beta SI + (1-\epsilon)\beta V(t-\tau)I - (\delta + \kappa + \mu)I,$$

and

$$\begin{aligned} \widehat{G}Z &= PZ - GZ \\ &= \beta SI + (1-\epsilon)\beta V(t-\tau)I - (\delta + \kappa + \mu)I \\ &\quad -(\beta SI + (1-\epsilon)\beta V(t-\tau)I - (\delta + \kappa + \mu)I) \\ &= 0 \end{aligned}$$

Since conditions H1 and H2 are satisfied, the disease free equilibrium is therefore globally asymptotically stable when $R_v < 1$ and unstable whenever $R_v > 1$. □

If there is a large perturbation on the system, it will still return to the disease free equilibrium.

3.2.6 The Local Stability of Endemic Equilibrium (E.E.)

The Jacobian matrix at the endemic equilibrium E^* can be expressed as

$$J = \begin{pmatrix} a_1 & a_2 & a_3 \\ a_4 & a_5 e^{-\lambda\tau} + a_6 & a_7 \\ a_8 & a_5 e^{-\lambda\tau} & a_9 \end{pmatrix}$$

where,

$$a_1 = -(\beta I^* + \gamma + \mu)$$

$$a_2 = \omega$$

$$a_3 = -\beta S^*$$

$$a_4 = \gamma$$

$$a_5 = -(1-\epsilon)\beta I^*$$

$$a_6 = -(\omega + \mu)$$

$$a_7 = (1-\epsilon)\beta V^*$$

$$a_8 = \beta I^*$$

$$a_9 = \beta S^* + (1-\epsilon)V^* - (\delta + \kappa + \mu)$$

We compute the following determinant:

$$\begin{vmatrix} \lambda - a_1 & a_2 & a_3 \\ a_4 & \lambda - [a_5 e^{-\lambda\tau} + a_6] & a_7 \\ a_8 & a_5 e^{-\lambda\tau} & \lambda - a_9 \end{vmatrix} = 0$$

which gives the characteristic equation given as

$$(\lambda - a_1)(\lambda - [a_5 e^{-\lambda\tau} + a_6])(\lambda - a_9) = 0, \tag{3.43}$$

which simplifies to

$$\lambda^3 + M_2\lambda^2 + M_1\lambda + M_0 + (N_2\lambda^2 + N_1\lambda + N_0)e^{-\lambda\tau} = 0, \tag{3.44}$$

where

$$M_2 = -(a_1 + a_6 + a_9)$$

$$M_1 = (a_6a_9 + a_1a_6 + a_1a_9)$$

$$M_0 = (-a_1a_6a_9)$$

$$N_2 = -a_5$$

$$N_1 = (a_5a_9 + a_1a_5)$$

$$N_0 = (-a_1a_5a_9).$$

Multiplying both sides of equation (3.44) by $e^{\lambda\tau}$, we obtain

$$(\lambda^3 + M_2\lambda^2 + M_1\lambda + M_0)e^{\lambda\tau} + N_2\lambda^2 + N_1\lambda + N_0 = 0 \tag{3.45}$$

When $\tau = 0$, equation (3.45) can be expressed as

$$\lambda^3 + M_{02}\lambda^2 + M_{01}\lambda + M_{00} = 0, \tag{3.46}$$

where

$$M_{02} =(M_2 + N_2)$$

$$M_{01} =(M_1 + N_1)$$

$$M_{00} =(M_0 + N_0).$$

Based on Routh Hurwitz theorem [38], it can be concluded that all the roots of equation (3.46) are in the open left half plane if and only if the following condition holds:

$C1 : M_{02} > 0, M_{00} > 0$ and $M_{02}M_{01} > M_{00}$. If $\tau = 0$ and $C1$ holds for equation (3.44) then the endemic equilibrium is locally asymptotically stable.

For $\tau > 0$, we let $\lambda = iw$, for $w > 0$ be a root of equation (3.45). Substituting $\lambda = iw$ into (3.44) we obtain

$$(-iw^3 - M_2w^2 + iM_1w + M_0)((\cos(w\tau) + i\sin(w\tau)) - N_2w^2 + iN_1w + N_0 = 0 \quad (3.47)$$

On separating the real and imaginary parts of equation (3.47) we obtain

$$\begin{aligned} p_1(w)\cos(w\tau) - p_2(w)\sin(w\tau) &= p_3(w) \\ P_4(w)\sin(w\tau) + p_5(w)\cos(w\tau) &= p_6(w), \end{aligned} \quad (3.48)$$

where

$$\begin{aligned} p_1(w) &= -M_2w^2 + M_0 \\ P_2(w) &= M_1w - w^3 \\ p_3(w) &= N_2w^2 - N_0 \\ p_4(w) &= M_0 - M_2w^2 \\ p_5(w) &= M_1w - w^3 \\ p_6(w) &= -N_1w \end{aligned}$$

Solving equation (3.48), we obtain

$$\begin{aligned} \cos(w\tau) &= \frac{p_{01}(w)}{p_{00}(w)} \\ \sin(w\tau) &= \frac{p_{02}(w)}{p_{00}(w)}, \end{aligned} \quad (3.49)$$

where

$$\begin{aligned} p_{00} &= M_2 w^4 - (2M_0M_2 - M_1^2)w^2 - w^6 + M_0 + 2M_1 w^4 \\ p_{01} &= (M_0N_2 + N_0M_2 - M_1N_1)w^2 - (M_2N_2 - N_1)w^4 - N_0M_0 \\ P_{02} &= (M_1N_2 - N_0)w^3 - N_2w^5 - N_0M_1w \end{aligned}$$

Squaring and adding the two equations in equation (3.49), we get

$$p_{01}^2(w) + p_{02}^2(w) - p_{00}^2(w) = 0 \tag{3.50}$$

Suppose that $C2$: equation (3.50) has at least one positive root, w_0, then equation (3.46) will definitely have pure imaginary roots $\pm iw_0$. For w_0 we obtain the critical value of time delay as shown below

$$\tau_0 = \frac{1}{w_0} \arccos\left(\frac{p_{01}(w_0)}{p_{00}(w_0)}\right) \tag{3.51}$$

Differentiating equation (3.45) implicitly with respect to τ we obtain

$$\begin{aligned} &\left(3\lambda^2 + 2M_2\lambda + M_1\right) e^{\lambda\tau}\frac{d\lambda}{d\tau} \\ &+ \left(\lambda + \tau\frac{d\lambda}{d\tau}\right)\left(\lambda^3 + M_2\lambda^2 + M_1\lambda + M_0\right) e^{\lambda\tau} \\ &+ \left(2N_2\lambda + N_1\right)\frac{d\lambda}{d\tau} = 0, \end{aligned} \tag{3.52}$$

which can be arranged in the form of

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{Q_1(\lambda)}{Q_2(\lambda)} - \frac{\tau}{\lambda}, \tag{3.53}$$

where

$$\begin{aligned} Q_1 &= \left(3\lambda^2 + 2M_2\lambda + M_1\right) e^{\lambda\tau} + 2N_2\lambda + N_1 \\ Q_2 &= \lambda\left(\lambda^3 + M_2\lambda^2 + M_1\lambda + M_0\right) e^{\lambda\tau}. \end{aligned}$$

Taking real component of $\left(\frac{d\lambda}{d\tau}\right)^{-1}$ at $\tau = \tau_0$, with $\lambda = iw$, we have

$$Re\left[\frac{d\lambda}{d\tau}\right]^{-1}_{\tau=\tau_0} = \frac{B_R N_R + B_I N_I}{N_R^2 + N_I^2},$$

where

$$\begin{aligned}
B_R &= 3w^2\cos\tau_0 w_0 - 2M_2 w^2\cos\tau_0 w_0 - M_1\sin\tau_0 w_0 - 2N_2 w^2 - \tau(w^4\cos\tau_0 w_0 \\
&\quad - M_2 w^2\cos\tau_0 w_0 + M_2 w^3\sin\tau_0 w_0 - M_0 w\sin\tau_0 w_0); \\
B_I &= 3w^3\cos\tau_0 w_0 + 2M_2 w^2\sin\tau_0 w_0 - M_1 w\cos\tau_0 w_0 - N_1 w + \tau(w^4\sin\tau_0 w_0 \\
&\quad + M_2 w^3\cos\tau_0 w_0 + M_w^2\sin\tau_0 w_0 - M_0 w\cos\tau_0 w_0); \\
N_R &= -w^5\sin\tau_0 w_0 + M_2 w^4\cos\tau_0 w_0 + M_1 w^3\sin\tau_0 w_0 - M_0\cos\tau_0 w_0 \\
N_I &= w^5\cos\tau_0 w_0 + M_2 w^4\sin\tau_0 w_0 - M_1 w^3\cos\tau_0 w_0 - M_0 w^2\sin\tau_0 w_0
\end{aligned}$$

Observe that if $C3 : B_R N_R + B_I N_I \neq 0$ holds, then $Re\left[\frac{d\lambda}{d\tau}\right]^{-1}_{\tau=\tau_0} \neq 0$. Following the workings above and the Hopf bifurcation theory in [**?**], we have the theorem below

Theorem 3.2.4. *If conditions $C1-C3$ hold, then the endemic equilibrium $E^*(S^*, V^*, I^*)$ of the system* (3.20) *is locally asymptotically stable when $\tau \in [0, \tau_0]$; the system undergoes a Hopf bifurcation at $E^*(S^*, V^*, I^*)$ when $\tau = \tau_0$ and a family of periodic solutions bifurcate from $E^*(S^*, V^*, I^*)$.*

CHAPTER 4

NUMERICAL SIMILATIONS AND DISCUSSIONS

Simulations to validate the analytical findings and illustrate the long term dynamics of system (3.20) have been carried out. The parameter values are the same as the ones used in [29] with only τ being varied with time as indicated in the figures.

Parameter	**Value**
Λ	4.109x10^3people per day
ρ	1.884x 10^{-3}people per day
μ	2.537 x 10^{-5}day^{-1}
δ	4.466 x 10^{-1}day^{-1}
β	variable day^{-1}
κ	9.5 x $10^{-4} day^{-1}$Estimated
ϵ	1.0 x 10^{-3}day^{-1}Assumed
ω	2.778 x 10^{-3}day^{-1}
γ	1.884 x 10^{-3}day^{-1}

Figure (4.1) shows that the disease free equilibrium is globally asymptotically stable when $R_v = 0.7692$ which is clearly less than unity.

Figure (4.2) shows that the endemic equilibrium $E^*(35.7321, 45.5913, 6.3217)$ is locally asymptotically stable when $\tau \in [0, \tau_0 = 31.1725]$. This is in line with Theorem 3.2.4.

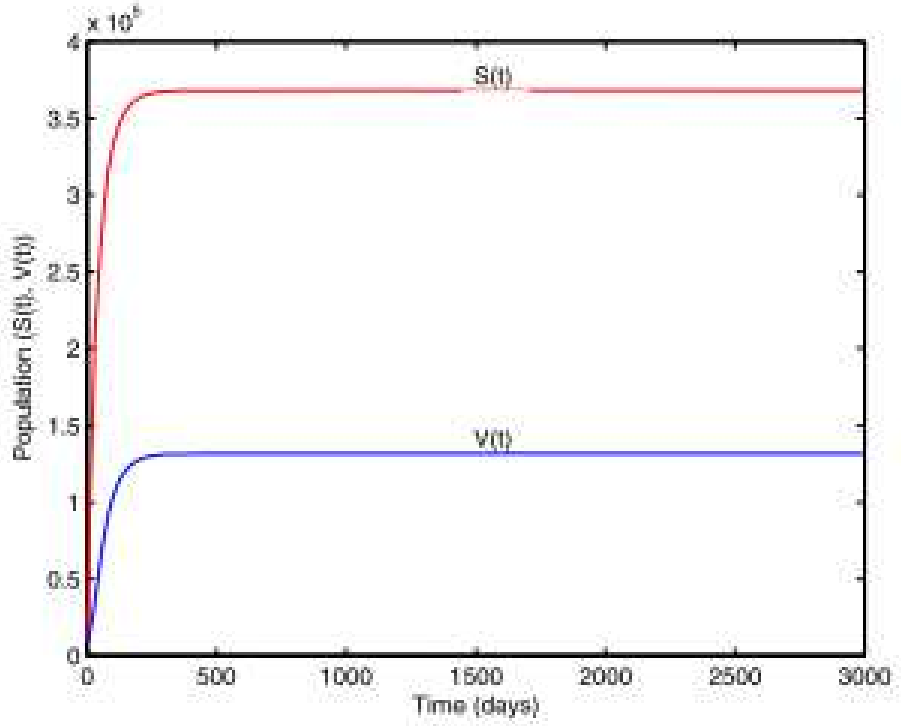

Figure 4.1: Simulation of system (3.20) shows the global stability of the disease-free equilibrium when $R_v = 0.7692$

In Figure (4.2)(a), we can clearly see that when $\epsilon = 0.0127$, $\tau = 5.76$ and $R_v = 4.5672$, the number of infectives are quite high as compared to Figures (4.2)(b) and (c) when $\epsilon = 0.91855, \tau = 1.257, R_v = 1.7261$ and $\epsilon = 0.4123, \tau = 3.1267, R_v = 3.1672$ respectively. This is a proof enough that rotavirus infections can be easily contained by introducing vaccine with high efficacy rates and a shorter delay time .

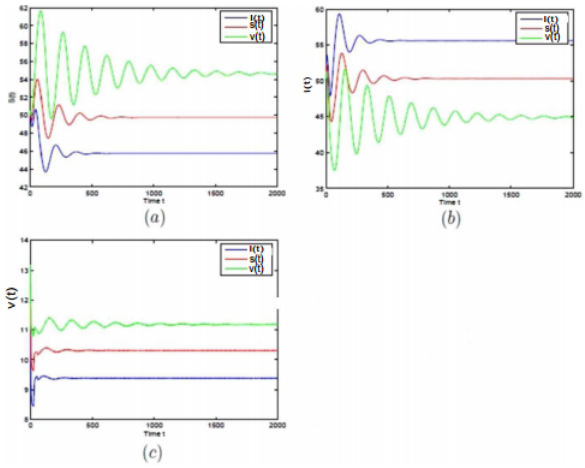

Figure 4.2: The effects of ϵ on all classes with (a) $\epsilon = 0.0127$, $\tau = 5.76$ and $R_v = 4.5672$, (b) $\epsilon = 0.91855, \tau = 1.257, R_v S = 1.7261$ and (c) $\epsilon = 0.4123, \tau = 3.1267, R_v = 3.1672$.

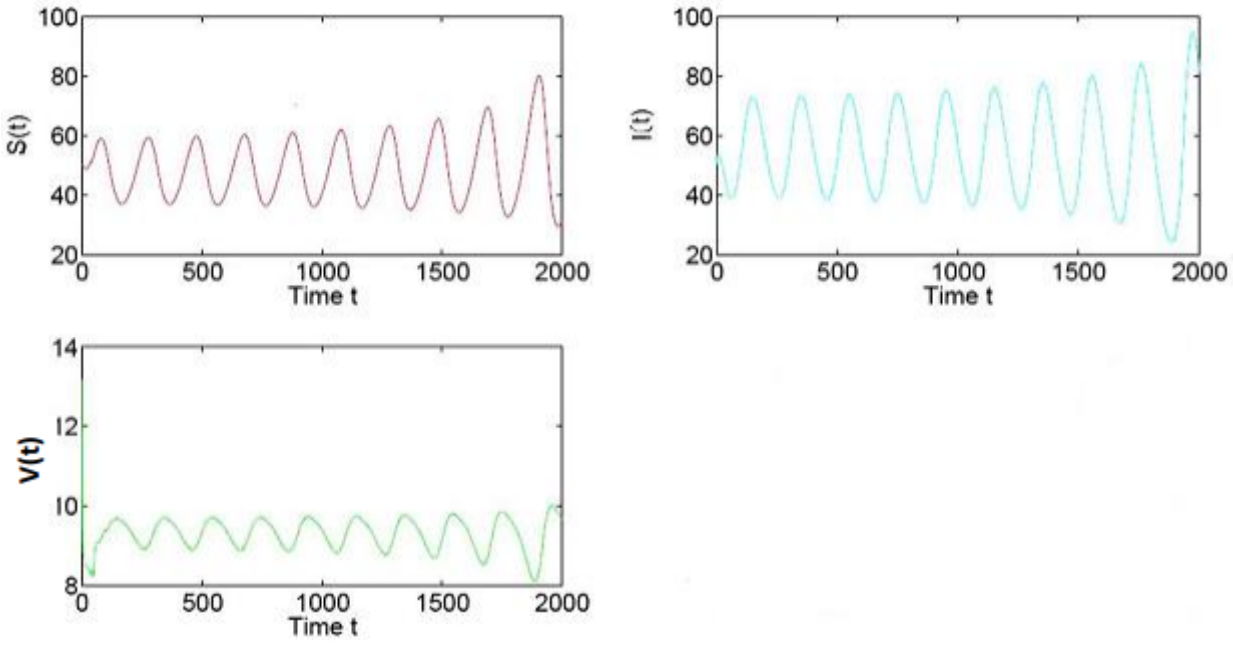

Figure 4.3: Time plots of S, V and I with $\tau = 36.125 > \tau_0 = 31.1725$

Figure 4.3 that a family of periodic solutions bifurcate at $E^*(35.7321, 45.5913, 6.3217)$. This phenomenon is also illustrated by Figure 4.4

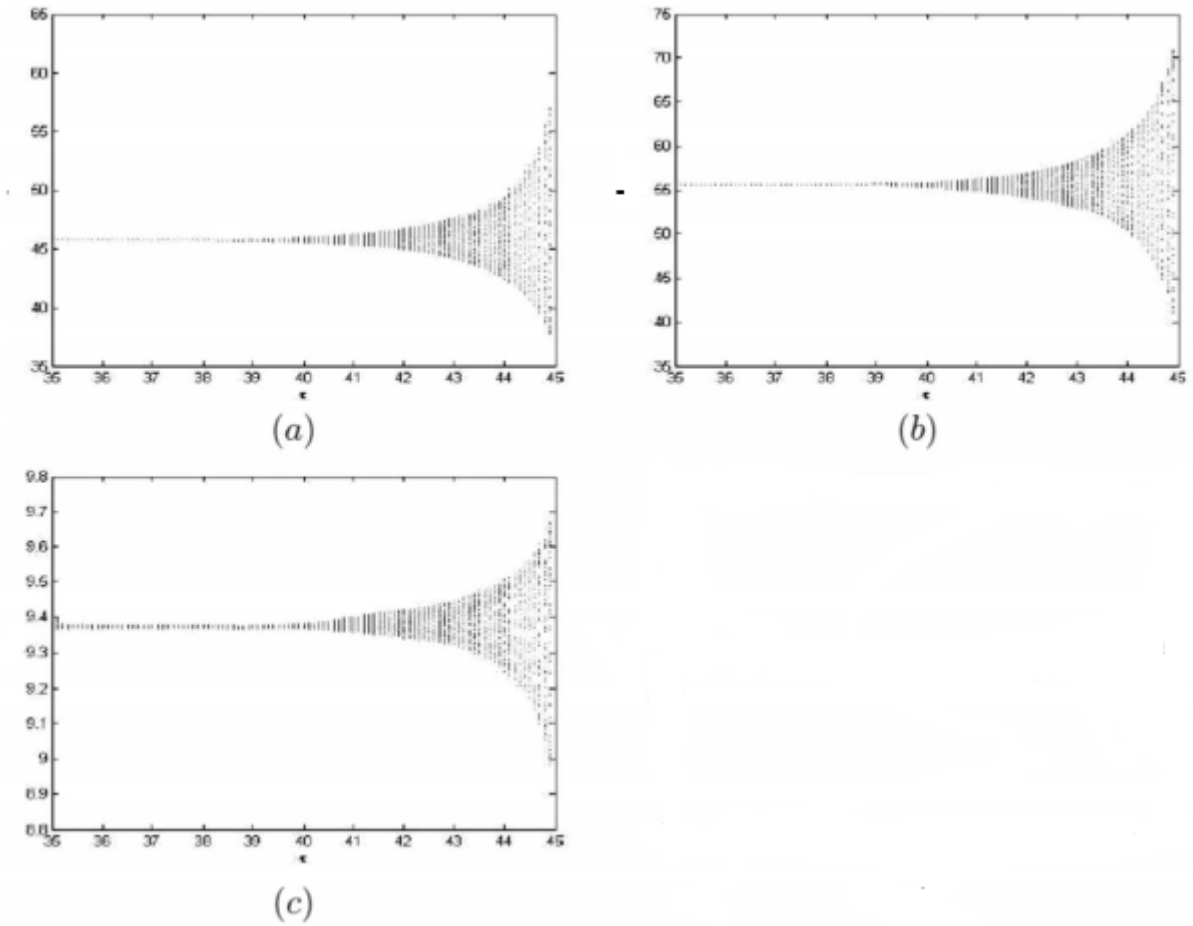

Figure 4.4: Bifurcation diagrams of system (3.20) with respect to τ (a)S, (b) V and (c) I

CHAPTER 5

CONCLUSION AND RECOMENDATION

5.1 Conclusion

The main objective of this study was to formulate a mathematical model for rotavirus incorporating time delay in the effects of vaccination. In this work, we have formulated a mathematical model for rotavirus incorporating time delay in the effects of vaccination. We have established the existence of both disease free and endemic equilibria. The disease free equilibrium has been proved to be both locally and globally stable. The endemic equilibria is proved to be locally stable whenever $\tau = 0$ and undergoes a Hopf bifurcation if $\tau > 0$. From the analytical and simulation results, we observed that when vaccine with low efficacy rates and a longer delay time is used there is an outbreak and when vaccine with high efficacy rates and a shorter delay time rotavirus infections are controlled effectively. We conclude that vaccine with high efficacy rates and a shorter delay time

should be introduced in order to effectively control rotavirus infections.

5.2 Recommendations

From the analytical and simulation results, we recommend that policy makers and health practitioners should plan and allocate vaccine with high efficacy rates and a shorter delay time in order to effectively control rotavirus infections. As a future work, the endemic equilibria is proved to be locally stable whenever $\tau = 0$ and undergoes a Hopf bifurcation if $\tau > 0$. We propose that the directions of Hopf bifurcation derived in this work be established.

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