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COLLEGE OF NATURAL AND COMPUTATION SCIENCES

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THESIS 0N MATHEMATICAL ANALYSIS OF THE TRANSMISSION DYNAMICS OF NOROVIRUS INFECTION MODEL

A Thesis Submitted to Department of Mathematics in Addis Ababa University for Partial Fulfillment of The Masters Degree In Mathematics .

By : Desalegn Kitil Abdi

Advisor : Manalebish Debalike (PhD)

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Abstract

The mathematical modeling of the transmission dynamics of norovirus in a population is designed and rigorously analyzed using some dynamical system theories and techniques. The model was used to gain insight into the disease dynamics and to evaluate control strategies of the norovirustransmission . The model has both global asymptotic stability and local asymptotic stability whenever the reproduction number is less than one. Numerical simulations of the model show that the use of basic control measure strategy is more effective than the treatment strategy while the combination of the two control strategies has a good effective impact on the community in controlling the transmission of the virus .

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CHAPTER ONE

INTRODUCTION

1.1Back-ground

Before the official genus name of norovirus, they were previously called the Norwalk-like viruses[fDCPa]. Norwalk-like virus is the first virus that was recognized to be the cause of gastroenteritis (infection that affects the stomach and the small intestine) in human [fDCPa]. Now a day , norovirus is considered to be the leading cause of the endemic of gastroenteritis and also the most common cause of viral gastroenteritis (it is also called stomach flu) in ages [gR]. Norovirus is known as a small blue rounded structured virus and it belongs to the family of caliciviridae [SPS08]. The name was gotten from a Latin word known as calyx (means cup-like) and it can be traced back to the hollow surface of the virus [Mar].The caliciviridae family of viruses are found in water [Kno]. Examples of foods that norovirus can be found are leafy greens (such as lettuce), fresh fruits, shellfish, oysters, and plankton [Kno].

Norovirus are divided into 5 genogroups which are genogroup I, II,III, IV and V [Kno] . The genogroups of noroviruses that can infect humans are genogroup I (example of the viruses in this group are: norwalk virus, desert shield virus and southhampton virus), genogroup II (examples of the viruses in this group are Bristol virus, Lordsdale virus, Torontovirus, Mexico virus, Hawaii virus and snow mountain) and genogroup IV while genogroup III infects the bovine species(e.g cattle) and genogroup V infects the mice. The genogroups associated with human are further divided into genotypes(or clusters) and then strains . The outbreak of the viral gastroenteritis that circulate across the globe is caused by the norovirus from genogroup II and genotype 4 (it can represented as GII.4) [Ao10] [Kno].

The first description of norovirus was given by a pediatrician called Dr. J. Zahorsky [fDCPa]. Because of the virus was not known as norovirus , he gave an account of the periodic cases (during the month of March-May) of vomiting and watery diarrhea in his patients[fDCPa]. The identification of the virus occurred in the year 1972 and it was being detected in the sampled stool from the outbreak [fDCPa][SPS08]. In 1968, the first recorded outbreak of the viral gastroenteritis infection occurred in an elementary school in the American town of Norwalk, Ohio [fDCPa]. The outbreak of the virus affected both the children and staff at the elementary school [fDCPa]. The name of the virus was coined from the place of the first outbreak. Many other discoveries occurred, and the viruses were named based on the location of the strain or by their physical appearances. Examples are: Montgomery County, Snow Mountain, Mexico Hawaii and Toronto viruses. In 2002, the official genus name norovirus was approved by the International Committee of Taxonomy of Virus due to further understanding of their taxonomy using modern molecular techniques (like the electron microscopy). By 2012, scientific bodies, media and health authorities referred the outbreak of the disease as Norwalk [fDCPa]. Annually, there are approximately 267,000,000 cases of the infection and over 200,000 deaths. Most of these deaths occurred mostly in developing countries, children, elderly and immune suppressed individuals.

According to some previous studies , in Africa, Noroviruses outbreaks and associated gastroenteritis were first reported in South Africa in 1993 with the two strains Norwalk and Hawaii .

In Ethiopia the study was conducted in children attending a health center in Awassa , southern Ethiopia over six month period from December 2008 to May 2009 . The result indicates ,Norovirus was detected in 16 (8%) of 200 cases and in 4 (7%) of 57 controls . Norovirus GII.3 was the strain most commonly detected in 8 (40%) of 20 and ten other genotypes were also detected .

1.2 Mode of NorovirusTransmission

Norovirus is a highly contagious virus, when introduced in a host it attach to the outside cells of the small intestine and transfers its genetic material into the human cells [Mar]. Then, the norovirus multiplies, kill the human cells and attaches to more cells of the small intestine[Mar]. Virions that is less than 10-100 is sufficient to create an infection and rate at which they spread is really fast [SPS08]. During peak sheddig in feces, an approximate of 5 million doses might be contained in each gram [Mar]. Human are known to be the main host of this virus [SPS08]. The transmission of the norovirus infection occurs through several routes and it can be either be through a direct or indirect route. The primary mode of transmission is through direct person-person contact for example caring, sharing utensils or food with an infected person. An indirect mode of transmission is through food borne or water borne transmission [LGP+12]. 50 percent of the outbreak of norovirus infected is caused by food borne transmission. For example it can occur through ingestion of contaminated water and food [Mar][LGP+12]. Another means is through the environment for example the spread of virus through aerosolized vomit into the environment. Virus can stay outside the human host for a long period of time and this depends on the surface they stay and the temperature [Wel]. An infected person is contagious from the day they begin to feel ill till when they recover. The norovirus is mostly shed in stool but it can be found in the vomit of an infected person [Mar]. After the infection, the peak viral shedding of the virus to the environment occurs between 2-5 days [HVL+11], 30 percent of the norovirus infections are asymptotic. In this case an asymptotic person can shed the virus but the virus shed in asymptotic person is less than symptomatic person [HVL+11] .

Norovirus is the leading cause of acute gastroenteritis in human for all ages. The incubation of the virus is between 12-48 hours but less often it might be down to 12 hours. Symptoms associated with this virus are nausea, non blooding diarrhea, vomiting and abdominal cramp [HVL+11]. Healthy individuals can get better from the illness between 1-3 days but the illness can be severe. Illness lasting for more than 4-6 days occur in young children, elderly persons and hospitalized patients [HVL+11] . The infection can lead to malnutrition, severe diarrhea which can be life threatening. Diarrhea and vomiting caused by the virus leads to dehydration and this can be very serious for infected children and elderly ones. When dehydration is ignored or not treated then the symptoms tends to be life threatening in both the children and elderly ones [gR].

1 .3 Control Strategies

The spread of norovirus infection can be prevented through some control strategies. The main two control strategies are treatment strategy and basic control measures strategy .

1.3.1 Treatment Strategy

Norovirus cannot be treated with antibiotics because it is not a bacterial infection and there is no treatment available for norovirus [Mar] but the treatments administered to an infected person aims to help in avoiding the complications that comes along with the illness. One of the complication is dehydration which is the loss of water from the body as a result of frequent vomiting and diarrhea. As a result of dehydration, patients maybe be hospitalized. Symptoms associated with the dehydration are dry mouth and throat, dizziness and reduced urination. Patients are advised to drink plenty fluid such as water, gatorade and children should take pedialyte. Drinks with high sugar content, alcohol, caffeine are advised to be avoided during this period because they can alter an increase in diarrhea.

1.3.2 Basic Control Measures Strategy

In order to reduce the level of norovirus infection in a community, the basic control measures are hand hygiene and cough etiquette, the usage of personal preventive equipments, proper disinfection and cleaning of contaminated surfaces, washing of items that is contaminated with stools and vomits, foods should not be handled by an infected person.

1.4 Objective Of The Thesis

The objective of this thesis is to study the transmission dynamics of norovirus in a population. In particular, thedeterministicmodel will be designed and used to gain qualitative insight into the disease dynamics and to evaluate control strategies. The model will be rigorously analyzed using some dynamical system theories and techniques. The numerical simulations the model will also be carried out . The thesis outline is organized as in chapter one the epidemiological properties of norovirus is briefly described , in chapter two some theories used for the analysis of the model are summarized , in chapter three the model is formulated and qualitatively analyzed , in chapter four numerical simulations are reported , in chapter five the result of the thesis is generated and in chapter six conlusions of the thesis described .

Some of the questions to be addressed in this thesis are:

i . What are the qualitative features of the model of the transmission dynamics of the norovirusinfection. We will be determinethe stability of the equilibra of the model.

ii . To determine the best control strategy that helps in controlling the spread of the viral

infection.

iii . To determine the community impact of the two combined control strategies :The treatment and basic control measure strategies.

1 .5 Norovirus Transmission Dynamics Modeling Review

Norovirus is one of the leading causes of viral gastroenteritis worldwide and responsible for substantial morbidity, mortality and healthcare costs. To further understanding of the epidemiology and control of norovirus, there has been much recent interest in describing the transmission dynamics of norovirus through mathematical models. In this study, we review the current modelling approaches for norovirus transmission. We examine the data and methods used to estimate these models that vary structurally and parametrically between different epidemiological contexts. Many of the existing studies at population level have focused on the same case notification dataset, whereas models from outbreak settings are highly specific and difficult to generalise. In this review, we explore the consistency in the description of norovirus transmission dynamics and the robustness of parameter estimates between studies. In particular, we find that there is considerable variability in estimates of key parameters such as the basic reproduction number, which may mean that the effort required to control norovirus at the population level may currently be underestimated.

The majority of norovirus transmission models take a compartmental approach where the population is split by disease state. Most commonly, the population is divided into susceptible, infected and recovered classes (SIR). A latent, or exposed, compartment (E) is also commonly included in models for norovirus. The latent compartment is necessary to examine the potential effectiveness of controls targeting infected individuals . Within such an SEIR model, the population is distributed into four states where susceptible individuals may become exposed if they come into contact with infected individuals. Once exposed, individuals progress to be infectious and then recovered or removed. In the simplest case, transitions are assumed to occur at a rate inversely proportional to the duration of time spent in each compartment . The number of individuals in each disease state at any time can be described by a set of coupled ordinary differential equations as ,

$\dot{S} = \mathrm{N} - \beta SI - \mu S$,

$\dot{E} = \beta SI - \alpha E - \mu E$,

$\dot{I} = \alpha E - \gamma I - \mu I$,

$\dot{R} = \gamma I - \mu R$,

where ,

μ is the per-capita birth or death rate; β, the transmission rate; α, the rate of latency loss and γ , the recovery rate.

This basic framework can be adapted to include age or spatial structure, stochastic transitions or additional infectious states such as asymptomatic infection. The duration of immunity to re-infection with norovirus is likely to be short lived. This basic SEIR structure may suffice for describing single epidemics of norovirus, but modelling the longer term between season dynamics of norovirus requires additional flows to describe this waning of immunity .

CHAPTER TWO

SOME MATHEMATICAL PRELIMINARIES

In this thesis some definitions and the main theories used are briefly described in this chapter .

2.1 EquilibriumOf Autonomous Ordinary Differential Equations

Biological processes are being described by autonomous (or non-autonomous) differential equations [not] .

In this thesis ,the autonomous ordinary differential equation system that will be considered is

$$\frac{dy}{dt} = f(y) \quad , \; y \in \mathbb{R}^n \, .$$

The differential equation is called autonomous because the vector function does not have an explicit dependence on the independent variable t [not] .

Definition : [Izh] If we have an autonomous differential equation $\frac{dy}{dt} = f(y)$**,** then an equilibrium point of the autonomous system is a state $\bar{y} \in \mathbb{R}$ satisfying $f(\bar{y}) = 0$.

2.2 Stability

The equilibrium point $\bar{y}$ of the autonomous differential equations can be either unstable (that is close by trajectories move away from the equilibrium point) or stable nearby trajectories can either move closer or they do not move from the equilibrium point).

Definition : [MLSS94] An autonomous system of equilibrium point of state $\bar{y} \in \mathbb{R}^n$ is said to be $stable$ if for any neighborhood N of the equilibrium there exist a neighborhood N' contained in N such that all the solutions that start in N' remain in N .

Definition : [MLSS94] An autonomous system of equilibrium point of state $\bar{y} \in \mathbb{R}^n$ is said to be $unstable$, if the equilibrium point of the system is not $stable$.

Definition : [MLSS94] An equilibrium point $\bar{y} \in \mathbb{R}^n$ is known to be $locally\ stable$ if all the solution that starts near the equilibrium point $\bar{y}$ remains near the equilibrium point .

Definition : [Pau] An equilibrium point $\bar{y} \in \mathbb{R}^n$ is known to be $globally\ stable$ if all the initial solutions of the model approaches the equilibrium as t approaches to infinity .

Definition : [MLSS94] An autonomous system of equilibrium point of the state $\bar{y}$ is said to be $asymptotically\ stable$ if it is $stable$ and there exists a neighborhood of the solution such that any solution starting in this neighborhood tends to the equilibrium point as t tends to infinity .

Definition : [MLSS94] An equilibrium point $\bar{y}$ is $locally\ asymptotically\ stable$ if the equilibrium point is $stable$ and as t tends to infinity all the solutions near the equilibrium point tends to the equilibrium point .

Definition : An equilibrium point is said to be in the basin of attraction if it consists of all points such that a solution that starts from the basin of attraction tends to the equilibrium .

2.3 Lyapunov Function Theory

In order to make conclusion about the trajectories of an autonomous ordinary differential equations without solving them , we use Lyapunov theory as follows .

1 .Definition : A function $V: \mathbb{R}^n \to \mathbb{R}$is said to be positive definite if

i)$V(x) > 0, \forall x \neq 0$

ii)$V(x) = 0\ , if\ and\ only\ if\ x = 0$.

2 .Definition : A function $V: \mathbb{R}^n \to \mathbb{R}$ is said to be a Lyapunov function if

i)V is positive definite

ii) The derivative is negative definite (or semi-definite) . That means $\dot{V} < 0, \dot{V}(0) = 0$

3 .Definition :[M.S][12] The LaSalle's principle : The LaSalle's principle is used explore the relationships between the state variables and also to show the asymptotic stability when the derivative of the definite function $V(x)$is only negative semi-definite .

Consider an autonomous system of the form

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

A set $M \subset \mathbb{R}_n$ is an invariant set if $x(0) \in M\ implies\ x(t) \in M, \forall t$ and it is said to be positively invariant set if $x(0) \in M\ implies\ x(t) \in M, \forall t \geq 0$.

4 .**Theorem (LaSalle's Invariance Principle**) [[Sch]] : Let $\Omega \subset D \subset \mathbb{R}^n$ be a compact set that is positively invariant of the system $\frac{dy}{dt} = f(y), y \in \mathbb{R}^n$ and let $V: D \to \mathbb{R}$ be a differentiable function such that $\dot{V}(x) \leq 0$ in Ω . Let $E \subset \Omega$be the set of all points in Ω where $\dot{V}(x) = 0$

Let $M \subset E$ be the largest invariant set in E . Then every solution starting in Ω approaches M as $t \to \infty$.

CHAPTER THREE

MATHEMATICAL FORMULATION OF THE MODEL

3.1 Model Formation

The model for the transmission dynamics of norovirus infection in a population of people in a community is designed by sub-dividing the total relevant population at time t, denoted by $N(t)$, into mutually-exclusive compartments of susceptible ($S(t)$), early exposed ($E_1(t)$), late exposed ($E_2(t)$), symptomatic ($I(t)$), treated ($T(t)$) and recovered ($R(t)$) individuals, so that

$$N(t) = S(t) + E_1(t) + E_2(t) + I(t) + T(t) + R(t).$$

The concentration of virus (norovirus) released into the environment, at time t, is denoted by D(t). The population of susceptible people ($S(t)$) is increased by recruitment of people into the community (by birth or immigration) at a rate Π_H and by the loss of infection-acquired immunity (at a rate ξ). It is diminished by direct person-to-person infection (at a rate β_H ; where $0 \leq \theta_E < 1$ is a modification parameter accounting for the assumed reduction in infectiousness of late exposed individuals in relation to symptomatic individuals) and by infection following contamination with viral particles in the environment at a rate $\lambda_V(t) = \beta_V \frac{D(t)}{K_D+D(t)}$, where$\beta_V$is the ingestion rate of viral particles by humans from contaminated sources (mostly from fecal, water or food contamination),Kis the half-saturation constant (carrying capacity) of the viral population. In this formulation, the Michaelis-mentenincidence function,$\frac{D(t)}{K_D+D(t)}$, is used to account for the probability that an individual acquires norovirus infection given a contact with a contaminated source. This population is further reduced by natural death (at a rate μ_H; this rate is assumed for all human compartments)

$$\frac{dS(t)}{dt} = \Pi_H + \xi R - \beta_H \left(\frac{\theta_E E_2 + I}{N}\right) S - \beta_V \left(\frac{D}{K_D + D}\right) S - \mu_H S \ .$$

The population of early-exposed individuals ($E_1(t)$) is generated following the infection of susceptible individuals. It is reduced by progression to the later-exposed class (at a rate γ) and by natural death, so that:

$$\frac{dE_1(t)}{dt} = \beta_H \left(\frac{\theta_E E_1 + I}{N}\right) S + \beta_V \left(\frac{D}{K_D + D}\right) - \gamma E_1 - \mu_H E_1.$$

The population of later-exposed individuals (E_2(t)) is generated at the rate γ. It is reduced by development of clinical symptoms of the infection (at a rate σ),recovery (at a rate ψ_E, and natural death. Thus,

$$\frac{dE_2(t)}{dt} = \gamma E_1 - \sigma E_2 - \psi_E E_2 - \mu_H E_2.$$

The population of individuals with norovirus symptoms ($I(t)$) is generated at the rate σ. It is diminished by treatment (at arate τ) recovery (at a rate ψ_I), natural death and disease-induced death (at a rate δ). Hence,

$$\frac{dI(t)}{dt} = \sigma E_2 - \tau I - \psi_I I - \mu_H I - \delta I.$$

The population of treated individuals (T(t)) is generated at the rate τ . It is reduced by recovery (at a rate $\psi_T > \psi_I$), natural death and disease-induced death (at a rate $\delta_T < \delta_I$). Thus,

$$\frac{dT(t)}{dt} = \tau I - \psi_T T - \mu_H T - \delta_T T.$$

The population of recovered individuals (R(t)) is generated following the recovery of late-exposed, symptomatic and recovered individuals (at the rates ψ_E, $\psi_I$and ψ_T respectively). It is decreased by loss of infection-acquired immunity (at the rate ξ) and natural death, so that:

$$\frac{dR(t)}{dt} = \psi_E E_2 + \psi_I I + \psi_T T - \xi R - \mu_H R ,$$

The norovirus viral concentration in the environment (D(t)) is increased by the natural growth of the virus (at a rate Π_D and by the excretion of the virus by later-exposed, symptomatic and treated individuals (at the rates ϕ_E, $\phi_I$and ϕ_T respectively). This population is decreased by the natural loss of the viral particles (at a rate μ_D).

Hence,

$$\frac{dD(t)}{dt} = \Pi_D D + \phi_E E + \phi_I I + \phi_T T - \mu_D D.$$

It follows, based on the above derivation that the model for the transmission dynamics of norovirus infection in a population is given by the following deterministic system of nonlinear differential equations:

$$\frac{dS(t)}{dt} = \Pi_H + \xi R - \beta_H \left(\frac{\theta_E E_2 + I}{N}\right) S - \beta_V \left(\frac{D}{K_D + D}\right) S - \mu_H S,$$

$$\frac{dE_1(t)}{dt} = \beta_H \left(\frac{\theta_E E_2 + I}{N}\right) S + \beta_V \left(\frac{D}{K_D + D}\right) S - \gamma E_1 - \mu_H E_1 \,,$$

$$\frac{dE_2(t)}{dt} = \gamma E_1 - \sigma E_2 - \psi_E E_2 - \mu_H E_2 \,,$$

$$\frac{d\mathrm{I}(t)}{dt} = \sigma E_2 - \tau I - \psi_I I - \mu_H I - \delta I \,, \quad (3.1.1)$$

$$\frac{dT(t)}{dt} = \tau \mathrm{I} - \psi_{\mathrm{T}} \mathrm{T} - \mu_{\mathrm{H}} \mathrm{T} - \delta_{\mathrm{T}} \mathrm{T} \,,$$

$$\frac{dR(t)}{dt} = \psi_E E_2 + \psi_I I + \psi_T T - \xi R - \mu_H R \,,$$

$$\frac{dD(t)}{dt} = \Pi_D D + \phi_E E_2 + \phi_I I + \phi_T T - \mu_D D \,.$$

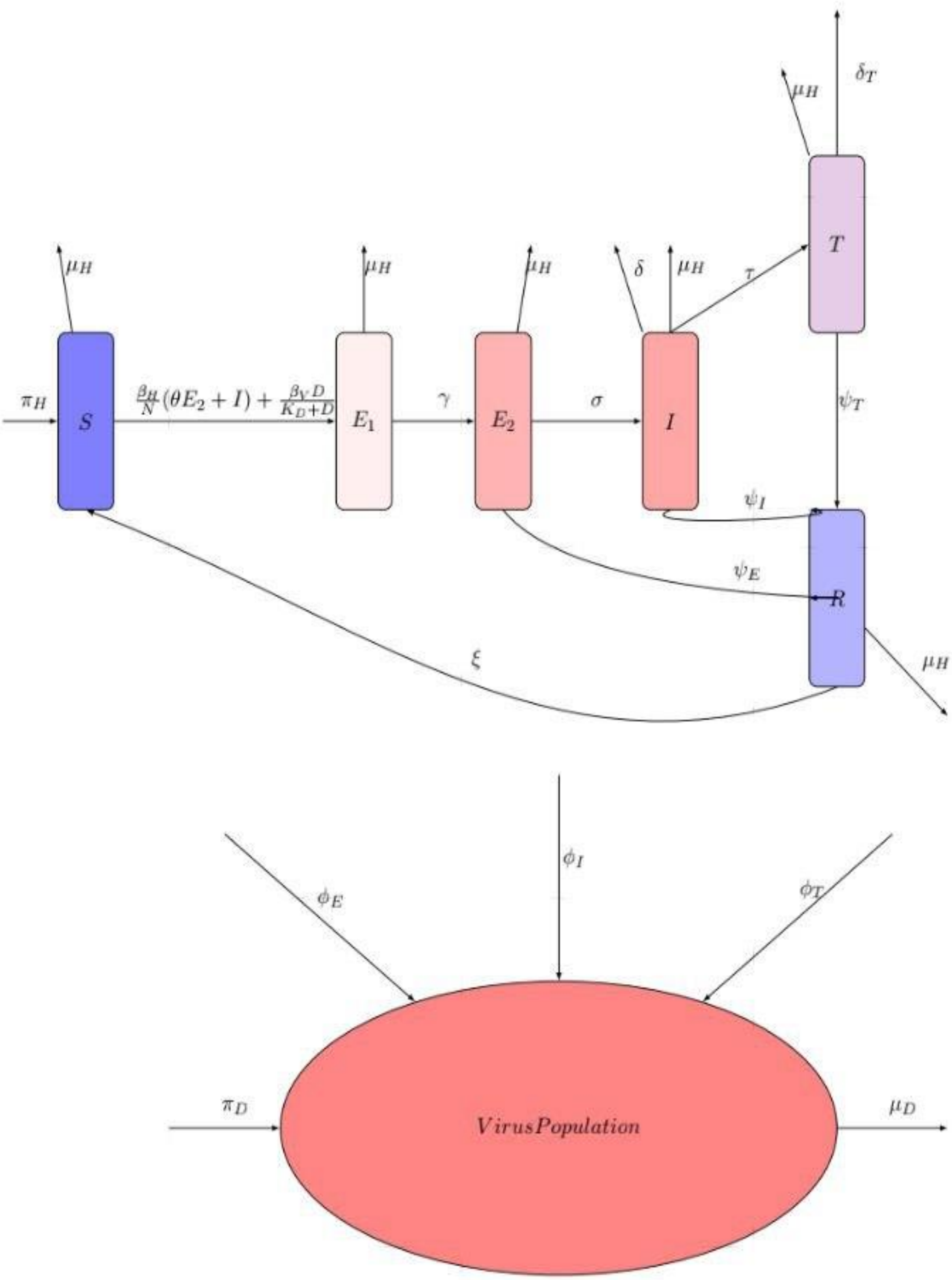

Figure 3 : Diagram of the model

State variables descriptions of the model :

$S(t)$ Population of susceptible individuals

$E_1(t)$ Population of early-exposed individuals

$E_2(t)$ Population of late-exposed individuals

$I(t)$ Population of symptomatic individuals

$T(t)$ Population of treated individuals

$R(t)$Population of recovered individuals

$D(t)$Viral concentration in the environment.

Descriptions of parameters of the model:

Π_H Recruitment rate of susceptible individuals

ξ Rate of loss of infection-acquired (natural) immunity

β_HRate of direct human-to-human transmission

θ_EModification parameter for reduction of infectiousness of late-exposed individuals

β_V Infection rate from contaminated sources

K Carrying capacity of viral concentration in the environment

μ_HNatural death rate

γ Progression rate to late-exposed stage

σ Rate of development of clinical symptoms

τ Rate of Infected individuals.

ψ_E Recovery rate of late-exposed individuals

ψ_{I}Recovery rate of symptomatic individuals

ψ_{T}Recovery rate of treated individuals

ϕ_{E}Viral shedding rate by late-exposed individuals

ϕ_{I}Viral shedding rate by symptomatic individuals

ϕ_{T}Viral shedding rate by treated individuals

δ Disease-induced death rate for symptomatic individuals

δ_TDisease-induced death rate for treated individuals

Π_DNatural growth rate of viral particles in the environment

μ_DNatural death rate of viral particles in the environment .

3.2 Analysis Of The Model

In this thesis , the model monitors the population of people in a community and all its associated parameters are non-negative . Then the following non-negativity result holds .

Theorem : The variables of the model (3.1.1) are non-negative for all time . In other words , solutions of the model system (3.1.1) with positive initial data remain positive for all $t > 0$.

Proof .

Let $t_1 = sup\{t > 0 : S > 0, E_1 > 0, E_2 > 0, I > 0 , T > 0 , R > 0 , D > 0\}$. Then $t_1 > 0$.

Now , let we start from the first equation of the model (3.1.1) as ;

$\frac{dS}{dt} = \Pi_H + \xi R(t) - \lambda(t)S(t) - \mu_H S(t) \geq \Pi_H - (\lambda(t) + \mu_H)S(t)$, (3.2.1) where ,

$\lambda(t) = \frac{\beta_H(\theta_E E_2+I)}{N} + \frac{\beta_V D}{K_D D}$, (3.2.2)

Thus , inequality (3.2.1) can be re-write as

$$\frac{dS}{dt} \geq \Pi_H - (\lambda(t) + \mu_H)S(t)$$

This implies that $\frac{dS}{dt} + (\lambda(t) + \mu_H)S(t) \geq \Pi_H$.

Multiplying both sides by integrating factor $I.F = exp\left\{\mu_H t + \int_0^t \lambda(x)dx\right\}$, then the above inequality becomes

$$\frac{d}{dt}\left[S(t)exp\left\{\mu_H t + \int\limits_0^t \lambda(x)dx\right\}\right] \geq \Pi_H exp\left\{\mu_H t + \int_0^t \lambda(x)dx\right\}$$

Integrating both sides of the inequality , then it follows that

$$S(t_1)exp\left\{\mu_H t_1 + \int_0^{t_1} \lambda(x)dx\right\} - S(0) \geq \int_0^{t_1} \Pi_H exp\left\{\mu_H y + \int_0^{y} \lambda(x)dx\right\} dy$$

So that ,

$S(t) \geq S(0)exp\left\{-\mu_H t_1 - \int_0^{t_1} \lambda(x)dx\right\} + \left[exp\left\{-\mu_H t_1 - \int_0^{t_1} \lambda(x)dx\right\}\right] \int_0^{t_1} \Pi_H exp\{\mu_H y + \int_0^{y} \lambda(x)dx\}dy > 0$.

This implies that ,

$S(t) > 0$, which completes the proof.

Similarly , it can be shown that all other variables (E_1, E_2, I, T, R, D) of the model are non-negative for all time t greater than zero .

The above result can also be established by considering the region :

$$\mathcal{D} = \mathcal{D}_H \times \mathcal{D}_V \subset \mathbb{R}_+^6 \times \mathbb{R}_+ \ ,$$

with ,

$\mathcal{D}_H = \left\{(S, E_1, E_2, I, T, R) \in \mathbb{R}_+^6 : S + E_1 + E_2 + I + T + R = N \leq \frac{\Pi_H}{\mu_H}\right\}$, and

$\mathcal{D}_V = \left\{D : D \leq \frac{\Pi_H(\phi_E + \phi_I + \phi_T)}{\mu_H(\mu_D - \Pi_D)}\right\}$.

Then , we claim the following result .

Lemma : The feasible region $\mathcal{D} = \mathcal{D}_H \times \mathcal{D}_V \subset \mathbb{R}_+^6 \times \mathbb{R}_+$is positively-invariant set for the model (3.1.1) .

The proof of the above Lemma is as follows .

We start by adding the first six equations of the model (3.1.1) , that means

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dE_1}{dt} + \frac{dE_2}{dt} + \frac{dI}{dt} + \frac{dT}{dt} + \frac{dR}{dt}$$

$$= \Pi_H + \xi R - \frac{\beta_H(\theta_E E_2 + I)}{N} S - \frac{\beta_V D}{K_D + D} S - \mu_H S + \frac{\beta_H(\theta_E E_2 + I)}{N} S + \frac{\beta_V D}{K_D + D} S$$
$$- \gamma E_1 - \mu_H E_1 + \gamma E_1 - \sigma E_2 - \psi_E E_2 - \mu_H E_2 + \sigma E_2 - \tau I - \psi_I I - \mu_H I - \delta I + \tau I$$
$$- \psi_T T - \mu_H T - \delta_T T + \psi_E E_2 + \psi_I I + \psi_T T - \xi R - \mu_H R$$

$$= \Pi_H - \mu_H S - \mu_H E_1 - \mu_H E_2 - \mu_H I - \mu_H T - \mu_H R - \delta I - \delta_T T$$

$$= \Pi_H - (S + E_1 + E_2 + I + T + R)\mu_H - (\delta I + \delta_T T)$$

$$= \Pi_H - N\mu_H - (\delta I + \delta_T T)$$

$$\leq \Pi_H - N\mu_H.$$

This implies that ,

$$\frac{dN}{dt} \leq \Pi_H - \mu_H N \ .$$

It follows that ,

$$\frac{dN}{dt} \leq 0 \ , \ if \ \ \Pi_H - \mu_H N \leq 0 \ .$$

And hence ,

$\Pi_H - \mu_H N \leq 0$, implies$-\mu_H N \leq -\Pi_H$, this true when $N \geq \frac{\Pi_H}{\mu_H}$.

Thus ,

$$\frac{dN}{dt} \leq 0 \ if \ N \geq \frac{\Pi_H}{\mu_H} \ .$$

Now , considering

$$\frac{dN}{dt} \leq \Pi_H - \mu_H N \ ,$$

Implies ,

$$\frac{dN}{\Pi_{H-\mu_H N}} \leq dt$$

This is the same as saying ,

$$\int_0^t \frac{dN}{\Pi_H - \mu_H N} \leq \int_0^t dy$$

$$\frac{\Pi_H - \mu_H N}{\Pi_H - \mu_H N(0)} \geq exp\{-\mu_H t\} = e^{-\mu_H t}$$

$$\Pi_H - \mu_H N \geq e^{-\mu_H t}\big(\Pi_H - \mu_H N(0)\big)$$

$$-\mu_H N \geq e^{-\mu_H t}(\Pi_H) - e^{-\mu_H t}\big(\mu_H N(0)\big) - \Pi_H$$

$$N(t) \leq \frac{N(0)\mu_H e^{-\mu_H t}}{\mu_H} + \frac{\Pi_H(1 - e^{-\mu_H t})}{\mu_H}$$

$$N(t) \leq N(0)e^{-\mu_H t} + \frac{\Pi_H}{\mu_H}(1 - e^{-\mu_H t})$$

In particular ,

$N(t) \leq \frac{\Pi_H}{\mu_H}\ \ if\ N(0) \leq \frac{\Pi_H}{\mu_H}$.

Consider the last equation of the model (3.1.1) as

$\frac{dD}{dt} = \Pi_D D + \phi_E E_2 + \phi_I I + \phi_T T - \mu_D D$(3.2.3)

By using $E_2 \leq \frac{\Pi_H}{\mu_H}$, $I \leq \frac{\Pi_H}{\mu_H}$, $T \leq \frac{\Pi_H}{\mu_H}$ in the above equation (3.2.3) ,

$$\frac{dD}{dt} = \Pi_D D + \phi_E E_2 + \phi_I I + \phi_T T - \mu_D D$$

$$\leq \Pi_D D + \phi_E \frac{\Pi_H}{\mu_H} + \phi_I \frac{\Pi_H}{\mu_H} + \phi_T \frac{\Pi_H}{\mu_H} - \mu_D D$$

$$= \frac{\Pi_H(\phi_E + \phi_I + \phi_T)}{\mu_H} - (\mu_D - \Pi_D)D$$

This implies ,

$$\frac{dD}{dt} \leq \frac{\Pi_H(\phi_E + \phi_I + \phi_T)}{\mu_H} - (\mu_D - \Pi_D)D$$

$$dD \leq \left(\frac{\Pi_H(\phi_E + \phi_I + \phi_T)}{\mu_H} - (\mu_D - \Pi_D)D\right)dt$$

$$\frac{dD}{\frac{\Pi_H(\phi_E+\phi_I+\phi_T)}{\mu_H} - (\mu_D - \Pi_D)D} \leq dt$$

Integrating both sides of the inequality ,

$$\int_0^t \frac{dD}{\frac{\Pi_H(\phi_E+\phi_I+\phi_T)}{\mu_H} - (\mu_D - \Pi_D)D} \leq \int_0^t dy$$

$$\frac{\Pi_H(\phi_E + \phi_I + \phi_T) - \mu_H(\mu_D - \Pi_D)D(t))}{\Pi_H(\phi_E + \phi_I + \phi_T) - \mu_H(\mu_D - \Pi_D)D(0))} \geq exp\{-(\mu_D - \Pi_D)t\}$$

$$\Pi_H(\phi_E + \phi_I + \phi_T) - \mu_H(\mu_D - \Pi_D)D(t) \geq exp\{-(\mu_H - \Pi_D)t\}\big(\Pi_H(\phi_E + \phi_I + \phi_T) - \mu_H(\mu_D - \Pi_D)D(0)\big)$$

$$-\mu_H(\mu_D - \Pi_D)D(t) \geq exp\{-(\mu_D - \Pi_D)t\}\big(\Pi_H(\phi_E + \phi_I + \phi_T) - \mu_H(\mu_D - \Pi_D)D(0)\big) - \Pi_H(\phi_E + \phi_I + \phi_T)$$

$$D(t) \leq D(0)exp\{-(\mu_D - \Pi_D)t\} + \frac{\Pi_H(\phi_E + \phi_I + \phi_T)}{\mu_H(\mu_D - \Pi_D)}(1 - exp\{-(\mu_D - \Pi_D)\})$$

Therefore

$D(t) \leq \frac{\Pi_H(\phi_E+\phi_I+\phi_T)}{\mu_H(\mu_D-\Pi_D)}$ $if\ D(0) \leq \frac{\Pi_H(\phi_E+\phi_I+\phi_T)}{\mu_H(\mu_D-\Pi_D)}$. □

Hence , the region $\mathcal{D}$ is positively-invariant (so that it is sufficient to consider the dynamics of the flow generated by the model (3.1.1) in $\mathcal{D}$) . In this region , the model will be considered mathematically and epidemiologically well-posed [HH] .

3. 3 Disease-free equilibrium of the model

The disease-free equilibrium (DFE) of the model (3.1.1) exist at the point

ε_0= (S^* , ${E_1}^*$, ${E_2}^*$, I^* , T^* , R^* , D^*)

= ($\frac{\Pi_H}{\mu_H}$, 0, 0, 0, 0, 0, 0) .

The disease-free equilibrium is composed of only the susceptible population because there is no infection at this equilibrium state. At this state the infected population is zero.

Lemma :The disease free equilibrium of the model is locally-asymptotically stable at the point ε_0 , whenever the reproduction number is less than unity.

The above lemma implies that norovirus can be eliminated from the community (when the reproduction number is less than unity) if the initial sizes of the sub-population of the model are in the basin of attraction of the disease free equilibrium(ε_0) .

3.4 The Basic Reproduction Number

The basic reproduction number denoted by $R_0$and is defined as the expected number of secondary infections per generation given one infected individual is introduced to an entirely susceptible population . The reproduction number measures the average number of new infections generated by an infectious person and a single diarrheal particle in a population where infectious individuals are treated .The reproduction number allows to predict whether the disease will become endemic or die out and also to determine the effective control measure . If $R_0 > 1$, then each infected individual produce more than one secondary infected individuals and as a result of this , the disease will spread into the susceptible population . If $R_0 < 1$, then each individual produces on average less than one infected individual [SG13] .Then basic reproduction number of the model is given by :

$$R_0 = \frac{\gamma\beta_H(\theta_E k_3 k_4 k_5 + \sigma k_4 k_5)}{\prod_{i=1}^{5} k_i} + \frac{\Pi_H \gamma \beta_V(\phi_E k_3 k_4 + \phi_I \sigma k_4 + \phi_T \sigma \tau)}{\mu_H K_D \prod_1^5 ki}$$

where ,

$$k_1 = \gamma + \mu_H \text{ , } k_2 = \sigma + \psi_E + \mu_H \text{ , } k_3 = \tau + \psi_I + \mu_H + \delta \text{ ,} k_4 = \psi_T + \mu_H + \delta_T, \quad k_5 = \mu_D - \Pi_D$$

This reproduction number is derived from the next generation operation method . The next generation operation is a simple approach for determining the local stability of a linear system of ordinary differential equations (ODEs) and is used when the population is divided in to mutually-exclusive n [SG13] . So that , the local stability of disease-free equilibrium (ε_0) of the model (3.1.1) will be described using the next generation operator method [DHM90, dDW] . By using the notation in [dDW] , the non-negative matrix F of the new infection terms and the

M-matrix ,V of the transition terms associated with the model (3.1.1) are given respectively by

$$F = \begin{pmatrix} 0 & \beta_H\theta_E & \beta_H & 0 & \frac{\beta_V\Pi_H}{K_D\mu_H} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \text{and} V = \begin{pmatrix} k_1 & 0 & 0 & 0 & 0 \\ -\gamma & k_2 & 0 & 0 & 0 \\ 0 & -\sigma & k_3 & 0 & 0 \\ 0 & 0 & -\tau & k_4 & 0 \\ 0 & -\phi_E & -_{\phi_I} & -\phi_T & k_5 \end{pmatrix}.$$

Then the basic reproduction number of the model denoted by ,$R_0 = \rho(\mathrm{F}V^{-1})$, where ρ is the spectral radius and is given as above formula .

3.4.1 Interpretation Of The Basic Reproduction Number

The terms which are the first term $\left(\frac{\gamma\beta_H(\theta_E k_3 k_4 k_5 + \sigma k_4 k_5)}{\prod_{i=1}^{5} k_i}\right)$and the second term $\left(\frac{\Pi_H\beta_V\gamma(\phi_E k_3 k_4 + \phi_I \sigma k_4 + \phi_T \sigma\tau)}{\mu_H K_D \prod_{i=1}^{5} k_i}\right)$ in the expression for basic reproduction number can be interpreted as follows .

The first term in the basic reproduction number accounts for viral contribution by infectious humans (that is in the classes of E_2 *and* I) . The average number of new cases generated by individuals in the late-exposed (E_2) class near the disease free equilibrium , denoted by C_E , is the product of the infection rate of late-exposed individuals ($\frac{\theta_E\beta_H S^*}{N^*}$) , the probability that an early-exposed individual survives the early-exposed (E_1) stage and move to the late-exposed (E_2) stage ($that\ is\ \frac{\gamma}{\gamma+\mu_H} = \frac{\gamma}{k_1}$) and the average duration in the late-exposed class ($that\ is\ \frac{1}{\sigma+\psi_E+\mu_H} = \frac{1}{k_2}$) . Thus , noting that at the disease free equilibrium $S^* = N^*$,

$$C_E = \frac{\gamma\theta_E\beta_H}{k_1 k_2}$$

Similarly , the number of infectious generated by infectious individuals in the symptomatic class ($I\ class$) near the disease free equilibrium , denoted by C_I , is the product of the infection rate of symptomatic individuals ($\beta_H \frac{S^*}{N^*}$) , the probability that a late-exposed individual survives the late-exposed (E_2) stage and move to the symptomatic stage ($\frac{\gamma\sigma}{(\gamma+\mu_H)(\sigma+\psi_E+\mu_H)} = \frac{\gamma\sigma}{k_1 k_2}$) and the average duration in the symptomatic (I) class ($\frac{1}{\gamma+\psi_I+\mu_H+\delta} = \frac{1}{k_3}$) .Thus

, $$C_I = \frac{\gamma\sigma\beta_H}{k_1 k_2 k_3}$$

The sum of C_E *and* $C_I$gives the first term in R_0 . That is

$$C_E + C_I = \frac{\gamma\beta_H\theta_E}{k_1k_2} + \frac{\gamma\beta_H\sigma}{k_1k_2k_3} = \frac{k_3(\gamma\beta_H\theta_E) + \gamma\beta_H\sigma}{k_1k_2k_3} = \frac{\gamma\beta_H\theta_E k_3 + \gamma\beta_H\sigma}{k_1k_2k_3} = \frac{\gamma\beta_H(\theta_E k_3 + \sigma)}{k_1k_2k_3}$$

$$= \left(\frac{\gamma\beta_H(\theta_E k_3 + \sigma)}{k_1k_2k_3}\right)\left(\frac{k_4k_5}{k_4k_5}\right) = \frac{\gamma\beta_H(\theta_E k_3 + \sigma)k_4k_5}{k_1k_2k_3k_4k_5} = \frac{\gamma\beta_H(\theta_E k_3k_4k_5 + \sigma k_4k_5)}{\prod_{i=1}^{5} k_i}$$

This implies that

$C_E + C_I = \frac{\gamma\beta_H(\theta_E k_3k_4k_5 + \sigma k_4k_5)}{\prod_{i=1}^{5} k_i}$, which is the first term in R_0 .

The second term in R_0 (the basic reproduction number) accounts for $viral\ shedding\ to\ the\ environment\ by\ infected\ individuals$. The viral shedding by individuals in the late-exposed (E_2) class , denoted by V_E , is the product of the infection (via contamination) rate $\left(\beta_V \frac{S^*}{K_D} = \beta_V \frac{\Pi_H}{\mu_H \mathrm{K}_D}\right)$, the probability that an individual in the early-exposed(E_1) class survives and move to the late-exposed (E_2) class $\left(\frac{\gamma}{\gamma+\mu_H} = \frac{\gamma}{k_1}\right)$, the average duration in the late-exposed (E_2) class $\left(\frac{1}{\sigma+\psi_E+\mu_H} = \frac{1}{k_2}\right)$ and the net of viral secretion by individuals in the late-exposed (E_2) class $\left(\frac{\phi_E}{\mu_D-\Pi_D} = \frac{\phi_E}{k_5}\right)$.

And hence ,

$$V_E = \frac{\beta_V\Pi_H\phi_{E\gamma}}{\mu_H K_D k_1k_2k_5}$$

Similarly , viral shedding to the environment by individuals in the I class is the product of the infection rate $\left(\beta_V \frac{S^*}{K_D}\right)$, the probability that an individual in the early-exposed (E_1) class survives and move to the late-exposed (E_2) class $\left(\frac{\gamma}{\gamma+\mu_H} = \frac{\gamma}{k_1}\right)$, the probability that an individual in the late-exposed (E_2) class survives and move to the I class $\left(\frac{\sigma}{\sigma+\psi_I+\mu_H} = \frac{\sigma}{k_2}\right)$, the average duration in the I class $\left(\frac{1}{\tau+\psi_I+\mu_H+\delta} = \frac{1}{k_3}\right)$ and net viral secretion by I individuals $\left(\frac{\phi_I}{\mu_D-\Pi_D} = \frac{\phi_I}{k_5}\right)$. Thus ,

$$V_I = \frac{\beta_V\Pi_H\gamma\sigma\phi_I}{\mu_H K_D k_1k_2k_3k_5} \ .$$

Finally , viral shedding by treated individuals is the product of the infection rate $\left(\beta_V \frac{S^*}{K_D}\right)$, the probability that an individual in the early-exposed (E_1) class survives and moves to the late-exposed (E_2) class $\left(\frac{\gamma}{\gamma+\mu_H} = \frac{\gamma}{k_1}\right)$, the probability that an individual in the late-exposed (E_2) class survives and move to the I class $\left(\frac{\gamma}{\gamma+\psi_I+\mu_H} = \frac{\gamma}{k_2}\right)$, the probability that an individual in the

I class survives and moves to the treated class $\left(\frac{\tau}{\tau+\psi_I+\mu_H+\delta} = \frac{\tau}{k_3}\right)$, the average duration in the T class $\left(\frac{1}{\psi_T+\mu_H+\delta_T} = \frac{1}{k_4}\right)$, and the net viral secretion by treated individuals $\left(\frac{\phi_T}{\mu_D-\Pi_D} = \frac{\phi_T}{k_5}\right)$.

Thus ,

$$V_T = \frac{\beta_V \Pi_H \gamma \sigma \tau \phi_T}{\mu_H K_D \prod_{i=1}^{5} k_i}$$

The sum $V_E + V_I + V_T$gives the second term of R_0 . That means :

$$V_E + V_I + V_T = \frac{\beta_V \Pi_H \gamma \phi_E}{\mu_H K_D k_1 k_2 k_5} + \frac{\beta_V \Pi_H \gamma \sigma \phi_I}{\mu_H K_D k_1 k_2 k_3 k_5} + \frac{\beta_V \Pi_H \gamma \sigma \tau \phi_T}{\mu_H \mathrm{K}_D k_1 k_2 k_3 k_4 k_5}$$

$$= \frac{k_3 k_4 (\beta_v \Pi_H \gamma \phi_E) + k_4 (\beta_V \Pi_H \gamma \sigma \phi_I) + \beta_V \Pi_H \gamma \sigma \tau \phi_T}{\mu_H K_D k_1 k_2 k_3 k_4 k_5}$$

$$= \frac{\beta_V \Pi_H \gamma (\phi_E k_3 k_4) + \beta_V \Pi_H \gamma (\phi_I \sigma k_4) + \beta_V \Pi_H \gamma \sigma \tau \phi_T}{\mu_H K_D k_1 k_2 k_3 k_4 k_5}$$

$$= \frac{\beta_V \Pi_H \gamma (\phi_E k_3 k_4 + \phi_I \sigma k_4 + \sigma \tau \phi_T)}{\mu_H K_D \prod_{i=1}^{5} k_i}$$

This implies the sum $V_E + V_I + V_T = \frac{\beta_V \Pi_H \gamma (\phi_E k_3 k_4 + \phi_I \sigma k_4 + \sigma \tau \phi_T)}{\mu_H K_D \prod_{i=1}^{5} k_i}$, which is the second term in the basic reproduction number R_0 .

Theorem . (Global Stability of DFE) : The disease free equilibrium of the model (3.1.1) is globally asymptotically stable in the set $\mathcal{D}$ whenever the reproduction number is less than unity .

Proof

Consider the Lyapunovfunction :

$\mathcal{F} = a_1 E_1 + a_2 E_2 + a_3 I + a_4 T + D$,

where ,

$a_1 = \frac{\gamma(\beta_H \theta_E k_3 k_4 k_5 + \beta_H \sigma k_4 k_5 + m_1 \phi_E k_3 k_4 + m_1 \sigma \phi_I k_4 + m_1 \sigma \tau \phi_T)}{k_1 k_2 k_3 k_4 m_1}$,

$a_2 = \frac{\beta_H \theta_E k_3 k_4 k_5 + \beta_H \sigma k_4 k_5 + m_1 \phi_E k_3 k_4 + m_{1\sigma} \phi_I k_4 + m_1 \sigma \tau \phi_T}{k_2 k_3 k_4 m_1}$,

$$a_3 = \frac{\beta_H k_4 k_5 + m_1 \phi_I k_4 + m_1 \tau \phi_T}{k_3 k_4 m_1},$$

$$a_4 = \frac{\phi_T}{k_4},$$

with , $m_1 = \frac{\beta_V \Pi_H}{K_D \mu_H}$,

The Lyapunov derivative (where dot represents differentiation with respect to time) is given by

$$\dot{\mathcal{F}} = a_1 \dot{E}_1 + a_2 \dot{E}_2 + a_3 \dot{I} + a_4 \dot{T} + \dot{D}$$

$$= \left[\frac{\gamma(\beta_H \theta_E k_3 k_4 k_5 + \beta_H \sigma k_4 k_5 + m_1 \phi_E k_3 k_4 + m_1 \sigma \phi_I k_4 + m_1 \sigma \tau \phi_T)}{k_1 k_2 k_3 k_4 m_1}\right] (\lambda S - k_1 E_1)$$

$$+ \left[\frac{\beta_H \theta_E k_3 k_4 k_5 + \beta_H \sigma k_4 k_5 + m_1 \phi_E k_3 k_4 + m_1 \sigma \phi_I k_4 + m_1 \sigma \tau \phi_T}{k_2 k_3 k_4 m_1}\right] (\gamma E_1 - k_2 E_2)$$

$$+ \left[\frac{\beta_H k_4 k_5 + m_1 \phi_I k_4 + m_1 \tau \phi_T}{k_3 k_4 m_1}\right] (\sigma E_2 - k_3 I) + \frac{\phi_T}{k_4} (\tau I - k_4 T) + \phi_E E_2 + \phi_I I + \phi_T T - k_5 D.$$

Since $S(t) \leq \frac{\Pi_H}{\mu_H}$ in the region D and $\frac{\beta_V}{K_D + D} \leq \frac{\beta_V}{K_D}$, it follows that

$$\lambda S = \frac{\beta_H (\theta_E E_2 + I) S}{N} + \frac{\beta_V D S}{K_D + D} \leq \beta_H (\theta_E E_2 + I) + \frac{\Pi_H \beta_V D}{\mu_H K_D} = \beta_H (\theta_E E_2 + I) + m_1 D \, .$$

Hence ,

$$\dot{\mathcal{F}} \leq \left[\frac{\gamma(\beta_H \theta_E k_3 k_4 k_5 + \beta_H \sigma k_4 k_5 + m_1 \phi_E k_3 k_4 + m_1 \sigma \phi_I k_4 + m_1 \sigma \tau \phi_T)}{k_1 k_2 k_3 k_4 m_1}\right] [\beta_H (\theta_E E_2 + I) + m_1 D]$$

$$+ \left[\frac{\beta_H \theta_E k_3 k_4 k_5 + \beta_H \sigma k_4 k_5 + m_1 \phi_E k_3 k_4 + m_1 \sigma \phi_I k_4 + m_1 \sigma \tau \phi_T}{k_2 k_3 k_4 m_1}\right] (\gamma E_1 - k_2 E_2) \tag{3.4.1}$$

$$+ \left[\frac{\beta_H k_4 k_5 + m_1 \phi_I k_4 + m_1 \tau \phi_T)}{k_3 k_4 m_1}\right] (\sigma E_2 - k_3 I) + \frac{\phi_T}{k_4} (\tau I - k_4 T) + \phi_E E_2 + \phi_I I + \phi_T T - k_5 D \, .$$

It can be easily seen that the coefficients of $E_1 \; and \; T$ in the inequality (3.4.1) equal zero .

Collecting the coefficients of E_2 , $I\ and\ D$ in (3.4.1) and then gives

$$\dot{\mathcal{F}} \leq \left[-\frac{\beta_H\theta_E k_5}{m_1}+\frac{\beta_H\theta_E\gamma(\beta_H\theta_E k_3k_4k_5+\beta_H\sigma k_4k_5+m_1\phi_E k_3k_4+m_1\sigma\phi_I k_4+m_1\sigma\tau\phi_T)}{k_1k_2k_3k_4m_1}\right]E$$

$$+\left[-\frac{\beta_H k_5}{m_1}+\frac{\beta_H\gamma(\beta_H\theta_E k_3k_4k_5+\beta_H\sigma k_4k_5+m_1\phi_E k_3k_4+m_1\sigma\phi_I k_4+m_1\sigma\tau\phi_T)}{k_1k_2k_3k_4m_1}\right]I$$

$$+\left[-k_5+\frac{\gamma(\beta_H\theta_E k_3k_4k_5+\beta_H\sigma k_4k_5+m_1\phi_E k_3k_4+m_1\sigma\phi_I k_4+m_1\sigma\tau\phi_T)}{k_1k_2k_3k_4}\right]D$$

$$=\left[-\frac{\beta_H\theta_E k_5}{m_1}+\frac{\beta_H\theta_E k_5\gamma(\beta_H\theta_E k_3k_4k_5+\beta_H\sigma k_4k_5+m_1\phi_E k_3k_4+m_1\sigma\phi_I k_4+m_1\sigma\tau\phi_T)}{k_1k_2k_3k_4k_5m_1}\right]E_2$$

$$+\left[-\frac{\beta_H k_5}{m_1}+\frac{\beta_H k_5\gamma(\beta_H\theta_E k_3k_4k_5+\beta_H\sigma k_3k_4+m_1\phi_E k_3k_4+m_1\sigma\phi_I k_4+m_1\sigma\tau\phi_T)}{k_1k_2k_3k_4k_5m_1}\right]I$$

$$+\left[-k_5+\frac{\gamma k_5(\beta_H\theta_E k_3k_4k_5+\beta_H\sigma k_4k_5+m_1\phi_E k_3k_4+m_1\sigma\phi_I k_4+m_1\sigma\tau\phi_T)}{k_1k_2k_3k_4k_5m_1}\right]D$$

$$=\left[\frac{\beta_H\theta_E k_5}{m_1}\left(-1+\frac{\gamma\beta_{H(\theta_E k_3k_4k_5+\sigma k_4k_5)}}{k_1k_2k_3k_4k_5}+\frac{\gamma m_1(\phi_E k_3k_4+\sigma\phi_I k_4+\sigma\tau\phi_T)}{k_1k_2k_3k_4k_5}\right)\right]E_2$$

$$+\left[\frac{\beta_H k_5}{m_1}\left(-1+\frac{\gamma\beta_H(\theta_E k_3k_4k_5+\sigma k_4k_5)}{\prod_{i=1}^{5}k_i}+\frac{\gamma m_1(\phi_E k_3k_4+\sigma\phi_I k_4+\sigma\tau\phi_T)}{\prod_{i=1}^{5}k_i}\right)\right]I$$

$$+\left[k_5\left(-1+\frac{\gamma\beta_H(\theta_E k_3k_4k_5+\sigma k_4k_5)}{\prod_{i=1}^{5}k_i}+\frac{\gamma m_1(\phi_E k_3k_4+\sigma\phi_I k_4+\sigma\tau\phi_T)}{\prod_{i=}^{5}k_i}\right)\right]D$$

$$=\left[\frac{\beta_H\theta_E k_5}{m_1}\left(-1+\frac{\gamma\beta_H(\theta_E k_3k_4k_5+\sigma k_4k_5)}{\prod_{i=1}^{5}k_i}+\frac{\gamma\Pi_H\beta_V(\phi_E k_3k_4+\sigma\phi_I k_4+\sigma\tau\phi_T)}{\mu_H K_D\prod_{i=1}^{5}k_i}\right)\right]E_2$$

$$+\left[\frac{\beta_H k_5}{m_1}\left(-1+\frac{\gamma\beta_H(\theta_E k_3k_4k_5+\sigma k_4k_5)}{\prod_{i=1}^{5}k_i}+\frac{\gamma\Pi_H\beta_V(\phi_E k_3k_4+\sigma\phi_I k_4+\sigma\tau\phi_T)}{\mu_H K_D\prod_{i=1}^{5}k_i}\right)\right]I$$

$$+\left[k_5\left(-1+\frac{\gamma\beta_H(\theta_E k_3k_4k_5+\sigma k_4k_5)}{\prod_{i=1}^{5}k_i}+\frac{\gamma\Pi_H\beta_V(\phi_E k_3k_4+\sigma\phi_I k_4+\sigma\tau\phi_T)}{\mu_H K_D\prod_{i=}^{5}k_i}\right)\right]D$$

$$=\frac{\beta_H\theta_E k_5}{m_1}(R_0-1)E_2+\frac{\beta_H k_5}{m_1}(R_0-1)I+k_5(R_0-1)D$$

$$=\frac{k_5}{m_1}(\beta_H\theta_E E_2+\beta_H I+m_1 D)(R_0-1)$$

This implies that ,

$\dot{\mathcal{F}} \leq \frac{k_5}{m_1}(\beta_H\theta_E E_2 + \beta_H I + m_1 D)(R_0 - 1)$.

Since all the parameters and variables of the model are non-negative , it follows that $\dot{\mathcal{F}} \leq 0$ for $R_0 \leq 1$ with $\dot{\mathcal{F}} = 0$ if and only if $E_2 = I = D = 0$. Hence , $\dot{\mathcal{F}}$ is a Lyapunov function on D . Thus it follows by the LaSalle's Invariance Principle [Hal] , that

$\lim_{t\to\infty} E_2(t) = 0$, $\lim_{t\to\infty} I(t) = 0$, $\lim_{t\to\infty} D(t) = 0$. (3.4.2)

It follows from the first equation of the model (3.1.1) that

$$\frac{dS}{dt} = \Pi_H + \xi R(t) - \lambda(t)S(t) - \mu_H S(t) \geq \Pi_H - (\lambda(t) + \mu_H)S(t),$$

where ,

$$\lambda(t) = \frac{\beta_H(\theta_E E_2 + I)}{N} + \frac{\beta_V D}{K_D + D},$$

$$\lim_{t\to\infty} \lambda(t) = 0 . \quad (3.4.3)$$

This implies , $\lim_{t\to\infty} sup\lambda = 0$, it follows that , for sufficiently small $\varpi^* > 0$, there exists constants $M_1 > 0$ such that $\lim_{t\to\infty} sup\lambda \leq \varpi^*$, $\forall t > M_1$. Hence , it follows the second equation of the model (3.1.1) that , for $t > M_1$,

$$\frac{dE_1}{dt} \leq \frac{\varpi^*\Pi_H}{\mu_H} - k_1 E_1$$

This implies , $\frac{\frac{dE_1}{dt}}{\frac{\varpi^*\Pi_H}{\mu_H} - k_1 E_1} \leq 1$

$$\left(\frac{\frac{dE_1}{dt}}{\frac{\varpi^*\Pi_H}{\mu_H} - k_1 E_1}\right) \leq 1$$

Now , integrating both sides of the inequality ,

$$\int_0^t \left(\frac{\frac{dE_1}{dt}}{\frac{\varpi^*\Pi_H}{\mu_H} - k_1 E_1}\right) \leq \int_0^t dx$$

Then we have ,

$$\frac{\frac{\varpi^* \Pi_H}{\mu_H} - k_1 E_1(t)}{\frac{\varpi^* \Pi_H}{\mu_H} - k_1 E_1(0)} \geq exp\{-K_1 t\} .$$

Therefore ,

$$\frac{\varpi^* \Pi_H}{\mu_H} - k_1 E_1(t) \geq (\frac{\varpi^* \Pi_H}{\mu_H} - k_1 E_1(0)) exp\{-K_1 t\}$$

$$E_1(t) \leq exp\{-K_1 t\} E_1(0) + \frac{\varpi^* \Pi_H}{k_1 \mu_H} (1 - exp\{-K_1 t\}$$

Hence ,

$$E_1^{\infty} = \lim_{t \to \infty} sup E_1 \leq \frac{\varpi^* \Pi_H}{k_1 \mu_H} ,$$

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

$$E_1^{\infty} = \lim_{t \to \infty} sup E_1 \leq 0. \qquad (3.4.4)$$

Similarly , it can be shown that

$$E_{1\infty} = \lim_{t \to \infty} inf E_1 \geq 0 . \qquad (3.4.5)$$

Thus , it follows from (3.4.4) and (3.4.5) above that

$$E_{1\infty} \geq 0 \geq E_1^{\infty} .$$

Hence ,

$$\lim_{t \to \infty} E_1 = 0 . \qquad (3.4.6)$$

Similarly , it can be shown that

$$\lim_{t \to \infty} S(t) = \frac{\Pi_H}{\mu_H} , \lim_{t \to \infty} T(t)=0 , \lim_{t \to \infty} R(t) = 0 . \qquad (3.4.7)$$

Thus , by combining equations (3.4.2) ,(3.4.6) and (3.4.7) , it follows that every solution of the equations of the model (3.1.1) , with initial conditions in D , approaches to the disease free equilibrium point (ε_0) as $t \to \infty$ (for $R_0 < 1$) .

The above result shows that norovirus can be eliminated from the community if the associated reproduction number of the model is less than unity . The figure below is a numerical simulations of the model (3.1.1) using different initial conditions when the reproduction number is less than unity . From the figure all solutions converges to the disease free equilibrium .

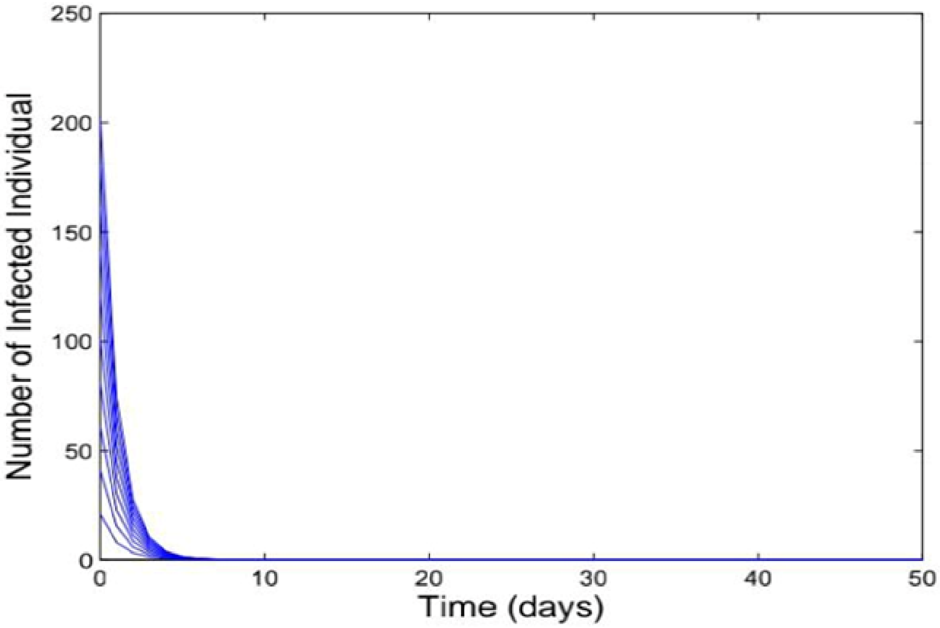

Figure 3.1 : Simulations of the model (3.1.1) showing the number of infected individuals as a function of time for $R_0 < 1$. Parameter values used are as given in table (4.1) with $\beta_H = 0.65$, $\beta = 0.00083$, $K_D = 10^7$, $and\ \ \gamma = 0.000325$, $so\ that\ R_0 = 0.6782 < 1$.

3.5 Endemic Equilibrium Point

The endemic(positive) equilibrium point of the model is equilibria where at least one of the infected components of the model is non-zero .

Let the endemic equilibrium point of the model represented by ϑ and defined as

$$\varepsilon_1 = (S^{**}, {E_1}^{**}, \qquad {E_2}^{**}, I^{**}, T^{**}, R^{**}, D^{**})$$

Then further define λ^{**} as

$\lambda^{**} = \frac{\beta_H(\theta_E {E_2}^{**} + I^{**})}{N^{**}} + \frac{\beta_V D^{**}}{K_D + D^{**}}$, (3.5.1)

(the force of infection of the model at steady-state) .

By solving the equations in the model (3.1.1) at steady-state , it follows that

$S^{**} = \frac{k_1 k_2 k_3 k_4 \mathrm{h} \Pi_H}{p_1 \lambda^{**} + p_2}$, ${E_1}^{**} = \frac{k_2 k_3 k_4 h \Pi_H \lambda^{**}}{p_1 \lambda^{**} + p_2}$, ${E_2}^{**} = \frac{k_3 k_4 h \gamma \Pi_H \lambda^{**}}{p_1 \lambda^{**} + p_2}$,

$I^{**} = \frac{k_4 h \sigma \gamma \Pi_H \lambda^{**}}{p_1 \lambda^{**} + p_2}$, $T^{**} = \frac{h \tau \sigma \gamma \Pi_H \lambda^{**}}{p_1 \lambda^{**} + p_2}$, $R^{**} = \frac{\gamma m \Pi_H \lambda^{**}}{p_1 \lambda^{**} + p_2}$, (3.5.2)

$$D^{**} = \frac{\gamma h m \Pi_H \lambda^{**}}{(p_1 \lambda^{**} + p_2) k_5} \ ,$$

where

$h = \xi + \mu_{\mathrm{H}}$,$m = \psi_{\mathrm{T}} \tau \sigma + \psi_{\mathrm{E}} k_3 k_4 + \psi_{\mathrm{I}} \sigma k_4, p_1 = k_1 k_2 k_3 k_4 h - \xi \gamma m$,

$p_2 = k_1 k_2 k_3 k_4 h \mu_H$(3.5.3)

Substituting the expressions in (3.5.2) into (3.5.1) , and noting (3.5.3) , shows that the non-zero equilibria of the model (3.1.1) satisfy the quadratic equation in terms of λ^{**} as follows.

$a(\lambda^{**})^2 + b(\lambda^{**}) + c = 0$, (3.5.4)

where ,

$$a = K_D k_5 p_1 \tau \sigma \gamma h + K_D k_5 p_1 k_4 k_3 k_2 h + \gamma^2 h \Pi_H m^2 + K_D k_5 p_1 \gamma k_4 k_3 h + K_D k_5 p_1 \gamma m$$

$$+ \gamma^2 h^2 \Pi_H m \sigma \gamma + K_D k_5 p_1 \sigma \gamma k_4 h + \gamma h^2 \Pi_H m k_4 k_3 k_2 + \gamma^2 h^2 \Pi_H m k_4 k_3$$

$+ \gamma^2 h^2 \Pi_D m \sigma k_4$,

$$b = \mathrm{K}_D k_5 p_2 k_4 k_3 k_2 h - \beta_H \gamma k_4 h \theta_E \sigma K_D k_5 p_1 - \beta_V \gamma h^2 \Pi_H m k_4 k_3 k_2 - \beta \gamma^2 h^2 \Pi_H m k_4 k_3$$

$$+ \gamma k_4 h k_3 K_D k_5 p_2 + \mathrm{K}_D k_5 p_2 \sigma \gamma k_4 h + K_D k_5 p_2 \tau \gamma h + K_D k_5 p_1 k_4 k_3 k_2 k_1 h$$

$$+ \gamma h^2 \Pi_H m k_4 k_3 k_2 k_1 - \beta_V \gamma^2 h^2 \Pi_H m \tau \sigma - \beta_V \gamma^2 h \Pi_H m^2 - \beta_H \gamma^2 k_4 h^2 \theta_E \sigma \Pi_H m$$

$$- \beta_V \gamma^2 h^2 \Pi_H m \sigma k_4 - \beta_H \gamma^2 k_4 h^2 k_3 \Pi_H m - \mathrm{\beta}_H \gamma k_4 h k_3 K_D k_5 p_1 + K_D k_5 p_2 \gamma m ,$$

$c = K_D k_5 \mu_H h^2 {k_1}^2 {k_2}^2 {k_3}^2 {k_4}^2 (1 - R_0)$.

The endemic equilibrium points can be obtained by substituting the positive roots of λ^{**} into the steady state (3.5.2) , it follows from (3.5.5) that $a > 0$ because of all the model parameters are non-negative . Further ,$c < 0$ whenever $R_0 > 1$. Thus , regardless of the sign for b in (3.5.5) , the following result is established . The figure below is a numerical simulations of the model (3.1.1) using different initial conditions when $R_0 > 1$. The figure shows the endemic state of the model when $R_0 (= 3.43 \times 10^7) > 1$.

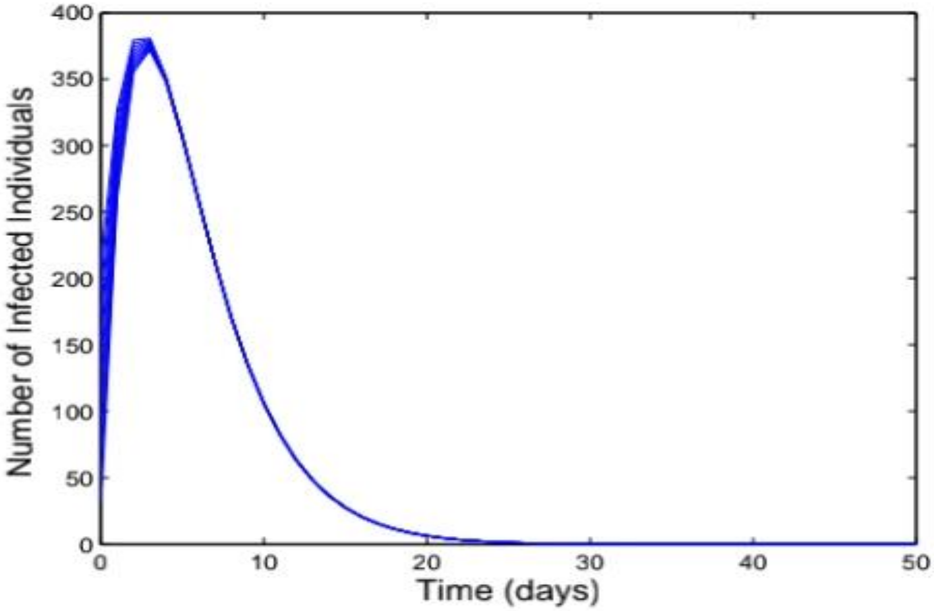

Figure 3.2 : Simulations of the model (3.1.1) showing the number of infected individuals as a function of time for $\boldsymbol{R_0 > 1}$. Parameter values used are in table (4.1) with $\boldsymbol{\beta_H = 0.65}$, $\boldsymbol{\beta = 0.06}$, $\boldsymbol{K_D = 10^{11}}$, $\boldsymbol{and \gamma = 0.325 (so that R_0 > 1)}$.

CHAPTER FOUR

NUMERICAL SIMULATIONS

In this numerical simulation part we will assess impact of the control strategies of transmission of norovirus at the population level . And hence under numerical simulation of the model of the transmission dynamics of norovirusthere are description of parameters of the model with values and their references mentioned below .

Parameter	Description of the parameter	Values	References
Π_H	Recruitment rate of susceptible individuals	10970 per day	[JBea15]
ξ	Rate of loss of infection-acquired (natural) immunity	[0.00137,0.005488] per day	$[TDJ^+]$
β_H	Rate of direct human to human transmission	[0.65, 0.82] per day	Assumed
θ_E	Modification parameter for reduction of infectiousness of late-exposed individuals	0.0035 per year	Assumed
β_V	Infection rate from contaminated sources	0.033 per gram	[PCP$^+$ 08]
K_D	Carrying capacity of viral concentration in the environment	$[10^5, 10^{11}]$	[Kir13]
μ_H	Natural death rate	0.0000342 /day	[Age]
γ	Progression rate to late-exposed stage	0.325 per day	Assumed
σ	Rate of development of clinical symptoms	[0.0000174,0.0000192] per day	[HVL$^+$11]
τ	Rate of infected individual	[0.00514,0.00651] per day	[fDCPb]
ψ_E	Recovery rate of late-exposed individuals	[0.33,1] per day	Assumed
ψ_I	Recovery rate of symptomatic individuals	[0.33,1] per day	[HVL$^+$11]
ψ_T	Recovery rate of treated individuals	0.05 per day	Assumed

ϕ_E, ϕ_I, ϕ_T	Viral shedding	[0.02,0.04]/day	[HVL$^+$11]
δ	Disease induced death rate of infected individuals	[0.46,0.64] per day	[fDCPb]
δ_T	Disease induced death rate of treated individuals	[0.46,0.64] per day	[fDCPb]
Π_D	Natural growth rate of viral particles in the environment	[0.46,0.64] per day	[Bay09]
μ_D	Natural death rate of viral particles in the environment	[0.0000332,0.0000386] per day	[LGP$^+$12

Table 4.1 : Descriptions of parameter values .

In this mathematical modeling of norovirus transmission dynamics ,we consider the control strategies as : basic control measure strategy , treatment strategy and the two combined strategy . And then we will see the numerical simulations of each of them one by one

4.1 The Basic Control Measure Strategy

The basic control measure strategy focuses on the prevention of the virus before infection . The best examples of it are proper food sanitation and personal hygiene . Then this strategy was being accounted for by the ingestion parameter β_V and the direct contact parameterβ_H .

That means an increase or decrease in β_V and $\beta_H$will leads to the increase or decrease in the contact rate of the population with the norovirus infection .

For the simulation of this strategy there are two effective levels considered with values are chosen arbitrary . These are :

i) Low effective level of basic control measure strategy with $\beta_H = 0.65$,$\beta_V = 0.83$

ii) High effective level of basic control measure strategy with $\beta_H = 0.065$,$\beta_V = 0.0083$

Below is the figure produced during the simulations of two effective levels considered

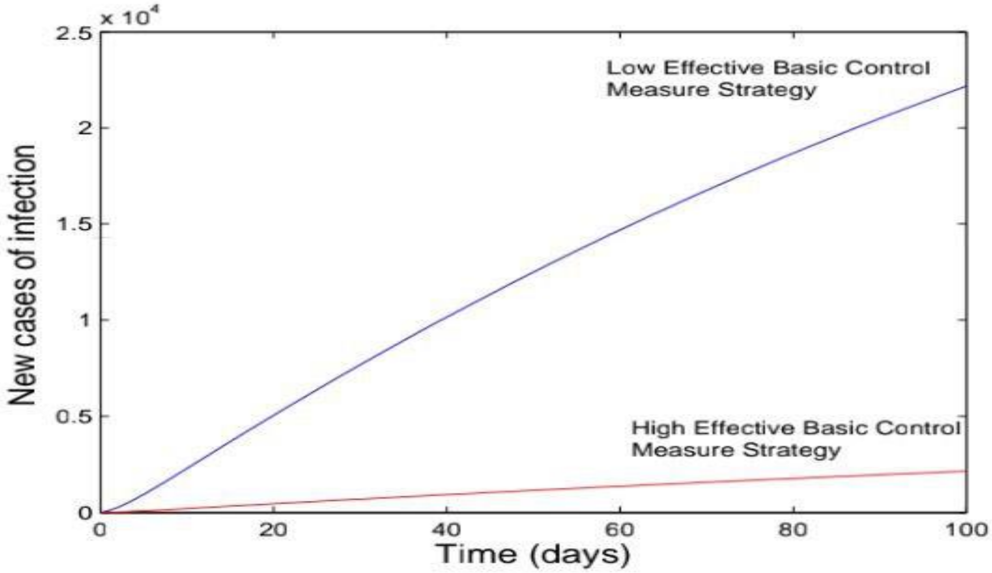

Figure 4.1 : simulations of the model (3.1.1) showing the two effective levels of the basic norovirus control measure strategy with parameter values used are used in table (4.1) and for high effective level of basic control measure strategy ,$\boldsymbol{\beta_H = 0.065}$,$\boldsymbol{\beta_V = 0.083}$,$\boldsymbol{\gamma = 0.00325}$,$\boldsymbol{K_D = 10^{10}}$ and for low effective level of basic control measure strategy are $\boldsymbol{\beta_H = 0.65}$,$\boldsymbol{\beta_V = 0.83}$,$\boldsymbol{\gamma = 0.00325}$,$\boldsymbol{K_D = 10^{10}}$.

In low effective level of the basic control measure strategy of norovirus transmission new cases of infection are increases significantly as more than 20000 cumulated new cases were being introduced within a year .In the case of high effective level of basic control measure strategy , there is a significant decrease of norovirus transmission (new cases of infection) and it indicates that less than 500 cumulative cases of infection were introduced within a year .

4.2 Treatment Strategy

Under this strategy the numerical simulations are focused to access the impact of the use of treatments to control the transmission of norovirus . There are two effective levels of the treatment strategy to be considered . These are :

i)Low effective level of the treatment strategy .

At this level the rate of infected individuals to be considered is $\tau = 0.0007$.

ii)High effective level of the treatment strategy . At this level the rate of infected

individuals to be considered is $\tau = 0.07$.

So that , the figure 4.2 below shows the one which has more efficiency in controlling (decreasing) new cases of infection by norovirus in the people of community .

The parameter values used for numerical simulations are in table (4.1) and for low effectiveness of the treatment strategy as well as high effectiveness of the treatment strategy

$$\mathrm{K}_D = 10^{11} , \gamma = 0.000325 .$$

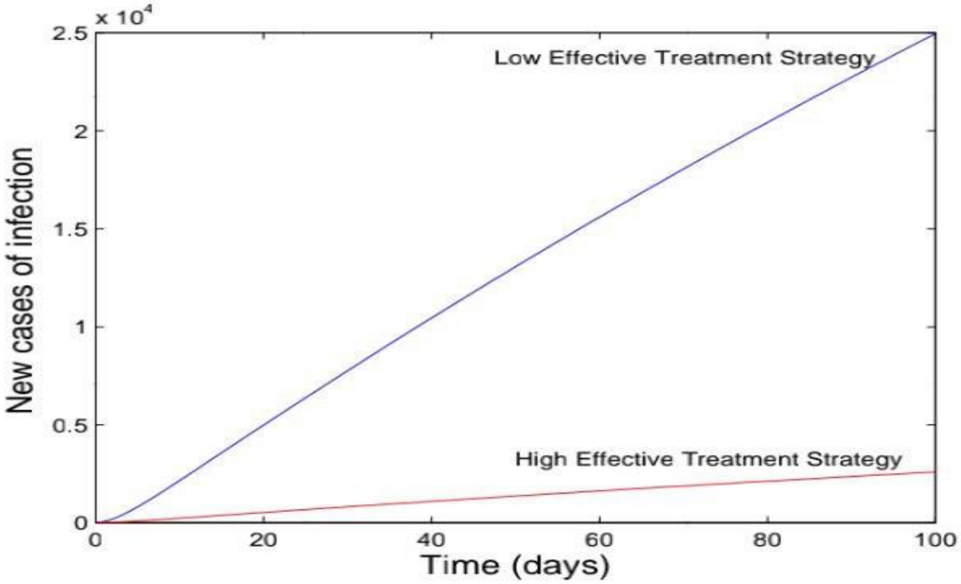

Figure 4.2 : Simulations of the model (3.1.1) showing the two effective levels of the treatment strategy . Parameter values used are given in table (4.1) .For low effectiveness of the treatment strategy $\boldsymbol{\tau} = \mathbf{0.0007}$, $\boldsymbol{K_D} = \mathbf{10^{11}}$, $\boldsymbol{\gamma}\mathbf{0.000325}$and effectiveness of the treatment strategy$\boldsymbol{\tau} = \mathbf{0.07}$, $\mathbf{K}_{\boldsymbol{D}} = \mathbf{10^{11}}$, $\boldsymbol{\gamma} = \mathbf{0.000325}$.

The figure 4.2 indicates that there is an increase in the cumulative number of new cases of the infection with norovirus introduced for low effective strategy and there is a decrease in the cumulative number of new cases of the infection introduced for high effective treatment strategy . Less than 500 cumulative new cases were introduced as a result of the high effectiveness of the treatment and 25000 cumulative new cases were introduced for the low effective strategy .

4.3 .The Combined Impact Of The Basic Control Measure And Treatment strategies

For the combined impact of basic control measure and treatment strategies , we compare the two effectiveness levels of basic control measure strategy and the two effective levels of treatment strategy . The two combined strategies are the following .

i) Low effective level of the basic control measure strategy and the treatment strategy

with parameter values as $\beta_H = 0.65$, $\beta_V = 0.83$, $\tau = 0.0007$.

ii) High effective level of the basic control measure strategy and the treatment strategy

with parameter values as $\beta_H = 0.065$, $\beta_V = 0.0083$, $\tau = 0.07$.

Below is the figure gotten from the simulation of the combined control strategies .

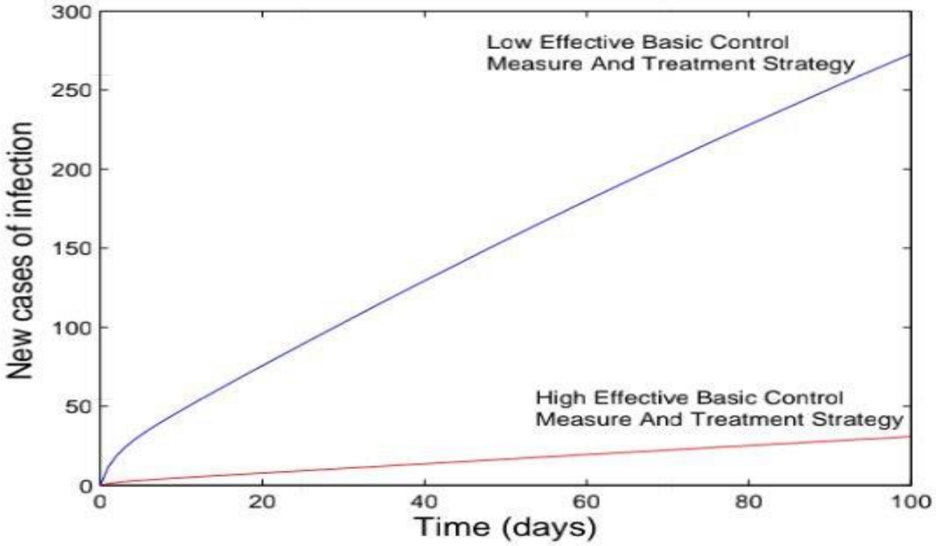

Figure 4.3 : Simulations of the model (3.1.1) showing the two effective levels of both the basic control strategy and the treatment strategy . Parameter values used are in table (4.1) . For low effectiveness of the basic control strategy and treatment strategy $\beta_H = 0.65$, $\beta_V = 0.83$, $\tau = 0.0007$, $K_D = 10^{11}$, and $\gamma = 0.325$. For high effectiveness of the basic control and treatment strategies$\beta_H = 0.65$, $\tau = 0.07$, $K_D = 10^{11}$, $\gamma = 0.325$.

CHAPTER FIVE

SUMMARY

In this thesis , the model designed and analyzed accounts for the transmission dynamics of norovirus infection in the population . The model consists of seven mutually exclusive epidemiological compartments . The six compartments from the seven compartments are accounts for the human population and the remaining one is account for the virus population .The infection rate used for this thesis considers both the direct contact with an infected person and indirect contact with contaminated sources . The Michaelis-Menten incidence function was used for the ingestion rate of the virus through contaminated sources .

In the thesis ,some of the theoretical and epidemiological findings of the model of the transmission dynamics of norovirus infection made are :

i)The two equilibrium points which are the disease free equilibrium point and the endemic equilibrium point exist and determined .

ii) The model is globally asymptotically stable at the disease free equilibrium if the basic reproduction number is less than unity .

Deduction made from the numerical simulations in the study are :

1) The cumulative new cases of norovirus infection decreases if there is a high effective Basic control measure strategy .

2) The number of the cumulative new cases introduced into the environment decreases if thereisa high effective treatment strategy .

3) The basic control measure strategy helps better in controlling the spread of the viral disease in the community .

4) The best effective method is the high control basic measure and the high treatment strategy . The combination of the two control strategies helps in reduction of the infection impact in a community .

CHAPTER SIX

CONLUSION

In conclusion , in order to have a disease free equilibrium in a community or the community with a norovirus a high effective basic control measure strategy should be put into consideration and a proper treatment strategy should be administered to an infected person in a community in order to reduce the rate of mortality and the transmission rate of the norovirus infection . This means that if high effective level of basic control measure strategy is introduced(or taken) it will reduces the rate of infected people and that will help the community in controlling the spread of norovirus in the community . Similarly , high effective treatment strategy decrease new cases of infected individuals by norovirus in the population .

In addition since the virus has no vaccine like bacteria , then the implication of the two controlling strategies of the spread of norovirus in a community have a better impact in decreasing of its transmission dynamics . As the numerical simulations shows (or indicates) the combined impact of basic control measure strategy and the treatment strategy in decreasing (or even in controlling) the norovirus transmission (or spread) in a community .

Matlab Code For The Control Strategies

```
function yeardfe11

ep=[10:10:100];

for i=1:1:1

 [t,y]=ode45(ɵf,[0:100], [900000000;50000; 1000; 5*ep(i); 2*ep(i); 2*ep(i); 6* ep(i);0]);

 [t,z]=ode45(ɵg,[0:100], [900000000;50000; 1000; 5*ep(i); 2*ep(i); 2*ep(i); 6* ep(i);0]);

plot(t,y(:,8)); hold on ;

plot(t,z(:,8), r); hold on ;

xlabel(‘Time (days)’, FontSize’,14)

ylabel(‘Cumulative New cases of infection ‘ ,’FontSize’,14)

end

functiondydt = f(t,y)

piH= 11152

xi=0.0025;

betaH=0.65;

betaV= 0.83;

thetaE= 0.035;

kD=10^11;

muH=3.47*10^(-5);

gamma=0.000325;

sigma=1.7* 10^(-4);

tau= 5.5 * 10^(-7);
```

```
psiE = 0.35;
psiI= 0.4;
psiT = 0.5;
phiI= 0.02;
phiE= 0.02;
phiT= 0.02;
delta= 0.6;
deltaT = 0.46;
piD=3.5 * 10^(-5);
muD=0.000914
 k1=gamma + muH;
 k2=sigma+ psiE +muH;
 k3=tau + phiI + muH + delta;
 k4=psiT + muH + deltaT;
 k5=muD- piD;
 N = 320760000;
lambda = betaH/N *(thetaE* y(3) + y(4))- betaV *y (7)/(kD+ y(7));
 R_ 0 =( gamma * betaH *(thetaE* k3 * k4* k5 + sigma * k4* k5)/ k1* k2 * k3* k4 * k5 )+ piH *
gamma * betaV* (phiE * k3 * k4 + phiI* sigma*k4 + phiT* sigma* tau)/ muH* kD* k1* k2*k3 *
k4* k5;
 R_ 0
dydt = [piH + xi * y(6)- (lambda+ muH)* y(1);
lambda * y(1)- (gamma+ muH) * y(2);
gamma * y(2)- (sigma + psiE + muH) * y(3);
sigma*y(3)- (tau + psiI + muH + delta) * y(4);
```

```
tau * y(4)- (psiT+ muH + deltaT ) * y(5);

psiE * y(3) + psiI * y(4) + psiT * y(5)- (xi + muH) * y(6);

piD * y(7) + phiE * y(3) + phiI * y(4) + phiT * y(5)- muD * y(7);

lambda * y(1);];


functiondzdt = g(t,z)

piH= 10970

xi=0.0025;

betaH=0.065;

betaV= 0.0083;

thetaE= 0.035;

kD=10^11;

muH=3.42*10^(-5);

gamma=0.000325;

sigma=1.7* 10^(-4);

tau= 5.5 * 10^(-7);

psiE = 0.4;

psiI= 0.5;

psiT = 0.7;

phiI= 0.04;

phiE= 0.04;

phiT= 0.04;

delta= 0.64;

deltaT = 0.5;
```

```
piD=3.5 * 10^(-5);
muD=0.001
 k1=gamma + muH;
 k2=sigma+ psiE +muH;
 k3=tau + phiI + muH + delta;
 k4=psiT + muH + deltaT;
 k5=muD- piD;
 N = 320760000;
lambda = betaH/N *(thetaE* z(3) + z(4))- betaV *z (7)/(kD + z(7));
 R_ 0 =( gamma * betaH *(thetaE* k3 * k4* k5 + sigma * k4* k5)/ k1* k2 * k3* k4 * k5 )+ piH * gamma * betaV* (phiE * k3 * k4 + phiI* sigma*k4 + phiT* sigma* tau)/ muH* kD* k1* k2*k3 * k4* k5;
 R_ 0
dzdt = [piH + xi * z(6)- (lambda+ muH)* z(1);
lambda * z(1)- (gamma+ muH) * z(2);
gamma * z(2)- (sigma + psiE + muH) * z(3);
sigma*z(3)- (tau + psiI + muH + delta) * z(4);
tau * z(4)- (psiT+ muH + deltaT ) * z(5);
psiE * z(3) + psiI * z(4) + psiT * z(5)- (xi + muH) * z(6);
piD * z(7) + phiE * z(3) + phiI * z(4) + phiT * z(5)- muD * z(7);
lambda * z(1);];
```

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