MATHEMATICAL STUDIES ON INFLUENZA MODELS

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To my father…

ABSTRACT

In this thesis we studied three deterministic epidemic models consisting of multiple strains with different types of incidence rates.

The first model consists of two strains with bilinear incidence rate in one strain and non – monotonic incidence rate in the other. We found four equilibrium points; disease free equilibrium, endemic with respect to strain 1, endemic with respect to strain 2, and endemic with respect to both strains. The global stability analysis of the equilibrium points were carried out through the use of Lyapunov functions. Two basic reproduction ratios R_0^1 and R_0^2 are found, and we have shown that, if both are less than one, the disease dies out, and if both are greater than one epidemic occurs. Furthermore, epidemics occur with respect to any strain with basic reproduction ratio greater than one and disease dies out with respect to any strain with basic reproduction ratio less than one. It was also shown that, any strain with highest basic reproduction ratio will automatically outperform the other strain, thereby eliminating it. Numerical simulations were carried out to support the analytic result and to show the effect of parameter *k* in the non – monotonic incidence rate, which describes the psychological effect of general public towards the infective.

In the second model we studied two strain flu model in which one strain (resistance) is the mutation of the other (non – resistance) strain. We attributed different types of incidence rates to these strains; bilinear and saturated. The bilinear incidence rate is attributed to non - resistant strain, while the saturated incidence rate is attributed to resistant strain. The global stability analysis of the proposed model is carried out through the use of Lyapunov functions. Two basic reproduction ratios R_R and R_N are found, and we show that, if both are less than one, the disease dies out and the disease free equilibrium is globally asymptotically stable. If both are greater than one, epidemic occurs and the endemic equilibrium is globally asymptotically stable. More over epidemic occurs with respect to the strain with the largest basic reproduction ratio and their respective global asymptotic stability was shown. We also presented some numerical simulations to support the analytic results.

In the third model we considered three strains of influenza (I_1, I_2, and I_3) where we have vaccine for strain1 (V_1) only, and population has enough awareness of strain 2. There is neither vaccine nor awareness for strain 3. Our main aim is to mathematically analyze the effect of the vaccine for strain 1 and awareness of strain 2 on the dynamics of strain 3. It is also in our aim to study the coexistence of these three strains. Six equilibrium points were obtained and their global stability using Lyapunov functions was shown to depend on the magnitude of a threshold quantity, called basic reproduction ratio. It was shown that the

coexistence of strain 1 and strain 2 is not possible and the coexistence of the three strains was shown numerically. It can be observed from the numerical simulations that, although vaccine curtail the spread of strain 1, awareness curtail the spread of strain 2, but they both have negative effect on strain 3. This tells the relevant authorities whenever there is influenza epidemic to investigate thoroughly the possibilities of the existence of multiple strains, so as to provide vaccines and enough awareness on all the strains present.

Keywords: Epidemic model; influenza; basic reproduction ratio; incidence rate; multiple strains; vaccine; global stability

ÖZET

Bu tezde farklı insidans hızlarına sahip çok sayıda türlerden oluşan üç deterministik salgın modeli incelendi.

Birinci model, ikilidoğrusal insidans hızı ve monoton olmayan insidans oranı olmak üzere iki türden oluşur. Dört denge noktası bulduk; bu denge noktaları, hastalığın olmadığı denge noktası, 1'inci ve 2'inci türe göre salgın ve her iki tür için salgın noktalarıdır. Denge noktalarının küresel kararlılık analizi, Lyapunov fonksiyonlarının kullanımı ile gerçekleştirildi. İki tekrar çoğalma oranı R_0^1 ve R_0^2 bulundu ve bu oranların her ikisi de birden küçük ise hastalığın yok olduğunu ve her ikisin de birden büyük olması durumunda salgının gerçekleştiği gösterilmiştir. Bundan başka, tekrar çoğalma oranı birden büyük olan herhangi bir türle ilgili olarak salgınlar ortaya çıkar ve temel üreme oranı birden küçük olan herhangi bir tür için ise hastalık yok olur. Aynı zamanda, en yüksek tekrar çoğalma oranına sahip herhangibir türün otomatik olarak diğer türden daha iyi performans göstereceği ve böylece diğer türü ortadan kaldırıldığı gösterildi. Analitik sonucu desteklemek ve k parametresinin(toplumun psikolojik etki katsayısı) monotik olmayan insidans hızına etkisini göstermek için sayısal simülasyonlar kullanıldı. İkinci modelde, iki farklı tür grip inceledik. Bu iki türden biri dirençli diğeri ise mutasyon geçiren dirençsiz türdür.Bu türlere iki farklı insidans oranları varolduğunu kabul ettik; bu oranlar ikilidoğrusal ve doymuş. İkili doğrusal insidans oranı dirençsiz tür, doymuş insidans oranı ise dirençli tür diye isimlendirildi. Önerilen modelin küresel kararlılık analizi, Lyapunov fonksiyonlarının kullanımı ile gerçekleştirildi. R_R ve R_N olarak iki tekrar çoğalma oranı hesaplanmıştır ve her ikisinin de birden küçük olması durumunda, hastalığın yok olduğunu ve hasta olmayan küresel denge noktasının asimptotik kararlı olduğu gösterdik. Her ikisi birden büyük ise salgın olur ve yaygınlık denge noktası küresel asimptotik kararlılığı sağlar. Salgın üzerine daha fazla yorum yapmak gerekirse, salgın en büyük tekrar üreme oranı birden büyük olan türdede ortaya çıkmakta ve genel asimtotik kararlılık gösterilmektedir. Analitik sonuçları desteklemek için bazı sayısal simülasyonlar da kullanıldı.

Üçüncü modelde, üç tip terapi türü (I1, I2 ve I3) düşünündük ve yalnızca 1'inci tür (V1)'in terapisi olduğu kabul edildi ve 2'inci türün ise yeterince farkındalığı olduğu kabul edildi. 3'üncü tür için de ne terapisi ne de farkındalık vardır. Temel amacımız terapilerin 1'inci türün 3'üncü tür üzerindeki dinamik etkisini ve 2'inci türün ise yine 3'üncü tür üzerindeki farkındalığını analiz etmektir. Bir diğer amacımız ise bu üç türün birlikteliğini incelemektir. Altı denge noktası Lyapunov fonksiyonları kullanarak elde edildi. Tekrar üreme oranı olarak adlandırılan bir eşik miktarı hesaplandı ve bunun büyüklüğe bağlı olduğu gösterildi. 1'inci tür

ile 2’inci türün bir arada bulunmasının mümkün olmadığını fakat üç türün bir arada var olabileceği sayısal olarak gösterdi. Sayısal simülasyonlar terapilerin varlığı 1’inci türün yayılmasını azalttı. Farkındalık ise 2’inci türün yayılmasını azalttı ama hem terapinin olması ve hem de farkındalık 3’üncü tür üzerine negatif bir etki yaptı. Bu sonuçlara gore eğer grip salgını varsa ilgili yetkililer hem yeterli terapi şekli olmalı ve hem de farkındalık sağlamak zorundadırlar ayrıca grip ile mücadelede çoklu türlerin etkilerinin de varolabileceğini düşünerek hareket etmelidir..

Keywords: Salgın modeli; grip; tekrar üreme oranı; hasta oranı; çoklu tür; terapi; küresel kararlılık

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LIST OF ABBREVIATIONS

SIR: Susceptible, Infected, Recovered

NP: Nucleoprotein

$\boldsymbol{R_0}$: Basic Reproduction Ratio

NGM: Next Generation Matrix

IVP: Initial Value Problem

$\boldsymbol{R_0^1}$: First Basic Reproduction Ratio

$\boldsymbol{R_0^2}$: Second Basic Reproduction Ratio

$\boldsymbol{R_0^3}$: Third Basic Reproduction Ratio

$\boldsymbol{R_R}$: Resistance Basic Reproduction Ratio

$\boldsymbol{R_N}$: Non – Resistance Basic Reproduction Ratio

$\boldsymbol{I_R}$: Resistance Strain

$\boldsymbol{I_N}$: Non – Resistance Strain

CHAPTER 1

INTRODUCTION

Influenza is termed as a serious cytopathogenic, infectious, drastic respiratory disease that is caused by influenza virus (Mohler et al., 2005). The virus is categorized into three main types; A, B, and C. This categorization is based on the differences that exist between matrix protein (M) and nucleoprotein (NP) (Tamura et al., 2005).

Type A can infect both humans, pigs, whales, birds and especially wild animals. It is the most acute of all the types. It is further subdivided into based on hemagglutinin (HA) and neuraminidase (NA) proteins found on the surface of the virus. There are 16 types of hemagglutinin (H1 – H16) and 9 types of neuraminidase (N1 – N9). Influenza virus subtypes are named according to the combination of these HA and NA present in them. For example H1N1 virus means, Influenza A that has an HA1 protein and NA1 protein. In humans only three of these combinations are most common; H1N1, H1N2, and H3N2. Type B can also infect humans and birds, and can cause epidemics. The last type (C) affects only humans and it can hardly be differentiated from common cold as it causes no epidemics (Webster et al., 2006).

Moreover influenza A and influenza B virus subtypes can be characterized into strains. There are two main ways in which a new strain of influenza appear; antigenic drift and antigenic shift (Michael et al., 1992). Antigenic drift occurs through gradual changes in the virus which happens over time. New strains arises which may then be new to the host antibodies. On the other hand antigenic shift is a sudden change in influenza A virus that results in a new strain that has never been seen before. Influenza A undergoes both changes, while B undergoes antigenic drift only (Michael et al., 1992).

1.1 History of Influenza Virus

The pandemics of influenza have been occurring for a quite long period of time (Major, 1995). Although records described some disease epidemics with clinical presentation similar to influenza, but one can't be certain that these epidemics were indeed as a result of influenza viruses. Nowadays avian reservoir is confirmed as the origin of the virus (Scholtissek, 1994).

Before 1500, Hypocratus in the "Book of Epidemics" described a disease with symptoms similar to influenza seen in Northern Greece (410 B.C). Monks also reported a similar epidemic 664AD which was caused by clerics travelling from a Syned in England (Creighton, 1965). In the year 1173 – 1174, England, France, and Italy suffered from a pandemic caused by a similar virus. This virus is termed a "Plague". Later in 1357 another similar epidemic took place in Italy from which for the first time the disease is termed as influenza (Major, 1945). Both in 1414 and 1427 two epidemics termed as "tac" or "horizon" and " dando" or "conqueluche" took place in France respectively (Creighton, 1965).

After 1500, the epidemic of influenza is well studied. During the summer of 1580, an epidemic started from Asia, spread to Africa, spread to Europe, and finally to Americas. A lot of people died in this influenza epidemic (Neustadt and Fineburg, 1983). European countries encountered series of influenza epidemics in the years 1658, 1679, 1708, and 1729 (Patterson, 1986). Bachaumont (a French doctor) reported another epidemic in London in the year 1775. It is reported that amidst this epidemic upto 12 deaths were recorded in Paris in a single day (De Lacey, 1993). In 1781 and then 1789 – 1790 another pandemic occurred which started from China and then across the entire Europe. This global pandemic resulted in the death of many young people. It infected more than half of the population of Rome and upto 30,000 incidences were recorded in one day in Saint Petersburg (Patterson, 1986). In 1889, another epidemic surfaced from Russia which resulted in approximately 40% of the world population been infected (Enserink, 2006). A mild pandemic was observed again in 1900 (Enserink, 2006).

Spanish flu (H1N1) which occurred in 1918 infected 30 – 50 % of the worlds' population (about 500 million – 1 billion) people (Niall et al., 2002). Origin of Spanish flu pandemic was

not clearly known but two places were suspected. The first place was China and then spread to United States due to immigration and later to the rest of the world (Lezzoni, 1999; Reid and Taubenberger, 2003). The second was United States from military camp in Furston and then in a prison in South Carolina (Soper, 1918).

Forty years after Spanish flu, another pandemic termed Asian flu (H2N2) took place in the year 1957. This pandemic also originated from a province called Kweichow in China (Bull, 1959). It started in February of 1957, it then spread to Yunan province and then the entire China, which resulted in morethan 500,000 infection. In March to April Mongolia, Hongkong and Singapore were hit, and all Asia were subsequently infected before mid – May (Bull, 1959). This virus was spread from Asia by ships and planes, and within 9 months only, this virus covered all other continents. The approximate number of deaths was estimated to be about two million (Cox and Subbaro, 2000).

Hong Kong flu (H3N2) was among the influenza pandemic that took place in history. It originated from Hong Kong in July 1968, and then spread to all parts of Asia, then Russia, then Europe, then Americas and subsequently to all parts of the world (Bull, 1969). Mechanism of appearance of this strain (H3N2) is similar to that of H2N2. It was also as a result of a genetic mix between avian and human virus (Scholtissek, 1994).

In 1977, a lot of young children were infected with H1N1 virus in a region in Russia. The virus only affected those that were not infected with the virus in 1957, and it was proved to be identical with H1N1 of 1954 (Kilbourne, 2006). Traces of these cases which was as a result of the virus coming from animals have been observed. In 1976, a soldier was infected with H1N1 virus in New Jersey USA, with the instant death of a soldier and the release of vaccines by US authorities no additional cases was recorded (Neustadt and Fineburg, 1983). A boy died of the virus in Hong Kong in the year 1997, and the virus was identified as H5N1 originated form domestic birds (Class et al., 1998). In 2003, eighty five cases of H7N7 were recorded in humans infected from domestic birds (Fouchier et al., 2004). H5N1 reemerged in 2003 (Li et al., 2004). H1N1 resurfaced again in 21st century as a result of recommendation of the two preexisting viruses (Garten et al., 2009; Morens et al., 2009). It was first detected in march

2009 in Mexico and later in the United States. It then spread worldwide with millions incidences and about 16, 813 deaths (WHO, 2009).

1.2 Epidemiology

This is the study of incidence, distribution, determinants as well as possible control measures of health – related occurrence in a specific population. The diseases causing epidemics can largely be divided into micro and macro parasites. Micro follows human to human transfer pattern examples are influenza, tuberculosis, gonorrhea etc. Macro follows humans to carrier to humans transfer pattern examples are malaria, black plague etc. It is also of significant importance to differentiate between these three important elements of epidemiology; endemic epidemic, and pandemic. Endemic refers to continual occurrence of a disease in a population. Epidemic refers to an unexpected upsurge of a disease in a population. Pandemic refers to a global epidemic affecting inflated number of populations.

There are ample means in which epidemic disease spread. These means include but are not limited to population explosion, missing sanitation in underdeveloped countries, and modern transportation which enables international boarders cross. Another important means by which disease spread is due to loss of natural immunity, this is due to pills we take which contain synthesis vitamins instead of the vitamins we get from natural resources. There are many more means by which diseases spread which are not easy to be listed and studied in a single research.

1.2.1 History of mathematical epidemiology

Mathematical epidemiology can be traced to over three hundred years back. John Graunt was the first to publish a book in 1662 with a title " Natural and political observations made upon the bills of mortality" in 1662. It was problems concerning demography problems in Britain mainly in the seventeenth century. He calculated the risk of death of some certain diseases

using the records of the death they caused. This analysis was the first to provide a systematic method of estimating the risk of death due to plague. This serves as the genesis of the theory of competing risks. Almost hundred years later that is in 1760 Daniel Bernoulli published a paper with the first epidemiological model. The aim of the model was to demonstrate the effect of inoculating patients with smallpox in reducing the progression. One year later, that is in 1761 D'Alembert developed another method of handling competing risks of death.

Hamer in the year 1906 was believed to be the inventor of modern mathematical biology. He applied mass action principle on deterministic epidemic model. Rose in 1911 proposed another simple epidemic model for malaria and in 1927 Kermack and Mckendrick proposed a generalized epidemic model (Ross, 1911). Nowadays these models are being modified by taking into account various epidemic units like chemotherapy, vaccination, migration, immunity, quarantine, resistance, non – monotonicity of incidence rates etc. Another important modification was that by Anderson and May in 1982 (Anderson and May, 1982). In their model they considered non - homogeneous mixing in the population. This leads to another discovery by Liu et al. in 1987 in which he considered non – linear incidence rate instead of the usual bilinear incidence rates as in the previous models. Many models were formed and analyzed over the years for diseases such as influenza, AIDS, SARS, malaria, cholera, measles, smallpox, rubella, diphtheria, gonorrhea etc.

1.2.2 Stochastic and deterministic models

The most important models useful in the study of epidemiology are the stochastic and deterministic models.

Stochastic models are used especially in small or isolated populations when known heterogeneities are important. They consider minute population especially when every individual is significant in the model as such stochastic models are termed as individual level – models. These types of models can be arduous to make, sometimes need a lot of simulations to make predictions, and contribute very little in explaining disease dynamics.

Deterministic models sometimes referred to as compartmental models describe the dynamics of the disease at the population level. They categorize individuals into compartments or groups. For example SIR model has three compartments; susceptible, Infectious, and recovered. There are mathematical parameters between each compartment that describes the transition rate of individuals from one compartment to another. Deterministic models are easy to set up, and require less data, hence they are the most widely used epidemiological models. Nowadays complex deterministic models exist in literature which can integrate stochastic elements such as demographic etc.

1.2.3 SIR epidemic model

The most basic model that describes whether or not an epidemic will occur and how it occurs in a population is the SIR epidemic model. It was first developed by Kermack and Mckendrick in 1927 (Britton, 2003; Murray, 2004; Ellner and Guckenheimer, 2006). Modification of this model exist in literature, examples of this can be found in a book by Hethcote (Hethcote, 2000), Dieckmann and Heesterbeek (Dieckmann and Heesterbeek, 2000), Anderson and May (Anderson and May, 1992), and Murray (Murray, 2004).

SIR model consists of three compartments; S, I, and R. S is the compartment of susceptibles, I is the compartment of infectives, and R is the recovered compartment. Figure 1, gives the description of the model and Table 1 provides the meaning of all the parameter as presented in equation (1.1).

Figure 1.1: Description of model 1

Table 1: Parameters of model 1.1

List of Parameter	Meaning of the parameters
S	Susceptibles
I	Infectives
R	Recovered
β	Rate at which susceptibles become infected
ɣ	Rate at which infected become recovered

The following system of equations represents the model

$$\frac{dS}{dt} = -\beta SI,$$

$$\frac{dI}{dt} = \beta SI - \gamma I, \tag{1.1}$$

$$\frac{dR}{dt} = \gamma I.$$

1.2.4 The Basic reproduction number (R_0)

R_0 is termed as the number of new infected individuals in a population that are infected as a result of one individual when everyone is susceptible and during the entire infection period. In simple models R_0 has the form given as

$$R_0 = (Number\ of\ contacts\ at\ a\ time)(Probability\ of\ infection\ in\ a\ contact)$$

$$(Period\ of\ epidemics)$$

In epidemiology, R_0 is considered as a threshold quantity, since $R_0 > 1$ implies epidemics and $R_0 < 1$ implies no epidemics. For many models $R_0 = 1$ implies transcritical bifurcation.

For complicated models that includes seasonality methods or heterogeneity the next generation matrix (NGM) method is used in computing the R_0. The NGM method was developed in 1990 by Diekmann et al. it was later after 12 years i.e in 2002 standardized by Van den Driessche and Watmough (Diekmann et al., 1900; Van Den Driessche and Watmough, 2002). It converts a system of ODE or PDE of an infectious disease model to an operator. The basic reproduction ratio here is defined to be the dominant eigenvalue (spectral radius) of this operator.

Consider the following deterministic model

$$\frac{dx_i(t)}{dt} = f_i(x), \qquad x(0) \in \overline{R_+^n}\,.$$

Where $x_i(t)$ stands for the number of individuals in compartment i at a given time t. Also let $x(0) \in \overline{R_+^n}$, where $\overline{R_+^n}$ is the nonnegative orthant of R^n. Let

$$X = \left\{x \in \overline{R_+^n} \backslash x_i = 0 \quad 1 \leq i \leq m\right\} \text{ where } m \leq n.$$

X: A set containing disease – free states.

Then

$$\frac{dx_i(t)}{dt} = F_i(x) - M_i(x),$$

where $F_i(x)$: Infection introduced into i compartment

$$M_i(x) = M_i^-(x) - M_i^+(x).$$

$M_i^+(x)$: Transfer into i compartment by other means.

$M_i^-(x)$: Transfer out of i compartment by other means.

The following assumptions hold true for these functions

i – The rate of movements are nonnegative, i.e if

$x \in \overline{R_+^n}$, then $F_i(x) > 0, M_i^+(x) > 0, M_i^-(x) > 0$ where $1 \leq i \leq n$.

ii – If a compartment is empty, then movement out of that compartment is not possible i.e if $x_i = 0$ then $M_i^-(x) = 0$.

iii – Movement of infection into non-infective class is not possible i.e

$$F_i(x) = 0 \quad for\ i > m.$$

iv – Disease free subspace is invariant, i.e when

$$x \in X\ both\ F_i(x) = 0, and\ M_i^+(x) = 0\ when\ \ 1 \leq i \leq m\ .$$

v – In the absence of new infection the disease free equilibrium is locally asymptotically stable i,e when $F(x) = 0$ all eigenvalues of the matrix at disease free equilibrium must be negative.

For disease free equilibrium of (1.1), we let square matrices $\overline{F}$ and $\overline{M}$ to be

$$\overline{F_{ij}} = \frac{\partial F_i}{\partial x_j} \quad when\ 1 \leq i, j \leq m,$$

$$\overline{M_{ij}} = \frac{\partial V_i}{\partial x_j} \quad when\ 1 \leq i, j \leq m.$$

Then $\bar{F}\bar{M}^{-1}$ is defined as NGM and $R_0 = \rho(\bar{F}\bar{M}^{-1})$ is the dominant eigenvalue (spectral radius) of the NGM.

1.3 Well – posedeness

A mathematical model is said to be well – posed if it satisfies the following three conditions

i – The model has a solution (existence of solution).

ii – The solution is unique (uniqueness of solution).

iii – The solution is stable (stability of solution).

If one of the above conditions failed, then the model is ill – posed.

1.3.1 Existence and uniqueness of solutions

Consider the initial value problem (IVP) defined as

$$\dot{x} = f(t, x),\ t \in R,$$

$$x(t_0) = a. \tag{1.2}$$

Here f is continuous and $domain(f)\ is\ contained\ in\ R \times R^n$, and (t_0, a) is constant.

Fundamental theorem of calculus implies that equation (1.2) is the same as

$$x(t) = a + \int_{t_0}^{t} f\big(s, x(s)\big)ds. \tag{1.3}$$

Now, our goal is to show that x(t) has a solution. We can do that by using either Picard iteration or Tonelli sequence.

For Picard iteration, an initial value is chosen for *x* and substituted in (1.3) and then the result is used to evaluate a new *x*. Setting $x_1(t) \coloneqq a$ then $x_{k+1}(t)$ is defined in terms of $x_k(t)$ where k >1 using equation

$$x(t) = a + \int_{t_0}^{t} f\big(s, x(s)\big)ds,\ k \geq 1, \qquad x_0(t) \text{ is given.}$$

If the absolute error $x_{k+1}(t)$ and $x_k(t)$ is less than the given tolerance value, take $x_k(t)$ as the result of the given problem.

For Tonelli sequence let $x_k(t)$ where $k \in N$ and for $t \geq t_0$ be defined by

$$x_k(t) = \begin{cases} a, & for\ \ t \in \left[t_0, t_0 + \frac{1}{k}\right], \\ a + \int_{t_0}^{t-\frac{1}{k}} f\big(s, x_k(s)\big)dx, & for\ t \in \left[t_0 + \frac{1}{k}, \infty\right), \end{cases} \tag{1.4}$$

for $t \geq t_0, x_k(t)$ is defined in the same manner. Here Tonelli sequence will be used to prove the existence theorem and Picard iterates to prove the uniqueness theorem. See Theorem 1.1 and 1.2.

Theorem 1.1 (Cauchy – Peano). let $f: [t_0 - \alpha, t_0 + \alpha] \times \overline{B(a, \beta)} \to R^n$ be a continuous and bounded function, then the solution exists on the interval $[t_0 - b, t_0 + b]$, for $b = min\left\{\alpha, {}^{\beta}/_{M}\right\}$ and $M > 0$ is the upper bound for f.

Proof. (Murray and Miller, 1976).

Theorem 1.2 (Picard – Lindelof uniqueness theorem). Let M be the upper bound of the continuous function $f: [t_0 - \alpha, t_0 + \alpha] \times \overline{B(a, \beta)} \to R^n$. Moreover, let L be a Lipschitz constant for all $t \in [t_0 - \alpha, t_0 + \alpha]$ of a Lipschitz continuous function $f(t, .)$, then (1.2) has a unique solution on $[t_0 - b, t_0 + b]$, and $b = \min\{\alpha, \frac{\beta}{M}\}$.

Proof. (Coddington and Levinson, 1955).

1.3.2 Stability of solutions

If for all $\varepsilon > 0$ and $t_0 \in R$ there exists δ depending on $\varepsilon \; and \; t_0$ such that if $\hat{x}(t) \; and \; x(t)$ are two solutions of (1.2) then

$$|x(t) - \hat{x}(t)| < \varepsilon, whenever \; |x(t_0) - \hat{x}(t_0)| < \delta \quad \forall t \geq t_0$$

then $\hat{x}(t)$ is a stable solution of (1.2).

If $\hat{x}(t)$ is stable and $\forall t_0 \in R \; \exists \delta = \delta(t_0) > 0$ such that for another solution say $x(t)$, $|x(t_0) - \hat{x}(t_0)| < \delta$ then $x(t) \to \hat{x}(t)$ as $t \to \infty$, then $\hat{x}(t)$ is asymptotically stable.

Since in this research we are more concerned with Lyapunov stability then what follow is a theorem and its proof on Lyapunov stability.

Theorem 1.3 (Lyapunov stability). Let D be a neighbourhood of $x(t)$ and V be a continuously differentiable positive definite function $V: R \times D \to R$, whose orbital derivative $\dot{V}$ is negative semi – definite, then x(t) is a Lyapunov stable solution of (1.2).

Proof. (Parks, 1992).

Theorem 1.4 (Asymptotic stability). Let D be the neighbourhood of $x(t)$ a solution of (1.2) and $V: R \times D \to R$ be a positive definite function whose orbital derivative $\dot{V}$ is negative definite. Furthermore, let $\widehat{W}: D \to R$ such that $V(t,x) \leq \widehat{W}(x) \ \forall (t,x) \in R \times D$, then x(t) is an asymptotically stable solution of (1.2).

Proof. (Parks, 1992).

Theorem 1.5 (LaSalle's invariance principle). Let D be a neighbourhood of x(t) and let $V: D \to R$ be a continuously differentiable positive definite function whose orbital derivative is negative semi definite. Let I be the union of complete orbits contained in $\{x \in D | \dot{V}(x) = 0\}$. Then there is U, a neighbourhood of $x(t)$ such that $\forall x_0 \in U, W(x_0) \subseteq I$.

Proof. (Parks, 1992).

1.4 Mathematical Modeling of Influenza

In literature many models were used to shade more light on the understanding of influenza mathematically, especially in the following areas

1. Provide insight into spatial – temporal transmission dynamics of the disease.
2. Make health policies in predicting the effect of public health.
3. Predict public health interventions effect in overcoming subsequent epidemics.

Most of influenza models were of the SIR form. Many extensions of the SIR model for influenza includes incorporating seasonality (Dushoff et al., 2004; Stone et al., 2007), as a spatial – temporal model (Rvachev, 1968), to show the effect of air travel on its pandemic

(Baroyan et al., 1971; Rvachev and Longini, 1985), and to show the importance of air travel on geographic spread (Flahault et al., 1994; Caley, 2007).

Mathematical models also provided insight into severity of past influenza epidemics (Chowell et al., 2007; Bootsma and Ferguson, 2007; Chowell et al., 2006; Mills et al., 2004; Vynnycky and Edmunds, 2008). Some models were used to investigate the three most devastating pandemics of influenza in history; Spanish flu (H1N1) 1918 – 1919, Asian flu (H2N2) 1957 – 1958, and Hong – Kong flu (H3N2) 1968 (Bootsma and Ferguson, 2007; Chowell et al., 2006; Mills et al., 2004; Vynnycky and Edmunds, 2008; Longini et al., 1986; Sattenspiel and Herring, 2003). It was shown using mathematical modeling the effect that interventions may have had in curtailing the H1N1 pandemics of 1918 – 1919 (Bootsma and Ferguson, 2007; Chowell et al., 2006; Mills et al., 2004; Vynnycky and Edmunds, 2008; Longini et al., 1986; Sattenspiel and Herring, 2003). The behavioral effects such as quarantine, imposing travel sanctions on the infected individuals, closing schools were also modeled (Cauchemez et al., 2008; Epstein et al. 2007). The effectiveness of biomedical interventions such as vaccines, therapeutic treatment, and prophylactic treatment were also shown using mathematical models (Arino et al., 2008; Longini et al., 2004).

Many models were also used to appraise the problem of anti – viral resistance (Lipsitch et al., 2007; Ferguson et al., 2003), to measure the relative efficacy of prophylaxis versus treatment plans (Longini et al., 2004), to describe the best plans for allocating vaccines (Riley et al., 2007). Some models went ahead to evaluate the effectiveness of combining behavioral and biomedical interventions (Longini et al., 2005; Ferguson et al., 2006). Varvadas et al. in 2007 and Galvani et al. also in 2007 studied the possible effect of human attitude in determining coverage of vaccine (Varvadas et al., 2007; Galvani et al, 2007). There studies illustrate how mathematical models can help in identifying the interventions strengths that are compulsory in epidemic controlling, but these goals may not necessarily be attained.

The parameter that measures transmission rate of a disease is termed as incidence rate. This parameter can be defined as the rate of emergence of new case of a disease in a unit time. Incidence rate is sometimes measured by categorizing a population under study using some

factors. These factors include; psychological inhibition, age, and social status. Strong relationship exists between annual risk of a disease, incidence rate and prevalence (Rvachev, 1968). Many models in literature have bilinear incidence rate (CDC Report). But there are also some other nonlinear incidence rates in the literature which include non-monotone, saturated, and fractional incidence rates.

Influenza, Dengue fever, Tuberculosis, and many other transmissible diseases can be caused by multiple pathogen strains. Many researchers studied epidemics caused by these types of diseases (Baroyan et al., 1971; Rvachev et al., 1985; Flahault et al, 1994). Basic reproduction ratio plays very significant role here, since it was also shown that, any strain with the largest basic reproduction ratio will outperform the other/others (Caley et al., 2007). Mostly mechanisms like exponential growth of the host population, co – infection, super - infection, vaccination, and mutation avail the strains coexistence (Choell et al., 2007; Bootsma and Ferguson, 2007; Chowell et al., 2006; Mills et al., 2004).

It is evident that most of the models with multiple strains in literature constitutes of bilinear incidence rates. This is not realistic, since the emergence of new strain will always have effect on the incidence rate of the old as well as the new strain itself. Our thesis studies this type of models, where one strain have a different incidence rate from the other.

1.5 Outline of the Thesis

This thesis is the compilation of three articles. These articles are self – contained and the corresponding chapters can be read separately. The central study subject in the thesis is modeling multiple strain influenza with nonlinear incidence rates.

Chapter 2: Global stability analysis of two strain epidemic model with bilinear and non – monotone incidence rates, I.A. Baba, E. Hincal, European Physical Journal Plus 132:208 (2017).

In this chapter a two strain epidemic model was formulated, with two different incidence rates, viz.: bilinear $f(I)$ and non - monotone $g(I)$

$$f(I) = \alpha I_1,$$
$$g(I) = \frac{\beta I_2}{1+kI_2^2}.$$

Chapter 3: Resistance and non – resistance strains of influenza: A mathematical model, I.A. Baba, E. Hincal, I. under review in A Mathematical Population Studies

In this chapter we give the first application of our study by studying a two strain model, with bilinear incidence rate $f(I)$ as a resistance strain and saturated incidence rate $g(I)$ as a non-resistance strain

$$f(I) = \alpha I_R,$$
$$g(I) = \frac{\beta I_N}{1+kI_N}.$$

Chapter 4: A model for influenza with vaccination and awareness, I.A. Baba, E. Hincal, Chaos, Solitons, and Fractals. 49:55 (2018).

In this chapter, we give the second application of our study by studying three strains of influenza in which there is vaccine for strain 1, and awareness for strain 2 (nonlinear incidence rate). Our goal is to study the effect of the vaccine for strain 1, awareness for strain 2 on the propagation dynamics of strain 3.

In chapter 5, we give summary and conclusion of the study.

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CHAPTER 2

GLOBAL STABILITY ANALYSIS OF TWO STRAIN EPIDEMIC MODEL WITH BILINEAR AND NON – MONOTONE INCIDENCE RATES

In this chapter we studied an epidemic model consisting of two strains with different types of incidence rates; bilinear and non – monotone. The model consist of four equilibrium points; disease free equilibrium, endemic with respect to strain1, endemic with respect to strain2, and endemic with respect to both strains.

The global stability analysis of the equilibrium points were carried out through the use of Lyapunov functions. Two basic reproduction ratios R_0^1 and R_0^2 are found, and we have shown that, if both are less than one, the disease dies out, and if both are greater than one epidemic occurs. Furthermore, epidemics occur with respect to any strain with basic reproduction ratio greater than one and disease dies out with respect to any strain with basic reproduction ratio less than one. It was also shown that, any strain with highest basic reproduction ratio will automatically outperform the other strain, thereby eliminating it.

Numerical simulations were carried out to support the analytic result and to show the effect of parameter *k* in the non – monotonic incidence rate, which describes the psychological effect of general public towards the infective.

2.1 Introduction

Let $S(t)$, $I(t)$, and $R(t)$ be the population of susceptible, infective, and removed individuals at time t, respectively. Most models of the SIR type have incidence rate that is of the bilinear form (Brauer and Castillo – Chaves, 2011). Many nonlinear incidence rates exist in the literature; some of which are the non-monotone incidence rate (Xiao and Ruan, 2007),

saturated incidence rate (Capasso V and Serio, 1978), and fractional incidence rate (Windarto and Anggriani, 2015).

Incidence rate measures the rate of transmission of diseases. It is defined as the rate of appearance of new cases of disease per unit time. Measurement of incidence rate is sometimes based on categorizing the population by a number of factors, which include social status, age, and psychological inhibition. Prevalence, incidence rate and the annual risk of a disease in any population are related (Styblo, 1985).

A common phenomenon in disease spreading is pathogen mutation. An example of this is the H1N1 influenza virus that emerged in Mexico and the United States in the year 2009, which is the mutation of the seasonal influenza. Many diseases such as Tuberculosis, HIV, Dengue fever, and some other sexually transmitted diseases are caused by more than one strain of pathogen. The dynamical analysis of the pathogen–host interactions with multiple strains has been considered by many researchers (Lin et al., 2003; Feng et al., 2002; Feng and Velasco-Hernandes, 1997). It is also shown that, any strain with the largest basic reproduction ratio will automatically outperform the other strains, thereby eliminating them (Bremermann and Thieme, 1989). Mechanisms like co – infection, super - infection, mutation, exponential growth of the host population, and vaccination promote coexistence among the strains (Martcheva and Pilyugin, 2006; Nowak and May 1994; Li et al., 2004; Lipsitch and Nowak, 1995; Martcheva et al., 2008).

The significance of studying multiple strain models is to identify the condition that enables the coexistence of the different strains. Many mechanisms related to this were studied in the literature; they include super infection (Castillo – Chavez et al., 1996; Ianneli et al., 2005; Wu et al., 2013), co – infection (Martcheva and Pilyugin, 2006; May and Norwak, 1995), mutation (Martcheva et al., 2007), and the effect of age (Martcheva, 2007).

Most of the related research in literature concentrate on models with homogeneous mixing; the assumption that each individual within a susceptible population has the same contact rate with an infective. This assumption is not always true in reality, thus there is need for incorporating

heterogeneous mixing in models. Some researchers considered heterogeneous mixing in there models (nonlinear incidence rates), but most of these researches are on single strain models (Fu et al., 2008; Li, 2005; Lou and Ruggeri, 2010; Moreno et al., 2002). Few researches on multiple strains with heterogeneous mixing exist in literature, but these researches considered heterogeneous mixing on all the strains (Wu et al., 2011; Wu et al., 2013). This is not always the case in reality; the type of mixing depends on the awareness of the population towards the disease in question. If strain1 is the mutation of strain 2, it is expected that the population is aware of strain 2 (heterogeneous mixing) but not strain 1 (homogeneous mixing).

The purpose of this section is to consider the global stability analysis of a two – strain model which incorporates both homogeneous and heterogeneous mixing, that is bilinear incidence rate in one strain $f(I)$ and non – monotone incidence rate $g(I)$ in the other

$$f(I) = \alpha I_1,$$

$$g(I) = \frac{\beta I_2}{1 + kI_2^2}.$$

In this section we are mainly concerned with a two – strain SIR model with a competing mechanism and bilinear incidence rate in the first strain and non – monotone incidence rate in the second strain. Each of these strains follow SIR model, and basic reproduction ratio for each strain is obtained. The stability of the disease free and endemic equilibria is examined by Lyapunov method. We also propose some conditions for the coexistence of the two strains. We will also show numerically the effect of the parameter k which describes the psychological effect of general public towards the infective in the case of non – monotone strain.

This section is organized as follows; Section 2.1 is the introduction. In section 2.2, we formulate the two strain model, with bilinear incidence rate in strain1 and non - monotone incidence rate in strain2. Section 2.3 is the existence of equilibria and the computation of basic reproduction numbers. Stability analysis of the equilibria follows in section 2.4, and section 2.5 is discussion of the results with numerical simulations to support the analytic results.

2.2 The Model

Two strain epidemics model consisting of system of four ordinary differential equations is considered. The compartments are S(t), I_1(t), I_2(t), and $R(t)$ which denotes the population of susceptible, infective with respect to strain1, infective with respect to strain2, and removed individuals at time t, respectively. Table 1 describes the variables and parameters of the model, and Figure 1 is the transfer diagram of the model.

Table 2.1: Description of variables and parameters of model (2.1)

Parameter	**Description**
Λ	Recruitment rate
$\frac{1}{d}$	Average life expectancy of the population
α	Infection rate of the resistant strain
β	Infection rate of the non – resistant strain
$\frac{1}{\mu}$	Average infection period of resistant strain
$\frac{1}{\gamma}$	Average infection period of non - resistant strain
k i	Parameter that measures the psychological or inhibitory effect of the population $k \in [0,1]$

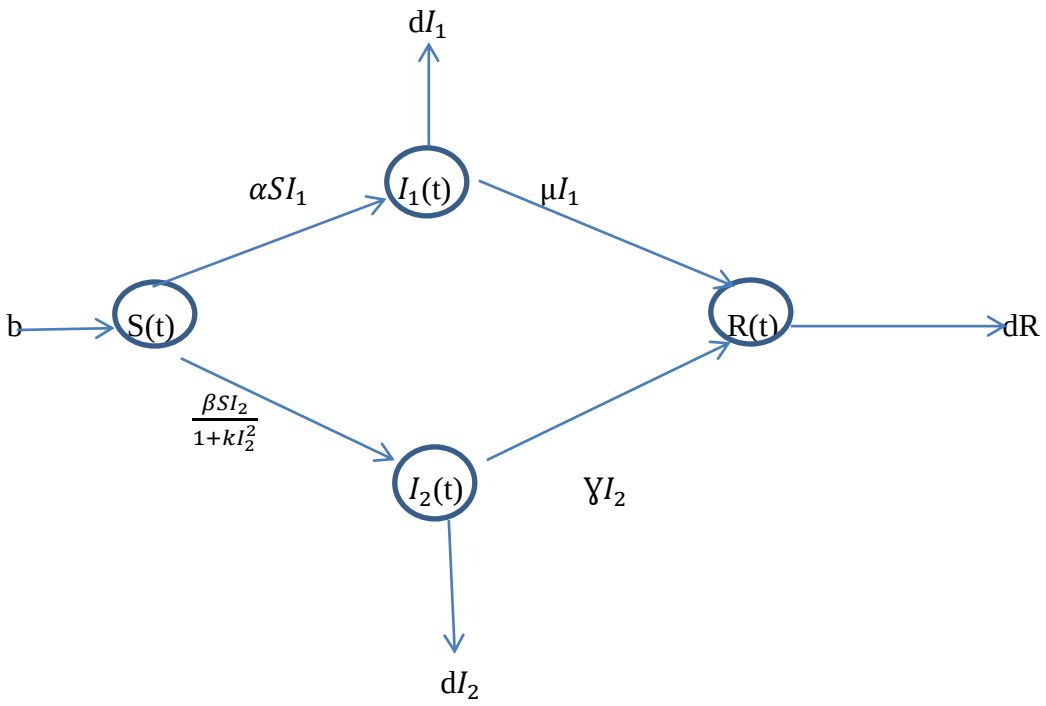

Figure 2.1: Transfer diagram of model (1)

2.2.1 Assumptions

The following assumptions are made in constructing the model

i) There is constant recruitment into susceptible class through birth or immigration.

ii) Once recovered from either of the strains, an individual remains in the recovery class.

iii) There is homogeneous and heterogeneous mixing with regard to strain 1 and strain 2 respectively.

Hence, we have the following system of ordinary differential equations representing the disease dynamics:

$$\frac{dS}{dt} = \Lambda - dS - \alpha S I_1 - \frac{\beta S I_2}{1 + k I_2^2},$$

$$\frac{dI_1}{dt} = \alpha S I_1 - (d + \mu) I_1,$$

$$\frac{dI_2}{dt} = \frac{\beta S I_2}{1 + k I_2^2} - (d + \gamma) I_2, \qquad (2.1)$$

$$\frac{dR}{dt} = \mu I_1 + \gamma I_2 - dR,$$

$N = S + I_1 + I_2 + R.$

2.3 Mathematical Analysis

We first present the following lemma;

Lemma 2.1: The plane $S + I_1 + I_2 + R = \frac{\Lambda}{d}$ is an invariant manifold of system (2.1), which is attracting in the first octant.

Proof: Summing the above equations in (2.1), we have

$$\frac{dN}{dt} = \Lambda - dS - \alpha S I_1 - \frac{\beta S I_2}{1 + k I_2^2} + \alpha S I_1 - (d + \mu) I_1 + \frac{\beta S I_2}{1 + k I_2^2} - (d + \gamma) I_2 + \mu I_2 + \gamma I_2 - dR,$$

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

This implies, $(t) = \frac{\Lambda}{d}$.

For any $N(t_0) \geq 0$, the general solution is

$$N(t) = \frac{\Lambda}{d} + ce^{-dt},$$

at $t_0 = 0$,

$$N(t_0) = \frac{\Lambda}{d} + c,$$

$$\therefore N(t) = \frac{\Lambda}{d} + \left(N(t_0) - \frac{\Lambda}{d}\right)e^{-dt},$$

Thus $\lim_{t\to\infty} N(t) = \frac{\Lambda}{d}$.

Since $N = S + I_1 + I_2 + R$, we can then focus on the following reduced system,

$$\frac{dS}{dt} = \Lambda - dS - \alpha S I_1 - \frac{\beta S I_2}{1 + kI_2^2},$$

$$\frac{dI_1}{dt} = \alpha S I_1 - (d + \mu) I_1,$$

$$\frac{dI_2}{dt} = \frac{\beta S I_2}{1+kI_2^2} - (d + \gamma) I_2.$$

2.3.1 Existence of equilibria

The four possible equilibrium points for the system (2.1) are

i) Disease free equilibrium

$$E_0 = (S_0, I_{1,0}, I_{2,0}) = \left(\frac{\Lambda}{d}, 0, 0\right).$$

Since $S_0, I_{1,0}, I_{2,0}$ are both greater than or equals to zero, the equilibrium exist.

ii) Strain1 endemic equilibrium

$$E_1 = (S_1, I_{1,1}, I_{2,1}) = \left(\frac{d+\mu}{\alpha}, \frac{\alpha\Lambda - d(d+\mu)}{d+\mu}, 0\right).$$

For the equilibrium to exists (biologically meaningful equilibrium), $I_{1,1}$ must be greater than or equals to zero, that is when $\Lambda\alpha - d^2 - d\mu \geq 0,$

which implies $\frac{\Lambda\alpha}{d(d+\mu)} \geq 1.$

iii) Strain2 endemic equilibrium

$$E_2 = (S_2, I_{1,2}, I_{2,2}),$$

where,

$$S_2 = \frac{(d+\gamma)(1+kI_{2,2}^2)}{\beta},\ I_{1,2} = 0,\ I_{2,2} = \frac{-\beta(d+\gamma)+\sqrt{\beta^2(d+\gamma)^2-4dk(d+\gamma)[-\Lambda\beta+d(d+\gamma)]}}{2dk(d+\gamma)}.$$

For the equilibrium to exists (biologically meaningful), $I_{2,2}$ must be greater than or equals to zero, that is when $-\beta(d+\gamma) + \sqrt{\beta^2(d+\gamma)^2 - 4dk(d+\gamma)[-b\beta + d(d+\gamma)]} \geq 0.$

This implies $\frac{\Lambda\beta}{d(d+\gamma)} \geq 1.$

iv) Endemic equilibrium

$$E_3 = (S_3, I_{1,3}, I_{2,3}),$$

where

$$S_3 = \frac{d+\mu}{\alpha}, I_{1,3} = \frac{\alpha\Lambda - d(d+\mu)}{\alpha(d+\mu)} - \frac{\beta I_{2,3}}{\alpha\left(1+kI_{2,3}^2\right)}, I_{2,3} = \sqrt{\frac{\beta(d+\mu)}{\alpha k(d+\gamma)} - \frac{1}{k}}.$$

For the equilibrium to exists (biologically meaningful equilibrium), $I_{1,3}$ and $I_{2,3}$ must be greater than or equals to zero, that is when

$$\frac{\alpha\Lambda - d(d+\mu)}{\alpha(d+\mu)} - \frac{\beta I_{2,3}}{\alpha\left(1+kI_{2,3}^2\right)} \geq 0.$$

This implies

$$\frac{\alpha\Lambda}{d(d+\mu)} \geq \frac{\beta I_{2,3}}{d\left(1+kI_{2,3}^2\right)} + 1,$$

and

$$\sqrt{\frac{\beta(d+\mu)}{\alpha k(d+\gamma)} - \frac{1}{k}} \geq 0.$$

This implies

$$\frac{\beta\Lambda}{d(d+\gamma)} \geq \frac{\alpha\Lambda}{d(d+\mu)}.$$

2.3.2 Basic reproduction ratio

This can be defined as the number of secondary infections caused by an infective individual in a completely susceptible population. Here we used the next generation matrix method to evaluate it.

Let

$$F = \begin{bmatrix} \alpha S I_1 \\ \dfrac{\beta S I_2}{1+kI_2^2} \end{bmatrix}, \qquad V = \begin{bmatrix} (d+\mu)I_1 \\ (d+\gamma)I_2 \end{bmatrix},$$

$$M = \partial F = \begin{bmatrix} \alpha S & 0 \\ 0 & \dfrac{\beta S}{1+kI_2^2} - \dfrac{2\beta k S I_2^2}{(1+kI_2^2)^2} \end{bmatrix}, \qquad N = \partial V = \begin{bmatrix} d+\mu & 0 \\ 0 & d+\gamma \end{bmatrix},$$

$$M(E_0) = \begin{bmatrix} \alpha \dfrac{\Lambda}{d} & 0 \\ 0 & \beta \dfrac{\Lambda}{d} \end{bmatrix},$$

$$MN^{-1} = \begin{bmatrix} \frac{\alpha\Lambda}{d(d+\mu)} & 0 \\ 0 & \frac{\beta\Lambda}{d(d+\gamma)} \end{bmatrix}.$$

The basic reproduction number is the spectrum radius of the matrix MN^{-1},

$$R_0 = \rho(MN^{-1}).$$

This implies $R_0 = R_0^1 = \frac{\alpha\Lambda}{d(d+\mu)}$, $\quad or \quad$ $R_0 = R_0^2 = \frac{\beta\Lambda}{d(d+\gamma)}$.

2.4 Global Stability Analysis

Here, we used the method of Lyapunov function to carry out the global stability analysis of the equilibria.

Theorem 2.2. The disease free equilibrium, E_0 is globally asymptotically stable if $\max\{R_0^1, R_0^2\} < 1$.

Proof. Consider the following Lyapunov function

$$V = (S - S_0 lnS) + I_1 + I_2 + C,$$

where $C = -S_0 + S_0 lnS_0$.

$$\dot{V} = \left(1 - \frac{S_0}{S}\right)\dot{S} + \dot{I}_1 + \dot{I}_2$$

$$= \left(1 - \tfrac{S_0}{S}\right)\left(\Lambda - dS - \alpha S I_1 - \tfrac{\beta S I_2}{1+kI_2^2}\right) + (\alpha S I_1 - (d+\mu)I_1) + \left(\tfrac{\beta S I_2}{1+kI_2^2} - (d+\gamma)I_2\right)$$

$$= dS_0 - dS - \frac{dS_0{}^2}{S} + dS_0 + I_1[\alpha S_0 - (d+\mu)] + I_2\left[\frac{\beta S_0}{1+kI_2^2} - (d+\gamma)\right]$$

$$= dS_0\left[2 - \frac{S}{S_0} - \frac{S_0}{S}\right] - I_1(d+\mu)\left[1 - \frac{\alpha\Lambda}{d(d+\mu)}\right] - I_2(d+\gamma)\left[1 - \frac{\beta\Lambda}{d(d+\gamma)}\right]$$

$$= dS_0\left[2 - \frac{S}{S_0} - \frac{S_0}{S}\right] - I_1(d+\mu)[1 - R_0^1] - I_2(d+\gamma)[1 - R_0^2]$$

This implies $\dot{V} < 0$, by the relation between geometric and arithmetic means and if $\max\{R_0^1,\ R_0^2\} < 1$.

Theorem 2.3. The strain1 endemic equilibrium, E_1 is globally asymptotically stable if $R_0^1 > \max\{1,\ R_0^2\}$.

Proof. Consider the following Lyapunov function

$$V = (S - S_1 lnS) + (I_1 - I_{1,1} lnI_1) + I_2 + C,$$

where $C = -\left[S_1 - S_1 lnS_1 + I_{1,1} - I_{1,1} lnI_{1,1}\right]$.

$$\dot{V} = \left(1 - \frac{S_1}{S}\right)\dot{S} + \left(1 - \frac{I_{1,1}}{I_1}\right)\dot{I}_1 + \dot{I}_2$$

$$= \left(1 - \tfrac{S_1}{S}\right)\left(\Lambda - dS - \alpha S I_1 - \tfrac{\beta S I_2}{1+kI_2^2}\right) + \left(1 - \tfrac{I_{1,1}}{I_1}\right)(\alpha S I_1 - (d+\mu)I_1) +$$
$$\left(\tfrac{\beta S I_2}{1+kI_2^2} - (d+\gamma)I_2\right)$$

$$= 2dS_1 - dS - \tfrac{dS_1{}^2}{S} + I_1\left(\alpha S_1 - (d+\mu)\right) + I_{1,1}(-\alpha S + (d+\mu)) + I_2\left(\tfrac{\beta S_1}{1+kI_2^2} - (d+\gamma)\right)$$

$$= dS_1\left(2 - \frac{S}{S_1} - \frac{S_1}{S}\right) + I_1\left(\alpha\frac{(d+\mu)}{\alpha} - (d+\mu)\right) - I_{1,1}(\alpha S - (d+\mu)) - I_2\left[(d+\gamma) - \frac{\beta\frac{(d+\mu)}{\alpha}}{1+kI_2^2}\right]$$

$$\leq dS_1\left(2 - \frac{S}{S_1} - \frac{S_1}{S}\right) - d[\alpha S - (d+\mu)]\left[\frac{\alpha\Lambda}{d(d+\mu)} - 1\right] - \frac{I_2}{\alpha}[\alpha(d+\gamma) - \beta(d+\mu)]$$

$$= dS_1\left(2 - \frac{S}{S_1} - \frac{S_1}{S}\right) - d[\alpha S - (d+\mu)][R_0^1 - 1] - \frac{I_2}{\alpha}[\alpha(d+\gamma) - \beta(d+\mu)].$$

Then $\dot{V} \leq 0$ by the relation between geometric and arithmetic means, if $R_0^1 > 1$, and if

$$\frac{\alpha(d+\gamma)}{\beta(d+\mu)} > 1.$$

That is $R_0^1 > R_0^2$.

Theorem 2.4. The strain2 endemic equilibrium, E_2 is globally asymptotically stable if $R_0^2 > \max\{1, R_0^1\}$.

Proof**.** Consider the following Lyapunov function

$$V = (S - S_2 lnS) + (I_2 - I_{2,2} lnI_2) + I_1 + C,$$

where $C = -\left[S_2 - S_2 lnS_2 + I_{2,2} - I_{2,2} lnI_{2,2}\right]$.

$$\dot{V} = \left(1 - \frac{S_2}{S}\right)\dot{S} + \left(1 - \frac{I_{2,2}}{I_2}\right)\dot{I}_2 + \dot{I}_1$$

$$= \left(1 - \frac{S_2}{S}\right)\left(\Lambda - dS - \alpha S I_1 - \frac{\beta S I_2}{1+kI_2^2}\right) + \left(1 - \frac{I_{2,2}}{I_2}\right)\left(\frac{\beta S I_2}{1+kI_2^2} - (d+\gamma)I_2\right) + \alpha S I_1 - (d+\mu)I_1$$

$$= 2dS_2 - dS - \frac{dS_2{}^2}{S} + I_1\big(\alpha S_2 - (d+\mu)\big) + I_2\left(\frac{\beta S_2}{1+kI_2^2} - (d+\gamma)\right) - I_{2,2}\left((d+\gamma) + \frac{\beta S}{1+kI_2^2}\right)$$

$$\leq dS_2\left[2 - \frac{S}{S_2} - \frac{S_2}{S}\right] - I_1[(d+\mu) - \alpha S_2] - I_2[(d+\gamma) - \beta S_2] - \left[\frac{\beta S}{1+kI_2^2} + (d+\gamma)\right] I_{2,2}.$$

This implies $\dot{V} \leq 0$ by the relation between geometric and arithmetic means and if

$$d + \mu > \alpha S_2, \tag{2.2}$$

$$d + \gamma > \beta S_2, \tag{2.3}$$

$$I_{2,2} > 0. \tag{2.4}$$

from (2.2), it implies

$$d + \mu > \frac{\alpha(d+\gamma)(1+kI_{2,2}^2)}{\beta}.$$

This implies

$$R_0^2 > R_0^1,$$

from (2.3), it implies

$$d + \gamma > \frac{\alpha(d+\gamma)(1+kI_{2,2}^2)}{\beta}.$$

This implies $I_{2,2} < 0$, which has no biological meaning.

From (2.4), it implies

$$I_{2,2} > 0.$$

This implies

$$R_0^2 > 1.$$

Theorem 2.5. The endemic equilibria E_3 is globally asymptotically stable if $R_0^1 = R_0^2 > 1$.

Proof. Consider the following Lyapunov function

$$V = (S - S_3 lnS) + (I_1 - I_{1,3} lnI_1) + (I_2 - I_{2,3} lnI_2) + C,$$

where $C = -\left[S_3 - S_3 lnS_3 + I_{1,3} - I_{1,3} lnI_{1,3} + I_{2,3} - I_{2,3} lnI_{2,3}\right]$.

$$\dot{V} = \left(1 - \frac{S_3}{S}\right)\dot{S} + \left(1 - \frac{I_{1,3}}{I_1}\right)\dot{I}_1 + \left(1 - \frac{I_{2,3}}{I_2}\right)\dot{I}_2$$

$$= \left(1 - \frac{S_3}{S}\right)\left(\Lambda - dS - \alpha S I_1 - \frac{\beta S I_2}{1 + kI_2^2}\right) + \left(1 - \frac{I_{1,3}}{I_1}\right)(\alpha S I_1 - (d + \mu) I_1)$$
$$+ \left(1 - \frac{I_{2,3}}{I_2}\right)\left(\frac{\beta S I_2}{1 + kI_2^2} - (d + \gamma) I_2\right)$$

$$\leq 2dS_3 - dS - \frac{dS_3{}^2}{S} - I_1[(d + \mu) - \alpha S_3] - I_{1,3}[\alpha S - (d + \mu)]$$
$$- I_2[(d + \gamma) - \beta S_3] - I_{2,3}\left[\frac{\beta S}{1 + kI_2^2} - (d + \gamma)\right]$$

$$= dS_3\left[2 - \frac{S}{S_3} - \frac{S_3}{S}\right] - I_2\left[(d + \gamma) - \beta\frac{(d + \mu)}{\alpha}\right] - [\alpha S - (d + \mu)] I_{1,3}$$
$$- \left[\frac{\beta S}{1 + kI_2^2} - (d + \gamma) I_{2,3}\right].$$

$\dot{V} \leq 0$ by the relation between geometric and arithmetic means and if

$$\frac{\beta(d+\mu)}{\alpha} - (d + \gamma) \leq 0, \tag{2.5}$$

$$I_{2,3} > 0, \tag{2.6}$$

$$I_{1,3} > 0. \tag{2.7}$$

From (2.5) it follows that

$$\beta(d + \mu) \leq \alpha(d + \gamma),$$

this implies

$$R_0^1 \geq R_0^2.$$

From (2.6), it follows that

$$\sqrt{\frac{\beta(d + \mu)}{k\alpha(d + \gamma)} - \frac{1}{k}} \geq 0.$$

This implies

$$R_0^2 \geq R_0^1.$$

From (2.7), it follows that

$$\frac{b}{d + \mu} > \frac{d}{\alpha} + \frac{\beta I_{2,3}}{\alpha(1 + kI_2^2)}.$$

This implies

$$R_0^1 > 1.$$

2.5 Discussions and Numerical Simulations

In this section we studied an epidemic model consisting of two strains with different type of incidence rates; bilinear and non – monotone incidence. Unlike in the research of Feng Z. et al in 2002 (Feng et al., 2002) and Li C. H. in 2005 (Li, 2005), where they respectively studied

multiple strain with bilinear incidence rates only and non – monotone incidence rates only, here we studied the combination of the two. In the former, they considered homogeneous mixing, while in the latter they considered heterogeneous mixing in the population respectively. This is not always the case in reality; the type of mixing depends on the awareness of the population towards the disease in question, and since here strain1 is mutation of strain2, we assumed that the population is aware of strain2 (heterogeneous mixing) but not strain1 (homogeneous mixing).

Four equilibrium points are found; the disease free equilibrium, strain specific endemic, and endemic with respect to both strains. The method of Lyapunov was used to carry out the global stability analysis of all the equilibria. This is an improvement of the research by Junyuan Y. and Chun – Hsein L. in 2016 (Junyuan and Chun – Hsein, 2016), where they couldn't show the global stability of the endemic equilibrium analytically.

The global analysis depends on the threshold quantities; basic reproduction ratios denoted by R_0^1 and R_0^2. If $max\{R_0^1, R_0^2\} < 1$ the disease dies out, and if $R_0^1 = R_0^2 > 1$ the epidemic occurs with respect to both strains. Furthermore, if $R_0^1 > \max\{1, R_0^2\}$, strain1 persists and strain2 dies out, and if $R_0^2 >> \max\{1, R_0^2\}$ strain2 persists and strain1 dies out. These results also agree with similar studies on HIV/AIDS dynamics by Qianqian L et al in 2012 (Qianqian et al., 2012), and Tuberculosis model by Moghadas SM and Gumel AB in 2002 (Moghadas and Gumel, 2002). It was also shown that, any strain with highest basic reproduction ratio will automatically outperform the other strain, thereby eliminating it. This is in agreement with the findings by Bremermann HJ and Thieme HR in 1989 (Bremermann and Thieme, 1989).

Numerical simulations were also carried out to support the analytic results. In Fig 2.2 both strains (I_1 and I_2) die out, this is because the basic reproduction ratios for the strains are both less than one ($R_0^1 = 0.75, and\ R_0^2 = 0.53$). In Fig 2.3 strain2 ($I_2$) dies out and strain1 ($I_1$) persists ($R_0^1 = 7.5, and\ R_0^2 = 0.53$), and in Fig 2.4 strain1 (I_1) dies out and strain2 (I_2) persists ($R_0^1 = 0.75, and\ R_0^2 = 6.2$). Lastly in Fig 2.5 both the two strains (I_1 and I_2) persist, this is because the basic reproduction ratios are equal and greater than one ($R_0^1 = R_0^2 = 7.5$).

It can also be observed from Figure 2.2 and Figure 2.5 that strain2 dies out faster, and the persistence of strain1 is higher than that of strain2. This is due to the effect of the parameter k, which describes the psychological effect of general public towards the infective. Although the effect of the parameter k is not shown by R_0^2 but it has been shown clearly using the above simulations.

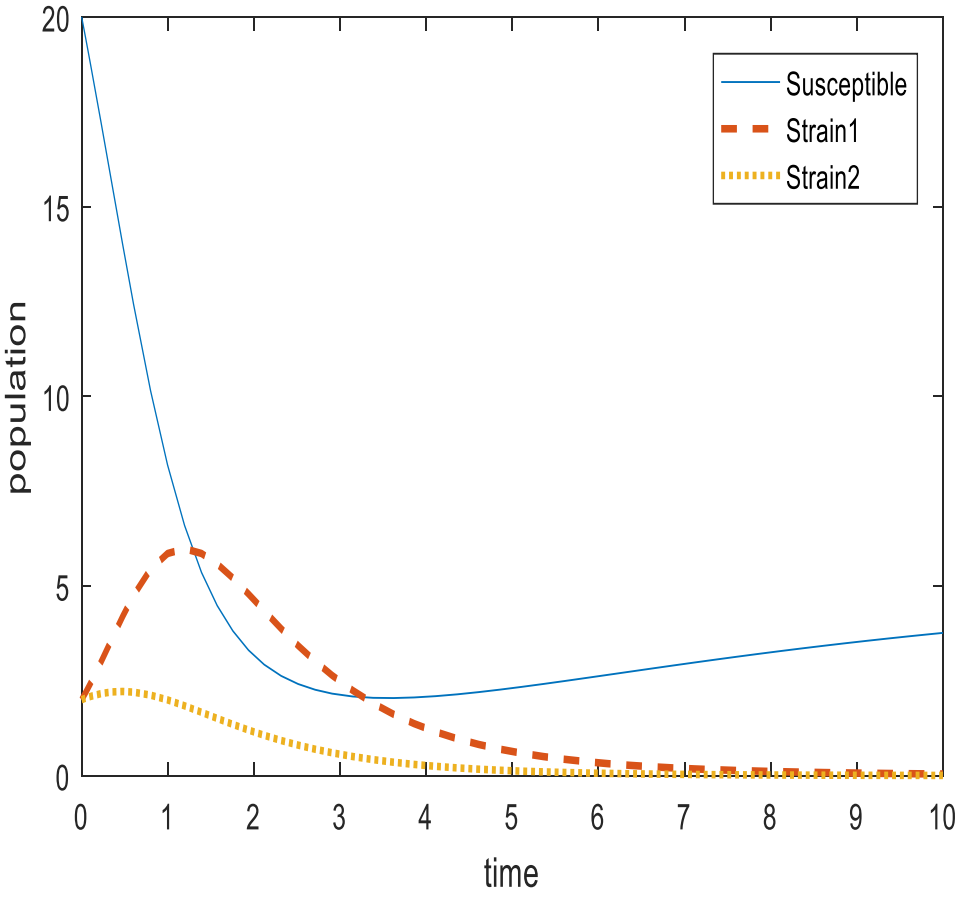

Figure 2.2: Both strains die out. Parameter values; $\Lambda = 1, d = 0.2, \alpha = 0.15, \mu = 0.8, \beta = 0.1, \gamma = 0.75, k = 0.1, R_0^1 = 0.75, and\ R_0^2 = 0.53.$

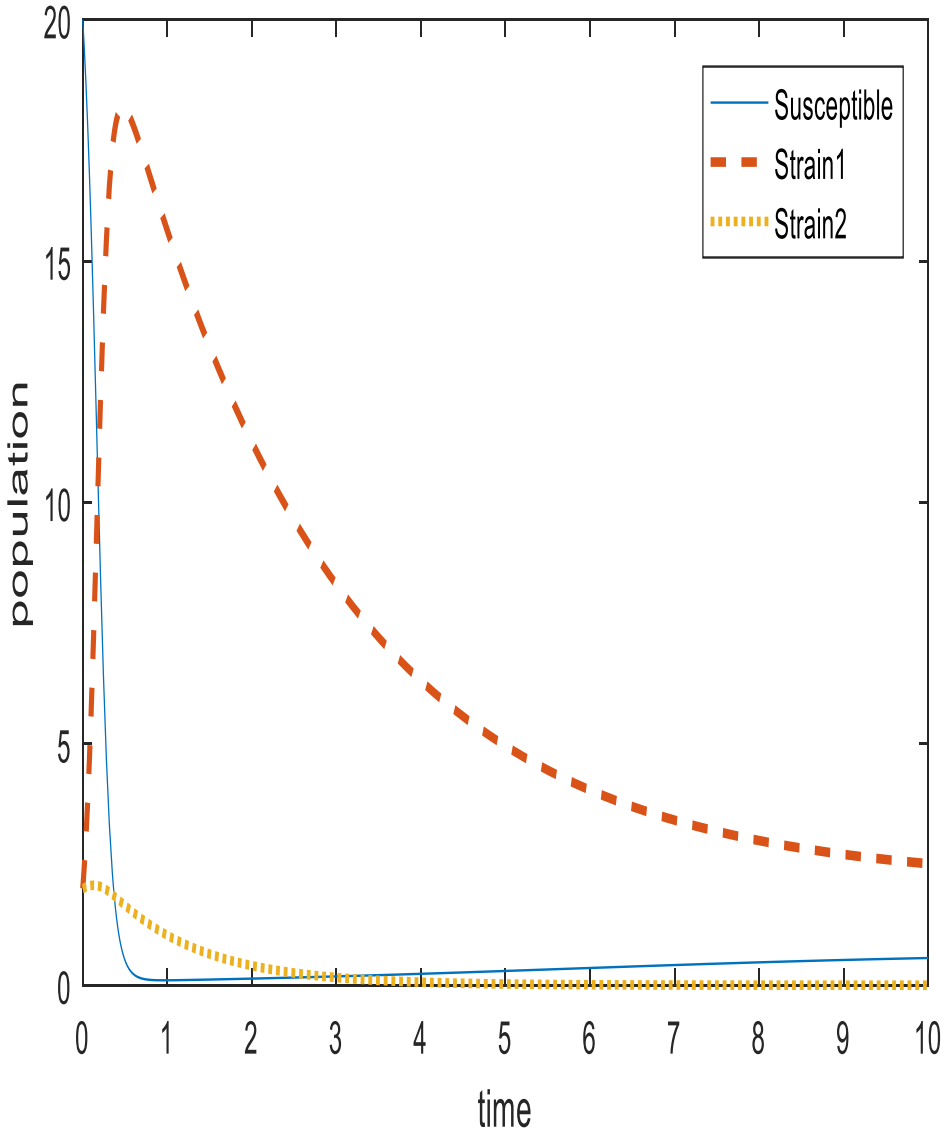

Figure 2.3: Persistence of strain1 only. Parameter values; $\Lambda = 1, d = 0.2, \alpha = 0.6, \mu = 0.2, \beta = 0.1, \gamma = 0.75, k = 0.1, R_0^1 = 7.5, and\ R_0^2 = 0.53.$

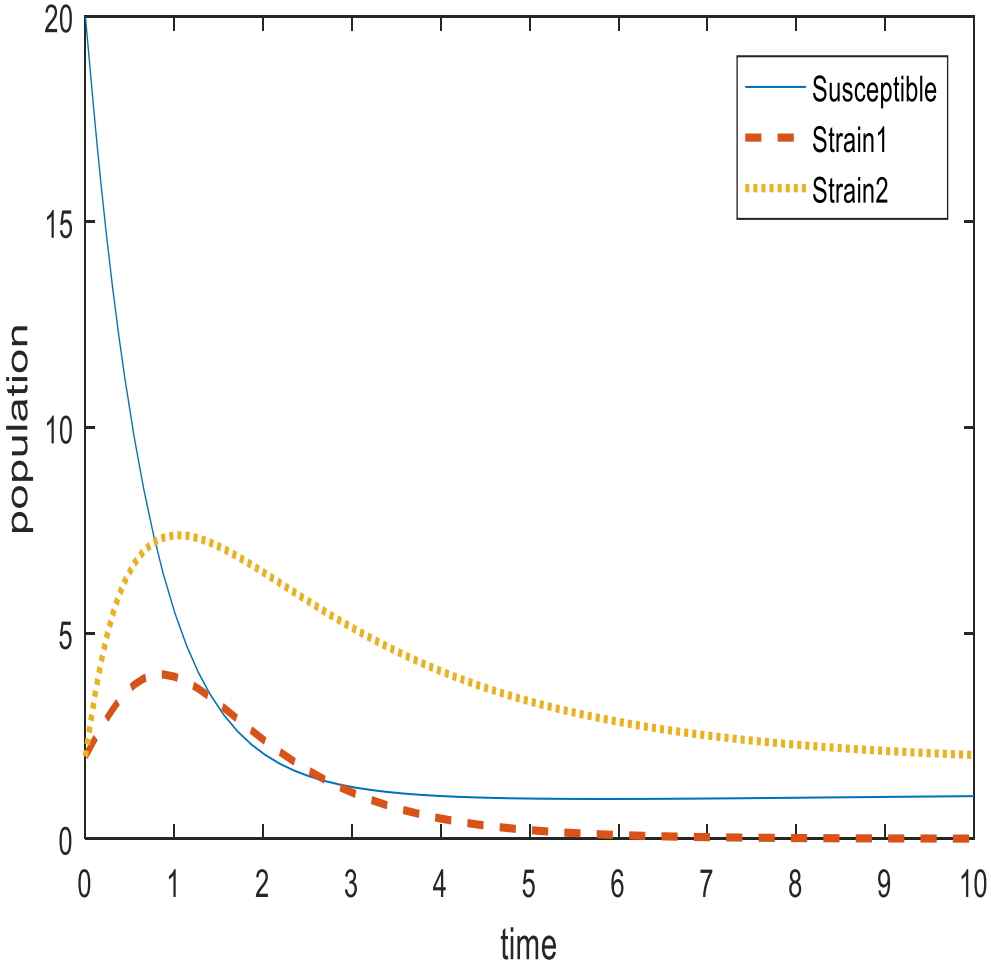

Figure 2.4: Persistence of strain2 only. Parameter values; $\Lambda = 1, d = 0.2, \alpha = 0.15, \mu = 0.8, \beta = 0.52, \gamma = 0.22, k = 0.1, R_0^1 = 0.75, and\ R_0^2 = 6.2.$

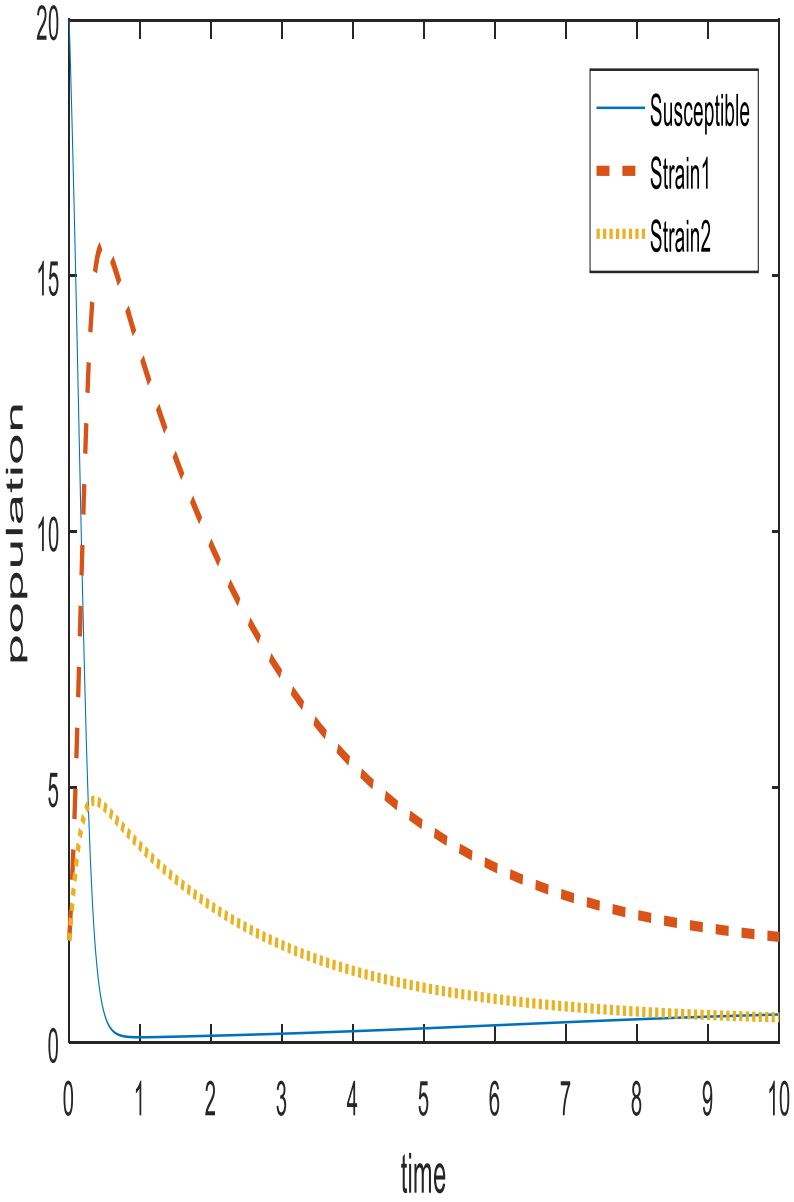

Figure 2.5: Both strains persist. Parameter values; $\Lambda = 1, d = 0.2, \alpha = 0.6, \mu = 0.2, \beta = 0.6, \gamma = 0.2, k = 0.1,\ R_0^1 = 7.5, and\ R_0^2 = 7.5.$

CHAPTER 3

RESISTANCE AND NON – RESISTANCE STRAINS OF INFLUENZA: A MATHEMATICAL MODEL

In this chapter we studied two strain flu model in which one strain (resistance) is the mutation of the other (non – resistance) strain. We attributed to each of the strains, a distinct incidence rate viz.; bilinear and saturated. Bilinear incidence rate is attributed to non - resistant strain, while the saturated incidence rate is attributed to resistant strain. Lyapunov functions were used to prove the global stability of the proposed model. R_R and R_N are the two basic reproduction ratios found. Analysis of the model shows that, if the maximum of the two ratios is less than one, an epidemic is controlled. If the minimum of the two ratios is greater than one, epidemic occurs. More over strain with higher magnitude of the basic reproduction ratio persists and dominate the other. Numerical simulations were presented, and their results were shown to support the analytic results.

3.1 Introduction

Caused by influenza virus, influenza is a serious cytopathogenic, infectious and drastic respiratory disease (Mohler et al., 2005). In general it has three forms: A, B, and C. They are identified based on their differences in terms of matrix protein (M) and nucleoprotein (NP) (Tamura et al., 2005).

Type A can infect both humans and animals especially wild animals. It is the most acute of all the types. It is further subdivided based on hemagglutinin (HA) and neuraminidase (NA) proteins found on the surface of the virus. There are 16 types of hemagglutinin (H1 – H16) and 9 types of neuraminidase (N1 – N9). Subtypes of influenza virus are named based on combination of their HA and NA. For example H1N1 virus means; influenza A that has an HA1 protein and NA1 protein. In humans only three of these combinations are most common:

H1N1, H1N2, and H3N2. Type B can also infect humans and birds, and its spread can be epidemics. The last type, type C, affects only humans and it can hardly be differentiated from common cold as its spread is not usually epidemic (Webster et al., 2016).

The subtypes of influenza A and B can further be characterized into strains. There are two main ways in which a new strain of influenza appear: antigenic drift and antigenic shift (Martcheva et al., 2007). Antigenic drift occurs through gradual changes in the virus which happens over time. It produces new strains which may then not be recognized by the host antibodies. On the other hand antigenic shift is a sudden change in influenza A virus that results in a new strain that has never been seen before. Influenza A undergoes both changes, while B undergoes antigenic drift only (Ward et al., 2005).

Although vaccination can prevent influenza infection, it is not useful against emerging subtypes of influenza. This is evident from the pandemic nature of the H1N1 influenza in 2009. Hence, to prevent the spread of an emerging influenza epidemic, there is a need for antiviral to inhibit the replication of the virus. The antiviral plays a vital role in the protection of seasonal influenza (Ward et al., 2005; Schünemann et al., 2007; Fiore et al., 2011). Nowadays, resistance cases of this virus are observed. Aminoadamantanes resistance in the case of H3N2 virus and Oseltamivir resistance in the case of H1N1 virus are some of these resistance cases observed (Carr et al., 2002; Monto et al., 2006; Baranovich et al., 2009). This situation is deadly and can lead to much influenza pandemic in the future, hence the need for the establishment of worldwide surveillance that can monitor the condition (Monto et al., 2006).

In general, risk of transmission of new influenza strain is believed to be minimal compared to that of original strain. This can be attributed to the fact that mutation reduces viral strength (Herlocher et al., 2002; Carr et al., 2002; Ives et al., 2002; Herlocher et al., 2004; Abed et al., 2004; Bouvier et al., 2008).

Whenever there is an epidemic, two important questions that need to be addressed are: what is the possible cause of the epidemic, and the most effective intervention measures to protect the

general public against the epidemic? Mathematical modeling helps in providing answers to these questions (Bornemann et al., 2009; Lipsitch et al., 2009; Kaymakamzade et al., 2016; Baba et al., 2017). In order to study the condition under which both resistant and the non-resistant strains can coexist; as well as the differences between the mode of spread of the two strains, we develop a mathematical model. We used numerical simulations to show how one of the strains can displace the other.

Incidence rate can be termed as the rate of emergence of a disease in a unit time. It is a very important unit of epidemiology. Our aim in this paper is to study the coexistence between two strains of flu in which one strain (resistant strain) is the mutation of the other (non-resistant strain). Since the risk of the resistant strain (mutated strain) is assumed to be minimal compared the non – resistant strain, we considered different incidence rates for the duo; saturated for the resistant strain and bilinear for the non-resistant strain. The choice of saturated incidence rate for the resistant strain is due to the fact that it is more logical than the bilinear incidence rate, since it grasps the negotiating alteration and swarming impact of the infected people and hinders the unboundedness of the interconnection rate by fitting parameters, which was reused in several epidemic issues (Liu et al., 2005; Gomes et al., 2005; Kar and Jana, 2013).

Each of these strains follow basic SIR model. We obtained two basic reproduction ratios - one for each strain. Global stability for each equilibrium point is shown using Lyapunov function. Analysis for the coexistence of the two strains was also carried out.

This chapter is organized along these lines: section 3.1 introduces the concept. Section 3.2 explains the formulation of the model. In section 3.3 we give the detail mathematical analysis of the model. In section 3.4, we carry out numerical simulations and, finally, we discuss the results in section 3.5.

3.2 Model Formulation

Two strain epidemic model with four compartments is considered. These compartments are leveled as S(t), I_R(t), I_N(t), and $R(t)$ standing respectively for susceptible, infective resistant, infective non – resistant, as well as removed individuals. In Table 3.1, the description of variables and parameters as used in the model are given and Figure 3.1 is the diagrammatical representation of the model.

Table 3.1: Parameters and variables of model (2)

Parameter	**Description**
b	Recruitment rate
$\frac{1}{d}$	Life expectancy
β	Infection rate of the resistant strain
α	Infection rate of the non – resistant strain
$\frac{1}{\gamma}$	Average infection period of resistant strain
$\frac{1}{\mu}$	Average infection period of non - resistant strain
k	Parameter that measures the psychological or inhibitory effect

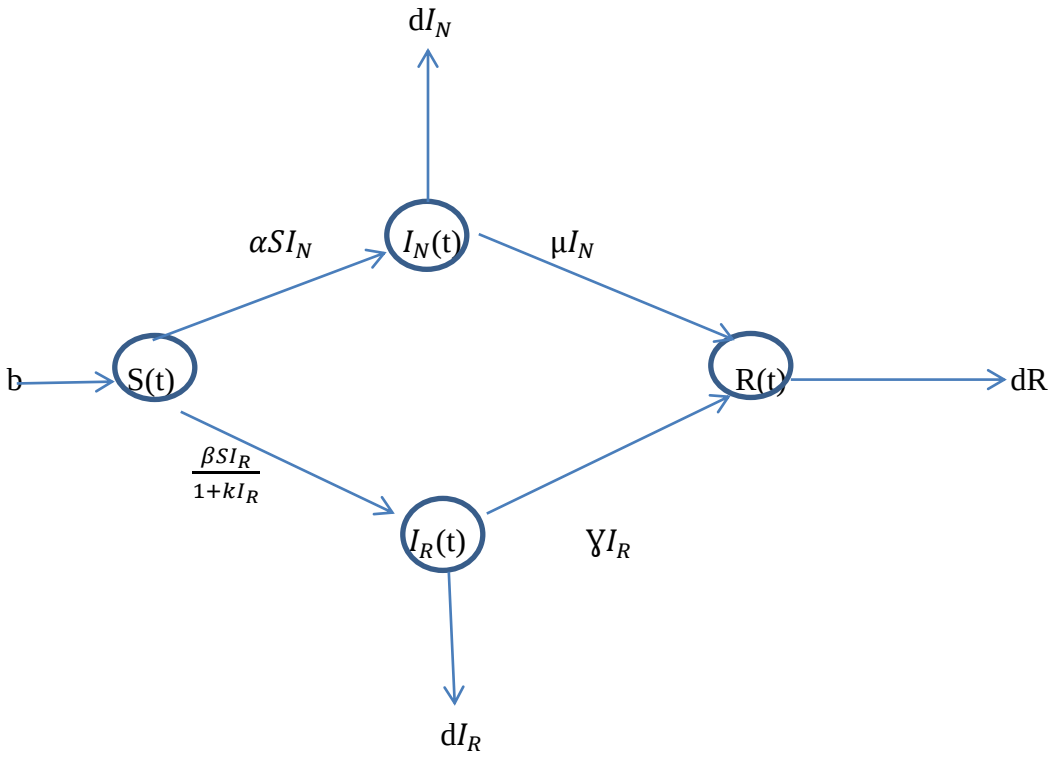

Figure 3.1: Diagrammatical representation of model (2)

The following assumptions are made

i) Recruitment into susceptible class is constant.

ii) There is no double infection.

iii) Once recovered from either resistant or non - resistant virus, an individual remains in the recovery class.

Hence the system of ordinary differential equations given by (3.1) describes the following model:

$$\frac{dS}{dt} = b - dS - \alpha SI_N - \frac{\beta SI_R}{1 + kI_R},$$

$$\frac{dI_N}{dt} = \alpha SI_N - (d + \mu)I_N,$$

$$\frac{dI_R}{dt} = \frac{\beta SI_R}{1+kI_R} - (d + \gamma)I_R, \tag{3.1}$$

$$\frac{dR}{dt} = \mu I_N + \gamma I_R - dR,$$

$$N = S + I_R + I_N + R,$$

3.3 Analysis of the Model

Here the mathematical analysis of the model is given. The following lemma is given at first.

Lemma 3.1. The plane $S + I_R + I_N + R = \frac{b}{d}$ is an invariant manifold of system (3.1), which is attracting.

Proof. Summing all four equations in (3.1);

$$\frac{dN}{dt} = b - dS - \alpha SI_N - \frac{\beta SI_R}{1 + kI_R} + \alpha SI_N - (d + \mu)I_N + \frac{\beta SI_R}{1 + kI_R} - (d + \gamma)I_R + \mu I_N + \gamma I_R - dR,$$

$$\frac{dN}{dt} = b - dN.$$

Considering $N(t_0) \geq 0$, then

$$N(t) = \frac{b}{d} + ce^{-dt}.$$

Taking $t_0 = 0$, we get

$$N(t_0) = \frac{b}{d} + c.$$

Therefore,

$$N(t) = \frac{b}{d} + \left(N(t_0) - \frac{b}{d}\right) e^{-dt}.$$

Hence $\lim_{t\to\infty} N(t) = \frac{b}{d}$

Since $N = S + I_R + I_N + R$, system (3.1) can be reduced to

$$\frac{dS}{dt} = b - dS - \alpha S I_N - \frac{\beta S I_R}{1 + k I_R},$$

$$\frac{dI_N}{dt} = \alpha S I_N - (d + \mu) I_N,$$

$$\frac{dI_R}{dt} = \frac{\beta S I_R}{1 + k I_R} - (d + \gamma) I_R.$$

3.3.1 Existence of equilibria

The system has four possible equilibria

i) Disease free, which always exist

$$E_0 = \left(\frac{b}{d}, 0, 0\right).$$

ii) Non – resistant equilibrium

$$E_1 = \left(\frac{d + \mu}{\alpha}, \frac{b\alpha - d^2 - d\mu}{\alpha(d + \mu)}, 0\right),$$

which exists when $b\alpha - d^2 - d\mu \geq 0$.

This implies $\frac{b\alpha}{d(d+\mu)} \geq 1$.

iii) Resistant equilibrium

$$E_2 = \left(\frac{d+\gamma+bk}{dk+\beta}, 0, \frac{b\beta - d^2 - d\gamma}{d\gamma k + d^2 k + \beta d + \beta\gamma}\right),$$

which only exists if $b\beta - d^2 - d\gamma \geq 0$.

This implies $\frac{b\beta}{d(d+\gamma)} \geq 1$.

iv) Endemic equilibrium

$$E_3 = \left(\frac{d+\mu}{\alpha}, \frac{-(d^2k + dk\mu + \beta d - \alpha d - \alpha\gamma + \beta\mu - bk\alpha)}{(d+\mu)\alpha k}, \frac{\beta d + \beta\mu - \alpha d - \alpha\gamma}{(d+\gamma)\alpha k}\right),$$

which only exists if

$$d^2k + dk\mu + \beta d - \alpha d - \alpha\gamma + \beta\mu - bk\alpha \leq 0 \qquad (3.1)$$

$$and \qquad \beta d + \beta\mu - \alpha d - \alpha\gamma \geq 0. \qquad (3.2)$$

From (*) it follows

$$[dk(d+\mu) - bk\alpha] + [\beta(d+\mu) - \alpha(d+\gamma)] \leq 0.$$

This implies $\frac{\alpha b}{d(d+\mu)} \geq 1$ and $\frac{\beta b}{d(d+\gamma)} \leq \frac{\alpha b}{d(d+\mu)}$.

From (**) it follows

$$\beta(d+\mu) \geq \alpha(d+\gamma).$$

This implies $\frac{\beta b}{d(d+\gamma)} \geq \frac{\alpha b}{d(d+\mu)}$.

From (*) and (**), endemic equilibrium E_3 exists only if

$$\frac{\beta b}{d(d+\gamma)} = \frac{\alpha b}{d(d+\mu)} \geq 1.$$

3.3.2 Basic reproduction ratio (R_0)

R_0 is defined as the number of new cases a single infected individual produced in a population of susceptible individuals. Here next generation matrix (NGM) method is used to obtain it.

If

$$F = \begin{bmatrix} \alpha S & 0 \\ 0 & \frac{\beta S}{1+kI_N} - \frac{\beta k S I_N}{(1+kI_N)^2} \end{bmatrix}, \qquad V = \begin{bmatrix} d+\mu & 0 \\ 0 & d+\gamma \end{bmatrix},$$

$$F(E_0) = \begin{bmatrix} \alpha\frac{b}{d} & 0 \\ 0 & \beta\frac{b}{d} \end{bmatrix},$$

$$FV^{-1} = \begin{bmatrix} \frac{\alpha b}{d(d+\mu)} & 0 \\ 0 & \frac{\beta b}{d(d+\gamma)} \end{bmatrix},$$

R_0 is the maximum eigenvalue of the matrix FV^{-1},

$$R_0 = \rho(FV^{-1}).$$

This implies $R_0 = R_N = \frac{\alpha b}{d(d+\mu)}$ *or* $R_0 = R_R = \frac{\beta b}{d(d+\gamma)}$.

3.3.3 Global stability analysis

Lyapunov function technique is used to prove the global nature of the equilibrium solutions.

Theorem 3.2. E_0 (disease free equilibrium) is globally asymptotically stable when $\{R_R, R_N\} < 1$.

Proof. The following Lyapunov function is constructed

$$V = (S - S_0 lnS) + I_R + I_N + C,$$

where $C = -S_0 + S_0 lnS_0$.

$$\dot{V} = \left(1 - \frac{S_0}{S}\right)\dot{S} + \dot{I}_R + \dot{I}_N$$

$$= \left(1 - \tfrac{S_0}{S}\right)\left(b - dS - \alpha S I_N - \tfrac{\beta S I_R}{1+kI_R}\right) + (\alpha S - (d+\mu)I_N) + \left(\tfrac{\beta S I_R}{1+kI_R} - (d+\gamma)I_R\right)$$

$$= dS_0 - dS - \frac{dS_0{}^2}{S} + (d+\mu)I_N\left(\frac{\alpha S_0}{d+\mu} - 1\right) + (d+\gamma)I_R\left(\frac{\beta S_0}{(d+\gamma)(1+kI_R)} - 1\right)$$

$$\leq dS_0\left(2 - \frac{S}{S_0} - \frac{S_0}{S}\right) + (d+\mu)I_N(R_N - 1) + (d+\gamma)I_R(R_R - 1)$$

If $R_R < 1$, $R_N < 1$ and by the geometric and arithmetic means inequality, it can be concluded $\dot{V} \leq 0$.

Theorem 3.3. Non – resistant virus equilibrium E_1 is globally asymptotically stable when $R_N > 1$ and $R_N > R_R$.

Proof. The following Lyapunov function is constructed

$$V = (S - S_1 lnS) + (I_N - I_{N1} lnI_N) + I_R + C,$$

here $C = -S_1 + S_1 lnS_1 - I_{N1} + I_{N1} lnI_{N1}$.

Taking the derivative, we get

$$\dot{V} = \left(1 - \frac{S_1}{S}\right)\dot{S} + \left(1 - \frac{I_{N1}}{I_N}\right)\dot{I}_N + \dot{I}_R$$

$$= \left(1 - \tfrac{S_1}{S}\right)\left(b - dS - \alpha S I_R - \tfrac{\beta S I_R}{1+kI_R}\right) + \left(1 - \tfrac{I_{N1}}{I_N}\right)(\alpha S - (d+\mu)I_N) + \left(\tfrac{\beta S I_R}{1+kI_R} - (d+\gamma)I_R\right)$$

$$= 2dS_1 - dS - \tfrac{dS_1{}^2}{S} + I_N\left(\alpha S_1 - (d+\mu)\right) + I_{N1}(-\alpha S + (d+\mu)) + I_R\left(\tfrac{\beta S_1}{1+kI_R} - (d+\gamma)\right)$$

$$= dS_1\left(2 - \tfrac{S}{S_1} - \tfrac{S_1}{S}\right) + I_N\left(\alpha\tfrac{(d+\mu)}{\alpha} - (d+\mu)\right) - I_{N1}(\alpha S - (d+\mu)) + I_R\left(\tfrac{\beta\frac{(d+\mu)}{\alpha}}{1+kI_R} - (d+\gamma)\right)$$

$$\leq dS_1\left(2 - \tfrac{S}{S_1} - \tfrac{S_1}{S}\right) + \left(\alpha S - (d+\mu)\right)\left(\tfrac{-\alpha b + d^2 + d\mu}{\alpha(d+\mu)}\right) + I_R\left(\tfrac{\beta(d+\mu)}{\alpha} - (d+\gamma)\right).$$

*B*y the geometric and arithmetic means inequality , we get

$$2 - \frac{S}{S_1} - \frac{S_1}{S} \leq 0.$$

Therefore, $\dot{V} \leq 0$, if

$$-\alpha b + d^2 + d\mu < 0 \quad \text{and} \quad \frac{\beta(d+\mu)}{\alpha} - (d+\gamma) < 0$$

This implies $R_N > 1$ and $R_N > R_R$.

Theorem 3.4. The resistant virus equilibrium E_2 is globally asymptotically stable when $R_R > 1$ and $R_R > \frac{b(dk+\beta)}{d(d+\gamma+bk)}$, $R_N > \frac{b(dk+\beta)}{d(d+\gamma+bk)}$.

Proof. The following Lyapunov function is considered

$$V = (S - S_2 lnS) + (I_R - I_{R2} lnI_R) + I_N + C,$$

where $C = -S_2 + S_2 lnS_2 - I_{R2} + I_{R2} lnI_{R2}$.

Taking the derivative, we get

$$\dot{V} = \left(1 - \frac{S_2}{S}\right)\dot{S} + \left(1 - \frac{I_{R2}}{I_R}\right)\dot{I}_R + \dot{I}_N$$

$$= \left(1 - \tfrac{S_2}{S}\right)\left(b - dS - \alpha S I_N - \tfrac{\beta S I_R}{1+kI_R}\right) + \left(1 - \tfrac{I_{R2}}{I_R}\right)\left(\tfrac{\beta S I_R}{1+kI_R} - (d+\gamma)I_R\right) + \alpha S - (d+\mu)I_N$$

$$= 2dS_2 - dS - \tfrac{dS_2{}^2}{S} + I_N(\alpha S_2 - (d+\mu)) + I_R\left(\tfrac{\beta S_2}{1+kI_R} - (d+\gamma)\right) + I_{R2}\left((d+\gamma) - \tfrac{\beta S}{1+kI_R}\right)$$

$$= dS_2\left(2 - \tfrac{S}{S_2} - \tfrac{S_2}{S}\right) + I_N\left(\tfrac{\alpha(d+\gamma+bk)}{dk+\beta} - (d+\mu)\right) + I_R\left(\tfrac{\beta(d+\gamma+bk)}{dk+\beta} - (d+\gamma)\right) + \left(\tfrac{\beta S}{1+kI_N} - (d+\gamma)\right)\left(\tfrac{-b\beta+d^2+d\gamma}{d\gamma k+d^2k+\beta d+\beta\gamma}\right).$$

*B*y the geometric and arithmetic means inequality , we get

$$2 - \frac{S}{S_2} - \frac{S_2}{S} \leq 0.$$

Therefore, $\dot{V} \leq 0$, if

$$\frac{d+\gamma+bk}{dk+\beta} < \frac{d+\mu}{\alpha}, \qquad \frac{d+\gamma+bk}{dk+\beta} < \frac{d+\gamma}{\beta}.$$

This implies $R_N > \frac{b(dk+\beta)}{d(d+\gamma+bk)}$, $\quad and \quad R_R > \frac{b(dk+\beta)}{d(d+\gamma+bk)}$.

and $-b\beta + d^2 + d\gamma < 0$, which implies $R_R > 1$.

Theorem 3.5. The endemic equilibria E_3 is globally asymptotically stable when $R_R = R_N > 1$.

Proof. The following Lyapunov function is considered

$$V = (S - S_3 lnS) + (I_R - I_{R3} lnI_R) + (I_N - I_{N3} lnI_N) + C,$$

Where $C = -S_3 + S_3 lnS_3 - I_{R3} + I_{R3} lnI_{R3} - I_{N3} + I_{N3} lnI_{N3}$.

$$\dot{V} = \left(1 - \frac{S_3}{S}\right)\dot{S} + \left(1 - \frac{I_{R3}}{I_R}\right)\dot{I}_N + \left(1 - \frac{I_{N3}}{I_N}\right)\dot{I}_N$$

$$= \left(1 - \frac{S_3}{S}\right)\left(b - dS - \alpha S I_N - \frac{\beta S I_R}{1 + kI_R}\right) + \left(1 - \frac{I_{N3}}{I_N}\right)(\alpha S - (d + \mu)I_N)$$
$$+ \left(1 - \frac{I_{R3}}{I_R}\right)\left(\frac{\beta S I_R}{1 + kI_R} - (d + \gamma)I_R\right)$$

$$= 2dS_3 - dS - \frac{dS_3{}^2}{S} + I_N(\alpha S_3 - (d + \mu)) + I_{N3}((d + \mu) - \alpha S)$$
$$+ I_R\left(\frac{\beta S_3}{1 + kI_R} - (d + \gamma)\right) + I_{R3}\left((d + \gamma) - \frac{\beta S}{1 + kI_R}\right)$$

$$\leq dS_3\left(2 - \frac{S}{S_3} - \frac{S_3}{S}\right) + (\alpha S - (d + \mu))\left(\frac{d^2k + dk\mu + \beta d - \alpha d - \alpha\gamma + \beta\mu - \alpha bk}{\alpha k(d+\mu)}\right) +$$
$$I_R\left(\frac{\beta(d+\mu)}{\alpha} - (d + \gamma)\right) + \left(\frac{\beta S}{1+kI_R} - (d + \gamma)\right)\left(\frac{-\beta d - \beta\mu + \alpha d + \alpha\gamma}{\alpha k(d+\gamma)}\right).$$

$\dot{V} \leq 0$ by the geometric and arithmetic means inequality and if

$$d^2k + dk\mu + \beta d - \alpha d - \alpha\gamma + \beta\mu - \alpha bk \leq 0, \tag{3.3}$$

$$\frac{\beta(d+\mu)}{\alpha} - (d + \gamma) \leq 0, \tag{3.4}$$

$$-\beta d - \beta\mu + \alpha d + \alpha\gamma \leq 0. \tag{3.5}$$

From (3.3), it follows that

$$(dk(d+\mu)-bk\alpha)+\big(\beta(d+\mu)-\alpha(d+\gamma)\big)\leq 0.$$

This yields $R_N \geq 1 \quad and\ R_N \geq R_R$.

From (3.4) it follows that

$$\beta(d+\mu)\leq \alpha(d+\gamma).$$

This yields $R_N \geq R_R$.

From (3.5) it follows that

$$\alpha(d+\gamma)\leq \beta(d+\mu).$$

This yields $R_R \geq R_N$.

From $(3.3), (3.4) and (3.5)$ it follows that

$$R_N = R_R = 1.$$

3.4 Numerical Simulations

In this section, some numerical simulations were carried out. In Fig 3.2 the strains (I_R and I_N) die out, since the basic reproduction ratios for the each strain is less than one ($R_N = 0.75, and\ R_R = 0.53$). Fig 3.3 shows resistant strain (I_R) dies out and non – resistant strain (I_N) persists ($R_N = 7.5, and\ R_R = 0.53$), and in Fig 3.4 non – resistant strain (I_N) dies out and resistant strain (I_R) persists ($R_N = 0.75, and\ R_R = 6.2$). Finally in Fig 3.5 the strains (I_N and I_R) persist ($R_N = R_R = 7.5$).

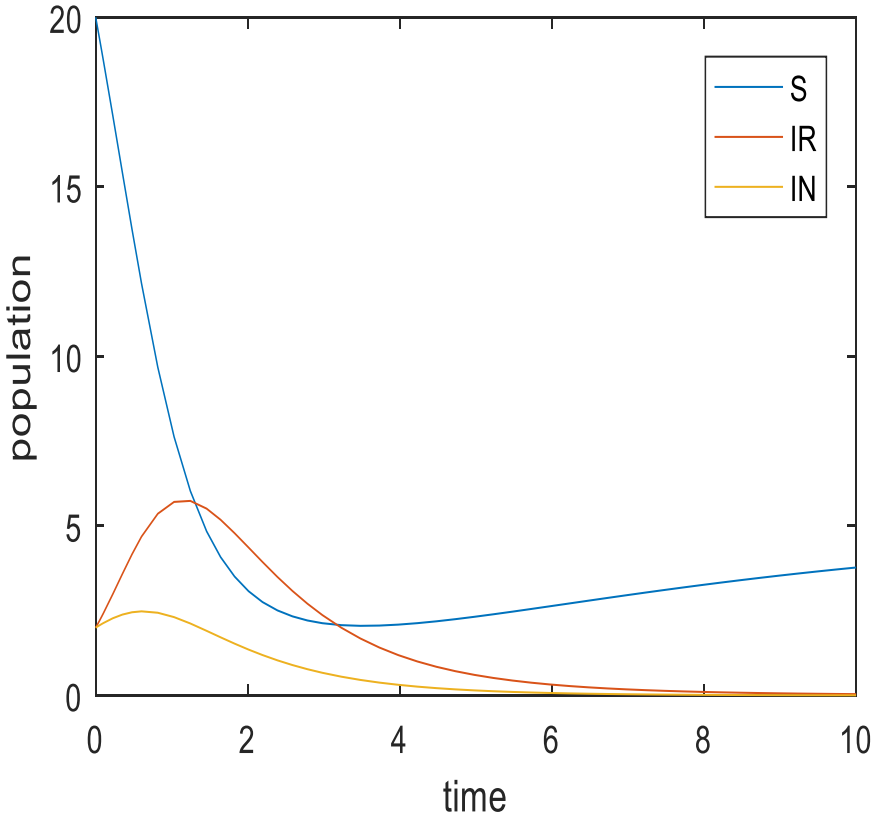

Figure 3.2: Disease - free equilibrium. Parameter values; $d = 0.2, b = 1, \mu = 0.8, \alpha = 0.15, \beta = 0.1, k = 0.1, \gamma = 0.75,\ R_N = 0.75, and\ R_R = 0.53.$

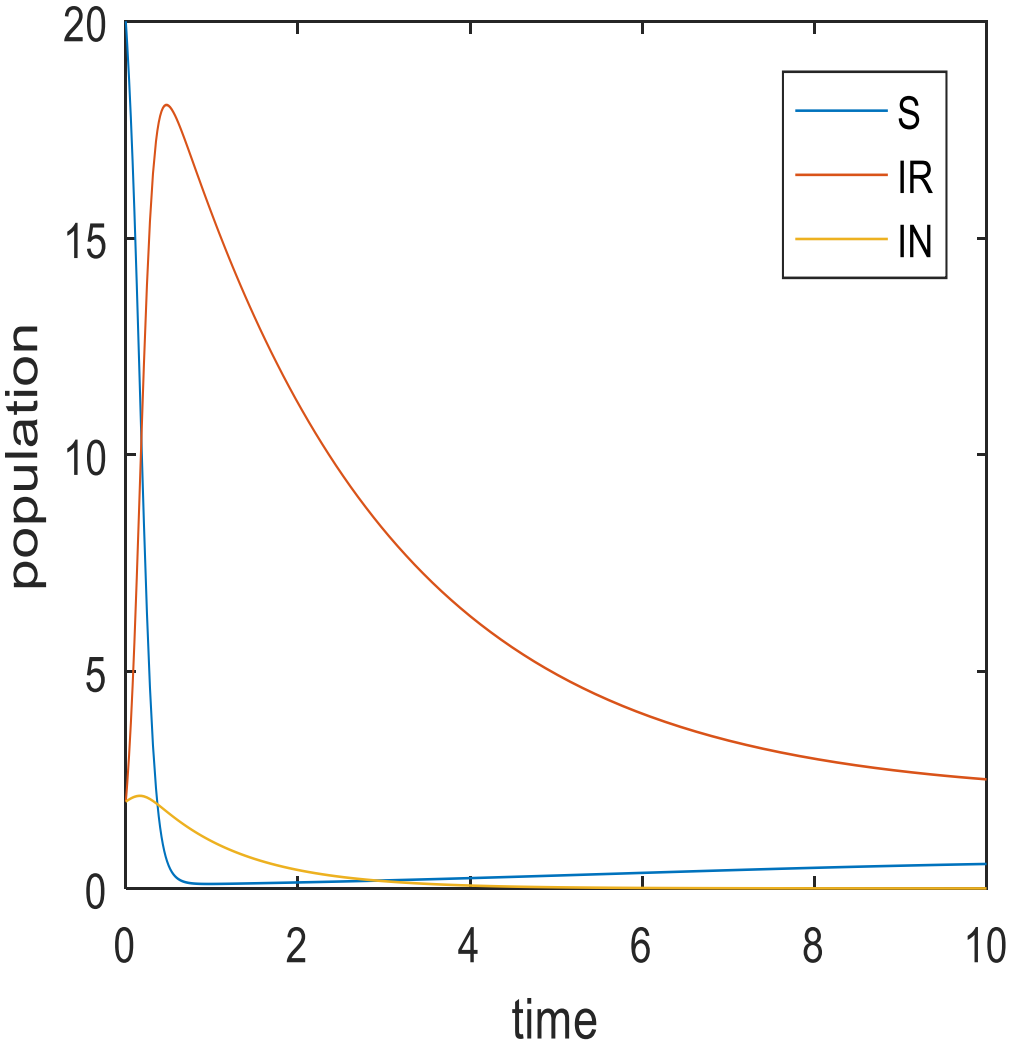

Figure 3.3: Resistant endemic equilibrium. Parameter values; $d = 0.2, b = 1, \mu = 0.2, \alpha = 0.6, \gamma = 0.75, \beta = 0.1, k = 0.1,\ R_N = 7.5, and\ R_R = 0.53.$

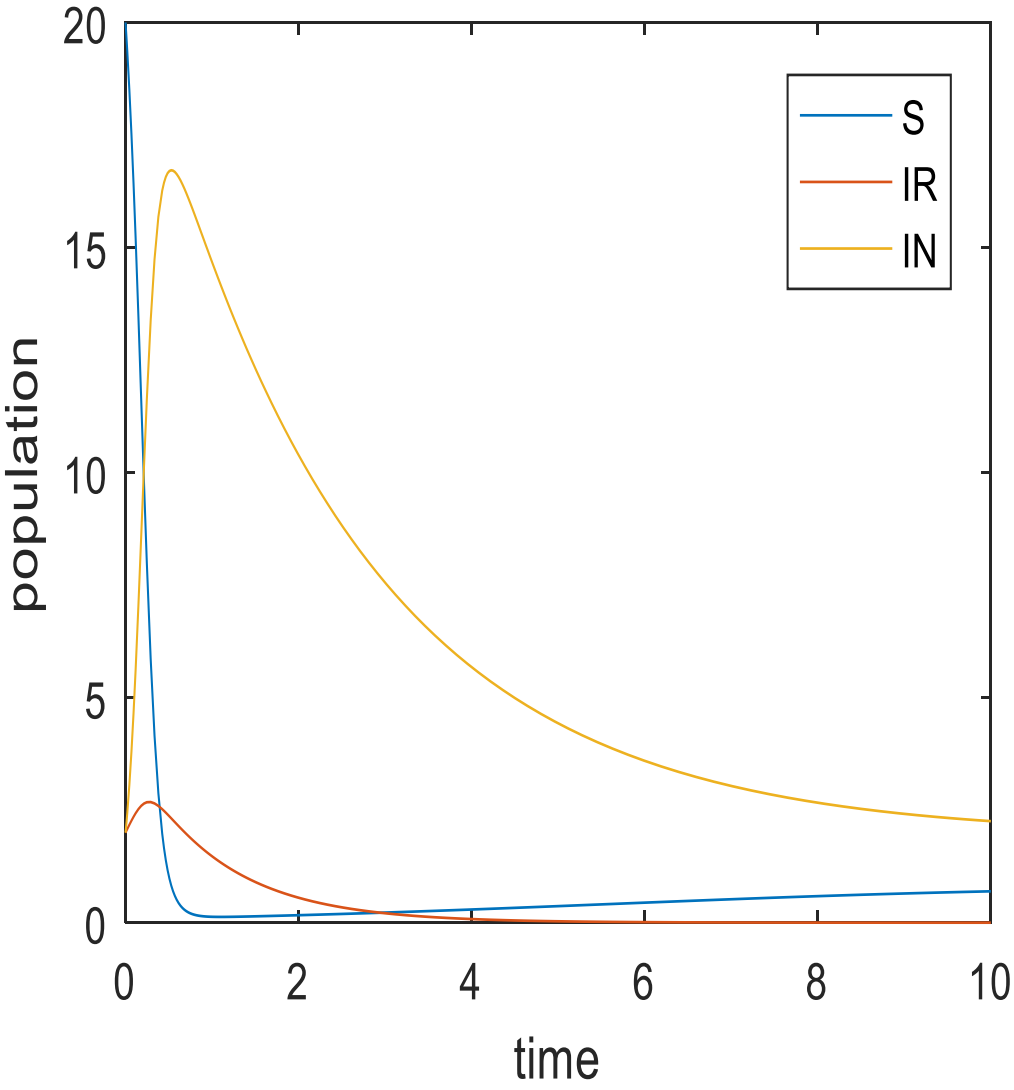

Figure 3.4: Non - Resistant endemic equilibrium. Parameter values; $d = 0.2, b = 1, \mu = 0.8, \alpha = 0.15, \gamma = 0.22, \beta = 0.52, k = 0,\ R_N = 0.75, and\ R_R = 6.2.$

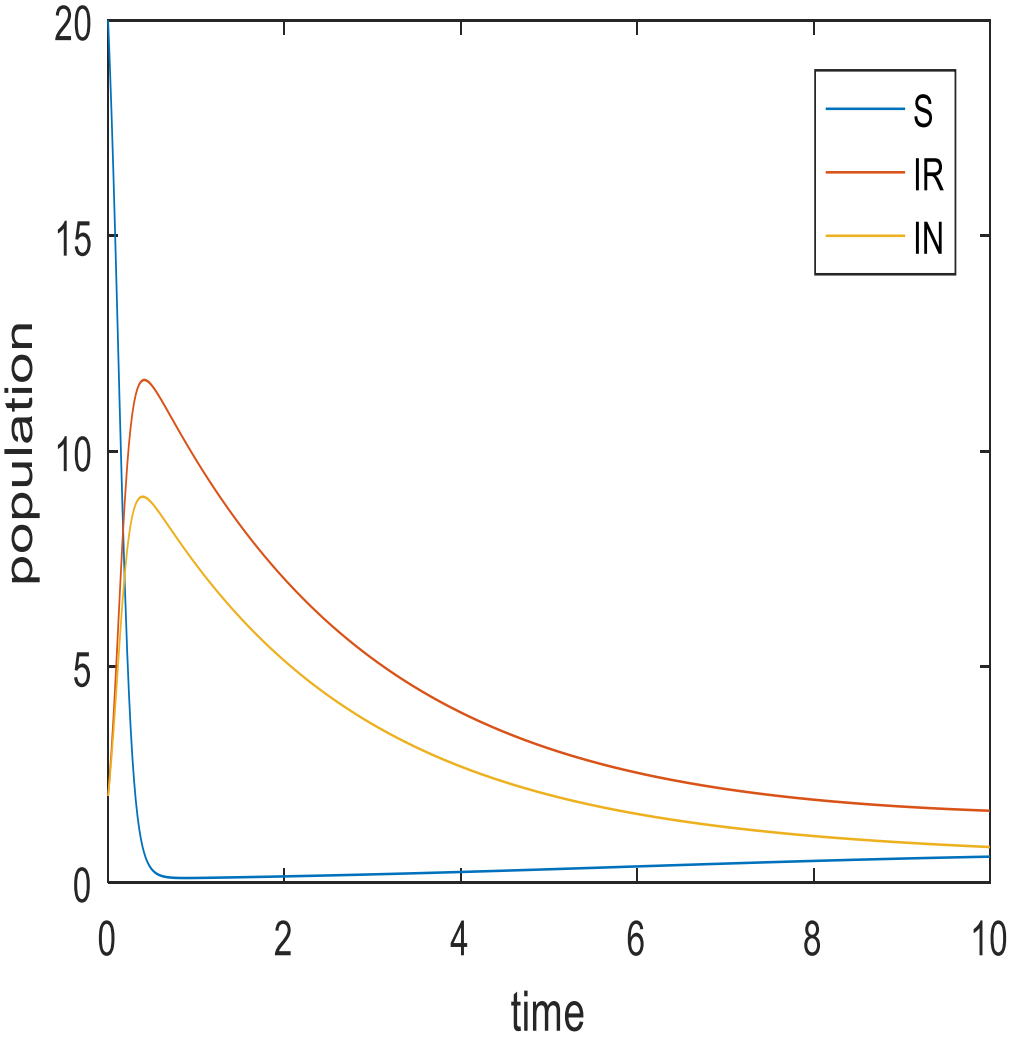

Figure 3.5: Endemic equilibrium. Parameter values; $d = 0.2, b = 1, \mu = 0.2, \alpha = 0.6, \beta = 0.6, k = 0, \gamma = 0.2,\ R_R = 7.5, and\ R_N = 7.5.$

3.5 Discussions

In this section we studied two strain flu model in which one strain (resistance) is the mutation of the other (non – resistance) strain. We attributed distinct incidence rates to these strains viz.; bilinear and saturated. Bilinear incidence rate is attributed to non - resistant strain, while

the saturated incidence rate is attributed to resistant strain. Lyapunov function was used to conduct the Stability analysis of the model. R_R and R_N are the basic reproduction ratios found. It was shown that, if the maximum of the two parameters is less than unity, the disease dies out and then the disease free equilibrium is globally stable, and if the minimum is greater than or equal to unity, epidemic occurs and the endemic equilibrium is globally stable. More over any strain with highest basic reproduction ratio is globally stable and will automatically outperform the other strain.

The numerical results obtained are similar to the analytic results. It can be observed from Figure 3.2 and Figure 3.5 that resistant strain dies out faster than non – resistant strain, and the number of Infectives are higher with respect to non - resistant strain. The reason can be attributed to the fact that mutations reduced viral fitness, and hence the effect of the mutation parameter k.

In conclusion coexistence conditions for two strains is given, and it was also have shown by numerical means that the rate of transmission of resistant virus which has saturated incidence rate is lower than that of the non – resistant virus which has bilinear incidence rate.

CHAPTER 4

A MODEL FOR INFLUENZA WITH VACCINATION AND AWARENESS

In this chapter we considered three strains of influenza (I_1, I_2, and I_3) where we have vaccine for strain1 (V_1) only, and population has enough awareness of strain 2. There is neither vaccine nor awareness for strain 3. Our main aim is to mathematically analyze the effect of the vaccine for strain 1 and awareness of strain 2 on the dynamics of strain 3. It is also in our aim to study the coexistence of these three strains. Six equilibrium points were obtained and their global stability using Lyapunov functions was shown to depend on the magnitude of a threshold quantity, called basic reproduction ratio. It was shown that the coexistence of strain 1 and strain 2 is not possible and the coexistence of the three strains was shown numerically. It can be observed from the numerical simulations that, although vaccine curtail the spread of strain 1, awareness curtail the spread of strain 2, but they both have negative effect on strain 3. This tells the relevant authorities whenever there is influenza epidemic to investigate thoroughly the possibilities of the existence of multiple strains, so as to provide vaccines and enough awareness on all the strains present.

Keywords: Three strain, global stability analysis, basic reproduction ratios, influenza

4.1 Introduction

Influenza is termed as a serious cytopathogenic, infectious, drastic respiratory disease that is caused by influenza virus (Mohler et al., 2005). Influenza is categorized into 3 main types; A, B, and C. This categorization is based on the differences that exist between matrix protein (M) and nucleoprotein (NP) (Tamura et al., 2005).

Type A can infect both humans, pigs, whales, birds and especially wild animals. It is the most acute of all the types. It is further subdivided into based on hemagglutinin (HA) and

neuraminidase (NA) proteins found on the surface of the virus. Hemagglutinin is divided into sixteen subtypes of (H1 – H16) and neuraminidase into nine subtypes (N1 – N9). Influenza virus subtypes are named based on their combination of HA and NA. For example H1N1 virus means, Influenza A that has an HA1 protein and NA1 protein. In humans three of these combinations are most common; H1N1, H1N2, and H3N2. Type B can also infect humans and birds, and can cause epidemics. The last type (C) affects only humans and it can hardly be differentiated from common cold as it causes no epidemics (Webster et al., 2016).

Most influenza models are of the SIR form. Many extensions of the SIR model for influenza includes incorporating seasonality (Dushoff et al., 2004; Stone et al., 2007), as a spatial – temporal model (Rvachev, 1968), to show the effect of air travel on its pandemic (Mohler et al., 2005; Baroyan, 1971), and to show the importance of air travel on geographic spread (Flahault et al., 1994; Caley, 2007).

Mathematical models also provided insight into severity of past influenza epidemics (Chowell et al., 2007; Bootsma and Ferguson, 2007). Some models were used to investigate the three most devastating epidemics of influenza viz.; Spanish flu (H1N1) 1918 – 1919, Asian flu (H2N2) 1957 – 1958, and Hong – Kong flu (H3N2) 1968 (Chowell et al., 2006; Mills et al., 2004; Chauchemez et al., 2008). It was shown using mathematical modeling the effect that interventions may have had in curtailing the H1N1 pandemics of 1918 – 1919 (Chowell et al., 2006). The behavioral effects such as quarantine, imposing travel sanctions on the infected individuals, closing schools were also modeled (Epstein et al., 2007; Arino et al., 2008). The effectiveness of biomedical interventions such as vaccines, therapeutic treatment, and prophylactic treatment were also shown using mathematical models (Longini et al., 2004; Riley et al., 2007; Lipsitch et al., 2007).

Many models were also used to determine the anti – viral resistance dilemma (Ferguson et al., 2006), to compare policies related to efficacy of prophylaxis and treatment (Riley et al., 2007), and to establish the best policies for budgeting vaccines (Lipsitch et al., 2007). Some models went ahead to evaluate the effectiveness of combining behavioral and biomedical

interventions for example Varvadas et al. considered the effect of human practice towards establishing vaccine broadcasting (Vardavas et al., 2007).

Influenza, Dengue fever, Tuberculosis, and many other transmissible diseases can be caused by multiple pathogen strains. Many researchers studied epidemics caused by these types of diseases (Baroyan et al., 1971; Rvachev et al., 1985; Flahault et al, 1994). Basic reproduction ratio plays very significant role here, since it was also shown that, any strain with the largest basic reproduction ratio will outperform the other/others (Caley et al., 2007). Mostly mechanisms like exponential growth of the host population, co – infection, super - infection, vaccination, and mutation avail the strains coexistence (Chowell et al., 2007; Bootsman and Ferguso, 2007; Chowell et al., 2006; Mills et al., 2004; Chauchemez et al., 2008; Kaymakamzade et al., 2016; Baba et al., 2017; Zhen et al., 2016; Han-Xin and Bing-Hong, 2016; Han-Xin and Zhen, 2016). Since new strains are still evolving, there is need for more studies on the coexistence of multiple strains.

In this section we considered three strains of influenza (I_1, I_2, and I_3) where we have vaccine for strain1 (V_1) only, and population has enough awareness of strain 2. There is neither vaccine nor awareness for strain 3. Our main aim is to mathematically analyze the effect of the vaccine for strain 1 and awareness of strain 2 on the dynamics of strain 3. It is also in our aim to study the coexistence of these three strains.

This section is formulated in such away; Section 4.1 introduces the problem. Formulation of the model follows in section 4.2. Calculation of basic reproduction number and study of existence of equilibria is conducted in section 4.3. Section 4.4 is the stability analysis of the equilibria, and finally in section 4.5 discussions numerical simulations results were given.

4.2 Model Formulation

Three strain influenza model with vaccination that consists of system of six first order ODE is constructed. The population of susceptible, infective with respect to strain 1, vaccine of strain

1, infective with respect to strain2, infective with respect to strain 3 and removed individuals at time t are represented by S(t), I_1(t), V_1(t), I_2(t), I_3(t) and $R(t)$ respectively.

Table 4.1: Definition of parameters and variables of the following model (4.1)

Parameter	**Description**
Λ	Recruitment rate
$\frac{1}{\mu}$	Average life expectancy of the population
β_1	Infection rate of strain 1
β_2	Infection rate of strain 2
β_3	Infection rate of strain 3
$\frac{1}{\gamma_1}$	Average infection period of strain 1
$\frac{1}{\gamma_2}$	Average infection period of strain 2
$\frac{1}{\gamma_3}$	Average infection period of strain 3
α	Parameter that measures the psychological effect
r_1	Rate of vaccination with strain1
v_1	Infection induced death rate of strain 1
k	Transmission coefficient of vaccinated individuals

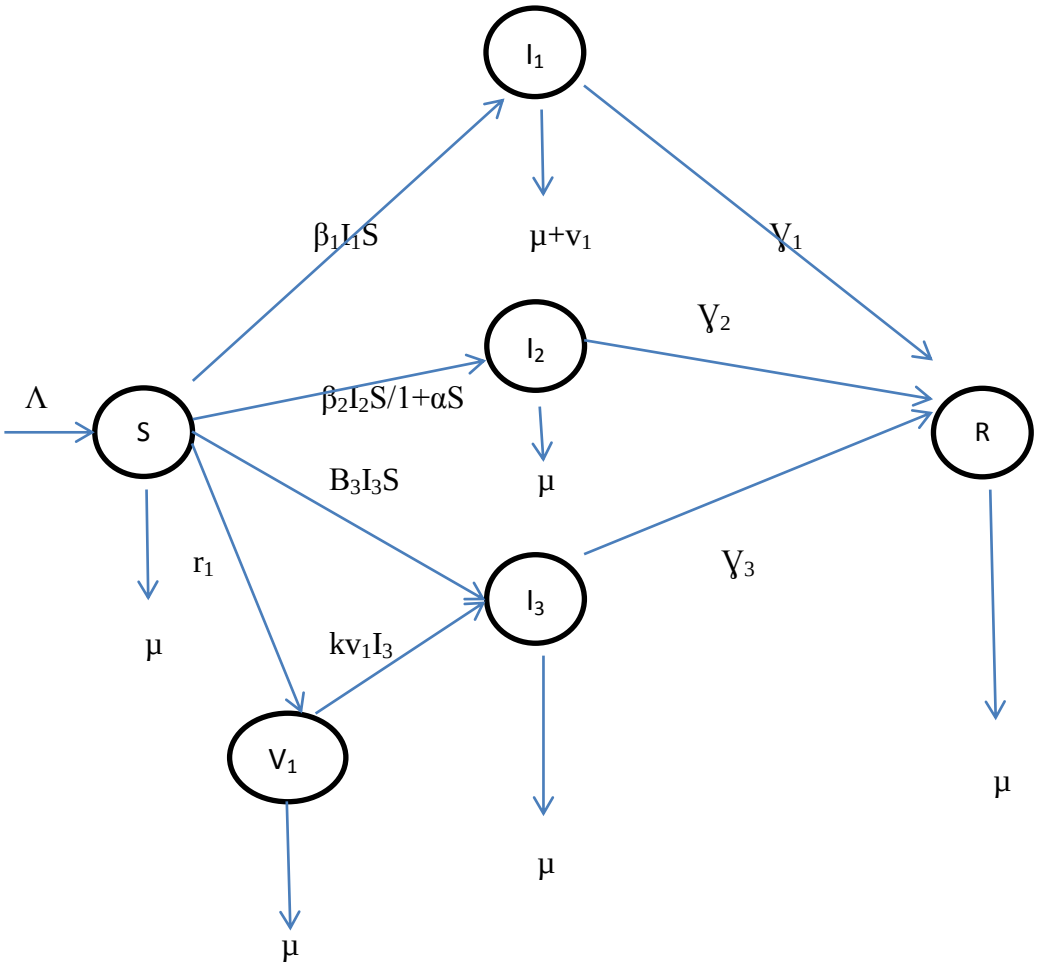

Figure 4.1: Transfer diagram of model (3)

Recruitment into suspectible class is assumed to be constant, and the possibility of double infection is ignored. The variables and parameters are positive and their meanings are given in Table 1, Figure 1 also gives the trasfer diagram of the model. With these assumptions the following model is considered:

$$\frac{dS}{dt} = \Lambda - \left(\beta_1 I_1 + \frac{\beta_2 I_2}{1+\alpha S} + \beta_3 I_3 + \Theta_1\right) S,$$

$$\frac{dV_1}{dt} = r_1 S - (kI_3 + \mu) V_1,$$

$$\frac{dI_1}{dt} = \beta_1 I_1 S - \Theta_2 I_1,$$

$$\frac{dI_2}{dt} = \frac{\beta_2 I_2 S}{1+\alpha S} - \Theta_3 I_2, \qquad (4.1)$$

$$\frac{dI_3}{dt} = (kV_1 + \beta_3 S) I_3 - \Theta_4 I_3,$$

$$\frac{dR}{dt} = \gamma_1 I_1 + \gamma_2 I_2 + \gamma_3 I_3 - \mu R,$$

where,

$$\Theta_1 = \mu + r_1,\ \Theta_2 = \mu + v_1 + \gamma_1, \Theta_3 = \mu + \gamma_2\ , \Theta_4 = \mu + \gamma_3,$$

and

$$N = S + V_1 + I_1 + I_2 + I_3 + R.$$

4.3 Equilibria, Boundedness, and Basic Reproduction Ratio

4.3.1 Existence of equilibrium solutions

Setting the system (4.1) to zero and solving the simultaneously we obtain the following equilibrium solutions

$$E_1 = \left\{S = \frac{\Lambda}{\Theta_1}, V_1 = \frac{\Lambda r_1}{\Theta_1 \mu}\ , I_1 = 0, I_2 = 0, I_3 = 0\ \right\}.$$

The equilibrium solution exists, since all the parameters in this equilibrium are at least equal to zero.

$$E_2 = \left\{S = \frac{\theta_2}{\beta_1}, V_1 = \frac{\theta_2 r_1}{\beta_1 \mu}\ , I_1 = \frac{-\Lambda\beta_1 + \theta_1\theta_2}{\theta_2\beta_1}, I_2 = 0, I_3 = 0\ \right\}.$$

This equilibrium solution exists only when $I_1 \geq 0$, that is when $\frac{\Lambda\beta_1}{\theta_1\theta_2} \geq 1$.

$$E_3 = \left\{S = \frac{-\theta_3}{-\beta_2+\alpha\theta_3}, V_1 = \frac{-\theta_3 r_1}{\mu(-\beta_2+\alpha\theta_3)}\ , I_1 = 0, I_2 = \frac{-\Lambda\beta_2+\alpha\Lambda\theta_3+\theta_1\theta_3}{\theta_2\beta_1}, I_3 = 0\ \right\}.$$

This equilibrium solution exists only when $S > 0, V_1 \geq 0, and\ I_2 \geq 0$

$$S > 0, \qquad if \quad \frac{\beta_2}{\alpha\theta_3} > 1,$$

$$V_1 \geq 0, I_2 \geq 0 \quad if \quad \frac{\beta_2}{\alpha\theta_3} \geq 1,$$

$$E_4 =$$
$$\left\{S = \frac{\Lambda}{\beta_3 I_3+\theta_1}, V_1 = \frac{r_1\Lambda}{(\beta_3 I_3+\theta_1)(kI_3+\mu)}\ , I_1 = 0, I_2 = 0, I_3 = \frac{1}{2}\frac{\alpha k\beta_3-\mu\theta_4\beta_3-k\theta_1\theta_4\pm\sqrt{\Omega_1}}{\theta_4\beta_3 k}\right\},$$

here,

$$\Omega_1 = \beta_3^2\Lambda^2k^2 - 2\beta_3^2\Lambda k\mu\theta_4 - 2\beta_3\Lambda k^2\theta_1\theta_4 + \beta_3^2\mu^2{\theta_4}^2 - 2\mu{\theta_4}^2\beta_3 k\theta_1 + {\theta_1}^2{\theta_4}^2k^2 + 4\theta_4\beta_3k^2r_1\Lambda.$$

This equilibrium solution exists only when $I_3 \geq 0$, that is when $\frac{kr_1\Lambda}{\mu\theta_1\theta_4} \geq 1$.

$$E_5 =$$
$$\left\{S = \frac{\theta_2}{\beta_1}, V_1 = \frac{-\beta_3\theta_2+\beta_1\theta_4}{k\beta_1}\ , I_1 = \frac{\Omega_2}{\theta_2\beta_1 k(-\beta_3\theta_2+\beta_1\theta_4)}, I_2 = 0, I_3 = -\frac{\Omega_3}{k(-\beta_3\theta_2+\beta_1\theta_4)}\right\},$$

here,

$$\Omega_2 = -\Lambda\beta_1 k\beta_3\theta_2 + \Lambda\beta_1^2 k\theta_4 - \beta_3\theta_2^2 r_1 k - \beta_3^2\theta_2^2\mu + \beta_3\theta_2\mu\theta_4\beta_1 + \theta_1\theta_2^2 k\beta_3 - \theta_1\theta_2\theta_4 k\beta_1,$$

and

$$\Omega_3 = -r_1 k\theta_2 - \mu\beta_3\theta_2 + \mu\theta_4\beta_1.$$

This equilibrium solution exists only when $V_1 \geq 0, I_1 \geq 0, and\ I_3 \geq 0.$

$$V_1 \geq 0 \quad if \quad \frac{\beta_1}{\theta_2} \geq \frac{\beta_3}{\theta_4},$$

$$I_1 \geq 0 \quad if \quad \theta_4\beta_1 - \beta_3\theta_2 \geq \frac{\beta_3\theta_2^2 r_1 k}{\Lambda\beta_1 k + \beta_3\theta_2},$$

$$I_3 \geq 0 \quad if \quad \mu\beta_3\theta_2 + r_1 k\theta_2 \geq \mu\theta_4\beta_1.$$

E_6

$$= \left\{ S = \frac{-\theta_3}{-\beta_2 + \alpha\theta_3}, V_1 = \frac{\alpha\theta_3\theta_4 + \beta_3\theta_3 - \beta_2\theta_4}{k(-\beta_2 + \alpha\theta_3)}, I_1 = 0, \right.$$
$$\left. I_2 = \frac{\Omega_4}{\theta_3 k(-2\beta_2\alpha\theta_3\theta_4 - \beta_2\beta_3\theta_3 + \beta_2^2\theta_4 + \alpha^2\theta_3^2\theta_4 + \alpha\beta_3{\theta_3}^2)}, I_3 = -\frac{\Omega_5}{k(\alpha\theta_3\theta_4 + \beta_3\theta_3 - \theta_4\beta_2)} \right\},$$

here,

$$\Omega_4 = -\beta_3^2{\theta_3}^2\mu - \alpha\beta_3{\theta_3}^2\mu\theta_4 - \beta_3{\theta_3}^2 r_1 k + \beta_2\beta_3\theta_3\mu\theta_4 - \beta_3\theta_3 k\Lambda\beta_2 + \alpha\beta_3{\theta_3}^2 k\Lambda + \alpha^2\theta_3^2\theta_4 k\Lambda + \beta_3{\theta_3}^2\theta_1 k - 2\alpha\theta_3 k\Lambda\beta_2\theta_4 + k\beta_2^2\theta_4\Lambda - k\beta_2\theta_1\theta_3\theta_4 + \alpha k\theta_1\theta_4{\theta_3}^2,$$

$$\Omega_5 = \alpha\mu\theta_3\theta_4 + k r_1\theta_3 + \mu\beta_3\theta_3 - \mu\beta_2\theta_4.$$

This equilibrium solution exists only when $S > 0, V_1 \geq 0, I_2 \geq 0, and\ I_3 \geq 0.$

$$S > 0 \qquad if \ \frac{\beta_2}{\alpha\theta_3} > 1,$$

$$V_1 \geq 0, I_3 \geq 0 \qquad if \ \frac{\beta_2}{\alpha\theta_3} \geq 1,$$

$$I_2 \geq 0 \qquad if \ \frac{\beta_3\theta_3}{\beta_2\theta_4} \geq 1.$$

4.3.2 Boundedness

The system trajectories are confined within a compact set. Consider

$$N(t) = S(t) + V_1(t) + I_1(t) + I_2(t) + I_3(t) + R(t)$$

Then

$$\frac{dN(t)}{dt}$$

$$= \Lambda - \left(\beta_1 I_1 + \frac{\beta_2 I_2}{1+\alpha S} + \beta_3 I_3 + \theta_1\right) S + r_1 S - (kI_3 + \mu)V_1 + \beta_1 I_1 S$$
$$- \theta_2 I_1 + \frac{\beta_2 I_2 S}{1+\alpha S} - \theta_3 I_2 + (kv_1 + \beta_3 S)I_3 - \theta_4 I_3 + \gamma_1 I_1 + \gamma_2 I_2$$
$$+ \gamma_3 I_3 - \mu R$$

$$= \Lambda - \mu(S + V_1 + I_1 + I_2 + I_3 + R) - v_1 I_1$$

$$\leq \Lambda - \mu N.$$

This implies

$$N(t) \leq \frac{\Lambda}{\mu} + ce^{-\mu t}.$$

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

4.3.3 Basic reproduction ratio (R_0)

R_0 is the number of new infections that are caused by a single infectious individual in a population where everyone is susceptible. Next generation matrix method is used here to obtain it

$$F = \begin{bmatrix} \beta_1 I_1 S \\ \dfrac{\beta_2 I_2 S}{1+\alpha S} \\ (kv_1 + \beta_3 S) I_3 \end{bmatrix}, \qquad V = \begin{bmatrix} \theta_2 I_1 \\ \theta_3 I_2 \\ \theta_4 I_3 \end{bmatrix},$$

It follows that

$$\partial F(E_1) = \begin{bmatrix} \beta_1 S_0 & 0 & 0 \\ 0 & \dfrac{\beta_2 S_0}{1+\alpha S_0} & 0 \\ 0 & 0 & kv_1 + \beta_3 S_0 \end{bmatrix}, \qquad \partial V(E_1) = \begin{bmatrix} \theta_2 & 0 & 0 \\ 0 & \theta_3 & 0 \\ 0 & 0 & \theta_4 \end{bmatrix},$$

$$\partial F(\partial V)^{-1} = \begin{bmatrix} \dfrac{\beta_1 S_0}{\theta_2} & 0 & 0 \\ 0 & \dfrac{\beta_2 S_0}{\theta_3(1+\alpha S_0)} & 0 \\ 0 & 0 & \dfrac{kv_1 + \beta_3 S_0}{\theta_4} \end{bmatrix},$$

$$R_1 = \frac{\beta_1 S_0}{\theta_2}, R_2 = \frac{\beta_2 S_0}{\theta_3(1+\alpha S_0)}, R_3 = \frac{kv_1 + \beta_3 S_0}{\theta_4}.$$

R_0 is the spectral radius of the matrix $\partial F(\partial V)^{-1}$. Therefore, $R_0 = max\{R_1, R_2, R_3\}$.

4.4 Stability Analysis

Global properties of the equilibria are studied in this section. Lyapunov function was used for the analysis.

Theorem 4.1. if $max\{R_1, R_2, R_3\} < 1$ and $\frac{r_1 S}{\mu V_1} \leq 1$, then the disease free equilibrium E_1 is globally asymptotically stable .

Proof. Lyapunov function of the following form is constructed

$$V(S, V_1, I_1, I_2, I_3) = g\left(\frac{S}{S_0}\right) + g\left(\frac{V_1}{V_{1,0}}\right) + I_1 + I_2 + I_3,$$

where $g(x) = x - 1 - lnx$. Since $I_1, I_2, I_3 > 0$.

We can easily see that $V(S, V_1, I_1, I_2, I_3) \geq 0$.

Now, we need to show $\dot{V} < 0$. Actually,

$$\dot{V} = \left(1 - \frac{S_0}{S}\right)\dot{S} + \left(1 - \frac{V_{1,0}}{V_1}\right)\dot{V}_1 + \dot{I}_1 + \dot{I}_2 + \dot{I}_3$$

$$= \left(1 - \frac{S_0}{S}\right)\left[\Lambda - \left(\beta_1 I_1 + \frac{\beta_2 I_2}{1 + \alpha S} + \beta_3 I_3 + \theta_1\right)S\right] + \left(1 - \frac{V_{1,0}}{V_1}\right)[r_1 S - (kI_3 + \mu)V_1]$$

$$+\beta_1 I_1 S - \theta_2 I_1 + \frac{\beta_2 I_2 S}{1 + \alpha S} - \theta_3 I_2 + (kv_1 + \beta_3 S)I_3 - \theta_4 I_3$$

$$= 2\theta_1 S_0 - \frac{\theta_1 {S_0}^2}{S} - \theta_1 S + (\beta_1 S_0 - \theta_2)I_1 + \left(\frac{\beta_2 S_0}{1 + \alpha S} - \theta_3\right)I_2$$

$$+ (kv_1 + \beta_3 S_0 - \theta_4)I_3 + r_1 S\left(1 - \frac{V_{1,0}}{V_1}\right) + (V_{1,0} - V_1)\mu$$

$$\leq \theta_1 S_0\left(2 - \frac{S_0}{S} - \frac{S}{S_0}\right) - \theta_2 I_1(1 - R_1) - \theta_3 I_2(1 - R_2) - \theta_4 I_3(1 - R_3)$$

$$- \mu(V_{1,0} - V_1)\left(1 - \frac{r_1 S}{\mu V_1}\right).$$

By the relation between arithmetic and geometric means $2 - \frac{S_0}{S} - \frac{S}{S_0} < 0$.

Theorem 4.2. If $R_1 \geq 1$, $max\{R_2, R_3\} < 1$ and $\frac{r_1 S}{\mu V_1} \leq 1$ then E_2 is globally asymptotically stable .

Proof. The following Lyapunov function is considered

$$V(S, V_1, I_1, I_2, I_3) = g\left(\frac{S}{S_1}\right) + g\left(\frac{V_1}{V_{1,1}}\right) + g\left(\frac{I_1}{I_{1,1}}\right) + I_2 + I_3,$$

where $g(x) = x - 1 - lnx$. Since $I_2, I_3 > 0$.

It can easily be seen that $V(S, V_1, I_1, I_2, I_3) \geq 0$.

Now, we need to show $\dot{V} < 0$. Really,

$$\dot{V} = \left(1 - \frac{S_1}{S}\right)\dot{S} + \left(1 - \frac{V_{1,1}}{V_1}\right)\dot{V_1} + \left(1 - \frac{I_{1,1}}{I_1}\right)\dot{I_1} + \dot{I_2} + \dot{I_3}$$

$$= 2\theta_1 S_1 - \frac{\theta_1 {S_1}^2}{S} - \theta_1 S + (\beta_1 S_1 - \theta_2) I_1 + \left(\frac{\beta_2 S_1}{1 + \alpha S} - \theta_3\right) I_2$$
$$+ (kv_1 + \beta_3 S_1 - \theta_4) I_3 + r_1 S\left(1 - \frac{V_{1,1}}{V_1}\right) + \left(V_{1,1} - V_1\right)\mu$$
$$+ I_{1,1}(\theta_2 - \beta_1 S_1).$$

Since $\beta_1 S_1 - \theta_2 = 0$,

$$\dot{V} \leq \theta_1 S_1 \left(2 - \frac{S_1}{S} - \frac{S}{S_1}\right) - \theta_2 I_{1,1}(R_1 - 1) - \theta_3 I_2(1 - R_2) - \theta_4 I_3(1 - R_3)$$
$$- \mu\left(V_{1,1} - V_1\right)\left(1 - \frac{r_1 S}{\mu V_1}\right),$$

$2 - \frac{S_1}{S} - \frac{S}{S_1} < 0$ by the relation between arithmetic and geometric means.

Theorem 4.3. If $R_2 \geq 1,\ max\{R_1, R_3\} < 1$ and $\frac{r_1 S}{\mu V_1} \leq 1$ then E_3 is globally asymptotically stable .

Proof. The Lyapunov function of the following form is considered

$$V(S, V_1, I_1, I_2, I_3) = g\left(\frac{S}{S_2}\right) + g\left(\frac{V_1}{V_{1,2}}\right) + I_1 + g\left(\frac{I_2}{I_{2,2}}\right) + I_3,$$

where $g(x) = x - 1 - lnx$. Since $I_1, I_3 > 0$.

It can easily be shown that $V(S, V_1, I_1, I_2, I_3) \geq 0$.

Now, we need to show $\dot{V} < 0$. Actually,

$$\dot{V} = \left(1 - \frac{S_2}{S}\right)\dot{S} + \left(1 - \frac{V_{1,2}}{V_1}\right)\dot{V}_1 + \left(1 - \frac{I_{2,2}}{I_2}\right)\dot{I}_2 + \dot{I}_1 + \dot{I}_3$$

$$= 2\theta_1 S_2 - \frac{\theta_1 {S_2}^2}{S} - \theta_1 S + (\beta_1 S_2 - \theta_2) I_1 + \left(\frac{\beta_2 S_2}{1 + \alpha S} - \theta_3\right) I_2$$
$$+ (k v_1 + \beta_3 S_2 - \theta_4) I_3 + r_1 S\left(1 - \frac{V_{1,2}}{V_1}\right) + (V_{1,2} - V_1)\mu$$
$$+ I_{2,2}\left(\theta_3 - \frac{\beta_2 S_2}{1 + \alpha S}\right)$$

Since $\frac{\beta_2 S_2}{1+\alpha S} - \theta_3 = 0$,

$$\dot{V} \leq \theta_1 S_2\left(2 - \frac{S_2}{S} - \frac{S}{S_2}\right) - \theta_2 I_1(1 - R_1) - \theta_3 I_{2,2}(R_2 - 1) - \theta_4 I_3(1 - R_3)$$
$$- \mu(V_{1,2} - V_1)\left(1 - \frac{r_1 S}{\mu V_1}\right),$$

$2 - \frac{S_2}{S} - \frac{S}{S_2} < 0$ by the relation between arithmetic and geometric means.

Theorem 4.4. If $R_3 \geq 1,\ max\{R_1, R_2\} < 1$ and $\frac{r_1 S}{\mu V_1} \leq 1$ then E_4 is globally asymptotically stable .

Proof. The following Lyapunov function is considered

$$V(S, V_1, I_1, I_2, I_3) = g\left(\frac{S}{S_3}\right) + g\left(\frac{V_1}{V_{1,3}}\right) + I_1 + I_2 + g\left(\frac{I_3}{I_{3,3}}\right),$$

where $g(x) = x - 1 - lnx$. Since $I_1, I_2 > 0$.

It can easily be seen that $V(S, V_1, I_1, I_2, I_3) \geq 0$.

Now, we need to show $\dot{V} < 0$.

$$\dot{V} = \left(1 - \frac{S_3}{S}\right)\dot{S} + \left(1 - \frac{V_{1,3}}{V_1}\right)\dot{V}_1 + \left(1 - \frac{I_{3,3}}{I_3}\right)\dot{I}_3 + \dot{I}_1 + \dot{I}_3$$

$$= 2\theta_1 S_3 - \frac{\theta_1 {S_3}^2}{S} - \theta_1 S + (\beta_1 S_3 - \theta_2) I_1 + \left(\frac{\beta_2 S_3}{1 + \alpha S} - \theta_3\right) I_2$$
$$+ (k v_1 + \beta_3 S_3 - \theta_4) I_3 + r_1 S\left(1 - \frac{V_{1,3}}{V_1}\right) + \left(V_{1,3} - V_1\right)\mu$$
$$+ I_{3,3}(\theta_4 - k v_1 + \beta_3 S_3)$$

Since $k v_1 + \beta_3 S_3 - \theta_4 = 0$,

$$\dot{V} \leq \theta_1 S_3\left(2 - \frac{S_3}{S} - \frac{S}{S_3}\right) - \theta_2 I_1(1 - R_1) - \theta_3 I_2(1 - R_2) - \theta_4 I_{3,3}(R_3 - 1)$$
$$- \mu\left(V_{1,3} - V_1\right)\left(1 - \frac{r_1 S}{\mu V_1}\right)$$

By the relation between arithmetic and geometric means $2 - \frac{S_3}{S} - \frac{S}{S_3} < 0$.

Theorem 4.5. If $min\{R_1, R_3\} \geq 1, R_2 < 1$ and $\frac{r_1 S}{\mu V_1} \leq 1$ then E_5 is globally asymptotically stable .

Proof. The following Lyapunov function is considered

$$V(S, V_1, I_1, I_2, I_3) = g\left(\frac{S}{S_4}\right) + g\left(\frac{V_1}{V_{1,4}}\right) + g\left(\frac{I_1}{I_{1,4}}\right) + I_2 + g\left(\frac{I_3}{I_{3,4}}\right)$$

where $g(x) = x - 1 - lnx$. Since $I_2 > 0$,

it can easily be seen that $V(S, V_1, I_1, I_2, I_3) \geq 0$.

Now, we need to show $\dot{V} < 0$.

$$\dot{V} = \left(1 - \frac{S_4}{S}\right)\dot{S} + \left(1 - \frac{V_{1,4}}{V_1}\right)\dot{V}_1 + \left(1 - \frac{I_{1,4}}{I_1}\right)\dot{I}_1 + \dot{I}_1 + \left(1 - \frac{I_{3,4}}{I_3}\right)\dot{I}_3$$

$$= 2\theta_1 S_4 - \frac{\theta_1 {S_4}^2}{S} - \theta_1 S + (\beta_1 S_4 - \theta_2)I_1 + \left(\frac{\beta_2 S_4}{1 + \alpha S} - \theta_3\right)I_2$$
$$+ (kv_1 + \beta_3 S_4 - \theta_4)I_3 + r_1 S\left(1 - \frac{V_{1,4}}{V_1}\right) + (V_{1,4} - V_1)\mu$$
$$+ I_{3,4}(\theta_4 - kv_1 + \beta_3 S_3) + I_{1,4}(\theta_2 - \beta_1 S_4)$$

Since $kv_1 + \beta_3 S_4 - \theta_4 = 0$, and $\beta_1 S_4 - \theta_2 = 0$

$$\dot{V} \leq \theta_1 S_4\left(2 - \frac{S_4}{S} - \frac{S}{S_4}\right) - \theta_2 I_{1,4}(R_1 - 1) - \theta_3 I_2(1 - R_2) - \theta_4 I_{3,4}(R_3 - 1)$$
$$- \mu(V_{1,4} - V_1)\left(1 - \frac{r_1 S}{\mu V_1}\right)$$

By the relation between arithmetic and geometric means $2 - \frac{S_4}{S} - \frac{S}{S_4} < 0$.

Theorem 4.6. If $min\{R_2, R_3\} \geq 1, R_1 < 1$ and $\frac{r_1 S}{\mu V_1} \leq 1$ then E_6 is globally asymptotically stable .

Proof. The following Lyapunov function is considered

$$V(S, V_1, I_1, I_2, I_3) = g\left(\frac{S}{S_5}\right) + g\left(\frac{V_1}{V_{1,5}}\right) + I_1 + g\left(\frac{I_2}{I_{2,5}}\right) + g\left(\frac{I_3}{I_{3,5}}\right),$$

where $g(x) = x - 1 - lnx$. Since $I_1 > 0$, It can easily be seen that, $V(S, V_1, I_1, I_2, I_3) \geq 0$.

Now, we need to show $\dot{V} < 0$. Really,

$$\dot{V} = \left(1 - \frac{S_5}{S}\right)\dot{S} + \left(1 - \frac{V_{1,5}}{V_1}\right)\dot{V}_1 + \left(1 - \frac{I_{1,5}}{I_1}\right)\dot{I}_1 + \dot{I}_1 + \left(1 - \frac{I_{3,5}}{I_3}\right)\dot{I}_3$$

$$= 2\theta_1 S_5 - \frac{\theta_1 {S_5}^2}{S} - \theta_1 S + (\beta_1 S_5 - \theta_2)I_1 + \left(\frac{\beta_2 S_5}{1 + \alpha S} - \theta_3\right)I_2$$
$$+ (kv_1 + \beta_3 S_5 - \theta_4)I_3 + r_1 S\left(1 - \frac{V_{1,5}}{V_1}\right) + (V_{1,5} - V_1)\mu$$
$$+ I_{3,5}(\theta_4 - kv_1 + \beta_3 S_3) + I_{2,5}\left(\theta_3 - \frac{\beta_2 S_5}{1 + \alpha S}\right).$$

Since $kv_1 + \beta_3 S_5 - \theta_4 = 0$, and $\frac{\beta_2 S_5}{1+\alpha S} - \theta_3 = 0$, we have that

$$\dot{V} \leq \theta_1 S_5\left(2 - \frac{S_5}{S} - \frac{S}{S_5}\right) - \theta_2 I_1(1 - R_1) - \theta_3 I_{2,5}(R_2 - 1) - \theta_4 I_{3,5}(R_3 - 1)$$
$$- \mu(V_{1,5} - V_1)\left(1 - \frac{r_1 S}{\mu V_1}\right).$$

By the relation between arithmetic and geometric means $2 - \frac{S_5}{S} - \frac{S}{S_5} < 0$.

4.5 Discussion, Conclusion, and Numerical Simulations

In this section, dynamics of three strains influenza model is studied. We obtained the following six equilibrium points;

E_1: disease free equilibrium, I_1, I_2, and I_3 are both zero.

E_2: endemic equilibrium for I_1 only, I_2 and I_3 are both zero.

E_3: endemic equilibrium for I_2 only, I_1 and I_3 are both zero.

E_4: endemic equilibrium for I_3 only, I_1 and I_2 are both zero.

E_5: coexistence of I_1 and I_3, I_2 is zero.

E_6: coexistence of I_2 and I_3, I_1 is zero.

It can be observed that, coexistence of I_1 and I_2 is not possible. This is because as soon as any strain has basic reproduction ratio greater than 1, it will surpass the other, thereby eradicating it. Though, the coexistence of the three strains can't be shown analytically but we show and analyze it numerically.

We also used next generation matrix method to obtain three threshold quantities R_1, R_2, and R_3 called the basic reproduction ratios for strain 1, 2, and 3 respectively. It was shown that the stability of each of the equilibrium solution depends on the magnitude of these threshold quantities. Lyapunov function was used to show the global stability of the equilibria. When $\max\{R_1, R_2, R_3\} < 1$ the disease free equilibrium is globally asymptotically stable and the disease dies out. It was also shown that the disease equilibriums are globally asymptotically stable when the respective strains have a basic reproduction ratio greater than unity.

Numerical analysis were conducted to investigate coexistence of the three strains, and to analyze the effect of vaccine for strain 1 and awareness of strain 2 on the dynamics of strain 3. The results are as follows;

Figure 4.2. There is vaccine for strain 1 and awareness of strain 2. Strain 1 and 2 die out and the population of people with strain 3 disease is about 4000.

Figure 4.3. Vaccine for strain 1 is available, so it dies out. Strain 2 and 3 persist and the population of people with strain 3 diseases is about 2500.

Figure 4.4. There is awareness for strain 2 only. Strain 2 dies out, strain 1 and 3 persist and the population of people with strain 3 diseases is about 3000.

Figure 4.5. There is neither vaccine for strain 1 nor awareness of strain 2. Both strains persist and the population of people with strain 3 diseases is around 2000.

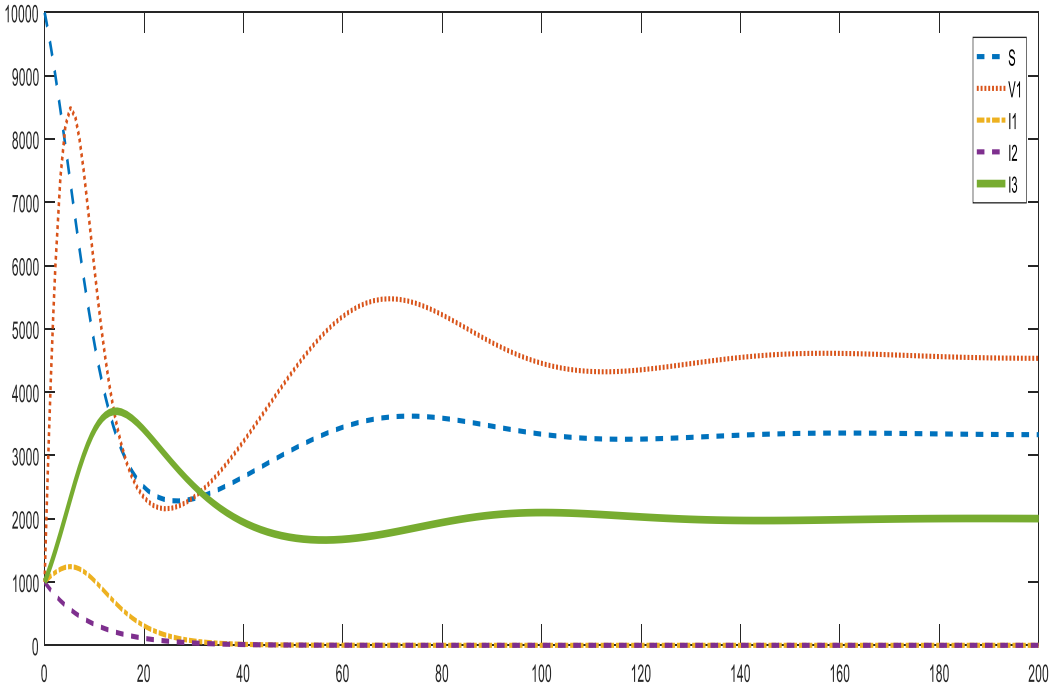

Figure 4.2: Vaccine for strain1 and awareness of strain2 are present: Parameter values; $\beta_1 = 0.00003, \beta_2 = 0.00003, \beta_3 = 0.00003, \Lambda = 200, r_1 = 0.3, \theta_1 = 0.32, \theta_2 = 0.22, \theta_3 = 0.11, \theta_4 = 0.10, k_1 = 0.0001, \mu = 0.02, v_1 = 0.1, \alpha = 0.7$

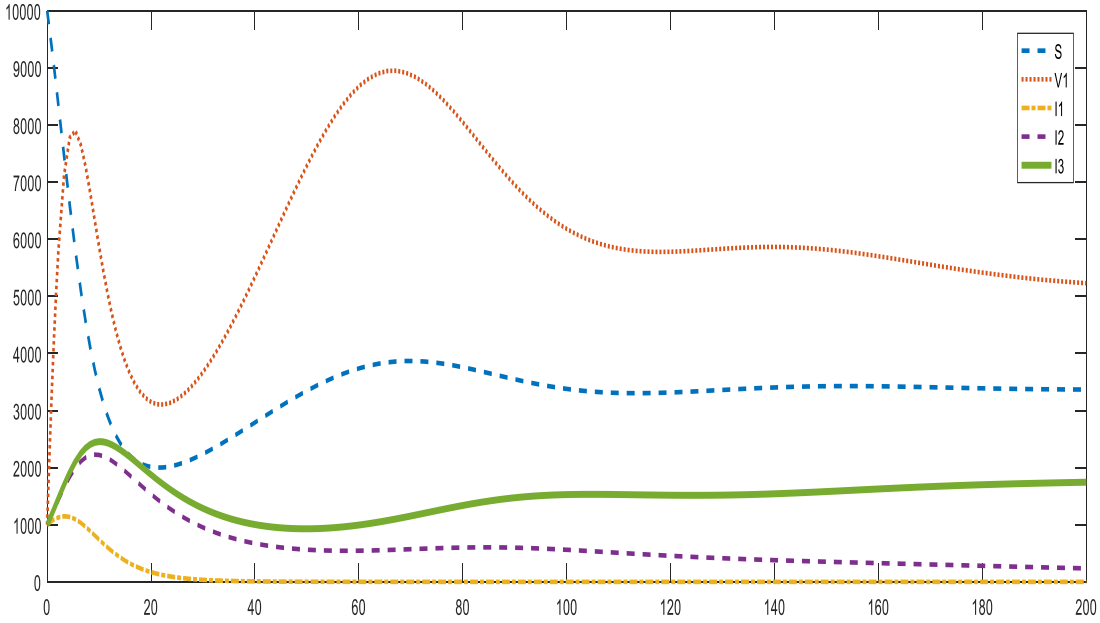

Figure 4.3: Presence of vaccine for strain1 only: Parameter values; $\Lambda = 200,\ \beta_1 = 0.00003, \beta_2 = 0.00003, \beta_3 = 0.00003, r_1 = 0.3,\ \theta_1 = 0.32, \theta_2 = 0.12, \theta_3 = 0.11, \theta_4 = 0.10,\ k_1 = 0.0001, \mu = 0.02, v_1 = 0.1, \alpha = 0.$

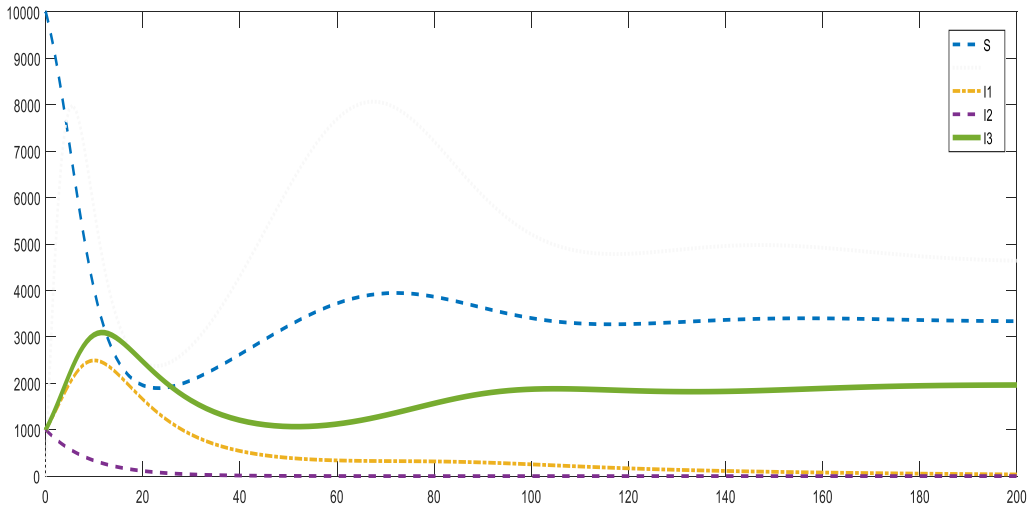

Figure 4.4: Awareness for strain2 only is present: Parameter values; $\Lambda = 200,\ \beta_1 = 0.00003, \beta_2 = 0.00003, \beta_3 = 0.00003, r_1 = 0.3,\ \theta_1 = 0.32, \theta_2 = 0.22, \theta_3 = 0.11, \theta_4 = 0.10,\ k_1 = 0.0001, \mu = 0.02, v_1 = 0, \alpha = 0.7.$

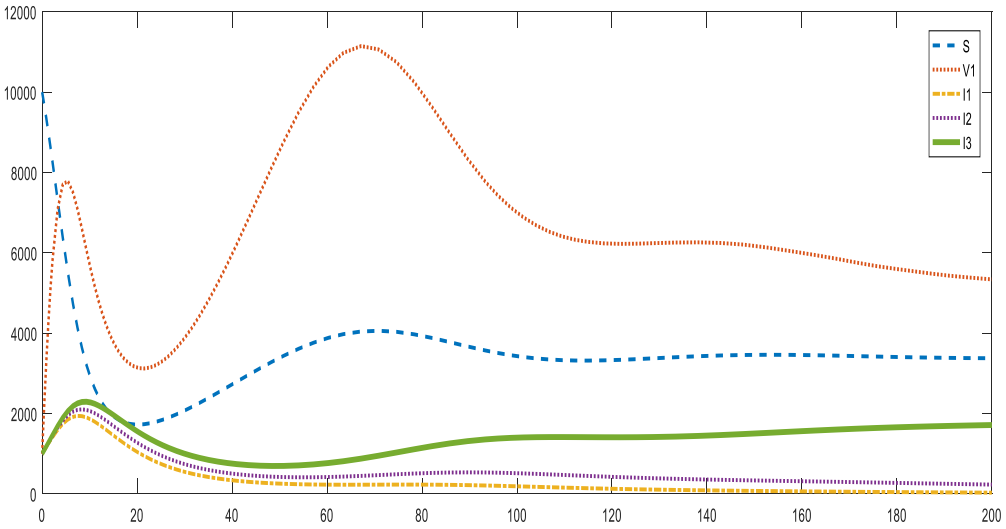

Figure 4.5: No effect of vaccine or awareness: Parameter values; $\Lambda = 200,\ \beta_1 = 0.00003, \beta_2 = 0.00003, \beta_3 = 0.00003, r_1 = 0.3,\ \theta_1 = 0.32, \theta_2 = 0.12, \theta_3 = 0.11, \theta_4 = 0.1\quad k_1 = 0.0001, \mu = 0.02, v_1 = 0, \alpha = 0.$

M. E. Alexander constructed and studied a model with vaccination for influenza transmission dynamics (Alexander et al., 2004). They show that if combining vaccine effectiveness and vaccination rate reaches a certain threshold then the disease will automatically be controlled.. S.M. Ashrafur Rahman and Xingfu Zou (Ashrafur Rahman and Xingfu, 2010) proposed a two strain model that investigated the effect of vaccine for strain one on the dynamics of second strain.

In our case we studied three strains in which there is vaccine for strain 1, awareness for strain 2, and neither vaccine nor awareness for strain 3. It can be observed that although vaccine curtail the spread of strain 1, awareness curtail the spread of strain 2, but they both have negative effect on strain 3. The population of people living with strain 3, increases from 2000 when there is neither vaccine for strain 1 nor awareness of strain 2, to 2500 when there is only awareness of strain 2, to 3000 when there is only vaccine for strain 1 and to 4000 when there is both vaccine for strain 1 and awareness of strain 2. This result is in agreement with the result obtained by T. Cohen et al. (Coheren et al., 2008), M. Martcheva et al. (Martcheva et al., 2007), and P.P. Ewan et al. (Ewan et al., 2017).

This tells the relevant authorities whenever there is influenza epidemic to investigate thoroughly the possibilities of the existence of multiple strains, so as to provide vaccines and enough awareness on all the strains present. There is also need for more studies on this issue possibly related to the complication of spatial epidemics. This will help in providing useful understanding into disease determent and control.

CHAPTER 5

CONCLUSION

In conclusion, in this thesis we studied three models about influenza. Both models considered multiple strains of influenza in which one strain have incidence rate different from the other. The first model has two strains in which one has bilinear incidence rate and the other non – monotone incidence rate. The second model is the first application of the first model where we considered the problem of resistance. In the second model we also considered two strains where one strain is the resistance strain attributed with bilinear incidence rate and the other is non – resistance strain attributed with saturated incidence rate. The third model is the second application of the first model where we considered three strains of influenza (I_1, I_2, and I_3). Here, we have vaccine for strain1 (V_1) only, and population has enough awareness of strain 2. There is neither vaccine nor awareness for strain 3. Our main aim is to mathematically analyze the effect of the vaccine for strain 1 and awareness of strain 2 on the dynamics of strain 3.

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WORK EXPERIENCE

Year	Place	Enrollment
2017 – present	Department of Mathematics	Lecturer
2012 – 2017	Department of Mathematics	Teaching Assistant
2006 – 2011	Department of Mathematics	Teacher

FOREIGN LANGUAGES

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PUBLICATIONS IN INTERNATIONAL REFEREED JOURNALS (IN COVERAGE OF SSCI AND SCI – EXPANDED):

- Baba, IA., Kaymakamzade, B., & Hincal, E. (2018). Two – strain Epidemic Model with Two Vaccinations. *Chaos, Solitons & Fractals*, 107, 15 – 21
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PUBLICATIONS IN INTERNATIONAL REFEREED JOURNALS (IN COVERAGE OF WEB OF SCIENCE AND SCOPUS):

- Kademi, HI., Baba, IA.& Saad, FT. (2017). Modelling the dynamics of toxicity associated with aflatoxins in foods and feeds . *Toxicology Reports* 4, 358 – 363
- Baba, IA.& Saad, FT. (2017). Global stability analysis of three strain influenza virus model. *Far East Journal of Mathematics* (Accepted)

BULLETIN PRESENTED IN INTERNATIONAL ACADEMIC MEETINGS AND PUBLISHED IN PROCEEDING BOOKS:

- Kaymakamzade, B., Baba, IA. & Hincal E. (2016). Global stability analysis of oseltamivir–resistant influenza virus model . 12th International Conference on

Application of Fuzzy Systems and Soft Computing, ICAFS 2016, 29-30 August 2016, Vienna, Austria. *Procedia Computer Science* 102 (2016) 333 – 341

THESIS

Master

- Baba, I.A. (2014). Unconstrained Optimization and Nonlinear Systems of Equations Review and Analysis Using Excel. Unpublished Master Thesis, Near East University, Faculty of Arts and Sciences, Nicosia, Cyprus

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