Mathematical Modeling on Control of Infectious Diseases and its Impact on Population Dynamics

Thesis

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Declaration of Authorship

I, hereby declare that the presented work in the thesis entitled "Mathematical Modeling on Control of Infectious Diseases and its Impact on Population Dynamics" in fulfilment of degree of **Doctor of Philosophy (Ph. D.)** is outcome of research work carried out by me under the supervision of Dr. Preety Kalra, working as Associate Professor, in the Department of Mathematics at School of Chemical Engineering and Physical Sciences of Lovely Professional University, Punjab, India. In keeping with general practice of reporting scientific observations, due acknowledgements have been made whenever work described here has been based on findings of other investigator. This work has not been submitted in part or full to any other University or Institute for the award of any degree.

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Certificate

This is to certify that work reported in the Ph.D thesis entitled "Mathematical Modeling on Control of Infectious Diseases and its Impact on Population Dynamics" submitted in fulfillment of the requirement for the reward of degree of **Doctor of Philosophy, (Ph.D)**, in Mathematics, is a research work carried out by Indu Ratti (41700268), is a bonafide record of her original work carried out under my guidance and supervision and no part of this thesis has ever been submitted for any other degree, diploma or equivalent course.

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Abstract

In the proposed work, the study carried out involves infectious diseases. Inspite of advancement in the field of medicine till date, infectious diseases still play havoc to large population around the world. So, in this work, the transmission of contagious/infectious disease, the factors affecting that transmission and measures to control the spread of these infectious diseases will be studied. The system is then formulated and analyzed, setting the borders by defining major components involved, characterising the variation in the form of mathematical equations and then interrelating the respective equations to form the model of system under study. For the study, the formation of dynamic mathematical model is done by fabricating differential (ordinary) equations which then help in prediction of the changes resulting in interrelated attributes of the system. The disease dynamics is modelled by taking factors such as transmission, transition, treatment, preventive measures, control measures etc. into consideration and then these disease models are used to prognosticate the efforts of prevention, treatment, awareness and latent/incubation period of the disease on the spread of the infection. Once the model is formulated, it will be analyzed for stability, bifurcation and persistence of system. Sensitivity analysis will be done by estimating sensitivity of model parameters with respect to state variables. The results will be demonstrated analytically and using graphs with the help of software like MATLAB.

The outcome of the proposed work will help us in predicting the disease dynamics based on the eigenvalues and the threshold parameter, that is, basic reproduction number. It will help epidemiologists and health care workers to predict if there will be epidemic or the disease dies out in the population. In case of outbreak, control strategies like isolation, vaccination, prevention, treatment etc. can be planned depending upon the disease.

The objectives of this research work includes the study of:

1. Mathematical modeling on control of communicable/infectious diseases and their effect on single population.

2. Mathematical modeling on control of communicable/infectious diseases and their effect on two species.

3. Mathematical modeling on control of co-infectious diseases.

4. Mathematical modeling on communicable/infectious disease including delay in its control.

In chapter 1, general introduction to infectious diseases is given. Their dynamics, how they propagate, through which medium they travel, how they spread in population, factors affecting the transmission like temperature, season, travel history, geographical conditions, human behaviour etc. are discussed. In this view, it is required to take some preventive measures like usage of insecticide to control the transmission in case of vector-borne disease, awareness about the disease, treatment, vaccination etc. to eliminate or reduce the amplitude of the infection. The research work done in the field by some noteworthy researchers till date has been discussed. In the view of this literature review, the research gaps have been identified leading to the formation of objectives of the study. The terms used in the work, mathematical preliminaries in the study have been described in this chapter. The chapter has been concluded with summary of all the chapters embodied in the work.

In chapter 2, vector borne infectious disease yellow fever has been taken for study. A non-linear vector-host compartmental model having variables as susceptible population, protective class taking preventive measures having temporary protection, infected class and recovered class for humans have been taken. For mosquitoes, separate compartments for susceptible and infected mosquitoes have been taken into consideration. The effect of insect repellent and vaccination of humans are introduced as control measures. Through numerical simulation and sensitivity analysis, it has been shown that if the threshold value of basic reproduction number is monitored, the disease can be controlled with the help of various control

parameters. The results obtained have been validated with the statistical and mathematical work done previously in the field.

In chapter 3, the infectious disease yellow fever has been taken to study the effect of awareness programmes conducted through media to make human population aware and control of vector population through usage of pesticide by proposing a compartmental model for the yellow fever. It is shown that aware population makes effort which results in controlling the disease. Moreover, the usage of insecticide also help in decreasing vector/mosquito population. Stability analysis and calculation of R_0 has been performed. It is further observed that awareness programmes have high impact on spread of disease. The results obtained analytically are further supported by numerical simulation.

In the same chapter, the infectious disease chikungunya is taken under study. A non-linear compartmental model is proposed and is studied for the effects of control measures on both human and mosquitoes. The control measures taken are mainly preventive strategies, usage of insecticide and vaccination. Results of stability analysis and simulation part shows that under the effect of insect repellent cream/sprays along with vaccination for humans, the dosage of insecticide can be minimized to large extent for mosquitoes. It has been observed that the value of insecticide ($q = 0.01$) is sufficient to contain the disease as compared to the value of insecticide used by authors in [1] where the value of q is in the range 0.2 to 0.7. Also, the value of threshold parameter R_0 has been calculated.

In chapter 4, the co-infection of two diseases namely malaria and rotavirus has been studied. In this chapter, the effects of malaria treatment, rotavirus treatment, treatment of co-infection along with role of insecticide has been studied. From the numerical simulation, it has been observed that co-infection decreases sharply if we apply all the treatments and it takes longer if the individual treatments are applied. The value of basic reproduction number of rotavirus-only model and malaria-only model is evaluated which resulted in the calculation of basic reproduction number for the main co-infection model. To understand the dynamics of co-infection, the stability analysis for infection-free equilibrium and

basic reproduction number is evaluated. Bifurcation analysis is performed for full co-infection model along with that of malaria model. Both malaria model and rotavirus model are found to be globally asymptotically stable. Sensitivity indices have been calculated to visualise the influence of parameters used in the model on the basic reproduction number. Results are illustrated with numerical simulation.
In chapter 5, a non-linear SEIR delay model is formulated by incorporating the incubation period of an infectious disease as delay in the model. The analysis is performed to check the stability at disease-free and endemic equilibrium. The critical value of delay parameter (τ) has been calculated and further it was observed that endemic equilibrium is stable if this value is less than the critical value calculated and system undergoes hopf-bifurcation if the value is greater than the critical value. It has been also observed through numerical simulation that transmission rate plays a significant role in dynamics of the disease. Since, incubation period is very important factor associated with dynamics of disease. It is worth calculating to control the disease. The critical value of τ is found to be 19.5 days. This work has been supported by [2] in which the value of incubation period of a virus named hantavirus is $7 - 39$ days with median value 18 days. This has also been validated as the incubation period of an infection named listeriosis may vary from $3 - 70$ days [3]. In the present work, it is being observed that as the value of incubation period (τ) is increased from 19.4 to 19.7 while assuming all other parameters involved in the model fixed, this system looses the stability transforming stable solutions to oscillatory solutions.
In the end, the problems taken under study have been well grounded by bibliography in the concluding part of the thesis.

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List of Abbreviations and Notations

WHO	World Health Organisation
YF	Yellow Fever
CHIKV	Chikungunya Virus
RV Infection	Rotavirus Infection
COVID-19	CoronaVirus Disease 2019
R_0	Basic Reproduction Number
YEL-AVD	Yellow Fever Vaccine-Associated Viscerotropic Disease
IPCC	Intergovernmental Panel on Climate Change
LAS	Local Asymptotic Stability
GAS	Global Asymptotic Stability

Chapter 1

General Introduction

1.1 Introduction

Infectious diseases have always threatened and invaded human populations. Apart from the loss of human lives, they create a big burden on the economy of the country in the sense of money, medical facilities, equipment for treatment and human efforts. Looking back in history of these diseases, poor sanitation, inaccessibility of preventive control measures in time, the level of interaction of human population with the pathogen, geographical area, weather etc. are some of the factors on which blame of an epidemic can be put on. However, many of the diseases still exists and spread inspite of taking precautions. Study of factors that determine the frequency and influence of a disease or other health related problems, their cause, formulation of preventive strategies, establishing programmes in a defined human population is known as epidemiology. It can be categorized as descriptive epidemiology and analytic epidemiology. The first one is the stage in which the disease occurred is examined by taking into account the time, place where it has occurred and symptoms of the person affected are considered. Hypothesis regarding the cause of disease are made in this stage. In the second one, the hypothesis made above are tested. Further, the diseases can be categorized in two groups: communicable diseases and non-communicable diseases. Communicable disease are those diseases which pass from one person to another by direct transmission or indirect transmission and

can be caused by bacteria, fungus, yeast, viruses and parasites. These infectious/-communicable diseases can spread through water, air and direct/indirect contact. For example Syphilis, Gonorrhea, AIDS are sexually transmitted diseases. Nosocomial infections, Rhinovirus cold, Brucellosis (slaughter house contact), Hepatitis B virus are few examples of infections by contact. Cholera, Giardiasis, Listeriosis, Campylobacter are few examples of food/water borne infections. Airborne infections can give rise to Tuberculosis, Influenza, Measles, Mumps, Rubella, Pertussis (childhood disease), Para influenza and many more types of diseases. Some vector borne infections are malaria, Dengue, Yellow Fever, Rocky mountain spotted fever and other. The infectious diseases can be transmitted through human, animal, soil and water reservoirs. AIDS, Syphilis, Shigellosis, herpes simplex virus take human as reservoirs. Rabies, Plague, Anthrax etc. are examples of diseases with animals as reservoirs. Tetanus, Botulism, Histoplasmosis travel through soil as reservoir. Some infections with water as reservoir are UTI, hot tub folliculitis etc. The other category of disease is non-communicable which is also known as chronic. To begin with, cardiovascular diseases, non-infectious diseases of respiratory track, diabetes, cancer are four types of non-communicable diseases. It is known fact that unhealthy diet, smoking, lack of exercise and abuse of alcohol are few important causes of this type of diseases. Further, cervical cancer is a communicable disease caused by human papilloma virus which conveys that there is a thin line separating communicable and non-communicable diseases. Communicable disease or infectious disease have been important part of history because there were epidemics that have attacked population, causing deaths very often, then disappearing to re-occur after certain times, possibly in decreasing severity as people develop immunity against them. For example, black deaths (bubonic plague) in fourteenth century propagated in many waves from Asia to Europe and almost one third of population died. Also, there are many diseases which become endemic causing many deaths. For example, in developing countries, diseases like measles, diarrhea, respiratory infections and many other which claim millions of people. Diseases like cholera, dengue, malaria are endemic in several parts of

world. Therefore, the impact of high mortality with effect on average life period and disease burden on financial state of countries is a serious issue. In Europe, bubonic plague claimed 2.5 million people out of 100 million in fourteenth century. In 1520, the Aztecs lost half of their population to small pox. Looking at the brighter side, in 1980, $2,600,000$ deaths reduced to $160,000$ in 2011 due to measles vaccine [4]. It has been observed that despite decrease in mortality, the frequency and magnitude of these diseases is increasing. The aim of studying infectious disease through mathematical modeling is to control and eradicate the infection from the given population by knowing and understanding the disease dynamics. There may be many factors associated with disease transmission like human behaviour, temperature, geographical conditions, contact rate of susceptible with infective, availability of control measures like vaccination and their frequency. The growth of these diseases within an individual commonly known as individual-level dynamics and their propagation in population, that is, population scale epidemic require different types of interventions. To study population level dynamics, two parameters are required. The first one is the basic reproduction number. It is the average number of secondary infections from an individual in a naive population. The second one is the time duration of infection which is infectious period and exposed time period in SEIR models. It has been observed that the above two factors have huge variability in epidemiological modeling. For example, childhood diseases like rubella, measles or chickenpox have very high R_0 (basic reproduction number). Further, it was found that in 1945 to 1965, the value of R_0 is ≈ 17 for cough (whooping) and measles in Wales and England with period of infection being small (less than one month). In contrast, for HIV cases in United Kingdom R_0 is ≈ 4 for homosexual population and R_0 is ≈ 11 for female prostitutes in Kenya and period of infection is lifelong [5].

The pioneer of study of infectious disease was John Graunt, who analyzed various causes of deaths. To start with, the initial model in mathematical epidemiology was contributed by Daniel Bernoulli $(1700 - 1782)$ which was inoculation against small pox. Again in 1855, John Snow gave the knowledge that disease like cholera

is transmitted by water. Furthermore, in 1873, William Budd explained the transmission of disease with compartmental modeling which was further explained by Sir R.A. Ross, Mechandrick, Kermack and Hamer in 1902 in which Ross demonstrated the dynamics of malaria transmission through compartmental modeling. The classic Kermack-McKendrick model [6] is explained as:

Here, the total population N is assumed to be constant approximately. The population is divided in groups or compartments namely susceptible, infected and recovered or immune compartments. They are denoted by S, I and R. The susceptible class is one who can catch infection, infected class contracts infection and transmits it and recovered class is one who recovers/gets immune. This progress of infection can be represented in the form:

$$S \to I \to R$$

In the model given below, the input in the infected class is proportional to the number of susceptible as well as infected persons, that is, rSI, r being the rate. The rate of transfer of infected individuals to the recovered compartment is a, which contributes the term aI in the recovered class. Here, it is assumed that all the pair of individuals have equal chance of mixing together. Also, it is supposed that the incubation period of disease is insignificant, that is, the person who catches infection becomes infective immediately. With these assumptions the model is presented in the form of equations.

$$\begin{aligned} \dot{S(t)} &= -rSI \\ \dot{I(t)} &= rSI - aI \\ \dot{R(t)} &= aI \end{aligned}$$

Here S, I and R are bounded by N as $S(t) + I(t) + R(t) = N$ and the initial conditions are $S(0) = S_0 > 0, I(0) = I_0 > 0$ and $R(0) = 0$.

It is important to note that the number of compartments depends upon the disease under study. For example, in SI models, there are only two compartments,

susceptible and infected whereas $SEIR$ models have one extra class, that is, latent class. Similarly, depending upon the problem under study there can be various classes like vaccinated class, aware class, protected class, quarantined class etc.

This development of compartmental modeling for infectious disease helped mathematicians and health professionals in different ways as their goals being better understanding of disease transmission and practical procedures for management of disease. Taking this work to the next level, the idea of disease transmission and further its spread was explained only in twentieth century with a mathematical model of non-linear differential equations for dynamics of infectious disease [7]. There were hundreds of outbreaks in animals as well as humans that have been reported in the last two centuries among them the most numerous are dengue ([8], [9]), cholera [10], malaria, SARS, measles [11–14], rotavirus, yellow fever [15], small pox [16], COVID-19 [17] and various food borne and airborne outbreaks and many more [18–22]. Yellow fever being an old disease was considered to have been controlled in mid 1900s by vaccination but it returned ([23], [24]). For example, chikungunya has a long history of transmission in Sub-Saharan Africa and then it re-occurred in America in 2013. Similarly, rotavirus infection has claimed so many young children in developing countries as compared to the countries where mortality rate are low.

A lot of work has been done in the fields of various diseases by different researchers. Most work has been done in the field of control measures of the infectious diseases but still there is scope to study many infectious diseases for the control strategies. In this work, we will mainly focus on control measures for the infectious diseases like yellow fever, chikungunya, co-infection of rotavirus and malaria.

1.2 Review of Literature

The history of the infectious diseases is highly affected by the accomplishments of the mankind. They are the second leading cause of mortality worldwide [25]. The emergence and reemergence of these diseases have high impact globally. Many of

these diseases like malaria, HIV/AIDS, dengue etc. have become endemic in many parts of the world. This shifts our focus on the prevention of these diseases, challenges of vaccines for them, economic challenges, scientific challenges and many more to mention. Inspite of conquered many of them, we are working hard in many fields to have proper command over them. There are fields where various treatments, vaccines, therapies have been successful but still there are many where we are striving hard. In the present work, we will be working on the control strategies of these infectious diseases in which there is still scope for advancements by taking examples of some of these diseases like yellow fever, chikungunya, the co-infection of diseases etc.

Yellow fever is a vector borne disease caused by biting of mosquito species named *Aedes aegypti*. This is a life threatening disease which is endemic in many parts of the world. It is transmitted through a virus to humans through mosquitoes. Regarding its epidemiology, it occurs in tropical Southern America, Sub-Saharan Africa where it is otherwise endemic and intermittently epidemic. The first outbreak of yellow fever occurred in 1647 in Islands of Caribbean and afterwards at least 25 major cities in America. In 1793, more than 9% of total population died in Philadelphia. In 1878, epidemic in Mississippi river valley claimed $20,000$ people approximately [26]. The risk of acquiring yellow fever can be related to several factors like status of vaccination, location travelled, temperature, season, time period of exposure to virus, activities during travel and rate of virus transmission. Researchers like Inwang started working on control through mathematical modeling. In the work, mathematical formulae for two things were established one out of which is resistance potential of mosquitoes/insects to DDT with target of $80\% - 90\%$ mortality. Second was the number of generations which must be subjected to insecticide to attain DDT resistance for *Aedes aegypti* [27]. Taking the work further, a model to control *Aedes aegypti* mosquito by the method of sterile insect technique was introduced by Esteva et al. It is a method in which normal insects/mosquitoes are radiated with gamma rays to make them sterile. These sterile insects when released in normal environment mate with normal females to

produce eggs that do not hatch, thus making that native population extinct. The sterile male technique was used in 1958 in Florida and was successful. It was observed that effectiveness of SIT depends on two factors, one is mating competitiveness of sterile mates and the other is to make sure that sterile mosquitoes are dispersed near breeding site, so that they can have fair chance of mating. It was observed that SIT will be effective depending upon the ratio of sterile mosquitoes release, displacement of natural mosquitos in the environment and effect of immigration of females who already have laid fertile eggs and nullified the sterile releases [28]. This study of yellow fever was taken to another level by observing the temperature dependence of mosquitoes and incubation period of the virus in them. Also, distributions of incubation period is quantitatively studied with the help of four models statistically using historic data. It has been estimated that extrinsic incubation period for urban vector *Aedes aegypti* at 25 degree has median value 10 days and intrinsic incubation period has a median value 4.3 days [29]. Further, it was noticed that the first outbreak of yellow fever after 1942 in South America in metropolitan Asuncion, Paraguay resulted in nine confirmed cases. Stochastic modeling and probabilistic modeling was done and value of R_0 was calculated considering various factors. It was found through simulation, that in this outbreak in 2008, there were 12.8% local outbreaks and 2% international spread through airline travellers. Also, the calculation of probabilities of introduction of YF epidemic and autochthonous transmission was done by considering factors like rates of travel, number of persons infected, values of R_0 and vaccination coverage rates [30].

Furthermore, it was observed that yellow fever has been largely controlled by widespread vaccination programmes in which a live attenuated vaccine is administered in single shot [26]. The only vaccine available for YF is live attenuated vaccine in 17 D lineage, which is mainly used to protect not only population in endemic areas but also persons travelling to those areas. But the occurrence of YF-17 D vaccine-associated viscerotropic disease (YEL-AVD) questioned the safety of

YF vaccine. As, it was being observed that there is dominance of YEL-AVD infections in young females and persons who are susceptible to YEL-AVD depending on the genetic setup or defect in immunity. Further, it was found that persons aged 60 years and above are at higher risks of SAEs (Serious adverse events) to YF 17 D and 17 DD vaccines. In Africa, it was observed that wild type YF infections are more prevalent than risk of adverse events. One interesting thing observed was that, in Africa, the risk of YF infection during epidemic is more than the risk of vaccine injury, where as, in contrast to that in Southern part of America, the risk of having YF during travel is almost the same or little higher than vaccine related risk. It was suggested that some safer alternative to 17 D vaccine should be there for travellers and population groups [31]. Taking the research forward, SAGE working group worked on many factors like need of booster dose against yellow fever after every 10 years, vaccine safety in elderly people with age more than 60 years, vaccine safety in HIV infected persons and in persons with other immune compromising situations, pregnant women, lactating women, whether the injection can be co-administered with other vaccines, routine vaccination and epidemic outbreak strategies ([32], [33]). Further, the estimate of disease burden in Africa was estimated by Garske et al. by taking various factors into account like the number of infections per year in any province, the force of infection, population and vaccination coverage in that area. It was ascertained that the factors affecting the estimates regarding burden of disease are uncertainty in demographic data, uncertainty regarding spatial distribution of yellow fever, its occurrence in different countries [34]. Furthermore, the yellow fever vaccination outbreak in Sao Paulo, Brazil in 2009 was studied by Ribeiro et al. It was observed that at the time of outbreak one million people were vaccinated which resulted in 11 deaths due to vaccine-induction and there were 28 yellow fever cases reported in outbreak. Their work helped by finding the areas to be vaccinated and proportion of people to be vaccinated in order to minimize the deaths. They updated the literature by working on vaccination strategy to minimize the number of vaccine induced mortality [35]. Further, taking the research to next level, Bonin et al. worked on

immune response to vaccine of yellow fever [36]. Also, Sakamoto et al. explored that the risk of yellow fever in travellers visiting Brazil is increased by importing the infection of yellow fever to different international destinations. It was found that in June 2018, death of 394 persons and 1257 confirmed cases were reported after the outbreak. Also, the calculation of relative risk of travellers visiting Brazil concluded that they are at 2.1-3.4 times high risk as compared to others. The countries with lower GDP per capita than countries at better financial status are at $2.5 - 2.8$ times higher risk of importing infection. To prevent the spread, it was advised that the travellers should be well informed about the area of infection transmission. In addition, it was suggested that if they cannot avoid going to these destination, then prior vaccination should be strongly advised to prevent infection [37]. Working further in the field was estimation of number of Chinese worker who were not vaccinated against yellow fever during outbreak in Angola in 2016 and it was observed that $25,900$ Chinese workers in Angola were not vaccinated despite yellow fever immunization made mandatory by International Health Regulatory bodies. Their results about the documented record of 11 Chinese workers who imported the infection of yellow fever to their home land China were in agreement with each other. It was suggested that yellow fever vaccination should be ensured to the persons travelling to infected areas in order to prevent the international expansion of disease. Border controls should be tightened and proof of yellow fever vaccine should be produced on arrival from yellow fever endemic countries [38].

The next infectious disease under study is chikungunya. Chikungunya is a vector borne viral disease spread from human to human by mosquito *Aedes albopictus* also known as Asian tiger. The main symptoms of disease are joint pains, wrist pains etc. This virus was firstly identified in 1953 [39]. Firstly, it was considered as a tropical disease but now the disease poses threat to the public health globally. So, there is need to target the control measures to eradicate the disease. Researchers from every nook and corner of the world are investing their efforts to control the disease. For example, Dumont et al. worked on the outbreaks of chikungunya in Reunion Island in 2005 and 2006 with the help of mathematical

modeling. Compartmental models for humans as well as mosquitoes were studied to calculate basic reproduction number. Numerical simulation revealed that value of R_0 changed from < 1 to > 1 which is in agreement with the situation that there is no outbreak in 2005 and almost one third of population got affected in 2006. Values of basic reproduction number revealed that force of infection varies from place to place which can be controlled by destruction of breeding sites of mosquitoes [40]. Taking a step ahead was by Moulay et al. who studied the invasion of chikungunya in humans. Firstly, disease spread in mosquito population was studied and then transmission of virus in humans was discussed. For mosquitoes, stage structured model, that is, different stages like embryonic, larvae and adult were considered. For virus in humans, SI and SIR type of models were taken into account. Stability analysis of endemic equilibrium and values of R_0 was discussed. It has been concluded, we have to be careful about *Aedes albopictus* breed because in the last years it has developed its potential to adapt in non-tropical areas. It was suggested that chemical interventions can help reduce the number of vector as it increases the mortality rate. But this too has drawbacks such as bad effects on environment and moreover mosquitoes become resistant to insecticides. Also, it was recommended that better interventions are drying up of breeding sites and effort by human population like using mosquito nets, mosquito repellent, isolating patients in hospitals, using appropriate clothes [41]. Again, Dumont et al. studied the outbreak in Reunion Island in 2006 with the perspective of investigating possibility to stop the chikungunya episode through mosquito control tools. They investigated the control measures taken by government in 2006 to stop the epidemic. In the process, the use of adulticide, larvicides and other mechanical tools like eliminating the breeding sites were discussed. It was observed that larvicides are not enough as they control to a certain limit. Further, it was found that the adulticide do control but have detrimental effect on endemic species as well as environment. Simulation results predicted $R_0 < 1$ for 2005 because of which the outbreak was not of as much amplitude as in 2006. They further updated by studying the use of larvicide and adulticide mixture. It has been concluded that

combination of larvicide, adulticide and other mechanical tools like drying up of breeding sites will give interesting results [1]. The study on chikungunya virus transmission potential and control measures for outbreak in Italy 2007 was taken to a higher level by Poletti et al. The study revealed that in the first stage of epidemic, there were 161 confirmed laboratory cases were there in two neighbouring village with total 3968 inhabitants. The researchers employed two models, one for the main vector *Aedes albopictus* mosquito with its dependence on temperature and other for epidemic transmission in humans. It was found that chances of probability of epidemic was predicted to be $32\% - 76\%$ after a single infective case who has contracted disease from a relative from Kerela, India. It was further observed that the value of R_0 was $1.8 - 6$. Further, the model gave the values which predict the already known hypothesis that CHIKV outbreak in those humid climate countries is associated with high density of mosquitoes. Regarding the efficacy of control measures, it was observed that reduction of eggs, breeding sites and adulticide do not help as much as compared to larvicides which reduces the average from 73% to 40% as compared to former 73% to 60%. It was suggested that though the potential of CHIKV is high, epidemic can be controlled by timely interventions like larvicide, mosquito repellents, window screens etc. [42]. The introduction of chikungunya virus in United States was studied for three major parts of US that have wide seasonal temperature variation. For New York, Miami and Atlanta, the peak time of epidemic risk depending upon the temperature was calculated. For New York, it was found that if the introduction of a single infected individual is done after June 15th, till December, there is significant probability of outbreak. Similarly, for Atlanta, periods of outbreak were predicted depending upon time of introduction of CHIKV. But for Miami, outbreak was predicted after introduction of CHIKV at any time of the year as in locations like Miami where temperature supports mosquito growth, controlling mosquito population will not be sufficient strategy. It was further suggested that different intervention measures like lowering vector human ratio can predict to lower the probability and magnitude of outbreak and identifying different endemic and epidemic regions can help plan

better intervention measures [43]. Fischer et al. updated the transmission studies by climatic risk maps using the knowledge of climatic suitability of chikungunya virus. It was probed that global transport and travelling imported such exotic viruses to Europe which was earlier considered as tropical disease. The research in this paper helped in identifying the regions with climatic aptness of CHIKV transmission. The study predicted that there is increase in risk of disease for Western Europe along with many Mediterranean regions. The study was updated through climate change impacts projected in three time frames and climate scenarios from $IPCC$ [44]. Furthermore, Liu et al. studied chikungunya disease by incorporating time varying factors for Reunion Island. It was noticed that the birth rate of mosquitoes is switching factor which varies from dry reason to wet reason [45]. Taking the work ahead, Robinson et al. worked on the outbreak of chikungunya in rural Cambodia by proposing a mathematical model. In this outbreak, in village of Trapeang Roka Kampong spece province, 44% biologically confirmed cases of chikungunya were found. Data obtained through campaign conducted after 7 weeks of outbreak helped construct epidemic curve which included self reported confirmed cases and also those who are not sure about their fever onset date. The basic reproduction number evaluation came out be 6.46. It was concluded that the estimate was sensitive to mosquito longevity and changes in rate of biting of mosquito. The exclusion of asymptotic cases and those whose fever onset date was not documented lead to underestimation of R_0 which in turn have negative impact on control measures to be adopted by health authorities. It was suggested that proper documentation and route of disease introduction should be taken into account for better predictions [46].

One more disease in the list of infectious diseases is rotavirus. Rotavirus is the main cause of diarrhea and severe gastroenteritis in children aged less than 5 years. Almost 95% of children get infected by rotavirus before reaching 5 years age with peak incidence between 4 to 36 months. This virus got its name from word 'rota' which means wheel as its shape resembles wheel under microscope. The symptoms are watery diarrhea, fever, vomiting and nausea. Its incubation period is

around two days. It has been noticed that little ones having two natural infections had complete protection against future infections as each infection confers immunity. It is being seen that rotavirus claims 20% of diarrhea deaths under 5 years in developing countries. It was suggested by WHO in recommendation that its vaccine should be covered in vaccine chart of every country as its economic burden is substantial [47]. A lot of work has been done in the direction to control the disease. For example, Bishop et al. worked on the immunity conferred by rotavirus infection in new born babies. The study was conducted on 81 babies who were observed for about three years. 55% of babies with neonatal infection and 54% without it, had rotavirus infection and 54% without it had rotavirus infection in coming three years of life. It was concluded that neonatal infection of rotavirus does not grantee immunity for subsequent infections but protect against several clinically severe diseases during reinfection [48]. Further, the dynamics of rotavirus infection through mathematical modeling was studied by Shim et al. by incorporating the factors seasonality, breastfeeding and vaccination by studying the data from Australia. It was observed that different vaccines like Rotashield (1998, USA), RRV-TV, that is, Rhesus Rotavirus tetravalent, Rotrix, Rotateq are effective. It was also discovered that post breast feeding, vaccination is more effective than a neonatal one. It was suggested that quality of maternal antibodies should also be considered as an important factor along with breastfeeding as the same is different in different geographic regions [49]. Further, the study has been updated by estimating the number of death due to rotavirus infection for a data from England and Wales. The records were obtained from office of National Statistics of Deaths with any type of gastroenteritis [50]. Taking the research to new heights is done by studying the concept of herd immunity in rotavirus infection by Effelterre et al. by employing a mathematical transmission model. Their work helped in studying the impact of vaccination programmes for RV infection for five countries France, Germany, Italy, Spain and UK of European Union. It was concluded that when vaccination coverage is $70\%, 90\%$ and 95%, herd immunity along with direct effects of vaccination helped by respective reduction in the

infection. In their work, it was assumed that vaccination mimics natural RV infection which wanes from 100% to 0% from birth to age of 6 months [51]. Further, updating the work in the field, Zaleta et al. worked on modeling of nosocomial transmission of rotavirus in hospitals in pediatric wards. Along with calculation of basic reproduction number which was 0.870, it was observed that there is need of control measures like health care workers ($HCWs$) to patient ratio, better hygiene measures and vaccination. It was concluded that the above control measures definitely reduce nosocomial transmission but may not be that effective and feasible in every setting [52]. Further, the effects of national introduction of monovalent rotavirus vaccine were assessed and its impact on diarrhea in children with age less than two years in El Salvador, America, from January 2007 to June 2009 were evaluated. They surveyed seven hospitals and studied 323 children with age less than two years who were admitted to hospitals with confirmed rotavirus diarrhea. It was concluded that the vaccine was highly effective as it reduced the hospital admission. It was also observed that dose of vaccine was 51% effective as hospital admission under age five declined by 40% in 2008 and by 51% in 2009 after vaccination in 2006. It was indicated that direct effects of rotavirus vaccination can have benefits even in areas with highest incidence and poorest setting. Whereas, it was observed that the effectiveness of monovalent vaccine were lower (59%) in children aged $1-2$ years in contrast to those aged $6-11$ months (83%) predicting that immunity wanes with time [53]. Taking the research further, the effect of rotavirus vaccine in low socio-economic settings (SES) were also studied and it was observed that efficacy of vaccine of rotavirus ranges from 50% in low SES to $> 90\%$ in contrast to high socio-economic settings. During the research, data from diverse range, epidemiologically and demographically high, middle, low SES was taken. Through a mathematical model incorporating age, immunity and natural history of infection of rotavirus, it was predicted that for severe diseases, vaccines are very effective and their efficiency diminishes as child grows in low SES. It was observed that in contrast to middle as well as high SES, the proportions of infections in low SES does not decline with each infection. It was further probed that

vaccination for rotavirus impersonate primary and secondary infections but the infections occurring afterwards cannot be denied. It was suggested that modification in vaccination programmes and modifying the aspects of vaccine can help [54].

Another infectious disease under study is malaria, which is one of the significant cause of both social and economic burden. It is caused by protozoan parasites. It can be caused *plasmodium falciparum, plasmodium malariae, plasmodium ovale* and *plasmodium vivax* in humans. But *plasmodium falciparum* is mostly the causative parasite among humans. WHO estimated 229 million cases of malaria in 2019 with most deaths and around 90% of the global burden on Sub-Saharan Africa [55]. However, WHO recommends usage of artemisinin-based combination therapies (ACT's) for plasmodium genus. The guidelines for treatment for uncomplicated falciparum malaria are in accordance with WHO in non-endemic countries but drug resistance cannot be ruled out for returning travellers [56].

Further, there are various infections that may infect a host [57–59] and that may altogether. There are many examples of them involving HIV and TB [60], HIV and hepatitis B [61], malaria and HIV [62], malaria and rotavirus [63], chikungunya and dengue, HIV-HBV co-infection [64] and many more [65, 66]. Moreover, this infection may occur with different serotypes or various strains of same virus. Simultaneous infections may also occur even when it seems that there is no synergy between the two agents affecting the person. This dynamics of co-infection is important to study as the treatment of one infection affects the dynamics of the other infection. Disease, poverty, sanitation, health care, nutrition, access to facilities are various factors accountable for killing people with these infectious agents.

Various researchers have been working in the field of controlling these co-infections. For example, the co-infection of rotavirus and malaria is discussed by Omondi et al. in 2018 after a study conducted in Ghana which showed that 11.8 percent of 243 children examined were infected by both. A model for the co-infection was being studied and basic reproduction number was calculated which predicted that

if $R_{mve} \approx 0.733 < 1$ implies that co-infection can be controlled and disease free equilibrium is being stable. But $R_{mve} \approx 1.37431 > 1$ implies that co-infection can be endemic and can be controlled by medical interventions only. It has been observed that global stability for co-infection can be achieved if protection like mosquito nets for malaria and better sanitation in case of rotavirus is taken care of. Further studies found that vaccination as one of the factors is considered by Omondi et al [63]. The model was analyzed to find out the value of basic reproduction number and numerical simulation incorporating the data from Kenya showed that $R_v = 0.9692 < 1$ which indicated infection-free equilibrium is globally stable. It was suggested that disease being endemic in population should be controlled by preventive measures like vaccination, safe drinking water and maintaining hygiene. It is being recommended that all the new born should be vaccinated in order to control rotavirus infection effectively [47].

There are various factors that can help in controlling an infection. Sometimes, it is as simple as isolating an infected individual. The isolation of infected individuals can also be planned only if we know the incubation period of the disease. Since isolation can be the only strategy for unseen epidemics but it is not always implemented flawlessly. However, quarantine or isolation time can only be decided with the knowledge of incubation period. The incubation period of an infectious disease is the time gap from exposure with microorganisms to the onset of clinical symptoms. Modeling incubation period is important in calculating the future time scale of epidemic and also helps in designing control strategies for the disease. The outbreak investigations and public health area can benefit from the knowledge of distribution of incubation period of a disease. There are models that rely on the accuracy of incubation period for public health interventions. The recent public health emergency, that is, COVID-19, has been studied for incubation period by many researchers including the latest by [67]. The estimated value of incubation period was calculated to be 5.74. The incubation period of SARS-CoV-2 Omicron virus was also calculated to have better control over the epidemic by [68]. A study of comparison of incubation periods for Delta virus and non-Delta virus revealed

that the value is 3.7 days for Delta cases and 4.9 days for non-Delta cases in Japan [69]. Authors in [70] contributed by reviewing the data regarding the incubation period of five viruses that are significant for public health.

In the view of the above literature, therefore, the following problems related to infectious diseases with the purpose to control the disease transmission have been studied with the help of mathematical modeling in this thesis.

1.3 Proposed Objectives of the Work

It was observed that work done on infectious disease using mathematical models can be complemented in many areas. In earlier work done with statistical kind of models, mathematical analysis can be considered for better control of infectious diseases. In many models vaccination as a control strategy can be taken into account. Factors like treatments, delay, precautions can be taken into account in many models. The proposed research work related to disease dynamics will be carried out by using mathematical modeling by achieving following objectives:

1. Mathematical modeling on control of communicable/infectious diseases and their effects on single population.
2. Mathematical modeling on control of communicable/infectious diseases and their effect on two species.
3. Mathematical modeling on control of co-infectious diseases.
4. Mathematical modeling on communicable/infectious disease including delay in its control

1.4 Main Terms Used in the Thesis

- **Basic Reproduction Number**: It is the number of secondary infections produced by a single infected individual in a completely naive population over its infectious period. This is a threshold value and is denoted by R_0.

- **Disease-free State**: The state when there is no disease present or the disease dies out in long term is called disease-free state.
- **Endemic State**: The disease which is present within a geographic area with constant prevalence is called endemic disease.
- **Latent Period**: The time gap between getting infected by a microorganism or a pathogen and when the individual is infectious, that is, they are capable of transmitting the infection.
- **Incubation Period**: It is the time from exposure to infection and onset of clinical symptoms of the infection.
- **Nosocomial**: It is the infection acquired in hospitals. It is also known as hospital acquired infection (HAI).
- **Control Measures**: These are the strategies applied to control the disease. They can be medicines, preventive measures, vaccines etc.
- **Autochthonous Transmission**: It is a term which refers to transmission of an infection from one person and its acquisition by another person in the same place.

1.5 Mathematical Preliminaries

Definition 1.1. Autonomous and non-autonomous systems [71]
Autonomous system of ordinary differential equation is as

$$\dot{x} = f(x)$$

that is, function is not dependent on independent variable where as in non-autonomous systems

$$\dot{x} = f(x, t) \tag{1.1}$$

the function f is dependent on independent variable.

Definition 1.2. Definition of Stability [71]

The solution of the system (1.1) is stable if for given $\epsilon > 0$ there is δ depending on ϵ with condition that for any solution $\hat{x}(t) = x(t, t_0, \hat{x_0})$ of the system (1.1) $\|\hat{x} - x_0\| < \delta$ implies $\|\hat{x}(t) - x_0(t)\| < \epsilon$ for $t \geq t_0$.

Definition 1.3. Definition of Asymptotic Stability [71]

The solution $x(t)$ of (1.1) is asymptotically stable if it is stable and if there is a $\delta_0 > 0$ which implies $\|\hat{x}(t) - x_0(t)\| \to 0$ as $t \to \infty$.

Definition 1.4. Routh Hurwitz Criteria [71]

The necessary and sufficient condition for roots of characteristic polynomial, whose coefficients are real, to lie in left half side of complex plane. This criteria is used to investigate local asymptotic stability of steady states of system of non-linear differential equations. It is given in the form of theorem given below:

Theorem 1.5. *Let*

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + \ldots\ldots\ldots + a_{n-1}\lambda + a_n,$$

be polynomial, where $a_i's$ are real constants and $i = 1, 2...n$. Define n Hurwitz matrices as

$$H_1 = \begin{pmatrix} a_1 \end{pmatrix}, \; H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix}, \; H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix}$$

and

$$H_n = \begin{pmatrix} a_1 & 1 & 0 & 0.... & 0 \\ a_3 & a_2 & a_1 & 1.... & 0 \\ a_5 & a_4 & a_3 & a_2.... & 0 \\ . & . & . & .... & 0 \\ . & . & . & .... & 0 \\ 0 & 0 & 0 & 0.... & a_n \end{pmatrix}$$

Here, $a_k = 0$ for $k > n$ and all roots of $P(\lambda)$ are either negative or having negative real parts if and only if all the Hurwitz determinants are positive, that is, $detH_k > 0, k = 1, 2, 3...n$. For $n = 2, 3, 4$ the this Criteria is summarised as

For

$$n = 2, a_1 > 0, a_2 > 0, n = 3, a_1 > 0, a_3 > 0, a_1 a_2 > a_3,$$

$$n = 4, a_1 > 0, a_3 > 0, a_4 > 0, a_1 a_2 a_3 > a_3^2 + a_1^2 a_4 > 0.$$

Definition 1.6. Equilibrium Point

A point $x = x_0 \in R^n$ is equilibrium point or critical point of the system $\dot{x} = f(x)$ if $f(x_0) = 0$.

Definition 1.7. Jacobian of a System

For the system $\dot{x} = f(x); x \in R^n$ and $x = x_0 \in R^n$. The Jacobian of f at an equilibrium point x_0 is a matrix obtained by partial derivatives of f at x_0. This is denoted by $Df(x_0)$ and is given by

$$J(x_0) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1}(x_0) & .... & \frac{\partial f_1}{\partial x_n}(x_0) \\ ..... & .... & .... \\ ..... & .... & .... \\ \frac{\partial f_n}{\partial x_1}(x_0) & .... & \frac{\partial f_n}{\partial x_n}(x_0) \end{pmatrix}$$

Definition 1.8. Lyapunov Second Method of Stability [71]

Considering the autonomous system

$$\dot{x} = f(x) \tag{1.2}$$

where $f \in C(R^n, R^n), f = (f_1, f_2, f_3.....f_n), x = (x_1, x_2, x_3....x_n)$ and $x(t_0) = x_0$ for all $t \geq t_0$. Let f be smooth enough to ensure the uniqueness and existence of solutions of (1.2). Let $f(x) \neq 0$ for $x \neq 0$ and $f(0) = 0$ in the proximity of the origin so that origin is an isolated critical point of (1.2) and (1.2) admits the so called zero solution ($x = 0$). Let Λ be an open set in space R^n which contains origin. Let V(x) be a scalar continuous function in $(x_1, x_2, x_3....x_n)$ defined on Λ.

- The function V(x) is said to be positive definite on Λ iff $V(0) = 0$ and $V(x) > 0$ for $x \in \Lambda$ with $x \neq 0$.
- A function V(x) is positive semi-definite on Λ if V is positive throughout on Λ, except at points where the value is zero (including zero).
- A function V(x) is negative definite (or it is negative semi-definite) on Λ iff $-V(x)$ is positive definite (or it is positive semi-definite) on Λ.

Definition 1.9. Sensitivity Analysis

The calculation of sensitivity indices helps to measure the changes in the state variable corresponding to a changes in parameter value. The ratio of relative alteration in variable to the relative alteration in the value of parameter is termed as normalized forward sensitivity index of that variable to that parameter. This has been elaborated by Chitnis et al. [72]. The formula for calculation of normalised forward sensitivity index of any particular variable u (dependent on any parameter k) is given under:

$$\Upsilon_k^u = \frac{\partial u}{\partial k} \times \frac{k}{u}$$

Definition 1.10. Hopf Bifurcation

Bifurcation is closely associated to biological or mathematical threshold value of a system. It is the branching of solutions of system at a threshold value τ_0 of τ (a parameter) which causes the system to loose its stability. For $\tau < \tau_0$, the system shows stability and for $\tau > \tau_0$ it is unstable, that is, there is a switch of stability and hopf bifurcation happens. In particular, hopf bifurcation is observed if a pair of complex solutions or eigenvalues crosses the virtual axes at a speed which is non-zero. Let us consider the eigenvalues of the linearized system $A(\tau) = D_x F(x, \tau)$ of $\dot{x} = F(x, \tau)$ lies in open half plane initially. Now, as τ varies, say, one pair $\lambda = \alpha(\tau) \pm \iota\beta(\tau)$ crosses imaginary axes at $\tau = \tau_0$.

$$\alpha(\tau_0) = 0, \frac{d\alpha(\tau_0)}{d\tau} \neq 0, \beta \neq 0,$$

then near τ_0, the stable equilibrium bifurcates creating periodic cycles.

Definition 1.11. Next Generation Matrix Method [73]

This method is applied to calculate basic reproduction number in case of epidemiological models. This is briefly elaborated as:

Let the autonomous system having non-negative initial conditions be

$$\dot{x_i} = f_i(x) = F_i(x) - V_i(x) : i = 1, 2, 3...n, \tag{1.3}$$

where $V_i = V_i^- - V_i^+$. Let $X = \{x \geq 0 : x_i = 0 \text{ for } i = 1, 2, ...m\}$ be the set of all disease-free equilibrium points of the system (1.3). Here $x = (x_1, x_2, ...x_n)^t$: $x_i \geq 0$ is the number of persons in every compartment of the infectious disease model.

1. If $x \geq 0$ then F_i, V_i^- and V_i^+ are all ≥ 0.
2. If $x_i = 0$ implies $V_i^- = 0$.

   Particularly for $x \in X$, implies $V_i^- = 0$ when $i = 1, 2, ...m$.
3. $F_i = 0$ for $i > m$.
4. For $x \in X$, $F_i(x) = 0$ along with $V_i^+(x) = 0$ for all $i = 1, 2, ...m$.
5. If $F(x) = 0$ then all the eigenvalues of $Df(x_0)$ possess (negative) real parts.

Here, $F_i(x)$ represents new infections in the ith compartment, V_i^+ is transition rate of individuals into ith compartment and V_i^- is transition rate of going out of ith compartment for the individuals.

Theorem 1.12. *For a disease transmission model* (1.3) *where* $f(x)$ *satisfies the axioms* $(1)-(5)$. *Then* x_0 *is* DFE *of this system then* x_0 *is called* LAS *for* $R_0 < 1$ *whereas it is not stable for* $R_0 > 1$, *here* $R_0 = \rho(FV^{-1})$ *and* $\rho(A)$ *being the spectral radius of the matrix* A.

1.6 Summary of the Thesis

In the present work proposed, the study of the system comprising major components human population, mosquito population, infections, their treatments, control strategies for these infectious diseases is done. The system is studied and analyzed by defining its boundaries, characterizing the changes in the form of mathematical equations and then the original system is formed by interconnecting these representative equations. For the proposed work, system of ordinary differential equations is used for proposing models to understand the dynamics of disease. In this research work, both kinds of models, that is, with constant population [74] and variable population have been studied. The disease dynamics is modelled with involvement of the factors like effect of awareness about disease in the population, preventive measures taken to control the infection, treatment taken, vaccination etc. and then they help in prediction of disease transmission, the extent of transmission, whether the disease will die out or turn into an epidemic or remain endemic in the population. Once the differential equations forms the model, they are solved by assuming the initial conditions and positivity of the variables taken. Further, the system is analyzed for stability conditions. The local stability is checked through Routh-Hurwitz criteria and Next generation matrix method is applied to calculate threshold parameter known as basic reproduction number. Also numerical simulation using MATLAB is done to support the analytic results. Further, the results based on the model analysis are compared with the existing results whether experimental or statistical results available in the field. In the chapter 1, general introduction regarding various infectious diseases in the population under the effect of preventive measures, treatments, vaccination etc has been given. Noteworthy contribution of various researchers till date has been included in the literature review section. In the view of same, identification of research gaps has been done. Based on these gaps, the objectives of the proposed study has been formed. The terms used in the study and mathematical preliminaries have also been described in the chapter. The chapter has been concluded with summary of chapters comprising the thesis.

In chapter 2, Mathematical model for transmission of infectious disease yellow fever has been formulated by taking different compartments for human and mosquito. Through stability analysis and numerical simulation, it has been proved that infection can be controlled by reducing mosquito biting rate and disease transmission parameter. Further, it has also been shown that insect repellent also reduces the contact between humans and mosquito, thereby, reducing infection. After the calculation of basic reproduction number, the results obtained have been validated with the existing results available in the field.

In the chapter 3, the infectious disease yellow fever with of awareness through media has been considered and studied. It has been assumed that these awareness programmes make people aware about the infection and this aware category of people make themselves safe from infection and also make effort in reducing mosquito population. Stability analysis of infection-free state has been performed. The value of R_0 calculated has been shown to be affected by rate of dissemination of awareness programmes. Moreover, from the numerical simulation it has been observed that a lesser quantity of insecticide to control the mosquito is sufficient in the presence of awareness programmes. Consequently the damage to the environment can be reduced.

In the same chapter the infectious disease chikungunya has been studied. A nonlinear mathematical model consisting of separate compartments for human and mosquitos has been formulated and analyzed. Results obtained by performing stability analysis and numerical simulation for the model showed that simultaneous effect of insect repellent creams/sprays, vaccination for the disease and chemical insecticide can help control the disease. Further, it has been shown that a much lesser quantity of insecticide as compared to that used earlier in the same field has been found to be effective to the reduce the infection. Also, the threshold parameter, that is, R_0 has been calculated in the model.

In chapter 4, disease dynamics of co-infection of rotavirus and malaria has been studied. The co-infection has been studied to see the effects of control measures in the form of treatments for both human and mosquito compartment. Local stability

analysis for disease-free equilibrium and calculation of R_0 has been done. Firstly, R_0 has been calculated for the individual models and then the threshold value for the complete model has been calculated. Further, bifurcation, direction of bifurcation and sensitivity indices are calculated to probe the effect of certain parameters significant for the transmission of disease. It has been observed that collective treatment namely malaria-rotavirus treatment and insecticide for mosquito is efficient than only insecticide treatment. Further numerical simulation showed that cumulative treatment is better than any single treatment given to various infected classes.

In chapter 5, a compartmental model for infectious diseases is proposed. Since, the incubation period of a disease plays very important role in disease dynamics. It can guide policy makers and health officials to make policies to control an emerging disease. The model incorporates incubation period in its formulation in the form of delay. The conditions of local stability for the equilibrium points have been investigated. Further, it is observed that disease-free state is locally stable when $R_0 < 1$. Also, the endemic equilibrium is LAS for certain conditions including $\tau < \tau_0$, here τ_0 is threshold value of τ. It was also observed that there is phenomenon of hopf-bifurcation leading to periodic solutions for $\tau \geq \tau_0$. Further investigation leads us to the fact that transmission parameter plays a significant part in disease dynamics. Furthermore, while analysing the model, it was observed that infection can be managed or curbed provided particular level of recovery rate and incubation period is administered failing which can lead to epidemic. Analytic results have been supported by numerical examples.

In the end, the proposed work under study has been supported by the bibliography given at the end of the thesis.

Chapter 2

Control of Infectious Disease and its Effect on Single Population: A Yellow Fever Mathematical Model

2.1 Introduction

Infectious diseases have been studied through mathematical modelling by making compartments of the total population. They can be as simple as a SIR model and can be further extended to many compartments depending upon the study taken. Here, we have extended this basic model to incorporate the control measures taken to study the infectious diseases by taking an example of yellow fever. The similar kind of model can be extended to study other vector borne diseases like malaria, dengue etc. by making appropriate changes.

Yellow fever is viral haemorrhagic fever which is caused by biting of a mosquito *Aedes aegypti*, a vector for yellow fever of the urban cycle of the disease ([74], [75]). After incubation period of 3 to 6 days, the disease becomes symptomatic with symptoms like mild fever, jaundice, vomiting, muscle pain and the disease may aggravate to death in some cases. Yellow fever virus is the prototype member

of the genus Flavivirus. This group of viruses has been found to be transmitted between vertebrates by arthropod viruses [76]. They are mostly abundant in tropical regions belonging to South America as well as of Africa and it gets transmitted to primates by *Aedes spp.* and *Sabethes spp.* [29]. Mathematical modeling has played an important role in fighting against the infectious diseases. Health care policies and cost effective treatment are blessings of researchers doing epidemiological studies. Various researchers have contributed in the field of control of these diseases. The contribution of some noteworthy researchers is mentioned here. For example, mosquito control is also studied by many researchers like Kesselring et al. [77]. Regarding the control of infection in humans, there is no particular antiviral drug for the disease but timely detection and taking precautionary measures may increase the chances of patient's survival. Taking the work to new heights, Zaleta et al. [78] discussed a sample vaccination model by considering many endemic states. The authors studied factors like policies concerning vaccination, vaccine coverage rate, the waning period (i.e. the period after which the immunity due to vaccine fails) and effectiveness of vaccine. Furthermore, the factors like role of mosquito vector, the climate and human behaviour were included in the model for outbreak of yellow fever in Luanda, Angola in December 2015 to August 2016 by Shi Zhao et al. in 2018. It was concluded that vaccination saved 5.1 fold more people from death out of 941 observed cases. Further, the time series analysis of Luanda's yellow fever suggested that the outbreak occurred in two waves, which can be more likely if there were no vaccination. In addition to that, the study also concluded that the value of R_0 can be changed by changing factors like insecticide for vector control, travelling restrictions and precautions through media. It has been simulated with different vaccination schemes [79]. Working on better control measures, Bodine et al. [80] modelled yellow fever by taking vaccination, use of insect repellent, reapplication of repellent after its waning period and human's tendency to apply insect repellent according to their state as infected or recovered. Furthermore, Monath et al. studied the underlying cause of yellow fever infection to the travellers travelling to tropics. Travelling as an adventure to the

remote areas where yellow fever is endemic, the stay at the place, the exposure to yellow fever mosquitoes in places like forests of Africa, international health regulations, yellow fever vaccine availability, epidemiological silence were the key factors studied by the author. It is being observed that there is shortage of YF vaccine and we need more sources to have complete control over the disease. It is being observed that the risk of yellow fever infection cannot be measured accurately but it can be reduced by taking some precautions. It was suggested that travellers should be aware about the yellow fever endemic areas [81]. Along with the risk of yellow fever while travelling, the risk YF 17D vaccine has been assessed by the author after some serious and adverse cases are seen. It was predicted that in case epidemic occurs, the vaccine requirement will exceed its production [82]. Though vaccination is an effective measure to control the disease but there are certain limitations for vaccination like restricted access to health care facilities, immuno deficient persons, pregnant women, small children and belief system of person for vaccination. Various statistical and theoretical studies have been done in the direction by researchers [83–86]. It was suggested that whether to vaccinate or not should be decided by various factors like travel destination, local weather, exposure of individuals with vectors etc. It was observed that there are studies showing adverse effect of vaccine [31, 87]. The authors suggested that vaccination for yellow fever should be avoided keeping in view its adverse effects. Yellow fever vaccine cannot be made mandatory due to its detrimental effects. Similar studies were done by [88, 89]. Codecco et al. [90] probed the effects of pre-emptive vaccination to populations who have uncertainty regarding risk of infection. It was suggested that vaccination should be done if risk of epidemic is there otherwise ethical issues regarding vaccine does not make mind set of people ready for the vaccination.

Keeping in view the above factors, there is need to use other control measures like use of insect repellent, bed nets, decreasing interaction between humans and hosts, timings to visit the places where the disease is endemic. In our work, we will be using insect repellent as protective measure along with vaccine as control strategy.

To our knowledge, there have been no work in yellow fever compartmental modeling, in which protected class of individuals has been investigated and studied. Here, with this aspect, protected class for human population has been introduced in this model to whom temporary protection is given. The reason for taking this class is that the persons who travel to yellow fever endemic regions are normally non-immune. So, the common practice to have protection is in the form sprays or application of insect repellent.

2.2 Mathematical Model

To study the dynamics of yellow fever, firstly we will formulate the model in the form of differential equations by making different compartments of the population.

2.2.1 Model Formulation

A mathematical model for yellow fever transmission for mosquito and human populations has been proposed. It is being assumed that the two populations mixes deliberately without any obstruction. The total human population denoted by $N_h(t)$ is divided into different epidemiological compartments of individuals namely susceptible class $S_h(t)$, protected class $P_h(t)$, infected class $I_h(t)$ and temporary immune class $R_h(t)$, whereas the vector/mosquito population $N_m(t)$ is split into two classes, that is, susceptible class and infected class denoted by $S_m(t)$ and $I_m(t)$ respectively. The transfer between the compartments is denoted by different epidemiological parameters. The susceptible human population gets infected when they are bitten by infected mosquitoes. The susceptible human population is increased by constant birth rate b_h. Here θ $(0 \leq \theta \leq 1)$ is the proportion of susceptible human which are taken under preventive measures and are going to the protected class. It is being assumed that protection will reduce the likelihood of infection. The factor associated with it is denoted by ω. Here $\omega = 0$, the protection is effective and if $\omega = 1$, then the protection is not effective. This protection is

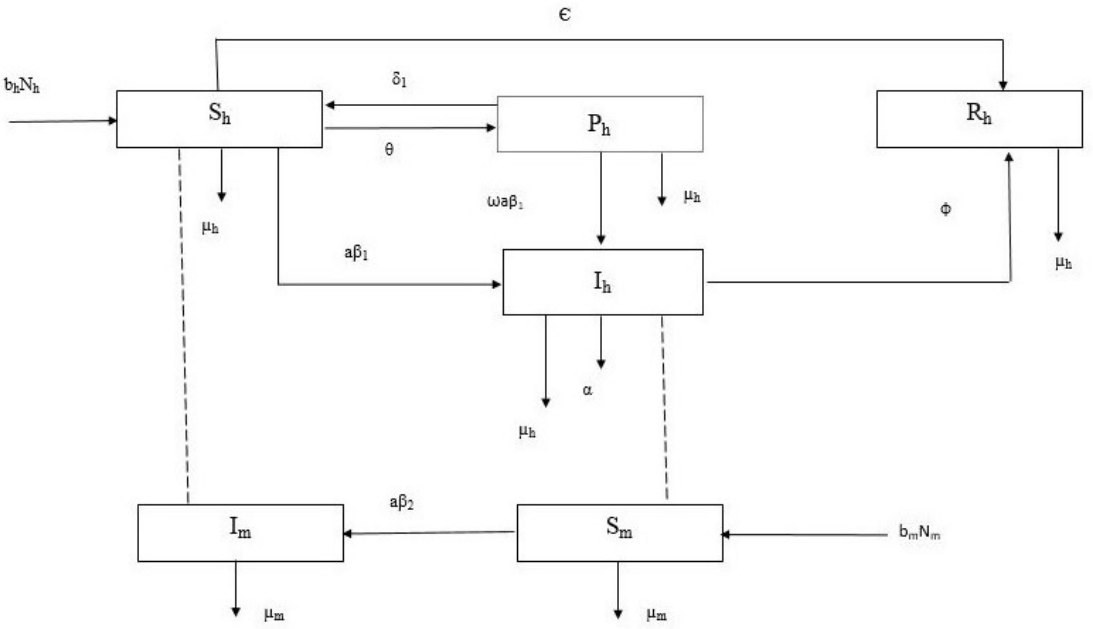

FIGURE 2.1: Flow diagram of the system

temporary as it wanes off with time. So, the protected humans return to the $S_h(t)$ at a constant rate δ_1. Infected humans acquire temporary immunity to increase the immune class at a constant rate ϕ. The disease does not transmit vertically and the human population have a constant rate of natural death denoted by μ_h. Also, infected humans die with disease death at a constant rate α. For mosquitoes, the recruitment is through constant birth rate b_m. Susceptible mosquitoes, when bite an infected individual at a constant rate a, gets infected with transmission probability β_2 and here β_1 is the transmission probability of getting infected from infected mosquito. There is no recovered class for vectors of the disease, that is, mosquitoes as they do not recover from the infection once they are infected. In the model, there is no difference between vaccinated and recovered humans as current yellow fever vaccine confers lifelong immunity which is same as recovery from disease.

Under these assumptions, the progress of the infection is given in the system of

equations:

$$\begin{aligned}
\dot{S_h} &= b_h N_h - a\beta_1 \frac{S_h I_m}{N_m} - \theta S_h + \delta_1 P_h - \mu_h S_h - \epsilon S_h, \\
\dot{P_h} &= \theta S_h - \omega a \beta_1 \frac{P_h I_m}{N_m} - (\delta_1 + \mu_h) P_h, \\
\dot{I_h} &= \frac{a\beta_1 S_h I_m}{N_m} + \omega a \beta_1 \frac{P_h I_m}{N_m} - (\phi + \alpha + \mu_h) I_h, \\
\dot{R_h} &= \phi I_h - \mu_h R_h + \epsilon S_h, \\
\dot{S_m} &= b_m N_m - a\beta_2 S_m \frac{I_h}{N_h} - \mu_m S_m, \\
\dot{I_m} &= a\beta_2 S_m \frac{I_h}{N_h} - \mu_m I_m.
\end{aligned} \tag{2.1}$$

Taking initial conditions $S_h(0) > 0, P_h(0) > 0, I_h(0) > 0, R_h(0) > 0, S_m(0) > 0$ and $I_m(0) > 0$.

It is quite evident that

$$\begin{aligned}
N_h &= S_h + P_h + I_h + R_h, \\
N_m &= S_m + I_m.
\end{aligned}$$

Also upon adding all the equations in the model (2.1) for human and mosquito populations, we get

$$\begin{aligned}
\dot{N_h} &= b_h N_h - \mu_h N_h - \alpha I_h, \\
\dot{N_m} &= b_m N_m - \mu_m N_m.
\end{aligned} \tag{2.2}$$

It is quite clear from first equation of (2.2), that in the absence of the disease ($\alpha = 0$), population N_h grows exponentially if $b_m > \mu_m$, N_h is constant if $b_h = \mu_h$, N_h decreases if $b_h < \mu_h$. Considering second equation of (2.2), $N_m = c_1 e^{(b_m - \mu_m)t}$, which implies that N_m is constant if $b_m = \mu_m$, N_m decreases if $b_m < \mu_m$ and it grows exponentially if $b_m > \mu_m$.

2.2.2 Description of Parameters in the Model

TABLE 2.1: Table for Description of Parameters in Yellow Fever Model.

Parameters	Value	Units
a	Average number of bites by mosquitoes to human	-
β_1	Transmission rate of YF from mosquito to human	day^{-1}
β_2	Transmission rate from human to mosquito	day^{-1}
θ	Proportion of susceptible individuals under protection	day^{-1}
δ_1	Rate of movement from protected class to susceptible class after protection wanes	day^{-1}
μ_h	Natural death rate for humans	day^{-1}
μ_m	Natural death rate for mosquitoes	day^{-1}
ϵ	Effective vaccination rate of susceptible humans	day^{-1}
ϕ	Constant rate to join temporary immunity class	day^{-1}
b_h	Birth rate of humans	day^{-1}
b_m	Birth rate of mosquitoes	day^{-1}
α	Yellow fever induced death rate	day^{-1}
ω	Factor related to infection, $\omega = 0$: protection is effective, $\omega = 1$: protection is ineffective	numeric value

2.3 Dynamical Behaviour of the Model

The dynamical behaviour of the model will be checked by exploring the boundedness and performing the stability analysis of the model.

2.3.1 Positivity and Boundedness of the Model

As we are dealing with dynamics of diseases, it is very important to ensure that all the variables in the model (2.1) are non-negative.
In this section, the positivity as well as boundedness of the variables will be discussed in the form given below:

Theorem 2.1. *Assuming the initial conditions of the model to lie in* τ*, where*

$$\tau = \{(S_h, P_h, I_h, R_h, S_m, I_m) \in R_+^6 : S_h \geq 0, P_h \geq 0, I_h \geq 0, R_h \geq 0, S_m \geq 0, I_m \geq 0\}.$$

then $\exists$ *a unique solution for the above system of equations* (2.1) *and the solution is retained in* τ *for* $t \geq 0$.

Proof. Considering right side of the equations (2.1) in the model are continuous with continuous partial derivatives in τ, we can prove that the system of equations has a unique solution for all $t \geq 0$. Thereby, it will be sufficient to prove that $S_h \geq 0, P_h \geq 0, I_h \geq 0, R_h \geq 0, S_m \geq 0$ and $I_m \geq 0$ for future time t. We will apply the same approach as applied in [74], [91] and [92].
Let

$$t_1 = sup\{t > 0 : S_h \geq 0, P_h \geq 0, I_h \geq 0, R_h \geq 0, S_m \geq 0, I_m \geq 0\}.$$

Therefore, $t_1 > 0$. Now, from first equation of (2.1) of the model, we have

$$\dot{S_h} = b_h N_h - a\beta_1 \frac{S_h I_m}{N_m} - \theta S_h + \delta_1 P_h - \mu_h S_h - \epsilon S_h. \tag{2.3}$$

The above written equation can be presented as

$$\dot{S_h} + [f(t) + (\theta + \epsilon + \mu_h)]S_h = F(t),$$

where $f(t) = \frac{a\beta_1 I_m}{N_m}$ and $F(t) = b_h N_h + \delta_1 P_h$.

So, $\frac{d}{dt}(S_h(t)[\exp{(\theta + \epsilon + \mu_h)t} + \int_0^t f(\eta)d\eta]) = F(t)\exp[(\theta + \epsilon + \mu_h) + \int_0^t f(\eta)d\eta]$.

Integrating both sides from $t = 0$ to $t = t_1$, the above equation becomes
$S_h(t_1)[\exp{(\theta + \epsilon + \mu_h)t_1} + \int_0^{t_1} f(\eta)d\eta] - S_h(0) = \int_0^{t_1}[F(\xi)\exp[(\theta + \epsilon + \mu_h)\xi + \int_0^{\xi} f(\eta)d\eta]d\xi$.

Therefore,

$$\begin{aligned} S_h(t_1) = {} & S_h(0)\exp[-((\theta + \epsilon + \mu_h)t_1 + \int_0^{t_1} f(\eta)d\eta)] \\ & + \exp[-((\theta + \epsilon + \mu_h)t_1 + \int_0^{t_1} f(\eta)d\eta)] \times \int_0^{t_1} F(\xi)\exp[(\theta + \epsilon + \mu_h)\xi + \int_0^{\xi} f(\eta)d\eta]d\xi. \end{aligned}$$

$S_h(t_1)$ being the sum of positive quantities is positive. Hence, $S_h(t_1) > 0$. Similarly, by the same argument, we can show that P_h, I_h, R_h, S_m and I_m are all positive for $t > 0$. □

Assuming that the two populations of humans and mosquitoes does not vary notably during the interval of time taken under study, we assume the two populations to be relatively constant ([74]). Hence, without loss of generality, the populations in each compartments can be scaled by total species of the respective population to make the model dimensionless. This is done by the transformations as $s_h = \frac{S_h}{N_h}, p_h = \frac{P_h}{N_h}, i_h = \frac{I_h}{N_h}, r_h = \frac{R_h}{N_h}, s_m = \frac{S_m}{N_m}, i_m = \frac{I_m}{N_m}$.

The system of equations reduces to

$$\begin{aligned}
\dot{s_h} &= b_h - a\beta_1 s_h i_m - \theta s_h + \delta_1 p_h - \mu_h s_h - \epsilon s_h,\\
\dot{p_h} &= \theta s_h - \omega a\beta_1 p_h i_m - (\delta_1 + \mu_h)p_h,\\
\dot{i_h} &= a\beta_1 s_h i_m + \omega a\beta_1 p_h i_m - (\phi + \alpha + \mu_h)i_h,\\
\dot{r_h} &= \phi i_h - \mu_h r_h + \epsilon s_h,\\
\dot{s_m} &= b_m - a\beta_2 s_m i_h - \mu_m s_m,\\
\dot{i_m} &= a\beta_2 s_m i_h - \mu_m i_m.
\end{aligned} \tag{2.4}$$

2.3.2 Equilibrium Points of the System

To check the behaviour of the system (2.4), we need to solve it to find the equilibrium points.

Now, we want to find equilibrium points of the system (2.4).

- Disease-free equilibrium is given by $E_0(s_h^{'}, p_h^{'}, 0, r_h^{'}, s_m^{'}, 0)$
  where $s_h^{'} = \frac{Db_h}{(\theta+\mu_h+\epsilon)-\theta\delta_1}, p_h^{'} = \frac{b_h\theta}{(\theta+\mu_h+\epsilon)-\theta\delta_1}, r_h^{'} = \frac{Db_h\epsilon}{(\theta+\mu_h+\epsilon)-\theta\delta_1}, s_m^{'} = \frac{b_m}{\mu_m}$.
  Here $s_h^{'} \geq 0, p_h^{'} \geq 0$ and $r_h^{'} \geq 0$ provided $(\theta + \mu_h + \epsilon) - \theta\delta_1 > 0$.

- Disease endemic equilibrium is given by $E^*(s_h^*, p_h^*, i_h^*, r_h^*, s_m^*, i_m^*)$ where
  $p_h^* = \frac{ABC}{\omega\alpha a^2\beta_2^2} - \frac{a\beta_1(a^2\omega\beta_1\beta_2+CD)}{\omega\alpha C\theta}$, $i_h^* = \frac{B}{a\beta_2}$,

$r_h^* = \frac{\phi B}{\mu_H a\beta_2} + \frac{\epsilon(a^2\omega\beta_1\beta_2 + CD)}{\mu_h \theta C}$, $i_m^* = \frac{a\beta_2}{a\beta_2 + b_m}$ where $s_h^* = 1 - p_h^* - i_h^* - r_h^*$ and $s_m^* = 1 - i_m^*$, here $A = \phi + \alpha + \mu_h$, $B = a\beta_2 + b_m - \mu_m$, $C = a\beta_2 + b_m$ and $D = \delta_1 + \mu_h$.

2.3.3 Stability Analysis

To proceed further, we will analyse the stability of the model at infection-free stationary point and disease endemic stationary point.

2.3.3.1 Local Stability at Disease-free Equilibrium

Firstly, firstly we will evaluate the threshold parameter R_0. We have computed R_0 by next generation matrix [93] and its value is

$$R_0 = \sqrt{\frac{a^2\beta_1\beta_2(\delta_1 + \mu_h + \theta\omega)}{(\phi + \alpha + \mu_h)((\theta + \mu_h + \epsilon)D - \theta\delta_1)}}.$$

Theorem 2.2. *The infection-free equilibrium* $E_0(s_h^{'}, p_h^{'}, 0, r_h^{'}, s_m^{'}, 0)$ *is locally asymptotically stable provided* $R_0 < 1$.

Proof. The local stability at E_0 is done by finding out the eigenvalues. The Jacobian of the system is given under

$$J_0 = \begin{pmatrix} -\omega a\beta_1 i_m - (\delta_1 + \mu_h) & 0 & -\omega a\beta_1 p_h \\ \omega a\beta_1 i_m & -(\phi + \alpha + \mu_h) & a\beta_1 s_h + \omega a\beta_1 p_h \\ 0 & a\beta_2 s_m & -\mu_m \end{pmatrix}$$

The Jacobian calculated at $E_0(s_h^{'}, p_h^{'}, 0, r_h^{'}, s_m^{'}, 0)$ is

$$J_0 = \begin{pmatrix} -(\delta_1 + \mu_h) & 0 & -\frac{\omega a \beta_1 b_h \theta}{(\theta+\mu_h+\epsilon)D-\theta\delta_1} \\ 0 & -(\phi + \alpha + \mu_h) & a\beta_1 s_h^{'} + \omega a \beta_1 p_h^{'} \\ 0 & a\beta_2 s_m^{'} & -\mu_m \end{pmatrix}$$

which contributes one of the eigenvalue as $\lambda = -(\delta_1 + \mu_h) < 0$.

The other eigenvalues are calculated from

$$\lambda^2 + (\phi + \alpha + \mu_h + \mu_m)\lambda - a^2\beta_1\beta_2 s_m^{'}(s_h^{'} + \omega p_h^{'}) = 0.$$

It can be written as $\lambda^2 + A_1\lambda + A_2 = 0$,

where $A_1 = \phi + \alpha + \mu_h + \mu_m > 0$,

and $A_2 = -a^2\beta_1\beta_2 s_m^{'}(s_h^{'} + \omega p_h^{'}) = (1 - (R_0)^2)\, A\frac{b_m}{\mu_m}$.

According to Routh-Hurwitz criteria, condition is $A_1 > 0$ along with $A_2 > 0$.

Clearly, $A_1 > 0$ and $A_2 > 0$ if $(1 - (R_0)^2)\, A\frac{b_m}{\mu_m} > 0$,

that is, $1 - (R_0)^2 > 0$, which implies, $R_0 < 1$. Therefore, the infection-free equilibrium E_0 is locally asymptotically stable for $R_0 < 1$. □

2.3.3.2 Stability Analysis at Endemic Equilibrium

Here, the local asymptotic stability at disease-endemic equilibrium is discussed using Routh-Hurwitz criteria.

Theorem 2.3. *The endemic equilibrium is locally stable if* $A_1 > 0, A_2 > 0$ *and* $A_1A_2 - A_3 > 0$ *conditions holds, where* A_1, A_2 *and* A_3 *are given below.*

Proof. The local stability of disease-endemic equilibrium is evaluated by the calculating eigenvalue of the model at the point E^* while assuming that $i_h \neq 0$.

Jacobian matrix J_1 for the given system is

$$J_1 = \begin{pmatrix} -a_{11} & a_{12} & -a_{13} \\ a_{21} & -a_{22} & a_{23} \\ a_{31} & a_{32} & -a_{33} \end{pmatrix}$$

where $a_{11} = \omega a \beta_1 i_m + (\delta_1 + \mu_h), a_{12} = 0, a_{13} = \omega a \beta_1 p_h, a_{21} = \omega a \beta_1 i_m,$
$a_{22} = (\phi + \alpha + \mu_h), a_{23} = a\beta_1 s_h + \omega a \beta_1 p_h, a_{31} = 0, a_{32} = a\beta_2 s_m, a_{33} = \mu_m.$
The equation giving values of λ for E^* is given by $det(J_1 - \lambda I_3) = 0,$
where I_3 is the identity matrix. Now for determining the stability at E^*, we will be using Routh-Hurwitz criteria to investigate the stability with the help of the characteristic equation given by $\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0,$
where the coefficients $A_i's$ are given by: $A_1 = (a_{11} + a_{22} + a_{33}),$
$A_2 = [a_{11}(a_{22} + a_{33}) + (a_{22}a_{33} - a_{23}a_{32})], A_3 = a_{11}(a_{22}a_{33} - a_{23}a_{32}) + a_{13}a_{21}a_{32}.$
According to Routh-Hurwitz criteria, endemic equilibrium will be LAS provided $A_1 > 0, A_2 > 0, A_3 > 0, A_1A_2 - A_3 > 0.$

□

2.4 Numerical Simulation and Discussion

Using initial conditions $S_h(0) = 100$, $P_h(0) = 20$, $I_h(0) = 10$, $R_h(0) = 10$, $S_m(0) = 120$, $I_m(0) = 20$ and parameters values: $b_h = 10, a = 1, \beta_1 = .001, \theta = 0.2, \delta_1 = 0.05, \mu_h = .01, \epsilon = 0.1, \omega = 1, \phi = 0.02, \alpha = 0.008, b_m = 0.051, \mu_m = 0.1, \beta_2 = 0.01$. To check the sensitivity of model outcomes to the changes in various parameters, the model was simulated for different scenarios. To check the effect of mosquito interaction with humans, the parameters relating to mosquito bite and transmission of yellow fever, that is, the values of a and β_1 were varied. The system changes from disease-free state to endemic state when the values $a = 1, \beta_1 = 0.0001$ were changed to $a = 4, \beta_1 = 0.01$ which reflected in the change of value of R_0 changing from 0.2749 to 1.0997 while keeping all other parameters fixed. This is shown in Figures 2.2 and 2.3.

TABLE 2.2: Table for Parameters for the Model for the Disease Yellow Fever.

Parameters	Value	Source
a	[1,12]	[94], [95]
β_1	0.001	assumed
β_2	0.01	[90]
θ	0.2	assumed
μ_h	0.01	assumed
μ_m	0.1	assumed
ϵ	0.1	[96], [97], [98]
b_h	10	assumed
b_m	0.051	[74]
δ_1	0.05	assumed
α	0.008	[34]
ϕ	0.02	assumed

Discussion on Number of Mosquito Bites

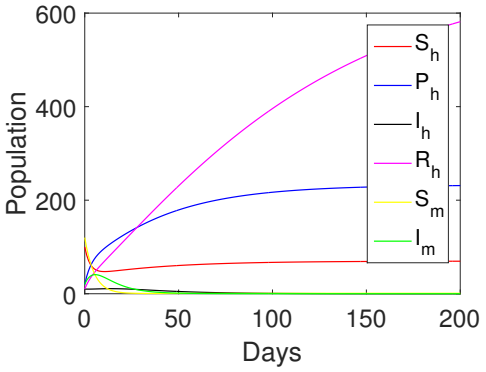

FIGURE 2.2: Simulation results for disease-free state for $a = 1, \beta_1 = 0.0001$, $R_0 = 0.2749$.

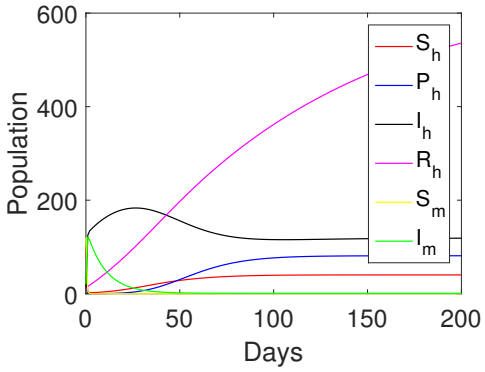

FIGURE 2.3: Simulation results for endemic state for $a = 4, \beta_1 = 0.01$, $R_0 = 1.0997$.

The simulation was done with varying values of a while keeping all other fixed. Depending upon $a \in [1, 12]$, R_0 varies from 0.0869 to 1.0433. It can be interpreted as the insect biting rate increases, the infection increases in human population as shown in Figures 2.4 and 2.5. The data used for the parameter related to mosquito bite in the model is largely consistent with the work done by [74, 94, 95] which gives validation to our work.

Discussion on Transmission Parameter

In our work, it has been shown that a slight change in the value of transmission

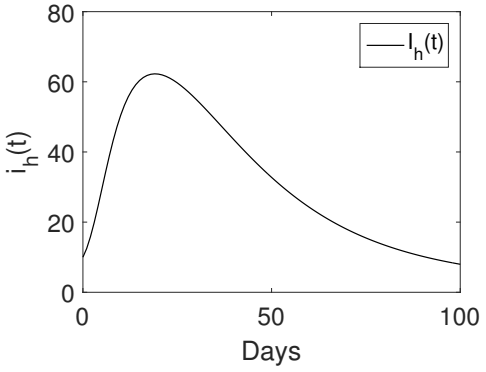

FIGURE 2.4: Simulation results for infective state humans for $a = 1$, $R_0 = 0.0869$.

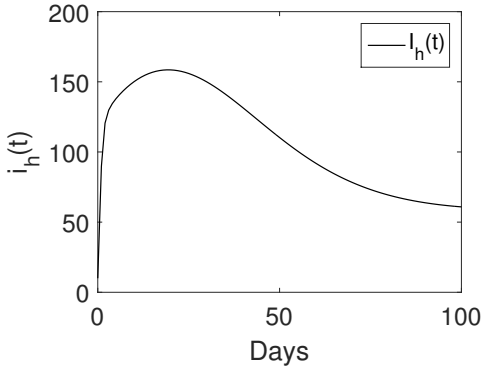

FIGURE 2.5: Simulation results for infective state humans for $a = 12$, $R_0 = 1.0433$.

parameter β_1 affects the value of R_0. As the yellow fever transmission parameter for humans, β_1 increases, there is increase in infection in human populations as can be seen in Figures 2.6 and 2.7. It is apparent from the simulation and verified numerically that as we increase β_1 from 0.001 to 0.002, the value of R_0 changes from $0.8694 < 1$ to $1.2295 > 1$. It is apparent that by reducing β_1, there will be reduction in severity of disease. These results are supported by a statical work done by [99] in which they used two models to estimate the intensity of transmission in African regions which are endemic to the disease. The results are also in line with the work done by Hamlet et al. [100] in which logistic regression model was used to predict the mosquito dependence on temperature. It was found that force of infection plays a strong role in the dynamics of the infection.

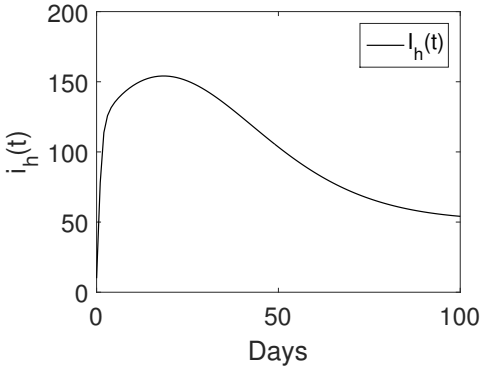

FIGURE 2.6: Simulation results for infective state of humans for $\beta_1 = 0.001$, $R_0 = 0.8694$.

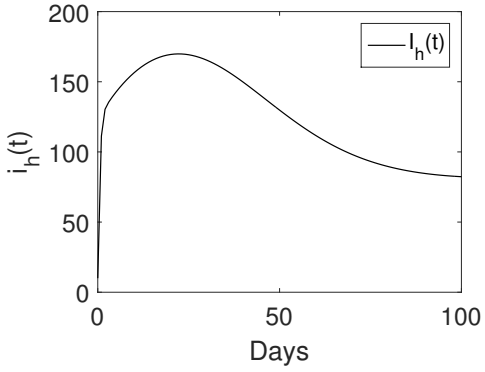

FIGURE 2.7: Simulation results for infective state of humans for $\beta_1 = 0.002$, $R_0 = 1.2295$.

Discussion on Insect Repellent

To examine the effects of temporary immunity attained through insect repellent on the severity of disease, all other parameters are fixed except the parameter for temporary imunity (ϕ). The value of R_0 decreases from 1.0039 to 0.8694 as we increased the value of ϕ from 0.01 to 0.02. It can be interpreted as that even the small amount of insect repellent has a dampening effect on the progress of disease. The peak of the curve decreases rapidly as is clear in the Figures 2.8 and 2.9.

Discussion on Vaccination Rate

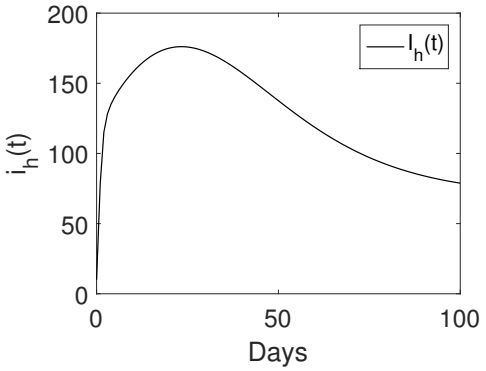

FIGURE 2.8: Simulation results for infective state of humans for $\phi = 0.01$, $R_0 = 1.0039$.

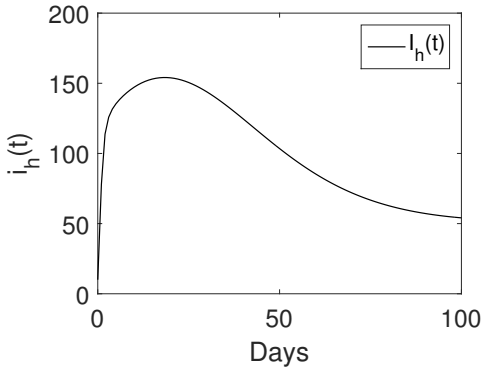

FIGURE 2.9: Simulation results for infective state of humans for $\phi = 0.02$, $R_0 = 0.8694$.

Various vaccination programmes can be incorporated to make the disease control in time. This can be done by starting vaccination programmes in the time before the activity of the mosquitoes reaches its maximum height, that is, during colder months. To model this, different values of vaccination rates were considered for simulation. Figures 2.10 and 2.11 represent the effect of vaccination rate ϵ on the infected population I_h. The greater the value of ϵ, the smaller is the infection in human population as is visible from the graphs. In our study, it was found that as the value of vaccination rate increases, the infection in the population decreases. These results are supported by study done by Garske et al. [34] in which the authors applied estimation method to study the impact of vaccination coverage through generalized linear models. The model has been validated with the fact that the value of the parameter taken for vaccination to control the disease is in

the range $[0, 1]$ which is consistent with the work done by [96–98].

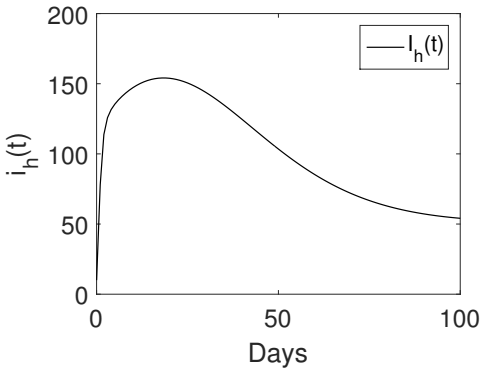

FIGURE 2.10: Simulation results for infective state of humans for $\epsilon = 0.1$.

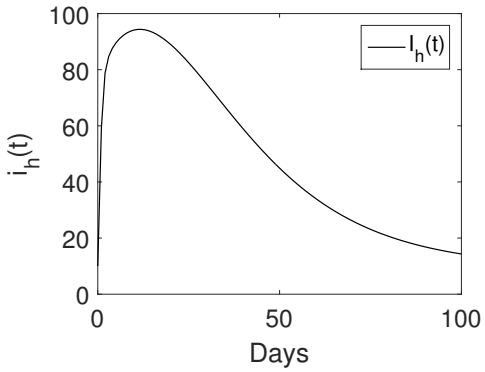

FIGURE 2.11: Simulation results for infective state of humans for $\epsilon = 0.9$.

2.5 Conclusion

A mathematical model for the disease dynamics of control of yellow fever is proposed and studied in which two populations namely humans and mosquitoes are considered. Disease-free equilibrium and endemic equilibrium are calculated and the local stability at these points have been investigated by applying Routh-Hurwitz criteria. Further, the value of basic reproduction has been calculated by using next-generation matrix method. The results showed that disease can be controlled by reducing mosquito biting rate, disease transmission parameter and vaccine coverage rate. Since, vaccines are not easily available in all areas which are affected by yellow fever and there are also rare adverse effects based on yellow fever vaccine. Therefore, the use of insect repellent to reduce the contact between mosquito and human is added as a precautionary measure which further can reduce the chances of epidemic. It has been shown numerically that preventive measures like application of insect repellent plays an important role along with vaccination. As we increased the value of parameter related to temporary protection through insect repellent, the value of R_0 changes from < 1 to > 1. The very significant factor used to predict the disease transmission, that is, (R_0) is shown to be highly

sensitive to this preventive measure giving temporary immunity. Numerical simulation is done for different scenarios by using MATLAB to support the analytic results.

Chapter 3

Mathematical Modeling on the Effect of Control Measures on Disease Dynamics of Two Species: A Study on Yellow Fever and Chikungunya

3.1 Introduction

Humans are susceptible to any kind of pathogen and the source of that infection can vary depending upon variety of factors. In vector-host interaction, when one species is infected, the other too gets infected after interaction. In a similar way, the control strategies applied on either one or both have impact on each other as they complete the circle. Here, we are studying the impact of control measures on disease dynamics of both the species by taking yellow fever and chikungunya as an example.

3.2 Model for Yellow Fever with Control Measures

Yellow fever is a zoonotic disease in a cycle of humans and non-human primates, where humans are the hosts and mosquitoes are vectors for the transmission cycle. It is endemic in Sub-Saharan Africa and Southern America. Its reemergence in mainly travellers travelling to endemic areas is a big reason to worry [101]. Mathematical modeling has emerged as a helping tool in framing various health policies which are cost effective that can reduce disease burden of these outbreaks. Many researchers have applied mathematical modeling for spread of these epidemics [102–105]. For example, Ankersen et al. [77] proposed a compartmental model for yellow fever epidemic through the effect of treatment of standing water on mosquito population. Yusuf et al. [74] formulated a deterministic model with multiple control measures for yellow fever outbreak. It was found that outbreak can be controlled if chemical and biological tools control mosquito population. Many researchers have studied yellow fever with effect of vaccine like Barrett [106] studied the availability of live attenuated vaccine 17D strain. It was suggested that occasional supply or insufficient supply of vaccine should be taken care of as there is literature available till date about vaccine shortage [107]. Although, there is a limited research supporting an alternative for shortage of YF vaccine [108] but much literature is not available. Also, yellow fever vaccine associated viscerotropic infection is although rare but it is fatal [109].

Among various control measures is control through awareness about infection as rise in the infection is accompanied by rise of awareness. This in turn make people change their behaviour as they try to isolate them or try to prevent the infection. These behavioural patterns can change in the patterns of transmission of the infection by reducing its pace. This awareness can be in any form like wearing face mask, having home remedies, having vaccination in time etc. Various researchers around the world have worked on the contribution of awareness in the control of disease. The contribution of some noteworthy researchers is included here. For example, awareness in population regarding vaccination required for international

travel was discussed in the [110]. It was observed in a study conducted at yellow fever vaccination clinic at Indian Institute of Medical Sciences, Bhubneswar, India that only 57.3 percent are aware of any requirements of travel vaccination. Whereas, 37.5 percent of the participants knew the fact that YF vaccine gives lifelong immunity. It was concluded that awareness about vaccination while travelling was also associated with occupation, higher education and history of any previous vaccination. Because of the fact that international travel exposes a person to wide spectrum of diseases, it was advised that the awareness regarding vaccination and prevention should be properly disseminated. The role of awareness has also been studied for HIV/AIDS by [111]. The role of awareness about gynecological health has also been taken seriously by [112]. The same kind of study on awareness is done by Jegede et al. [113]. It was concluded through a survey done by cross sectional study among 670 international travellers departing from Addis Ababa Bole international airport that uptake of recommended vaccines specifically DPT and influenza was low. There are variety of aspects involved in the vaccination programmes. In the work, the factors of religion and belief system were discussed. Considering the pivotal points, Mehta et al. [114] studied the factors like knowledge, attitude and precautionary measures taken regarding mosquito borne diseases by taking a sample from Bhavanagar, India. It was found that from sample of 135 persons, 88.1 percent of sample have awareness about these disease whereas 76.3 percent were aware about precautionary measures about the disease.

Although the YF vaccine confers lifelong immunity, there are adverse effects of vaccine that should be taken into consideration. The author in [115] emphasizes on the understanding the human behaviour response to the epidemics. He suggested that in epidemic modeling, society and disease both should be taken together as it is a co-evolution. It was suggested that there are many factors that change the behaviour of people like quarantine, closure of public places, control tracing etc. and these factors when included in a disease model can give better results. The authors in [116] studied the effects of connectivity between susceptible and

infective population. It was suggested that contact searching can be an effective tool in controlling the epidemic. The impact of SARS epidemic on the behaviour of population was also studied [117]. Through telephone survey done on 1603 adults in Hong Kong, it was noted that after the epidemic, majority of people adopted healthier lifestyle, spent more on health resources, practiced good health hygiene, measured healthy diet and opted for weight control practices. It was concluded that people opted for more healthy lifestyle to be safe. The authors in [118] studied that there is a relationship between health behaviour and risk perception. Moreover, there is a significant role of media in controlling the infectious diseases [119]. Further, this work was taken ahead by [120] in which the authors developed a SIS model for infection by incorporating media coverage. It was concluded that media coverage cannot fully eradicate infection but to an extent more awareness through media in a given population can reduce the number of infectives. Working further in the same field, Cui et al. [121] formulated three dimensional model for infectious disease. Stability analysis and numerical simulation shows that media coverage shortens the time of secondary peaks in the graphs. Taking the work to new heights, Funk et al. [122] analyzed and formulated a mathematical model to study the effect of awareness about the disease. It was concluded that if the infection rate is below some threshold value, the behavioral response in the proximity of the disease outbreak can stop the disease spread. It was observed that the factors like prediction of results of future of outbreak and interpreting disease parameters are very important. Furthermore, Funk et al. [123] studied endemic diseases of which population is aware or unaware. They studied the impact of various disease parameters under the effect of awareness among individuals. It was concluded that the correlations between disease and awareness at the local level is significant in the starting phase of any outbreak. Also, the investigation of spread of pathogen in disease transmission when the population changes behaviour being aware of infection was done. Moreover, compartmental model to study the dissemination of information in prevention of disease was studied by incorporating the level of responsiveness to information about disease [124].

A lot of work has been done to study the impact of awareness in the spread of various outbreaks of various diseases. But to our knowledge, there is still scope in this field regarding awareness for yellow fever. In the present work, we have proposed a mathematical model for yellow fever to study the effect of awareness programmes being executed by media along with control on vector population through insecticide. This awareness about infection will affect the susceptible class. Further, this susceptible class will be more on the precautionary side thereby forming a separate aware class.

3.2.1 Mathematical Model

In the upcoming section, a mathematical model is established by incorporating awareness through media among human population as a control measure and insecticide as a control strategy for vector population thereby showing the impact on both the species.

3.2.1.1 Model Formulation

Here, the total population of human $N_h(t)$ is segregated into three compartments susceptible, infected and aware. Here, $S_h(t)$ represents susceptible humans, $I_h(t)$ represents infected humans and $A_h(t)$ represents aware human class as regards to their awareness or disease status. The total vector population $N_v(t)$ is categorised into two classes namely susceptible vectors $S_v(t)$ and infected vectors $I_v(t)$. Here, $M(t)$ is the number of campaigns conducted by media to make people aware at that time. It is being assumed that the campaigns through media are considered to be dependent on the number of infected persons in the community. Further, the decrease in the media campaigns is also included in the model. This descent can be due to social causes, psychological reasons or monotonicity of these programmes. Not all, but a certain number of them are maintained in the system after some time as there is probability of presence of infected vectors in the system. It is being assumed that host and vector population mixes freely and disease spreads through

direct contact only. Further, it being a vector borne disease, to control the disease transmission, the vector control is very important factor. For this purpose, we have added insecticide as a control measure in the model. Under these assumptions, the progress of the disease is expressed by the set of differential equations:

$$\begin{aligned}
\dot{S_h} &= A - abS_hI_v - \beta MS_h + \delta A_h - d_1S_h,\\
\dot{I_h} &= abS_hI_v - (\alpha + d_1)I_h,\\
\dot{A_h} &= \beta MS_h - \delta A_h - d_1A_h,\\
\dot{S_v} &= b_v - acS_vI_h - \epsilon A_hS_v - (u_1 + d_2)S_v,\\
\dot{I_v} &= acS_vI_h - \epsilon A_hI_v - (u_1 + d_2)I_v,\\
\dot{M} &= \tau I_h - \tau_0(M - M_0).
\end{aligned} \tag{3.1}$$

Here, human population increases by birth or immigration rate A where a is the number of mosquito bites per human per unit time. The term b represents the transmission probability of getting infection from mosquito to host. Therefore, ab represents the rate at which susceptible host gets infection from mosquitoes. Similarly, c is the transmission probability of infection from human to mosquito. Therefore, ac is the rate at which mosquito gets infected from humans. b_v is the birth rate of mosquitoes. Here, the term α denotes the mortality rate of infected persons due to yellow fever. Again, β is the rate of dissemination of awareness programmes. These awareness programmes helps the population make a new class named aware class. It is being assumed that aware population will take all the precautions for their safety and are successful in doing so. δ is the rate at which aware class loose awareness because of fading away of memory or some social issues. ϵ is the rate at which aware population makes effort to reduce vector population by various efforts like proper of drainage of water, cleanliness etc. Moreover, u_1 is the control measure in the form of insecticides to reduce the vector population. Here, τ is the rate at which awareness programmes through media are executed. Again, τ_0 is the rate at which these programmes decline. M_0 is the number of baseline programmes maintained in the system.

3.2.1.2 Description of Parameters in the Model

TABLE 3.1: Table for Description of Parameters for Disease Yellow Fever with Awareness.

Parameters	Description	Units
a	Mosquito biting rate	per population per day
b	Transmission probability of YF from infected mosquito to human	-
c	Transmission probability of YF from infected human to mosquito	-
β	Rate of propagation of awareness	day^{-1}
δ	Rate at which individuals loose awareness due to memory fading	day^{-1}
d_1	Natural death rate for humans	day^{-1}
d_2	Natural death rate for mosquitoes	day^{-1}
α	Disease death rate of infected humans	day^{-1}
ϵ	Rate of making efforts to control mosquito population	per population per day
u_1	Pesticide control for mosquito population	day^{-1}
τ	Rate at which awareness is being spread through media	day^{-1}
τ_0	Rate at which media campaigns diminish	day^{-1}
M_0	Value of baseline number of programs maintained in system	-

3.2.2 Dynamical Behaviour of the Model

In the upcoming section, we will check the dynamic behaviour of model (3.1) by firstly investigating the boundedness and positivity of the solutions of the model.

3.2.2.1 Boundedness and Positivity of Model

The expressions for $N_h(t)$ and $N_v(t)$ can be attained from

$$N_h(t) = S_h(t) + I_h(t) + A_h(t),$$
$$N_v(t) = S_v(t) + I_v(t).$$

Adding the equations in (3.1), we get

$$\begin{aligned} \dot{N_h} &= A - d_1 N_h - \alpha I_h, \\ \dot{N_v} &= b_v - u_1 N_v - d_2 N_v. \end{aligned} \tag{3.2}$$

It is quite clear from first equation of (3.2), $N_h \leq \frac{A}{d_1}$ and N_v approaches $\frac{b_v}{u_1 - d_2}$ as time approaches infinity. As we are studying human and mosquito population, it is assumed that all the parameters involved are non-negative.

Theorem 3.1. *Assuming the initial conditions of the model to lie in T, where*

$$T = \{(S_h, I_h, A_h, S_v, I_v, M) \in R_+^6 : S_h \geq 0, I_h \geq 0, A_h \geq 0, S_v \geq 0, I_v \geq 0, M \geq 0\}.$$

$\exists$ a unique solution lying in T for $t \geq 0$.

Proof. Taking third equation of (3.1), $\dot{A_h} = \beta M S_h - \delta A_h - d_1 A_h$,
solving the above equation, we get $A_h \geq C_0 e^{-(\delta + d_1)t}$, C_0 being arbitrary constant, implying that $\forall$ t$\geq$ 0, $A_h \geq 0$.
Taking second last equation of (3.1), $\dot{I_v} = acS_v I_h - \epsilon A_h I_v - (u_1 + d_2) I_v$, solving the above equation, $I_v \geq C_1 e^{-(\epsilon + u_1 + d_2)t}$, C_1 being arbitrary constant, implying that $\forall$ t$\geq$ 0, $I_v \geq 0$.
Taking last equation of (3.1), $\dot{M} = \tau I_h - \tau_0 (M - M_0)$, solving, we get $M \geq C_2 e^{(-\tau_0)t}$, where C_2 is any constant. Therefore, $\forall$ t$\geq$ 0, $M(t) \geq 0$.
Now, considering first equation of (3.1), $\dot{S_h} = A - abS_h I_v - \beta M S_h + \delta A_h - d_1 S_h$.
It can be rewritten as $\dot{S_h} \geq -abS_h I_v - \beta M S_h - d_1 S_h$,
solving, $S_h \geq C_3 e^{-(f_1(t) + f_2(t) + d_1)t}$, where C_3 is any constant and $f_1(t) = abI_v$, $f_2(t) = \beta M(t)$ are positive as both $I_v \geq 0$ and $M(t) \geq 0$, which implies $\forall$ t$\geq$ 0, $S_h \geq 0$.
In the similar manner, it can be proved that $S_v \geq 0$ and $I_h \geq 0$ $\forall$ t$\geq$ 0. □

3.2.2.2 Analysis of Model

Firstly, we will analyse the model by finding the equilibrium points of the system (3.1) and then the value of R_0 will be evaluated to see the progression of the disease.

3.2.2.3 Disease-free Equilibrium

Here, we find the equilibrium states of the system. To find the disease-free equilibrium, that is, when there is no infection in the population, we put $I_h = 0, I_v = 0$. So, we get disease-free equilibrium $E^0(S_h^0, 0, A_h^0, S_v^0, 0, M^0)$.
Here, $S_h^0 = \frac{AC}{P}, A_h^0 = \frac{A\beta M_0}{P}$, $S_v^0 = \frac{Pb_v}{\epsilon A\beta M_0 + PD}, M^0 = M_0$.
Here, $C = d_1 + \delta, D = u_1 + d_2, P = d_1(\beta M_0 + C)$.

3.2.2.4 Basic Reproduction Number

To study the disease progression in the society, we derive the value of basic reproduction number, R_0. The value of R_0 decides whether a disease will die out or turn into an epidemic. To calculate R_0, we will be using Next Generation Matrix (NGM) given by [93]. For NGM, we have transmission matrix F and transition matrix V. Here F is transmission matrix describing production of new infection and V is the transition matrix denoting change in the state including death. The matrices F and V are given by

$$F = \begin{pmatrix} 0 & abS_h^0 \\ acS_v^0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} -(\alpha + d_1) & 0 \\ 0 & -\epsilon A_h^0 - u_1 - d_2 \end{pmatrix}$$

After calculating V^{-1}, $-FV^{-1}$ is calculated, where

$$FV^{-1} = \begin{pmatrix} 0 & \frac{-BabS_h^0}{Q} \\ \frac{-acS_v^0(\epsilon A_h^0 + D)}{Q} & 0 \end{pmatrix}$$

Here $B = \alpha + d_1, D = u_1 + d_2, Q = B(D + \epsilon A_h^0)$.

We compute the dominant eigenvalue of the matrix $-FV^{-1}$, that is, the spectral radius R_0.

$$R_0 = \sqrt{\frac{a^2 bcS_h^0 S_v^0}{Q}}$$

3.2.2.5 Local Stability Analysis at Infection-free Equilibrium

To check the stability at disease-free state, we check the Jacobian of the system (3.1). Jacobian is given by

$$J_0 = \begin{pmatrix} -abI_v - \beta M - d_1 & 0 & \delta & 0 & -abS_h & -\beta S_h \\ abI_v & -B & 0 & 0 & abS_h & 0 \\ \beta M & 0 & C & 0 & 0 & \beta S_h \\ 0 & -acS_v & -\epsilon S_v & -\epsilon A_h - D - acI_h & 0 & 0 \\ 0 & acS_v & -\epsilon I_v & acI_h & -\epsilon A_h - D & 0 \\ 0 & \tau & 0 & 0 & 0 & -\tau_0 \end{pmatrix}$$

where $C = \delta + d_1$.

The Jacobian for disease-free equilibrium E^0 is

$$J_0 = \begin{pmatrix} -\beta M_0 - d_1 & 0 & \delta & 0 & -abS_h^0 & -\beta S_h^0 \\ 0 & -B & 0 & 0 & abS_h^0 & 0 \\ \beta M_0 & 0 & C & 0 & 0 & \beta S_h^0 \\ 0 & -acS_v^0 & -\epsilon S_v^0 & -\epsilon A_h^0 - D & 0 & 0 \\ 0 & acS_v^0 & 0 & 0 & -\epsilon A_h^0 - D & 0 \\ 0 & \tau & 0 & 0 & 0 & -\tau_0 \end{pmatrix}$$

The eigenvalues given by above matrix are $\lambda = -\epsilon A_h^0 - D, -\tau_0$.

Remaining eigenvalues are given by

$$\begin{aligned} \lambda^2 + A_1\lambda + A_2 = 0, \\ \lambda^2 + l_1\lambda + l_2 = 0. \end{aligned} \tag{3.3}$$

Here $A_1 = B + D + \epsilon A_h^0, A_2 = B(D + \epsilon A_h^0) - a^2 bc S_h^0 S_v^0$

and $l_1 = C + \beta M_0 + d_1, l_2 = C(\beta M_0 + d_1) - \beta M_0 \delta$.

For the first equation of (3.3), applying Routh-Hurwitz criteria, for the system to be stable, the conditions are $A_1 > 0$ and $A_2 > 0$. Clearly $A_1 > 0$ and $A_2 > 0$ if $B(D + \epsilon A_h^0) > a^2 bc S_h^0 S_v^0$,

which implies

$$\frac{a^2 bc S_h^0 S_v^0}{B(D + \epsilon A_h^0)} < 1,$$

which means

$$R_0 < 1.$$

The above result is presented in the form of theorem below:

Theorem 3.2. *The disease-free equilibrium* $E^0(S_h^0, 0, A_h^0, S_v^0, 0, M_0)$ *is locally asymptotically stable if* $R_0 < 1$.

In the upcoming section, we will take numerical examples using MATLAB.

3.2.3 Numerical Simulation and Discussion

Here, we perform numerical simulation using different set of parameters for the model (3.1) to support the above results. Also, validation of basic reproduction number is done. These simulation help us understand the correlation between human and vector population in a better way. With initial conditions $S_h = 1000$, $I_h = 100$, $A_h = 50$, $S_v = 500$, $I_v = 100$, $M = 0$. The values of parameters have been presented in the form of table given in the form of the table. To have better understanding of effect of various aspects of programmes initiating awareness on

TABLE 3.2: Table for Parameters for the Model for the Disease Yellow Fever with Awareness.

Parameters	Value	Source
a	[1,12]	[94], [95]
b	0.1	assumed
c	0.01	[90]
β	0.001	[105]
d_1	0.0005	assumed
d_2	0.0005	assumed
ϵ	0.01	assumed
M_0	5	[105]
δ	0.05	assumed
α	0.005	[34]
τ	0.0015	[105]
τ_0	0.22	[105]

disease dynamics, we varied parameters like rate of propagation of awareness programmes (β) and rate of making efforts to control mosquito population (ϵ).

Discussion on Dissemination of Awareness Programmes

Firstly, we vary parameter for rate of propagation of awareness programmes (β) from $\beta = 0.1$ to $\beta = 0.5$. As we increased the value of β, the value of R_0 changes from $1.6612 > 1$ to $0.8575 < 1$. This indicates that R_0 is greatly affected by rate of dissemination of awareness programmes. The same impact has been be shown in Figures 3.1 and 3.2.

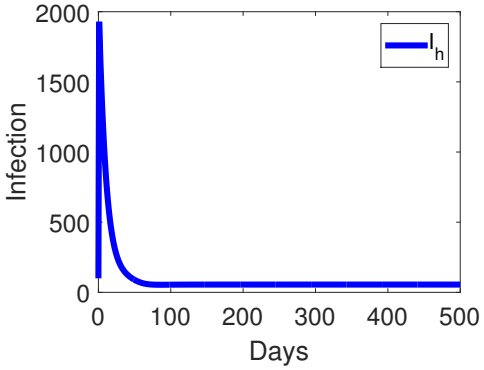

FIGURE 3.1: Simulation results for infectious human population for $\beta = 0.1$, $R_0 = 1.6612 > 1$.

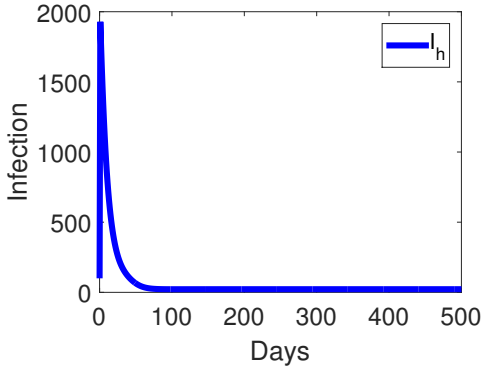

FIGURE 3.2: Simulation results for infectious human population for $\beta = 0.5$, $R_0 = 0.8575 < 1$.

Discussion on Efforts by Aware Population

Now, we varied the value of parameter for ϵ, the rate at which aware population

reduce vector population. It is verified from the figures that as there is increase in the efforts of aware population, there is decrease in mosquito population. As we increased the value of ϵ from $\epsilon = 0.001$ to $\epsilon = 0.01$. This resulted in decrease in the value of R_0 from 1.3276 to 0.8499 and if the value of R_0 is decreased below unity, this indicates decline in disease transmission. This is clear from Figures 3.3 and 3.4.

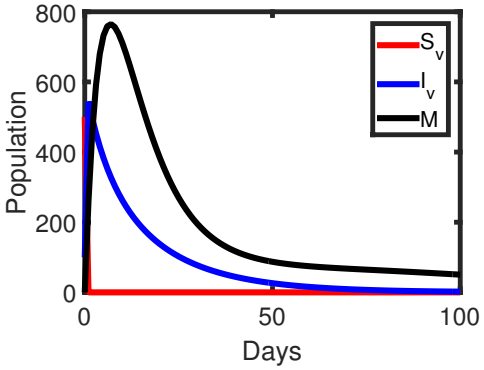

FIGURE 3.3: Simulation results for vector population for $\epsilon = 0.001$, $R_0 = 1.3276 > 1$.

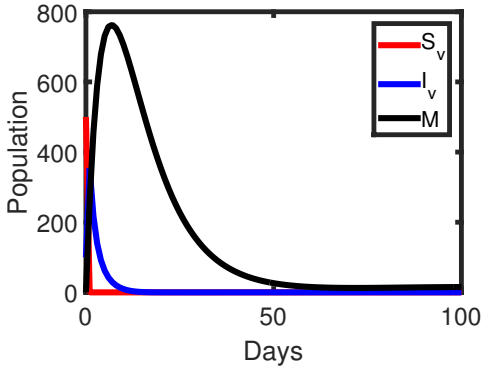

FIGURE 3.4: Simulation results for vector population for $\epsilon = 0.01$, $R_0 = 0.8499 < 1$.

Discussion on Usage of Insecticide

In the present model, we have also incorporated a factor of insecticide in the vector compartment to control the disease. It was observed that when we change the value of parameter for insecticide i.e. u_1 from 0.01 to 0.1, the value of R_0 decreases from 1.3276 to 0.8376. This indicates that if the value of parameter for insecticide is increased, then the value of R_0 decreases below unity. This indicates that increasing the control measure for mosquitoes, the disease transmission turns from epidemic to die off in the long run. For another vector borne disease [1], the value used for parameter for insecticide is in the range 0.2 to 0.7. We used a lesser quantity $u_1 = 0.1$, which still gives us $R_0 < 1$. This implies that by spreading awareness in the population, we can still control the disease by lesser amount of insecticide thereby saving environment from detrimental effects. This is shown in Figures 3.5 and 3.6.

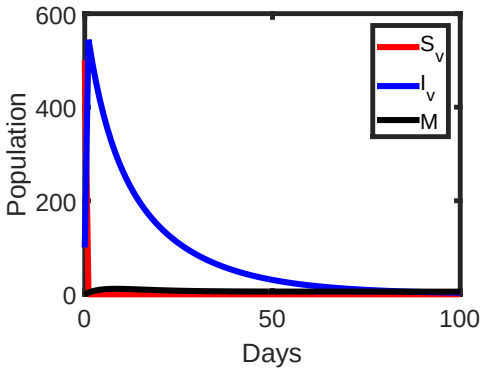

FIGURE 3.5: Simulation results for vector population for $u_1 = 0.01$, $R_0 = 1.3276 > 1$.

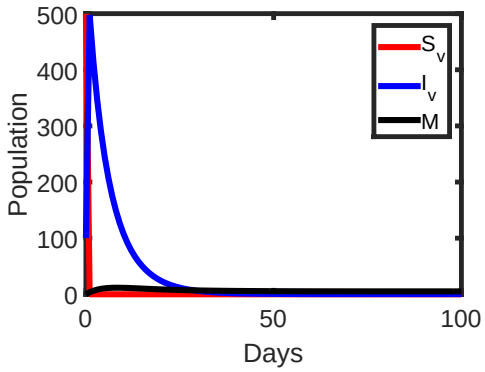

FIGURE 3.6: Simulation results for vector population for $u_1 = 0.1$, $R_0 = 0.8376 < 1$.

3.2.4 Conclusion

This work analyses the impact of awareness programmes on the dynamics of yellow fever infection in humans. It is being assumed that the programmes by media generate awareness implementing personal protection and control of vector population. Furthermore, the change in the behaviour of human population as a result of these programmes results in the fabricating of a separate compartment named aware class. This class not only protects themselves from infection through mosquitoes but also makes effort in reducing mosquito population. In this work, disease-free equilibrium and basic reproduction number has been calculated. Stability analysis at disease-free equilibrium has been performed. Disease-free equilibrium was found to be stable if $R_0 < 1$. Further, it was found that value of R_0 is affected by the rate of dissemination of awareness programmes. Moreover, it has been observed that the rate at which aware population reduces mosquitoes also affects the value of R_0. In the model, insecticide is also used as a control measure for yellow fever disease. It is found that lesser quantity of insecticide is sufficient to control the infection in addition to awareness programmes.

3.3 Model for Chikungunya Disease with Control Measures

Chikungunya is an alphavirus which affects humans by the bites of mosquito named *Aedes albopictus*. The cycle starts with the bite of an infected mosquito. The symptoms appear approximately after four days of incubation period and viremia usually persists for approximately 7 days in infected individuals. If in this period, a mosquito feeds on viremic host that can also get infected with chikungunya virus. The symptoms appear in 2 to 4 days including high fever, rash and chronic joint pain which can last for over a year [40]. The name of the virus has been derived from Makonde word of Southern Tanzania which means that which bends, as this results in bended posture because of multiple joint pains. The mortality rate due to chikungunya fever is low but can occur in persons having other health issues. After its reemergence after 20 years in various islands of Indian ocean, the first confirmed case of chikungunya was reported in Reunion island of Indian ocean in April 2005. This case was imported from Grande-Comore [45]. This turned into an outbreak consisting of two epidemic waves, one of which died in 2005 and turned to epidemic in 2006 producing $2,44,000$ estimated cases during outbreak. After the outbreak of this infection in Reunion island in 2005, in which one third of the total population got affected [40], the study of chikungunya was taken seriously by researchers. In 2012, Dumont et al. has done compartmental modeling by taking different classes for humans and vector while taking larvae compartment for mosquitoes for the first time. It was shown in their work that the value of R_0 changes from < 1 in 2005 to $R_0 > 1$ in 2006, which agreed with the situation in island as disease dies out in 2005 and turned out to be epidemic in 2006. The study was updated further by [41] by dividing mosquito population into eggs, larvae and adults stages. A case study of chikungunya outbreak in Italy has been studied by Poletti et al. in [42] in 2011 by a model taking into account the dynamics of mosquito, incorporating the climate factors. The value of R_0 was predicted to rise depending upon mosquito density. It was concluded that

epidemic can be under control by interventions in time besides high transmission capability of chikungunya virus. In a study, simulation was done by introduction of one infective person in different parts of the United States at different times of the years [43]. It was predicted that in August, if the chikungunya virus was introduced, the peak was at 38%, while the same was at 30% if it is from August to September. It was observed that changing time of introduction of infection in simulation does not work for areas like Miami, where the temperature support mosquito growth. Further, a study conducted in Europe revealed that the mosquito population can be reduced by the use of chemical larvicide, use of sprays like Deltamethrin, eliminating standing water in tires, buckets or destroying other breeding sites of mosquitoes [44]. But the use of adulticide like Deltamethrin and Fenirothion have been seem to harm the environment ([125], [126]) and in many areas the *Aedes* mosquito developed resistance to this adulticide. Further, to control the disease, pulse vaccination to susceptible population was studied by [127]. The same has been studied for different diseases [128–135]. There are many candidates in different stages of trial, but there is no vaccine available commercially [136–138]. Although there are some vaccines that have been tested on humans. Various trials for vaccine have been conducted by US Army Medical Research Institute. It was seen that in 85% of cases, neutralizing antibody titers were obtained after one year and there was seroconversation rate of 95% on day 28 [139]. But because of the emergence of threat of biological weapons in 2003, the trials for phase 3 of candidate vaccine was postponed [140]. One of the candidate, $VLA1553$, a live-attenuated vaccine candidate for active immunisation and prevention of disease caused by chikungunya virus seems to be promising vaccine [141].The effective vaccination depends on various factors like availability of vaccine, accessibility of health care facilities, belief system in humans for vaccination and proportion of population that can be vaccinated due to various constraints. In the absence of specific treatment, it can be controlled by mosquito control tools and symptomatic care of patients. So, the important way is to take the preventive measures like

reducing interaction with mosquitoes, controlling mosquito population. Insect repellent can also be used to reduce the interaction of mosquito to human and they are easily available and can be used by anyone. All the above factors discussed above if taken together can help reduce the amplitude of the epidemic curve.
Inspired from the discussion done, the target of this work is to control the spread of chikungunya by incorporating different control strategies. Here, in the present work, we have taken insecticide to control the vector population. It can be spray of chemical adulticide to reduce adult mosquito population or localized treatment of larvicides targeting the breeding sites of larvae before they mature. But chemical insecticide if used alone in massive quantity can harm the environment. Also, over time,*aedes* mosquitoes develop resistance to chemical insecticides. This necessitates us to study and to explore new control tools. Therefore, with the target to use it in minimum quantity, we are using insect repellent as temporary protection on humans to reduce the contact rate to control the disease. We take this into account as it is easy to handle and has no bad impact on environment. Further, vaccinating the susceptible population can also help in reduction of infection. So, total three types of controls have been considered in the model namely reducing the contact between humans and mosquitoes by application of insect repellent by humans, application of insecticides and vaccinating the susceptible population. Till now, there is no mathematical model incorporating these three control measures affecting both human and mosquito population in case of chikungunya virus.

3.3.1 Mathematical Model

Model formulation for chikungunya disease is done by making compartments of the population and then fabricating them in the form of differential equations.

3.3.1.1 Model Formulation

In this mathematical model for chikungunya virus, different compartments for human and mosquito population are considered. The human (host) population is

categorised into four epidemiological states, that is, susceptible, protected, infected and temporary immune class or recovered class denoted by $S_H(t)$, $P_H(t)$, $I_H(t)$ and $R_H(t)$ respectively. The vector population is split into two states namely susceptible $S_V(t)$ and infected $I_V(t)$. There is no recovered class for mosquitoes because if they get infected they never recover.

Here, it is assumed that the probability of a susceptible human to get infected from an infectious mosquito depends upon the density of human hosts and infectious mosquitoes [142].

It is being assumed that mosquito and human populations are mixed well and chikungunya is transmitted between humans and mosquitoes. Also, no vertical transmission in case of virus is assumed in the model. As the interaction between humans and mosquitoes can be reduced by the application of insect repellent. In our model, a protected class having temporary protection is taken by applying insect repellent. Here, b_H being the birth rate and μ_H being the natural mortality rate. The susceptible mosquitoes bite infected human beings at a rate a. Here, b is the proportion of the bites leading to infection. c being the probability that the vector becomes infected. The term γ $(0 \leq \gamma \leq 1)$ is the proportion of susceptible humans under temporary protection taken from mosquitoes per day. Since, the protection wanes off with time, therefore the individuals move from protected class to susceptible class $S_H(t)$ at rate δ. ω is the effective vaccination rate after which susceptible individuals goes to recovered/immune class. As the naive population travel to endemic areas with sprays and repellents to avoid mosquitoes. This gives them temporary protection for few hours after which it wanes off and we assume this protection reduces the likelihood of infection by a factor ϵ. Here $\epsilon = 0$, if the protection is effective and $\epsilon = 1$, if the protection is ineffective. θ is the rate of infected humans acquiring temporary immunity. The humans in infected class have disease death rate p. b_V and μ_V is the mosquito birth rate and death rates respectively. Further, q is the additional death rate of mosquitoes due to use of insecticide. Here, the term $\frac{abS_H I_V}{N_V}$ denotes the interaction of human host (S_H) and infected infected mosquito (I_V). The term $\frac{acS_V I_H}{N_H}$ denotes the interaction of

susceptible vector S_V with infected humans (I_H). With the assumptions discussed above, the model is constructed as:

$$\begin{aligned}
\dot{S_H} &= b_H N_H - ab\frac{S_H I_V}{N_V} - \gamma S_H + \delta P_H - (\mu_H + \omega)S_H,\\
\dot{P_H} &= \gamma S_H - \epsilon ab\frac{P_H I_V}{N_V} - (\delta + \mu_H)P_H,\\
\dot{I_H} &= ab\frac{S_H I_V}{N_V} + \epsilon ab\frac{P_H I_V}{N_V} - (\theta + p + \mu_H)I_H,\\
\dot{R_H} &= \theta I_H - \mu_H R_H + \omega S_H,\\
\dot{S_V} &= b_V N_V - ac\frac{S_V I_H}{N_H} - (\mu_V + q)S_V,\\
\dot{I_V} &= ac\frac{S_V I_H}{N_H} - (\mu_V + q)I_V.
\end{aligned} \tag{3.4}$$

along with the initial conditions $S_H(0) > 0$, $P_H(0) > 0$, $I_H(0) > 0$, $R_H(0) > 0$, $S_V(0) > 0$, $I_V(0) > 0$.

Here,

$$\begin{aligned}
N_H(t) &= S_H(t) + P_H(t) + I_H(t) + R_H(t),\\
N_V(t) &= S_V(t) + I_V(t).
\end{aligned}$$

Upon adding the equations (3.4) in the model, we get,

$$\begin{aligned}
\dot{N_H} &= b_H N_H - \mu_H N_H - pI_H,\\
\dot{N_V} &= b_V N_V - \mu_V N_V - qN_V.
\end{aligned} \tag{3.5}$$

It is quite clear from first equation in (3.5), that when disease is not present in the society ($p = 0$), population N_H grows exponentially if $b_H > \mu_H$, N_H is constant if $b_H = \mu_H$, N_H decreases if $b_H < \mu_H$.

Considering the second equation in (3.5), $N_V = c_1 e^{(b_V - \mu_V - q)t}$, which implies that N_V is constant if $b_V = \mu_V - q$, N_V decreases if $b_V < \mu_V - q$ and it grows exponentially if $b_V > \mu_V - q$.

3.3.1.2 Description of Parameters in the Model

TABLE 3.3: Table for Description of Parameters for Chikungunya Model.

Parameters	Description	Units
a	Mosquito biting rate	day^{-1}
b	Proportion of bites causing infection in mosquitoes	-
c	Probability of mosquito getting infected	-
θ	Rate at which infected individuals acquire temporary immunity	day^{-1}
δ	Rate at which susceptible humans move from P_H to S_H	day^{-1}
μ_H	Natural death rate of humans	day^{-1}
μ_V	Natural death rate for mosquitoes	day^{-1}
ω	Effective vaccination rate of susceptible humans	day^{-1}
b_H	Natural birth rate of humans	day^{-1}
b_V	Natural birth rate of mosquitoes	day^{-1}
p	disease induced death rate	day^{-1}
N_H	Total human population	-
N_V	Total mosquito population	-
γ	Proportion of individuals under temporary protection	day^{-1}
q	Mortality rate due to insecticide	day^{-1}
ϵ	0 if the protection is effective and 1 if the protection is ineffective	-

3.3.2 Dynamical Behaviour of the Model

We will analyse the model given by (3.4) firstly by making it dimensionless and then we will perform the stability analysis at equilibrium states of the system under study.

3.3.2.1 Positivity and Boundedness of the Model

Before moving further, we assume that parameters taken in the model are taken to be non-negative, as the interaction in the model is between mosquito and humans.

$$\Phi = \{(S_H, P_H, I_H, R_H, S_V, I_V) \in R_+^6 : S_H \geq 0, P_H \geq 0, I_H \geq 0, R_H \geq 0, S_V \geq 0, I_V \geq 0\}.$$

Assuming all the initial conditions in Φ there is a unique solution lying in Φ for $t \geq 0$.

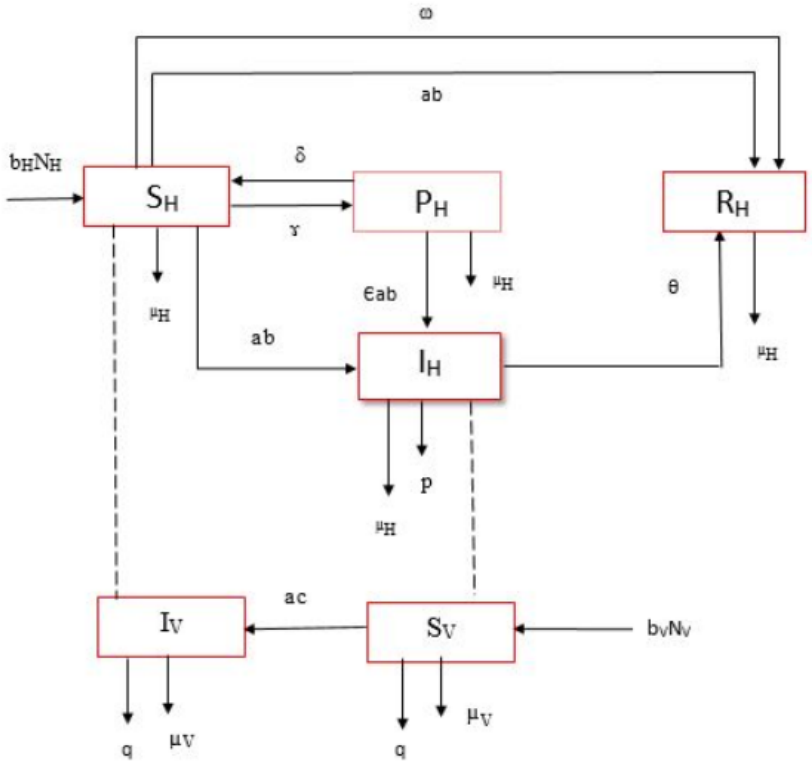

FIGURE 3.7: Flow diagram of the system

Theorem 3.3. *With the initial conditions of the system formulated to lie in* Φ*, where*

$$\Phi = \{(S_H, P_H, I_H, R_H, S_V, I_V) \in R_+^6 : S_H \geq 0, P_H \geq 0, I_H \geq 0, R_H \geq 0, S_V \geq 0, I_V \geq 0\}.$$

there exists a unique solution of the system of equations (3.4) *and this solution lies in* Φ *for* $t \geq 0$.

Proof. Assuming the right side of system to be continuous and has partial derivatives that too are continuous in the region Φ, we can prove that the set of equations in the system has a unique solution for $t \geq 0$. Thereby, it will be sufficient to demonstrate that $S_H \geq 0, P_H \geq 0, I_H \geq 0, R_H \geq 0, S_V \geq 0$ and $I_V \geq 0$ for all time t. We will apply the same approach as applied in [74], [91] and [92].

$$Let\ T = sup\{t > 0 : S_H \geq 0, P_H \geq 0, I_H \geq 0, R_H \geq 0, S_V \geq 0, I_V \geq 0\}.$$

Therefore $T > 0$. Considering first equation in (3.4) of the model, we have,

$$\dot{S_H} = b_H N_H - ab\frac{S_H I_V}{N_V} - \gamma S_H + \delta P_H - \mu_H S_H - \omega S_H. \tag{3.6}$$

We can rewrite it as

$\dot{S_H} + [f(t) + (\gamma + \omega + \mu_H)]S_H = F(t)$, where $f(t) = \frac{abI_V}{N_V}$ and $F(t) = b_H N_H + \delta P_H$.

$\frac{d}{dt}(S_H(t)[\exp{(\gamma + \omega + \mu_H)t} + \int_0^t f(\eta)d\eta]) = F(t)\exp[(\gamma + \omega + \mu_H)t + \int_0^t f(\eta)d\eta]$.

On integrating, the above equation becomes

$S_H(T)[\exp{(\gamma + \omega + \mu_H)T} + \int_0^T f(\eta)d\eta] - S_H(0) = \int_0^T [F(\xi)\exp[(\gamma + \omega + \mu_h)\xi + \int_0^\xi f(\eta)d\eta]d\xi$.

Therefore,

$$S_H(T) = S_H(0)\exp[-((\gamma + \omega + \mu_H)T + \int_0^T f(\eta)d\eta)]$$
$$+ \exp[-((\gamma + \omega + \mu_H)T + \int_0^T f(\eta)d\eta)] \times \int_0^T F(\xi)\exp[(\gamma + \omega + \mu_h)\xi + \int_0^\xi f(\eta)d\eta]d\xi.$$

Hence, $S_H(T)$ being sum of positive quantities is non-negative.

Therefore, $S_H(T) \geq 0$. Similarly, we can show that $P_H \geq 0$, $I_H \geq 0$, $R_H \geq 0$, $S_V \geq 0$ and $I_V \geq 0$ for all $t \geq 0$. □

3.3.2.2 Dimensionless Transformation

Here, it is assumed that the total human population and vector population does not vary significantly in the time interval taken under study. In a way, the population of both the species under study is assumed to be relative constant ([74]). Based on this it is interpreted that we can normalize the equations in the model

by scaling the population of each compartment by their respective species population. The transformations are given as under:

$$s_H = \frac{S_H}{N_H}, p_H = \frac{P_H}{N_H}, i_H = \frac{I_H}{N_H}, r_H = \frac{R_H}{N_H}, s_v = \frac{S_V}{N_V}, i_v = \frac{I_V}{N_V}.$$

On simplification, the system of equations reduces to

$$\begin{aligned}
\dot{s_H} &= b_H - abs_H i_v - \gamma s_H + \delta p_H - \mu_H s_H - \omega s_H, \\
\dot{p_H} &= \gamma s_H - \epsilon abp_H i_v - (\delta + \mu_H) p_H, \\
\dot{i_H} &= abs_H i_v + \epsilon abp_H i_v - (\theta + p + \mu_H) i_H, \\
\dot{r_H} &= \theta i_H - \mu_H r_H + \omega s_H, \\
\dot{s_v} &= b_v - acs_v i_H - (\mu_v + q) s_v, \\
\dot{i_v} &= acs_v i_H - (\mu_v + q) i_v.
\end{aligned} \tag{3.7}$$

3.3.2.3 Steady States

All the steady states of the system given by (3.7) are calculated by equating to zero the right side of the equations. The two equilibrium points of the system are evaluated as:

- Infection-free equilibrium point is $E^0(s_H^0, p_H^0, 0, r_H^0, s_v^0, 0)$

  where

  $s_H^0 = \frac{Db_H}{B}, p_H^0 = \frac{b_H \gamma}{B}, r_H^0 = \frac{D\omega b_H}{B\mu_H}, s_v^0 = \frac{b_v}{A}$

- Endemic equilibrium is $E^*(s_H^*, p_H^*, i_H^*, r_H^*, s_v^*, i_v^*)$

  where

  $s_H^* = \frac{(\epsilon a^2 bc + DE)Eb_H}{M}, p_H^* = \frac{\gamma E^2 b_H}{M}, i_H^* = \frac{B}{ac}, r_H^* = \frac{B\theta}{ac\mu_H} - \frac{N}{\mu_H},$
  $s_v^* = \frac{b_v}{E}, i_v^* = \frac{ac}{E}.$

  Where

  $A = \mu_v + q, B = ac + b_v - A, D = \delta + \mu_H, E = ac + b_v,$
  $L = \omega + \mu_H + \gamma, M = (a^2 bc + LE)(\epsilon a^2 bc + DE) - \delta\gamma E^2, N = \frac{\omega(\epsilon a^2 bc + DE)Eb_H}{M}.$

3.3.2.4 Stability Analysis

The local stability analysis of the model is done at both the equilibria along with the evaluation of R_0.

3.3.2.5 Stability Analysis at Disease-free Equilibrium E^0

Firstly, we will calculate R_0 by the approach by Van den Driessche [73]. Considering only those terms in which infection is in progress.
Infectious subsystem is taken as:

$$\begin{aligned}
\dot{p_H} &= \gamma s_H - \epsilon a b p_H i_v - (\delta + \mu_H) p_H, \\
\dot{i_H} &= a b s_H i_v + \epsilon a b p_H i_v - (\theta + p + \mu_H) i_H, \\
\dot{i_v} &= a c s_v i_H - (\mu_v + q) i_v.
\end{aligned}$$

This is segregated in two matrices T and $\sum$
where

$$T = \begin{pmatrix} -\epsilon a b i_v & 0 & -\epsilon a b p_H \\ \epsilon a b i_v & 0 & \epsilon a b s_H + \epsilon a b p_H \\ 0 & a c s_V & 0 \end{pmatrix}$$

and

$$\sum = \begin{pmatrix} -(\delta + \mu_H) & 0 & 0 \\ 0 & -(\theta + p + \mu_H) & 0 \\ 0 & 0 & -(\mu_v + q) \end{pmatrix}$$

Here, the matrix T is transmission matrix and is associated with number of secondary infections and Σ is transition matrix associated with rate of progress of infection. After calculating Σ^{-1} and $K = -T\Sigma^{-1}$.

$$K = \begin{pmatrix} -\epsilon a b i_v & 0 & \frac{-\epsilon a b p_H}{A} \\ \frac{\epsilon a b i_v}{D} & 0 & \frac{a b s_H + \epsilon a b p_H}{A} \\ 0 & \frac{a c s_v}{m} & 0 \end{pmatrix}$$

This matrix K is calculated at disease-free equilibrium and then the dominant eigenvalue of this $K = -T\Sigma^{-1}$ matrix will be the value of R_0.

Therefore,

$$R_0 = \sqrt{\frac{a^2 bcb_v b_H (D + \epsilon\gamma)}{A^2 Bm}}$$

where $m = (\theta + p + \mu_H)$.

Theorem 3.4. *The disease-free equilibrium $E^0(s_H^0, p_H^0, 0, r_H^0, s_v^0, 0)$ is locally asymptotically stable if $R_0 < 1$.*

Proof. The local stability at DFE is investigated from Jacobian matrix of the system.

$$J_0 = \begin{pmatrix} -abi_v - L & \gamma & abi_v & \omega & 0 & 0 \\ \delta & -\epsilon abi_v - D & \epsilon abi_v & 0 & 0 & 0 \\ 0 & 0 & -m & \theta & -acs_v & acs_v \\ 0 & 0 & 0 & -\mu_H & 0 & 0 \\ 0 & 0 & 0 & 0 & -aci_H & aci_H \\ -abs_H & -\epsilon abp_H & abs_H + \epsilon abp_H & 0 & 0 & -A \end{pmatrix}$$

where $L = \omega + \mu_H + \gamma$ and $D = \delta + \mu_H$.

Solving the above matrix to find the eigenvalues of the Jacobian at DFE, we get, $\lambda_1 = -A, \lambda_2 = -(\mu_v + q)$ which are negative definite.

Other eigenvalues are given by:

$$\begin{aligned} \lambda^2 + (L + D)\lambda + (LD - \gamma\delta) = 0, \\ \lambda^2 + (A + m)\lambda + Am - a^2 bcs_v^0 (s_H^0 + \epsilon p_H^0) = 0. \end{aligned} \tag{3.8}$$

Firstly, taking first equation of (3.8), we get $\lambda_3 = \frac{-(L+D)-\sqrt{disc}}{2}$ and $\lambda_4 = \frac{-(L+D)+\sqrt{disc}}{2}$.

Here, disc $= (L - D)^2 + 4\gamma\delta$, which is positive definite. λ_3 is negative definite.

λ_4 is negative if $(\mu_H + \omega)(\mu_H + \delta) + \mu_H\gamma > 0$ which is true.

Now taking second equation of (3.8), we get,

$\lambda_5 = \frac{-(A+m)-\sqrt{Disc}}{2}$, $\lambda_6 = \frac{-(A+m)+\sqrt{Disc}}{2}$.

Here, Disc > 0 if $(A - m)^2 + 4a^2 bcs_v^0 (s_H^0 + \epsilon p_H^0) > 0$.

λ_5 is negative definite and λ_6 is negative if

$(\mu_v + q)(\theta + p + \mu_H) > \frac{a^2 bcb_v b_H(D+\epsilon\gamma)}{AB}$ which implies,

$$\frac{a^2 bcb_v b_H(D + \epsilon\gamma)}{AB(\mu_v + q)(\theta + p + \mu_H)} < 1$$

$$\frac{a^2 bcb_v b_H(D + \epsilon\gamma)}{A^2 Bm} < 1,$$

i.e.

$$R_0^2 < 1 \Rightarrow R_0 < 1.$$

Therefore, disease-free equilibrium is stable if $R_0 < 1$. □

3.3.2.6 Stability Analysis at E^*

In this section, local stability analysis at the endemic equilibrium is discussed. The local stability conditions at endemic equilibrium is done by calculating the eigenvalues of the system. The Jacobian of the system is

$$J_1 = \begin{pmatrix} -l_1 & \gamma & l_3 & \omega & 0 & 0 \\ \delta & -l_2 & l_4 & 0 & 0 & 0 \\ 0 & 0 & -l_8 & \theta & -l_9 & l_{10} \\ 0 & 0 & 0 & -l_{12} & 0 & 0 \\ 0 & 0 & 0 & 0 & -l_7 & l_{11} \\ -l_{13} & -l_5 & l_6 & 0 & 0 & -A \end{pmatrix}$$

where

$l_1 = abi_v^* + L, l_2 = \epsilon abi_v^* + D, l_3 = abi_v^*$

$l_4 = \epsilon abi_v^*, l_5 = \epsilon abp_H^*, l_6 = abs_H^* + \epsilon abp_H^*$

$l_7 = aci_H^* + A, l_8 = m, l_9 = acs_v^*, l_{10} = acs_v^*$

$l_{11} = aci^*_H, l_{12} = \mu_H, l_{13} = abs^*_H$

On solving this, we get characteristic equation for endemic equilibrium

$$det(J_1 - \lambda I_6) = 0$$

where I_6 is 6×6 identity matrix. To investigate the stability at E^*, we will use the Routh-Hurwitz criteria. This criteria is applied on the characteristic polynomial to check the stability conditions. The solved characteristic equations is given below

$$p_6(\lambda) = \lambda^6 + a_1\lambda^5 + a_2\lambda^4 + a_3\lambda^3 + a_4\lambda^2 + a_5\lambda + a_6 \tag{3.9}$$

where $a_i's$ are given below

$a_1 = A - l_1 - l_2 - l_7 - l_8 - l_{12}$

$a_2 = (l_1 + l_2)(l_7 + l_8 + l_{12} - A) - \gamma\delta - Al_7 + (l_8 + l_{12})(l_7 - A) + l_8l_{12} - l_6l_{10}$

$a_3 = \delta\gamma(l_7 + l_8 + l_{12} - A) + (l_1 + l_2)[Al_7 + (A - l_7)(l_8 + l_{12}) + l_8l_{12}] + l_7A(l_8 + l_{12}) +$
$l_8l_{12}(A - l_7) - l_{10}(l_4l_5 - l_4l_6 + l_3l_13 - l_2l_6) + l_6(l_7l_{10} + l_{10}l_{12} + l_9l_{11})$

$a_4 = \gamma\delta(Al_7 + (A - l_7)(l_8 + l_{12}) + l_8l_{12}) - (l_1 + l_2)[Al_7 + (l_8 + l_{12}) + l_8l_{12}(A - l_7)] \quad -$
$Al_7l_8l_{12} - Rl_{10} + l_6(l_9l_{11}l_{12} - l_7l_{10}l_{12}) + (l_{10}l_7 + l_9l_{10}l_{11}l_{12})(l_4l_5 - l_1l_6 - l_2l_6 + l_3l_{13})$

$a_5 = Al_7l_8l_{12}(l_1 + l_2) - \gamma\delta[Al_7(l_8 + l_{12}) + l_8l_{12}(A - l_7)] + R(l_7l_{10} + l_{10}l_{12} + l_9l_{11}) +$
$(l_9l_{11}l_{12} - l_7l_{10}l_{12})(l_4l_5 - l_1l_6 - l_2l_6 + l_3l_{13})$

$a_6 = Al_7l_8l_{12}\gamma\delta + R(l_9l_{11}l_{12} - l_7l_{10}l_{12})$

$R = l_1l_2l_6 - l_1l_4l_5 - \delta\gamma l_6 + l_3l_5\delta + \gamma l_4l_{13} - l_2l_3l_{13}.$

By Routh-Hurwitz criteria all the eigenvalues of the Jacobian J_1 are negative or have negative real parts iff the Hurwitz determinants H_i are all positive. Which implies that the endemic equilibrium is locally asymptotically stable iff

$H_1 = a_1 > 0,\ H_2 = a_1a_2 - a_3 > 0,$

$H_3 = a_1a_2a_3 + a_1a_5 - a_1^2a_4 - a_3^2 > 0,$

$H_4 = (a_3a_4 - a_2a_5)(a_1a_2 - a_3) - (a_1a_4 - a_5)^2 > 0,$

$H_5 = a_5H_4 > 0,\ H_6 = a_6H_5 > 0.$

3.3.3 Numerical Simulation and Discussion

Using initial conditions $S_H(0) = 1000$, $P_H(0) = 20$, $I_H(0) = 10$, $R_H(0) = 10$, $S_V(0) = 140$, $I_V(0) = 20$ and parameters values: $b_H = 0.1, a = 5, b = 0.1, \theta = 0.2, \delta = 0.001, \mu_H = 0.000375, \epsilon = 0, \omega = 0.1, p = 0.1, c = 0.1, b_V = 0.01, \mu_V = 0.1, q = 0.01$. To check the sensitivity of model outcomes for different parameters, sensitivity analysis is done. We modelled different scenarios by varying different parameters and check the value of basic reproduction number.

Discussion on Mosquito Bites

TABLE 3.4: Table for Parameters for Model for the Disease Chikungunya.

Parameters	Value	Source
a	[1,12]	[95], [1], [40]
b	0.1	assumed
c	0.6	[46]
θ	0.2	assumed
δ	0.001	assumed
ω	0.1	assumed
b_H	0.1	assumed
b_V	0.01	assumed
μ_H	0.000375	[1]
μ_V	0.1	[46]
p	0.1	assumed
γ	0.5	assumed
q	0.017	assumed

Firstly, by changing the value of b, the proportion of mosquito bites causing infection, the variation in the Figures 3.8 and 3.9 can be seen. The values of b were varied from 0.1 to 0.9 which resulted in change in the value of R_0 from $0.6274 < 1$ to $1.8821 > 1$. It means that if the proportion of mosquito bites causing infection is decreased, then infection can be decreased.

Discussion on Insecticide

To check the system is sensitive to variations in parameter relating to mortality rate of mosquitoes due to insecticide. We varied that parameter q from 0.001 to 0.009 that resulted in change of R_0 from $3.8455 > 1$ to $0.7698 < 1$. As the value

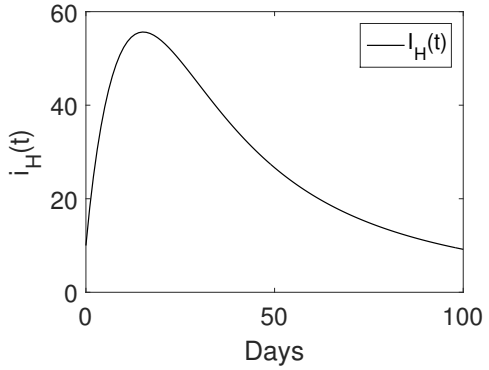

FIGURE 3.8: Simulation results for infective state of humans for $b = 0.1, R_0 = 0.6274 < 1$.

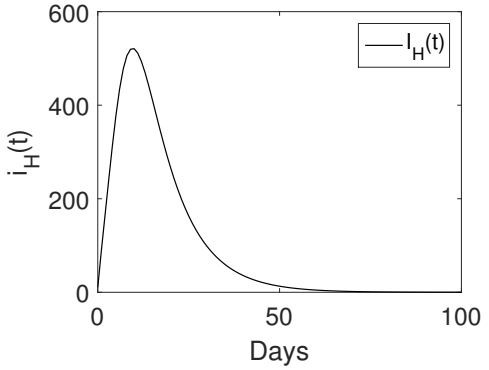

FIGURE 3.9: Simulation results for infective state of humans for $b = 0.9, R_0 = 1.8821 > 1$.

of q increases, infection in mosquitoes also reduces as shown in Figures 3.10 and 3.11, which in turn will reduce the transmission in humans. Value of R_0 indicate that as the value of q increases, disease will turn from epidemic state to dying off state.

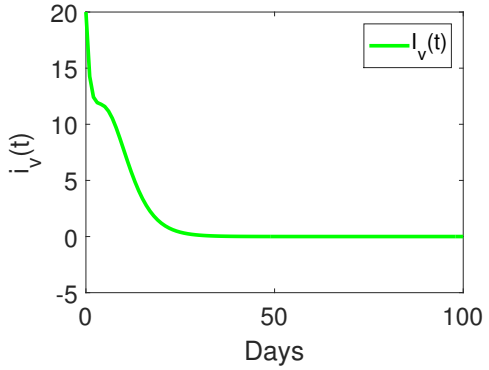

FIGURE 3.10: Simulation results for infective state of humans for $q = 0.001, R_0 = 3.8455 > 1$.

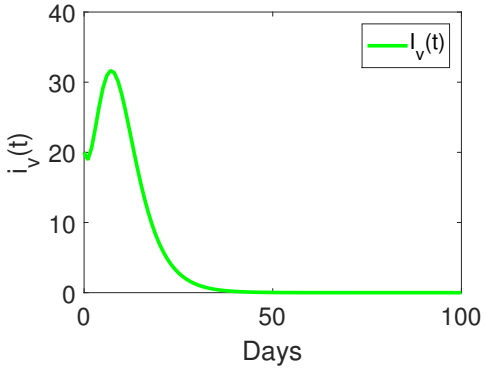

FIGURE 3.11: Simulation results for infective state of humans for $q = 0.009, R_0 = 0.7698 < 1$.

Discussion on Vaccination Rate

Another parameter involved in the model to control the disease is ω, that is, effective vaccination rate. As the value of ω is varied from 0.1 to 0.5, the peak of the curve of infection in humans decreases sharply as seen in Figures 3.12 and 3.13 indicating to be a successful measure of prevention.

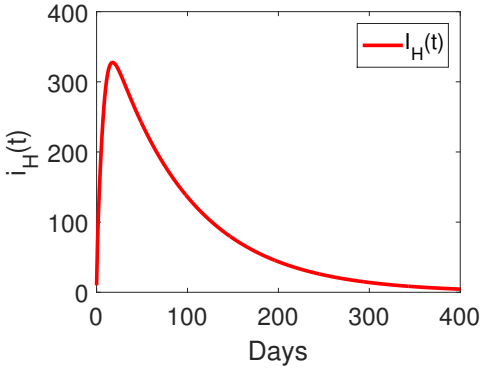

FIGURE 3.12: Simulation results for infective state of humans for $\omega = 0.1$.

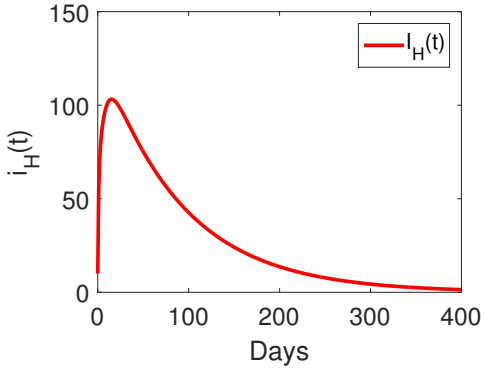

FIGURE 3.13: Simulation results for infective state of humans for $\omega = 0.5$.

Discussion on Insect Repellent

With the usage of insect repellent, the contact between mosquitoes and humans can reduced. This is well illustrated in the numerical simulation shown in Figures 3.14 and 3.15 when we changed the values of parameter a, that is, mosquito biting rate. The values of a were varied from 5 to 12 and this resulted in value of R_0 to change from $0.6274 < 1$ to $1.0178 > 1$. Figures 3.16 and 3.17 shows the graphs

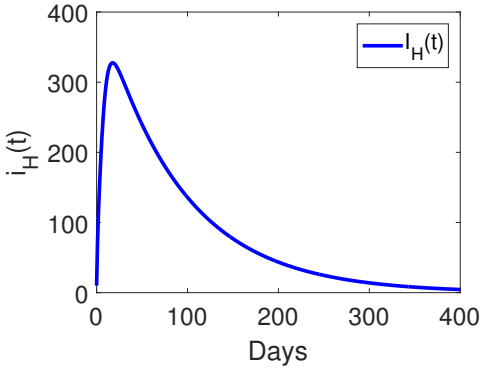

FIGURE 3.14: Simulation results for infected human for $a = 5, R_0 = 0.6274 < 1$.

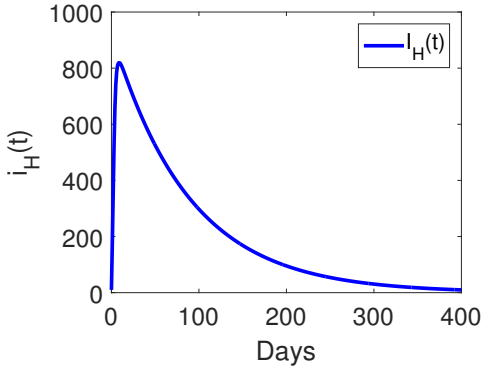

FIGURE 3.15: Simulation results for infected human for $a = 12, R_0 = 1.0178 > 1$.

of human population in disease-free state and endemic state. When the set of parameters a and b are varied from $a = 1, b = 0.1$ to $a = 8, b = 0.7$, the value of basic reproduction number R_0 changes from 0.3679 to 3.5902. It is quite clear that R_0 is very much affected by the factors a and b.

Discussion on Temporary Protection

Another control parameter introduced is γ, that is, proportion of individuals under

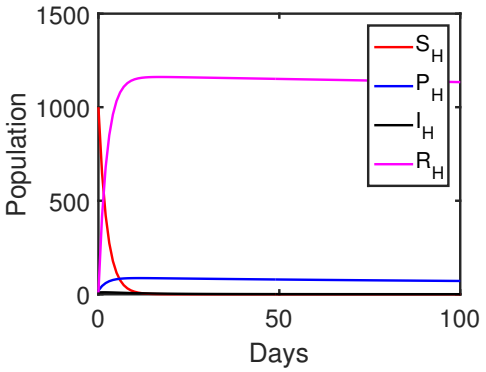

FIGURE 3.16: Simulation results for disease-free state when $a = 1, b = 0.1$.

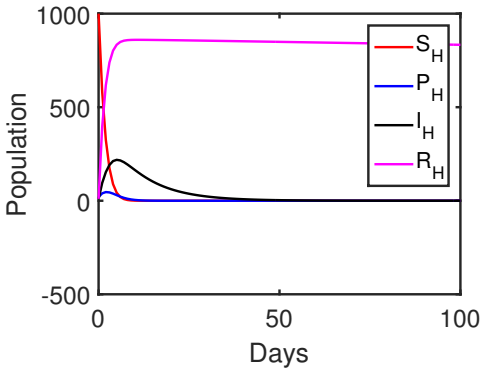

FIGURE 3.17: Simulation results for endemic state when $a = 8, b = 0.7$.

temporary protection of insect repellent. We changed the value of γ to check its sensitivity through simulation and found that on changing its value from 0.1 to 0.9, R_0 changes its value from $0.6274 < 1$ to $1.0419 > 1$. This can be interpreted that by the application of insect repellent, lesser mosquitoes will bite the person and hence chances of infection decreases. Since it is a circle of humans and mosquitoes for disease progression, this means that infection in humans and in vectors will decrease as is shown in Figures 3.18 and 3.19.

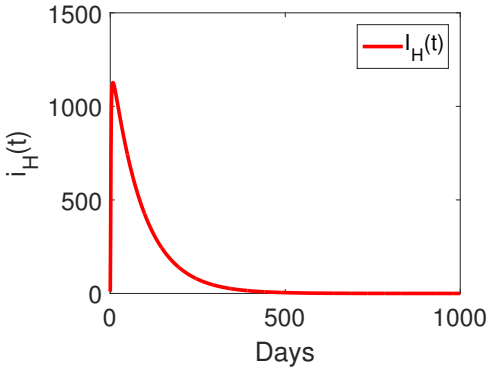

FIGURE 3.18: Simulation results for infective state of humans for $\gamma = 0.9$.

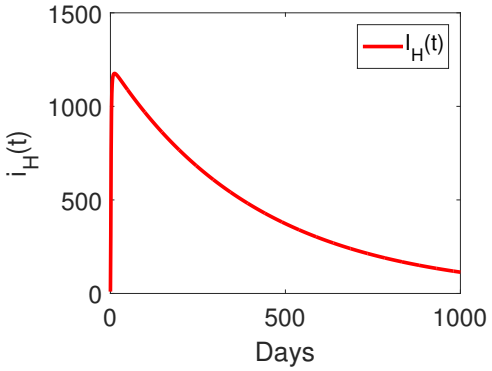

FIGURE 3.19: Simulation results for infective state of humans for $\gamma = 0.1$.

Discussion on Value of Insecticide

In [1], the authors used the range of the parameter q (which represents the effect of insecticide) from 0.2 to 0.7. However, we used q to be 0.01 which is a much lower value than the range used in [1]. We observed that a less effective insecticide ($q = 0.01$) is sufficient to kill the mosquito population in 50 days (see Figure 3.20)

because the mosquito human system is already considered to be under the effect of repellent also. Since, the use of insecticide is only an added control, less effective one would be sufficient. As we increase the value of q to be 0.2 to 0.7, the vector population dies off quickly (see Figures 3.21 and 3.22). The variation in value of

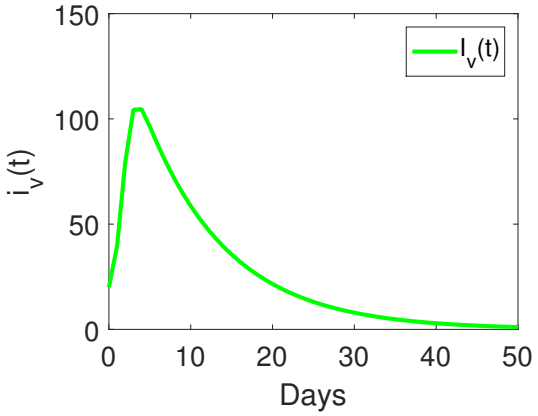

FIGURE 3.20: Simulation results for infected vector for $a = 5, q = 0.01$.

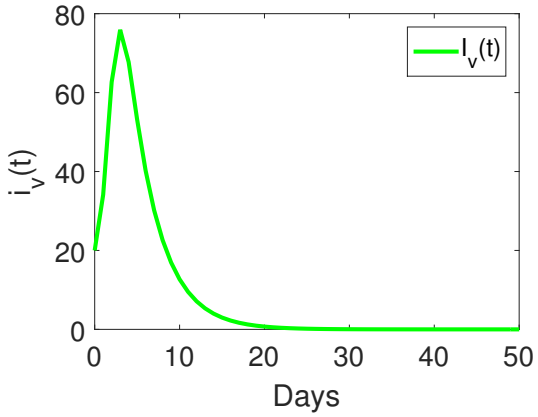

FIGURE 3.21: Simulation results for infected vector for $a = 5, q = 0.2$.

q is shown in the Figure 3.20, 3.21 and 3.22), which clearly interprets the effect of insecticide on the mosquito species. Further, this decrease in infection in infected mosquitoes decreases the infection in human population, thereby becoming the reason for decrease in chikungunya circle. The greater the value of insecticide, the greater is the mortality rate but the concern about the environment makes us turn towards safer alternative.

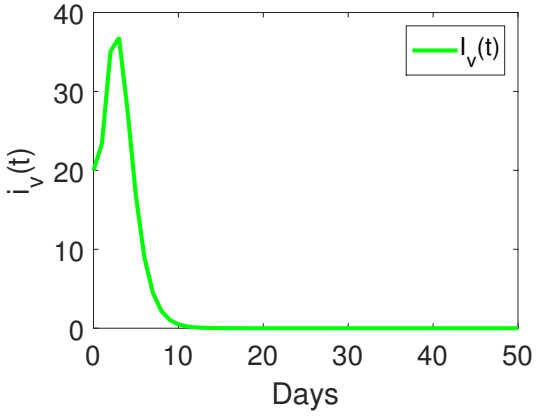

FIGURE 3.22: Simulation results for infected vector for $a = 5, q = 0.7$.

3.3.4 Conclusion

A mathematical model for chikungunya virus has been proposed and analysed. To control the disease transmission, various control measures are incorporated to eradicate the disease in both human and as well as mosquito population. This is possible only if the vector population is eradicated or disease can be controlled in human population. Further, to reduce the mosquito population, one of the most important intervention is reducing mosquitoes by using chemical insecticides. But keeping in view, the fatal consequences of these on environment, some other control measures are considered. Among the control strategies for humans, a preventive measure in the form of mosquito repellent creams/sprays are incorporated along with vaccination. The system is analysed for its equilibrium points for which further the stability analysis is performed using Routh-Hurwitz criteria. The threshold value, basic reproduction number is evaluated to see the progression of the disease. The impact of various control strategies on the value of R_0 have been studied. All these factors if taken together in right proportion and at right time can reduce impact of epidemic and hence R_0. It is concluded from simulation results that usage of insecticide can be reduced to a large extent if insect repellent sprays/creams and vaccination are used in support of insecticide. Hence, the environment can be saved to a great extent. The efficacy of these control measures were analysed using numerical simulation through MATLAB.

Chapter 4

Modelling the Effects of Control Strategies on Co-infection: A Mathematical Model on Rotavirus and Malaria

4.1 Introduction

Various infectious agents can infect a host and that too with different strains. The control/treatment of one affects the disease dynamics of other. Here, we have studied the effect of control measures on co-infection of two infectious diseases by taking an example of rotavirus and malaria.

Malaria and rotavirus co-infection is the cause of big burden of public health worldwide. The co-infection with malaria is typically difficult to understand and diagnose as the main species responsible for it is *Plasmodium falciparum* which is unicellular protozoan parasite infecting humans and it is the lethal species of Plasmodium causing malaria in humans. The main mosquito species responsible for malaria are *Plasmodium ovale, Plasmodium vivax, Plasmodium malariae and Plasmodium falciparum* but *P. falciparum* is most fatal to human kind. *P. falciparum* can cause asymptomatic infections, chronic and sometimes repeated acute

infection. Generally, an individual acquires a degree of immunity but if a febrile individual is co-infected with any other potential pathogen, it is hard to diagnose that *P. falciparum* is the sole cause of illness. It is the most important disease in the tropical regions with around 40% of world total population exposed to malaria in around 100 countries, it is a major health problem globally [143]. Its symptoms include severe headache, vomiting, nausea, fever, back pains, sweating and chills ([144], [145]). Malaria is responsible for about $70,000 - 2.7$ million causalities every year out of which 75% are African children with age under five years [72]. It is responsible for 30% of OPD, 19% of admissions to hospitals for various diseases and around 20% of mortality in children having age less than five years as seen in Kenya ([146], [147]). Prevention of malaria can be done through insect repellents, mosquito bed nets, draining of dirty water and spray of chemical insecticides etc. Many researchers have done a lot of work in the field of controlling the disease with different control measures.

On the other hand, the other infectious disease under study is rotavirus which is the most prevalent pathogen accountable for diarrhea among children [148]. It is transferred through fecal-oral route when person gets in contact with contaminated water, surface or object. It can also be transferred by respiratory route. Rotavirus causes severe infection of gastrointestinal tract and diarrhea in young children. It is the second main cause of mortality for children under five years [149]. Around the world, diarrhea claims $760,000$ deaths in children every year. Over 2.5% of admissions to hospitals are because of rotavirus. It has been diagnosed clinically that 38% of the children gets secured against further rotavirus infection after first natural infection [150]. It has been observed that various factors associated with rotavirus infection are seasonality, breast feeding, hygiene, sanitation etc. [151]. Water and sanitation improvements, management of oral rehydration solution and vaccines were suggested as control measures by Mulholland et al. [152].

It was further observed that in Northern Ghana, the main culprit of acute diarrhea is rotavirus. It was supported by a study conducted at Bulpeila health centre, that 15% of children with uncomplicated malaria has diarrhea. In Ghana,

it was found that 11.8% of the total number children have co-infection from *P. falciparum* and enteropathogens and in more than half of the infected persons rotavirus was common enteropathogen [153]. The study was further taken ahead by co-infection model for rotavirus and malaria by [63]. The work was progressed by another co-infection model for rotavirus and malaria developed by authors of [154]. In the work, effect of vaccination for rotavirus disease on co-infection dynamics was explored. It was further done by making SIR model for host and for vector (mosquito), there is SI model for malaria disease with control measure as vaccination only for rotavirus. The effect of rotavirus vaccination on malaria and rotavirus co-infection was explored. It was found that rotavirus only model was globally asymptotically stable where co-infection model exhibits backward bifurcation. Further, it was concluded that rotavirus vaccination helps reduce co-infection.

A mathematical model on co-infection of malaria and cholera has been formulated and analyzed by [155]. The model was exhibiting backward bifurcation. It was concluded that malaria infection can increase the risk of cholera infection but cholera infection does not accelerate risk of malaria. The effect of treatment of malaria on the infection of cholera has also been elaborately discussed. The work on co-infections of diseases has been taken to next level by researchers in [156] in which the conditions of optimal control for HIV-malaria are analyzed. Analysis of sub-models shows that malaria only model exhibits backward bifurcation. It was concluded that for optimal control of HIV-malaria, preventive control measures are the best form of strategy. To minimize the infection and cost associated with control measures, a dynamic model for the co-infection of dysentery and measles has been analyzed by Berhe et al. [157]. The controls like vaccination, treatment and sanitation of surroundings have been included. Further, the cost analysis has been done. Taking the work to next level, Tilahun et al. developed a mathematical model for Typhoid-Pneumonia co-infection [158]. Sensitivity index and bifurcation analysis has been done to check the most sensitive parameters. It was concluded that Pneumonia treatment cost least with prevention of typhoid fever.

The necessary conditions for optimal control have been also derived along with an optimality system. Cancer and hepatitis has been studied by authors in [159]. Malaria, rotavirus models have been studied individually ([49], [143] and [151]) and some researchers have worked to calculate the key factor R_0. From the previous studies, it is quite clear that there are models that studied malaria-rotavirus co-infection [154] in which treatment is given only to rotavirus infected class but still there is scope in the field. Further, in the work done by authors in [63], stability analysis of malaria-rotavirus co-infection model is done.

The model developed in the present study represents co-infection dynamics of rotavirus and malaria disease that is complete enough to consider all the possible control measures not only on humans but also for mosquitoes responsible for the spread of malaria. Here, control measures are taken for rotavirus infected human population, malaria infected human population, co-infected human population and insecticide is taken as control measure for mosquito population. Taken together, these control measures gives a picture that is likely to produce better results of co-infection control.

4.2 Formulation and Description of the model

We propose a model for rotavirus and malaria co-infection with various control measures. Since, we are dealing with vector-host interaction, there are separate compartments for host and vector in the formulation of model. In the proposed model, it is being assumed that a person can recover from malaria disease only, rotavirus disease only and also from the co-infection once co-infected with the diseases. It is also being assumed that all rotavirus recovered humans, malaria recovered humans and humans recovered from both the diseases are not permanently recovered. Therefore, they are susceptible to the diseases again. The total human population (N_h) is divided into different compartments namely susceptible class (S_h), class infected with rotavirus only (I_r), class infected with malaria only (I_m), class infected with both rotavirus and malaria (I_{mr}), only malaria recovered class

(R_m), only rotavirus recovered class (R_r), malaria-rotavirus recovered or removed class (R_{mr}). Similarly, the total vector population (N_v) is split in two compartments, that is, susceptible vector (S_v) and infected vector (I_v). In the model, A is the recruitment of susceptible human population and B is recruitment of susceptible mosquito population. It is being assumed that susceptible humans gets infected with malaria after the bite of malaria infected mosquito at biting rate a per day. So, susceptible person gets infection of malaria with a force $\lambda_m = \frac{abI_v}{N_h}$. Malaria infected individuals (I_m) recover naturally at a rate η_m and by treatment t_1. Malaria infected population gets reduced by disease death rate α_1 and natural death μ_h. Further, malaria recovered population become susceptible again at a rate β. Again, malaria is transmitted to susceptible vector population after coming in contact with malaria infected individual through biting. So, a susceptible mosquito gets infected at a rate $\lambda_v = \frac{ac(I_m+\theta_1 I_{mr})}{N_v}$. Mosquito population is reduced naturally at rate μ_v and by pesticide at a rate q. It is being assumed that there are no disease deaths in mosquitoes and also they do not recover from malaria once infected. So, there is no recovered compartment for mosquitoes.

Susceptible humans gets infected with rotavirus at a rate $\lambda_r = \frac{r(I_r+\theta_2 I_{mr})}{N_h}$ after coming in contact with rotavirus infectious human. Here, r is contact rate of susceptible population with rotavirus infected humans. Rotavirus infected population is diminished by natural recovery rate η_r and through treatment at rate t_2. It is also dwindled by disease death with rate α_2 and natural death rate μ_h. Here θ_2 models that humans co-infected with malaria-rotavirus both are more infectious than only-rotavirus infected [160]. Malaria infected individuals gets infected with rotavirus at rate $\delta\lambda_r$ and gets transferred to co-infected compartment. The parameter $\delta > 1$ is for increased susceptibility of individual getting infected with rotavirus than those who already have malaria. According to the authors in [161], there are chances of co-infection as malaria causes immunosuppression especially in young children. In the same way, humans having rotavirus infection gets infected with malaria at rate $\xi\lambda_m$ shifting the individual to co-infected compartment I_{mr}. Again, $\xi > 1$ accounts for increased susceptibility of malaria infection in human

having weak immune system due to rotavirus. Co-infected humans gets recovery from rotavirus at rate α_r and gets transferred to malaria infected class. Similarly, co-infected individuals recover from malaria and gets transferred to rotavirus-only infected compartment at rate α_m.

4.2.1 Model Equations

The model describes malaria-rotavirus co-infection with treatments for both malaria and rotavirus as control measures for humans and usage of insecticide for vector population to control malaria. The model equations are given as:

$$\begin{aligned}
\dot{S_h}(t) &= A - (\lambda_m + \lambda_r + \mu_h)S_h + \beta R_m + \beta R_r + \beta R_{mr},\\
\dot{I_m}(t) &= \lambda_m S_h + \alpha_r I_{mr} - (\delta\lambda_r + \eta_m + t_1 + \alpha_1 + \mu_h)I_m,\\
\dot{I_r}(t) &= \lambda_r S_h + \alpha_m I_{mr} - (\xi\lambda_m + \eta_r + t_2 + \alpha_2 + \mu_h)I_r,\\
\dot{I_{mr}}(t) &= \delta\lambda_r I_m + \xi\lambda_m I_r - (\alpha_3 + \eta_{mr} + \alpha_r + \alpha_m + t_3 + \mu_h)I_{mr},\\
\dot{R_m}(t) &= (\eta_m + t_1)I_m - (\mu_h + \beta)R_m,\\
\dot{R_r}(t) &= (\eta_r + t_2)I_r - (\mu_h + \beta)R_r,\\
\dot{R_{mr}}(t) &= (\eta_{mr} + t_3)I_{mr} - (\mu_h + \beta)R_{rm},\\
\dot{S_v}(t) &= B - \lambda_v S_v - (\mu_v + q)S_v,\\
\dot{I_v}(t) &= \lambda_v S_v - (\mu_v + q)I_v.
\end{aligned} \tag{4.1}$$

With initial conditions as

$S_h(0) > 0, I_m(0) > 0, I_r(0) > 0, I_{mr}(0) > 0, S_v(0) > 0, I_v(0) > 0.$

Here, the total population $N_h(t)$ and $N_v(t)$ satisfies

$$N_h(t) = S_h(t)+I_m(t)+I_r(t)+I_{mr}(t)+R_m(t)+R_r(t)+R_{mr}(t), N_v(t) = S_v(t)+I_v(t).$$

Upon adding the equations in (4.1) separately for humans and vectors, we get

$$\begin{aligned}
\dot{N_h} &= A - \mu_h N_h - \alpha_1 I_m - \alpha_2 I_r - \alpha_3 I_{mr},\\
\dot{N_v} &= B - \mu_v N_v - q N_v.
\end{aligned} \tag{4.2}$$

It is evident from equation (4.2), that when there is no disease in the population,

$$\dot{N_h} \leq A - \mu_h N_h.$$

After solving above equation and calculating as time approaches infinity, we have

$$\Omega_1 = \{(S_h, I_m, I_r, I_{mr}, R_m, R_r, R_{mr}, S_v, I_v) \in R_+^9 : 0 \leq N_h \leq \frac{A}{\mu_h}\}.$$

Similarly, for vector population, in case of no death due to insecticide

$$\dot{N_v} \leq B - \mu_v N_v.$$

After solving this equation as time tends to infinity, we get,

$$\Omega_2 = \{(S_v, I_v) \in R_+^{\mathbf{2}} : 0 \leq N_v \leq \frac{B}{\mu_v}\}.$$

The solution set of the system is bounded in $\Omega = \Omega_1 \times \Omega_2$.

4.2.2 Table for Description of Parameters for Co-infection Model

The terms in the model are presented in the tabular form:

Here,

$$\lambda_m = \frac{abI_v}{N_h}$$
$$\lambda_v = \frac{ac(I_m + \theta_1 I_{mr})}{N_v}$$
$$\lambda_r = \frac{r(I_r + \theta_2 I_{mr})}{N_h}.$$

4.3 Positivity and Boundedness of Solution of Co-infection Model

To perform the analysis of the model given by (4.1), it is significant to see the positivity and boundedness of the solutions of all the variables taken in the model.

TABLE 4.1: Table for Description of Parameters for Co-infection Model.

Parameters	**Description**
r	Effective contact rate of susceptible human with rotavirus infected human
β	The rate at which recovered population becomes susceptible again
η_m	Natural recovery rates from malaria
η_r	Natural recovery rates from rotavirus
η_{mr}	Natural recovery rates from malaria-rotavirus both
t_1	Effective treatment control on malaria
t_2	Effective treatment control on rotavirus
t_3	Effective treatment control on malaria-rotavirus both
α_r	Rate at which co-infected human recover from rotavirus and transfer to malaria infected
α_m	Rate at which co-infected human recover from malaria and transfer to rotavirus infected
α_1	Disease deaths due to malaria
α_2	Disease deaths due to rotavirus
α_3	Disease deaths due to malaria and rotavirus both
a	The average bites by mosquito on humans
b	Transmission rates per bite from malaria infected mosquito to susceptible human
c	Transmission rates per bite from malaria infected human to susceptible vector
μ_h	Natural mortality rates of humans
μ_v	Natural mortality rates of vectors
q	Mortality rate of mosquitoes due to insecticide
δ	For increase in human susceptible to rotavirus infection who is already malaria infected
ξ	Models increase in human susceptible to infection with malaria already infected with rotavirus
θ_1	For increase in probability of infection in vector from co-infected human [63]
θ_2	Models that co-infected are more contagious than that infected with only rotavirus [160]

*Table for Parameters

As the model proposed is for dynamics of mosquito and human, it is being supposed that all parameters taken in the model are positive.

Theorem 4.1. *Given the initial conditions proposed in the system to lie in T, where*

$$T = \{(S_h, I_m, I_r, I_{mr}, R_m, R_r, R_{mr}, S_v, I_v) \in R_+^9 : S_h \geq 0, I_m \geq 0, I_r \geq 0, I_{mr} \geq 0,$$
$$R_m \geq 0, R_r \geq 0, R_{mr} \geq 0, S_v \geq 0, I_v \geq 0\}.$$

then there is a unique solution for system of equations given by (4.1) and solution of above model remain in T for all time $t > 0$.

Proof. Taking first equation of co-infection model (4.1)

$$\dot{S_h}(t) = A + \beta R_m + \beta R_r + \beta R_{mr} - (\lambda_m + \lambda_r + \mu_h)S_h.$$

We will proceed by technique as applied by [162] and [163]. It is easy to prove that $S_h(t) > 0$ for all $t \geq 0$. Let us prove the contrary. If possible, let there exists a first time $t_0 > 0$ such that $S_h(t_0) = 0, S'(t_0) \leq 0$ and $S_h, I_m, I_r, I_{mr}, R_m, R_r, R_{mr}, S_v, I_v > 0$ for $0 < t \leq t_0$. Then from first equation of co-infection model (4.1), we have,

$$\begin{aligned}
\dot{S_h}(t_0) &= A + \beta R_m(t_0) + \beta R_r(t_0) + \beta R_{mr}(t_0) - (\lambda_m + \lambda_r + \mu_h)S_h(t_0),\\
\dot{S_h}(t_0) &= A + \beta R_m(t_0) + \beta R_r(t_0) + \beta R_{mr}(t_0) - 0,\\
\dot{S_h}(t_0) &> 0.
\end{aligned}$$

Which is a contradiction. Therefore, there does not exist any time t_0 such that $S_h(t_0) = 0$ and $S'(t_0) \leq 0$. Hence, $S_h(t) > 0$ for all $t > 0$.
Similarly, considering the next equation of co-infection model (4.1), if possible, let there exists a first time $t_0 > 0$ such that
$I_m(t_0) = 0, I'_m(t_0) \leq 0$ and $S_h, I_m, I_r, I_{mr}, R_m, R_r, R_{mr}, S_v, I_v > 0$ for $0 < t \leq t_0$.

$$\begin{aligned}
\dot{I_m}(t_0) &= \lambda_m S_h(t_0) + \alpha_r I_{mr}(t_0) - (\delta\lambda_r - \eta_m - t_1 - \alpha_1 - \mu_h)I_m(t_0),\\
\dot{I_m}(t_0) &= \lambda_m S_h(t_0) + \alpha_r I_{mr}(t_0),\\
\dot{I_m}(t_0) &> 0.
\end{aligned}$$

Which is a contradiction. Therefore, there does not exist any time t_0 such that $I_m(t_0) = 0$ and $I'_m(t_0) \leq 0$. Hence, $I_m(t) > 0$ for all $t > 0$. Similarly, by the same argument, we can prove that other variables are also positive and this proves the theorem. □

To proceed further, it is important to study and analyse the disease transmission of both the diseases individually. For this, we will study the co-infection model (4.1) in the absence of malaria disease (rotavirus model) and the same model in the absence of rotavirus (malaria model) separately. The individual models for both the diseases are given in the following section.

4.4 Models for Rotavirus and Malaria

We will study the individual models for rotavirus and malaria separately.

4.4.1 Model to Study Disease Dynamics of Rotavirus Only

By excluding terms related to malaria from the co-infection model given by (4.1), the single rotavirus-only model is given by

$$\begin{aligned}
\dot{S_h}(t) &= A - \lambda_r S_h - \mu_h S_h + \beta R_r, \\
\dot{I_r}(t) &= \lambda_r S_h - \eta_r I_r - t_2 I_r - \alpha_2 I_r - \mu_h I_r, \\
\dot{R_r}(t) &= \eta_r I_r + t_2 I_r - \mu_h R_r - \beta R_r.
\end{aligned} \tag{4.3}$$

4.4.2 Model to Study Disease Dynamics of Malaria Only

Leaving out the terms related to roatavirus in the co-infection model given by (4.1), we get malaria-only model

$$\begin{aligned}
\dot{S_h}(t) &= A - \lambda_m S_h - \mu_h S_h + \beta R_m, \\
\dot{I_m}(t) &= \lambda_m S_h - \eta_m I_m - t_1 I_m - \alpha_1 I_m - \mu_h I_m, \\
\dot{R_m}(t) &= \eta_m I_m + t_1 I_m - \mu_h R_m - \beta R_m, \\
\dot{S_v}(t) &= B - \lambda_v S_v - (\mu_v + q) S_v, \\
\dot{I_v}(t) &= \lambda_v S_v - (\mu_v + q) I_v.
\end{aligned} \tag{4.4}$$

In the upcoming section, the study of the main model given by (4.1) will be investigated by performing analysis of the two models given by equations (4.3) and (4.4).

4.4.3 Analysis of Individual Models

Here, we analyse the individual models by calculating their disease-free equilibrium points, basic reproduction numbers and stability at these points.

4.4.3.1 Analysis of the Model Considering Rotavirus Disease Only

First, we will start by calculating infection-free equilibrium of model (4.3) for rotavirus disease. Disease-free equilibrium of model dealing with rotavirus disease only is given by $E_{0r} = \left(\frac{A}{\mu_h}, 0, 0\right)$.

4.4.3.2 Basic Reproduction Number

The stability of disease-free equilibrium point of rotavirus-only model is checked by basic reproduction number. We apply the method given by Driessche [164]. We separate the transition terms and transmission terms from the infected compartment. Here, all the new infections are taken in the matrix named F and all other transitions are taken in the matrix named V. Let $F = [r]$ and $V = [-(\eta_r + t_2 + \mu_h + \alpha_2)]$. Then we calculate the matrix FV^{-1}. The spectral radius of the matrix FV^{-1} is denoted by R_0. It is given by

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

$$R_{0r} = \frac{r}{\eta_r + t_2 + \mu_h + \alpha_2} \tag{4.5}$$

Here, $R_{0r} < 1$ implies that $r < \eta_r + t_2 + \mu_h + \alpha_2$,
which means that effective contact rate of rotavirus from rotavirus infected human with susceptible human is less than total recovery rate (natural as well as with treatment) and death rate of human (natural death as well as disease death). This justifies the disease-free state that if transmission rate of any disease is less than its recovery, that disease will definitely die out .
In the upcoming sections, the local stability analysis and global stability analysis at disease-free equilibrium of rotavirus has been performed.

4.4.3.3 Local Stability Analysis of Disease-free State of Rotavirus Model

The result of disease-free state of rotavirus-only model can be written as:

Theorem 4.2. *The disease-free state of rotavirus-only model is locally asymptotically stable if* $R_{0r} < 1$ *and is not stable for* $R_{0r} > 1$.

Proof. We will find the stability conditions at disease-free equilibrium by calculating the variational matrix. The condition for stability of DFE is attained by applying Routh-Hurwitz criteria for stability at required points. The Jacobian of system (4.3) at disease-free equilibrium $E_{0r} = \left(\frac{A}{\mu_h}, 0, 0\right)$ is given as

$$J_0 = \begin{pmatrix} -\mu_h & -r & \beta \\ 0 & r - M & 0 \\ 0 & \eta_r + t_2 & -\mu_h - \beta \end{pmatrix}$$

where $M = \eta_r + t_2 + \mu_h + \alpha_2$.
The eigenvalues is $\lambda = -\mu_h, -\mu_h - \beta, r - M$.
First two eigenvalues are negative. For third eigenvalue to be negative, $r - M < 0$, which implies $\frac{r}{M} < 1$

$$R_{0r} < 1.$$

□

4.4.3.4 Global Stability Analysis of Disease-free Equilibrium of Rotavirus Model

The global stability analysis of rotavirus model is performed by considering a Lyapunov function and La Salle invariant principle [165].

Theorem 4.3. *The disease-free equilibrium E_{0r} of the sub-model (4.3) is globally asymptotically stable in Ω if $R_{0r} < 1$.*

Proof. Suppose a Lyapunov function for (4.3):

$$V(t) = (\eta_r + t_2 + \mu_h + \alpha_2)\, I_r$$

Let $(\eta_r + t_2 + \mu_h + \alpha_2) = M$, differentiating with respect to time, we have,

$$\begin{aligned} \dot{V(t)} &= (\eta_r + t_2 + \mu_h + \alpha_2)\dot{I_r} \\ &= M(\frac{rI_rS_h}{N_h} - MI_r) \\ &\leq M(r - M)I_r \\ &= M^2(R_{0r} - 1)I_r \\ &\leq 0. \end{aligned}$$

if $R_{0r} \leq 1$. It follows that $\dot{V(t)} \leq 0$ for $R_{0r} \leq 1$.
Clearly, $\dot{V} = 0$ is true if and only if $R_{0r} = 1$ or $I_r = 0$. Therefore, by Lyapunov Lasalle Principle [165], every solution of (4.3) in the feasible region approaches E_{0r} as time approaches infinity. □

4.4.3.5 Analysis of the Model Considering Malaria Disease Only

To have better clarity about the disease dynamics of malaria in the absence of rotavirus disease, we will perform stability analysis at disease-free stationary state of the model given by (4.4). Disease-free equilibrium is denoted as $E_{0m}\,(S_h^0, I_m^0, R_m^0, S_v^0, I_v^0)$ i.e $\left(\frac{A}{\mu_h}, 0, 0, \frac{B}{\mu_v+q}, 0\right)$.

4.4.3.6 Basic Reproduction Number

To see the disease dynamics, we need to calculate basic reproduction number by next generation matrix method given by Driessche [164]. We divide the coefficient matrix of infected compartment I_m and I_v of the system (4.4) into matrices F and V. The matrix F is for transmission, that is, new infections and transition terms are included in V.

$$F = \begin{pmatrix} 0 & ab \\ ac & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} -(\eta_m + t_1 + \alpha_1 + \mu_h) & 0 \\ 0 & -(\mu_v + q) \end{pmatrix}$$

Calculating the matrix $J = FV^{-1}$, we get,

$$J = FV^{-1} = \begin{pmatrix} 0 & -\frac{ab}{(\mu_v+q)} \\ -\frac{ac}{\eta_m+t_1+\alpha_1+\mu_h} & 0 \end{pmatrix}$$

The eigenvalues of the above determinant are calculated by

$$J - \lambda I = 0,$$

where,

$$J - \lambda I = \begin{pmatrix} -\lambda & -\frac{ab}{(\mu_v+q)} \\ -\frac{ac}{\eta_m+t_1+\alpha_1+\mu_h} & -\lambda \end{pmatrix}$$

Now, the spectral radius of the matrix named FV^{-1} is denoted by R_{0m}, that is

$$R_{0m} = \rho(FV^{-1}).$$

which implies

$$R_{0m} = \sqrt{\frac{a^2bc}{(\eta_m + t_1 + \alpha_1 + \mu_h)(\mu_v + q)}} \tag{4.6}$$

$R_{0m} < 1$ implies $a^2bc < (\eta_m + t_1 + \alpha_1 + \mu_h)(\mu_v + q)$. This can be interpreted that the collective transmission rate of malaria disease from infected human to susceptible mosquito and from infected mosquito to susceptible human along with mosquito biting rate is less than the cumulative recovery rate (natural as well as with treatment) and death rate (natural as well as with disease) which in turn justifies the disease-free state as transmission of any disease should be less than its recovery and death. Also, it is noteworthy that in case of vector-host models when an infectious mosquito or an infectious human is introduced in a completely naive population, the basic reproduction number is always in the form of square, that is, R_0^2. This is interpreted in a way that it takes two generations for infectious host/vector to reproduce itself [73]. In the upcoming section, local stability analysis is carried out at disease-free equilibrium states.

4.4.3.7 Local Stability Analysis of Malaria Model at Disease-free Equilibrium

By applying theorem 2 of Driessche and Watmough [73], the following result is stated:

Theorem 4.4. *The disease-free equilibrium of the model* (4.4) *for malaria disease only is locally asymptotically stable if* $R_{0m} < 1$ *and unstable if* $R_{0m} > 1$.

Proof. Firstly, we will calculate the variational matrix to see the local stability of disease-free equilibrium. Further, to calculate that, we need to find the eigenvalues of the system. The Jacobian matrix at $E_{0m}\,(S_h^0, I_m^0, R_m^0, S_v^0, I_v^0)$ i.e $E_{0m}\left(\frac{A}{\mu_h}, 0, 0, \frac{B}{\mu_v+q}, 0\right)$ is given as:

$$J_0 = \begin{pmatrix} -\mu_h & 0 & \beta & 0 & -ab \\ 0 & -L & 0 & 0 & ab \\ 0 & -(\eta_m + t_1) & -\mu_h - \beta & 0 & 0 \\ 0 & -ac & 0 & (\mu_v + q) & 0 \\ 0 & ac & 0 & 0 & -(\mu_v + q) \end{pmatrix}$$

where $L = \eta_m + t_1 + \alpha_1 + \mu_h$.

The eigenvalues are $\lambda = -\mu_h, -(\mu_v + q), -\mu_h - \beta$.

Other eigenvalues are given by

$$\lambda^2 + \lambda(L + \mu_v + q) + L(\mu_v + q) - a^2bc = 0.$$

It can be rewritten as

$$\lambda^2 + l_1\lambda + l_2 = 0,$$

where $l_1 = (L + \mu_v + q)$ and $l_2 = L(\mu_v + q) - a^2bc$.

According to Routh-Hurwitz criteria l_1 and l_2 should be both positive for the equilibrium to be stable. It is quite clear that $l_1 > 0$.

Now, $l_2 > 0$ implies $L(\mu_v + q) > a^2bc$, implying

$$\frac{a^2bc}{(\eta_m + t_1 + \alpha_1 + \mu_h)(\mu_v + q)} < 1,$$

which implies

$$R_{0m}^2 < 1.$$

□

4.4.3.8 Bifurcation Analysis of Malaria Model

The occurrence of bifurcation is investigated by applying centre manifold criteria for the set of equations in (4.4). Applying the Centre Manifold Theorem [166] along with [155], bifurcation analysis is carried out. This theorem by Castillo-Chavez and Song is given under.

Theorem 4.5. *Consider a system of differential equations with parameter* μ

$$\frac{dx}{dt} = f(x, \mu) \tag{4.7}$$

where $f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n$ *and* $f \in C^2(\mathbb{R}^n \times \mathbb{R})$ *and* $f(0, \mu) = 0$ *for every real* μ. *Let*

- $A = D_x f(0, 0)$, *which is linearization of the above system* (4.7) *around* 0 *and evaluated at* $\mu = 0$.
- *Here matrix* A *has simple eigenvalue zero and all other eigenvalues of* A *are having negative real parts.*
- *This matrix* A *has left and right eigenvectors* v *and* w *corresponding to zero eigenvalue with* $v.w = 1$.

Consider f_k *be the kth component of* f *and*

$$l = \sum_{k=i=j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0) \tag{4.8}$$

$$m = \sum_{k=i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \mu}(0, 0) \tag{4.9}$$

The local dynamics of (4.7) *around* 0 *is determined by the coefficients* l *and* m.

1. *For* $l > 0, m > 0$, *when* $\mu < 0$ *and* $\|\mu\| \ll 1$, 0 *is locally asymptotically stable and it assures a positive unstable equilibrium. When* $0 < \mu \leq 1, 0$ *is unstable and it assures a negative and locally asymptotically stable equilibrium.*
2. *For* $l < 0, m < 0$, *when* $\mu < 0$ *and* $\|\mu\| \ll 1$, 0 *is unstable; when* $0 < \mu \leq 1, 0$ *is locally asymptotically stable and this assures a positive unstable equilibrium.*
3. *For* $l > 0, m < 0$, *when* $\mu < 0$ *and* $\|\mu\| \ll 1$, 0 *is unstable and it assures a locally asymptotically stable negative equilibrium. When* $0 < \mu \leq 1, 0$ *is stable and there is appearance of a positive unstable equilibrium.*
4. *For* $l < 0, m > 0$, *when* μ *changes from negative to positive, there is switch in stability from stable to unstable at* 0. *Accordingly, a negative unstable equilibrium changes to positive and locally asymptotically stable equilibrium.*

To apply this theorem let us consider b^* as bifurcation parameter so that $R_{0m} = 1$. Here

$$b^* = \frac{L(\mu_v + q)}{a^2 c}.$$

Now, we transform the variables in (4.1) as:

$S_h = x_1,\ I_m = x_2,\ R_m = x_3,\ S_v = x_4,\ I_v = x_5.$

The system takes the form:

$$\begin{aligned}
\dot{x_1} &= A - (\lambda_m + \mu_h)x_1 + \beta x_3, \\
\dot{x_2} &= \lambda_m x_1 - (\eta_m + t_1 + \alpha_1 + \mu_h)x_2, \\
\dot{x_3} &= (\eta_m + t_1)x_2 - (\mu_h + \beta)x_3, \\
\dot{x_4} &= B - \lambda_v x_4 - (\mu_v + q)x_4, \\
\dot{x_5} &= \lambda_v x_4 - (\mu_v + q)x_5.
\end{aligned} \tag{4.10}$$

Where

$$\lambda_m = \frac{abx_5}{N_h}$$
$$\lambda_v = \frac{acx_2}{N_v}$$

Firstly, the Jacobian of the system (4.10) is calculated at E_{0m}, which is given by

$$J_{0m} = \begin{pmatrix}
-\mu_h & 0 & \beta & 0 & -p_1 \\
0 & -L & 0 & 0 & p_1 \\
0 & p_2 & -p_3 & 0 & 0 \\
0 & -p_4 & 0 & -p_5 & 0 \\
0 & p_4 & 0 & 0 & -p_5
\end{pmatrix}$$

where

$$p_1 = ab,\ p_2 = \eta_m + t_1,\ p_3 = \mu_h + \beta,\ p_4 = ac,\ p_5 = \mu_v + q.$$

Now, we will calculate the left and right eigenvectors of the Jacobian J_{0m}. Let us denote the left and right eigenvectors v and w, where $v = [v_1,\ v_2,\ v_3,\ v_4,\ v_5]^T$ and

$w = [w_1,\, w_2,\, w_3,\, w_4,\, w_5]^T$. We get,

$$w_1 = \left(\frac{w_2}{\mu_h}\right)\left(\frac{\beta p_2}{p_3} - \frac{p_1 p_4}{p_5}\right), w_2 = w_2,\; w_3 = \frac{p_2 w_2}{p_3},\; w_4 = \frac{-p_4 w_2}{p_5},\; w_5 = \frac{p_4 w_2}{p_5}$$

and

$$v_1 = v_3 = v_4 = 0,\; v_2 = v_2,\; v_5 = \frac{p_1 v_2}{p_5}.$$

After rigorous calculation and calculating the coefficients l and m from the theorem in [166], we have,

$$l = -w_5\left[\frac{v_2 w_2 a b^* \mu_h}{A} + \frac{v_2 w_3 a b^* \mu_h}{A} + \frac{v_5 w_2 a c(\mu_v + q)}{A}\right],$$

and

$$m = a v_2 w_5.$$

As the coefficient m is positive definite and $l < 0$. From the theorem in [166], the system undergoes forward bifurcation.

4.4.3.9 Global Stability Analysis for Malaria Model at Disease-free State

The global stability analysis of malaria model is done by La Salle invariant principle and considering a suitable Lyapunov function [165].

Theorem 4.6. *The disease-free equilibrium E_{0m} of the sub-model (4.4) is globally asymptotically stable in Ω if $R_{0m} < 1$.*

Proof. Let us consider a Lyapunov function for the set of equations (4.4):

$$V(t) = acI_m + (\eta_m + t_1 + \mu_h + \alpha_1)\, I_v.$$

Here $(\eta_m + t_1 + \mu_h + \alpha_1) = L$, Taking derivative with respect to time, we get,

$$\begin{aligned}
\dot{V(t)} &= ac\dot{I_m} + L\dot{I_v} \\
&= ac\left(\frac{abI_vS_h}{N_h} - LI_m\right) + L\left(\frac{acI_mS_v}{N_v} - (\mu_v + q)I_v\right) \\
&\leq a^2bcI_v - acLI_m + acLI_m - (\mu_v + q)LI_v \\
&= a^2bcI_v - (\mu_v + q)LI_v \\
&= (\mu_v + q)LI_v\left[\frac{a^2bc}{(\mu_v + q)L} - 1\right] \\
&= (\mu_v + q)LI_v\left[R_{0m}^2 - 1\right] \\
&\leq 0,
\end{aligned}$$

if $R_{0m} \leq 1$. It follows that $\dot{V(t)} \leq 0$ for $R_{0m} \leq 1$.

Clearly, $\dot{V} = 0$ is true if and only if $R_{0m} = 1$ or $I_v = 0$. Hence, by Lyapunov Lasalle Principle [165], every solution of (4.4) in the feasible region approaches E_{0m} as time approaches infinity. Therefore, the disease-free equilibrium E_{0m} of the (4.4) is GAS in Ω if $R_{0m} < 1$. Hence the theorem is proved. □

4.5 Analysis of Co-infection Model

The infection-free equilibrium of co-infection model is given by (4.1)

$E_{0rm}\left(S_h^0,\, I_m^0,\, I_r^0,\, I_{mr}^0,\, R_m^0,\, R_r^0,\, R_{rm}^0,\, S_v^0,\, I_v^0\right) = E_{0rm}\left(\frac{A}{\mu_h},\, 0,\, 0,\, 0,\, 0,\, 0,\, 0,\, \frac{B}{\mu_v+q},\, 0\right)$.

In the coming section, we will find the basic reproduction number of the main model given by (4.1) as it is the threshold value that help us to decides the dynamics of the disease. Also, the global stability analysis will be performed along with bifurcation analysis of the model. Sensitivity analysis is done to check whether the variation in parameters affect the behaviour of system as there may be some parameters for which system may be sensitive. It will be checked through sensitivity analysis and their effect on basic reproduction number is discussed.

4.5.1 Basic Reproduction Number of Co-infection Model

The basic reproduction number of co-infection model (4.1) is given by

$$R_0 = max\{R_{0r}, R_{0m}\},$$

where R_{0r} and R_{0m} are given by equations 4.5 and 4.6.

4.5.2 Global Stability Analysis of Co-infection Model

We study the global asymptotic stability for the system of equations (4.1) by Castillo-Chavez et al. approach in [166]. For that, we express the system of the equations given by (4.1) as:

$$\dot{X} = F(X, Z),$$

$$\dot{Z} = G(X, Z), G(X, 0) = 0.$$

Where X stands for uninfected population whereas Z stands for infected populations. Here, $X = (S_h, R_m, R_r, R_{mr}, S_v)$ and $Z = (I_m, I_r, I_{mr}, I_v)$. Let the disease-free equilibrium of the model be $E_0 = (X_0, 0)$, where $X_0 = \left(\frac{A}{\mu_h}, \frac{B}{\mu_v+q}\right)$. To make sure, the system is GAS, the conditions given by C_1 and C_2 must hold.
(C_1): For $\dot{X} = F(X, 0), X_0$ is globally asymptotically stable.
$(C_2) : G(X, Z) = BZ - \hat{G}(X, Z), \hat{G}(X, Z) \geq 0$ for $(X, Z) \in \Omega$.
Where $B = \frac{\partial}{\partial Z} G(X_0, 0)$.
If above two conditions holds for the model (4.1), then the following results holds.

Theorem 4.7. *The DFE of the model (4.1) is globally asymptotically stable for $R_0 < 1$ and conditions C_1 and C_2 are satisfied.*

Proof. For the model (4.1), $F(X,Z)$ and $G(X,Z)$ are given as:

$$F(X,Z) = \begin{pmatrix} A-(\lambda_m+\lambda_r+\mu_h)S_h+\beta(R_m+R_r+R_{mr}) \\ (\eta_m+t_1)I_m-(\mu_h+\beta)R_m \\ (\eta_r+t_2)I_r-(\mu_h+\beta)R_r \\ (\eta_{mr}+t_3)I_{mr}-(\mu_h+\beta)R_{mr} \\ B-\lambda_v S_v-(\mu_v+q)S_v \end{pmatrix}$$

and

$$G(X,Z) = \begin{pmatrix} \lambda_m S_h+\alpha_r I_{mr}-(\delta\lambda_r+\eta_m+t_1+\alpha_1+\mu_h)I_m \\ \lambda_r S_h+\alpha_m I_{mr}-(\xi\lambda_m+\eta_r+t_2+\alpha_2+\mu_h)I_r \\ \delta\lambda_r I_m+\xi\lambda_m I_r-(\alpha_r+\eta_{mr}+t_3+\alpha_3+\alpha_m+\mu_h)I_{mr} \\ \lambda_v S_v-(\mu_v+q)I_v \end{pmatrix}$$

Consider the system

$$F(X,0) = \begin{pmatrix} A-\mu_h S_h \\ 0 \\ 0 \\ 0 \\ B-(\mu_v+q)S_v \end{pmatrix}$$

It is clear that $X_0 = (\frac{A}{\mu_h}, \frac{B}{\mu_v+q})$ is globally asymptotically stable point of above equation of $F(X,0)$. This can be verified as the solution of above equation $S_h = \frac{A}{\mu_h}+(S_h(0)-\frac{A}{\mu_h})e^{-\mu_h t}$ and $S_v = \frac{B}{\mu_v+q}+(S_v(0)-\frac{B}{\mu_v+q})e^{-(\mu_v+q)t}$ approaches X_0 as time approaches infinity which implies global convergence of solution of system (4.1) in Ω.

$$B = \begin{pmatrix} -(\eta_m+t_1+\alpha_1+\mu_h) & 0 & \alpha_r & ab \\ 0 & r-(\eta_r+t_2+\alpha_2+\mu_h) & r\theta_2+\alpha_m & 0 \\ 0 & 0 & -(\eta_{mr}+t_3+\alpha_3+\alpha_m+\alpha_r+\mu_h) & 0 \\ ac & 0 & ac\theta_1 & -(\mu_v+q) \end{pmatrix}$$

Then $G(X,Z)$ can be written as $G(X,Z) = BZ - \hat{G}(X,Z)$, where

$$\hat{G}(X,Z) = \begin{pmatrix} \hat{G}_1(X,Z) \\ \hat{G}_2(X,Z) \\ \hat{G}_3(X,Z) \\ \hat{G}_4(X,Z) \end{pmatrix}$$

$$= \begin{pmatrix} abI_v(1-\frac{S_h}{N_h}) + \delta\lambda_r I_m \\ \lambda_r(N_h - S_h) + \xi\lambda_m I_r \\ -(\delta\lambda_r I_m + \xi\lambda_m I_r) \\ \lambda_v(N_v - S_v) \end{pmatrix}$$

Clearly $\hat{G}_3(X,Z) < 0$, implying $\hat{G}(X,Z) < 0$. Therefore, condition C_2 is not satisfied. Therefore, $E_0(X_0, 0)$ is not GAS for $R_0 < 1$. □

4.5.3 Bifurcation Analysis

We use method based on using Center Manifold Theory. For this theorem as mentioned in [166] (see also [158]), two main quantities are considered say a and b which decides the direction of bifurcation. Out of several conditions, one is: if $a < 0$ and $b > 0$, then system undergoes forward bifurcation whereas if $a > 0$ and $b > 0$, then system exhibits backward bifurcation. Applying this theorem, the following results can be concluded.

Theorem 4.8. *If* $a_0 = \frac{\beta k_9}{k_7} - \frac{k_3 k_{10}}{k_{12}} > 0$, *the system* (4.1) *undergoes backward bifurcation for* $R_0 = 1$. *If this inequality is inverted, then system undergoes forward bifurcation for* $R_0 = 1$.

Proof. To apply this theory, we consider two important coefficients b and r to be bifurcation parameters for $R_{0r} = 1$ and $R_{0m} = 1$ iff $r = r^*$ and $b = b^*$, where

$$r = r^* = \eta_r + t_2 + \mu_h + \alpha_2,$$

and

$$b = b^* = \frac{(\mu_v + q)(\eta_m + t_1 + \alpha_1 + \mu_h)}{a^2 c}.$$

Now, we transform the variables in the system (4.1) as:

$S_h = x_1,\ I_m = x_2,\ I_r = x_3,\ I_{mr} = x_4,\ R_m = x_5,\ R_r = x_6,\ R_{mr} = x_7,\ S_v = x_8,$

$I_v = x_9$.

Let $x = (x_1,\ x_2,\ x_3,\ x_4,\ x_5,\ x_6,\ x_7,\ x_8,\ x_9)^T$ and $F = (f_1,\ f_2,\ f_3,\ f_4,\ f_5,\ f_6,\ f_7,\ f_8,\ f_9)^T$, then the system given by (4.1) takes the form

$$\dot{dx} = F(x) \tag{4.11}$$

can be presented as:

$$\begin{aligned}
\dot{x_1} &= A - (\lambda_m + \lambda_r + \mu_h)x_1 + \beta x_5 + \beta x_6 + \beta x_7,\\
\dot{x_2} &= \lambda_m x_1 + \alpha_r x_4 - (\delta\lambda_r + \eta_m + t_1 + \alpha_1 + \mu_h)x_2,\\
\dot{x_3} &= \lambda_r x_1 + \alpha_m x_4 - (\xi\lambda_m + \eta_r + t_2 + \alpha_2 + \mu_h)x_3,\\
\dot{x_4} &= \delta\lambda_r x_2 + \xi\lambda_m x_3 - (\alpha_3 + \eta_{mr} + \alpha_r + \alpha_m + t_3 + \mu_h)x_4,\\
\dot{x_5} &= (\eta_m + t_1)x_2 - (\mu_h + \beta)x_5,\\
\dot{x_6} &= (\eta_r + t_2)x_3 - (\mu_h + \beta)x_6,\\
\dot{x_7} &= (\eta_{mr} + t_3)x_4 - (\mu_h + \beta)x_7,\\
\dot{x_8} &= B - \lambda_v x_8 - (\mu_v + q)x_8,\\
\dot{x_9} &= \lambda_v x_8 - (\mu_v + q)x_9.
\end{aligned} \tag{4.12}$$

Where $\lambda_m = \frac{abI_v}{N_h}$, $\lambda_v = \frac{ac(I_m + \theta_1 I_{mr})}{N_v}$

and $\lambda_r = \frac{r(I_r + \theta_2 I_{mr})}{N_h}$.

The Jacobian of the system (4.12) at disease-free equilibrium $(\frac{A}{\mu_h},\ 0,\ 0,\ 0,\ 0,\ 0,\ 0,\ \frac{B}{\mu_v + q},\ 0)$

is

$$J_2 = \begin{pmatrix} -\mu_h & 0 & -k_1 & -k_2 & \beta & \beta & \beta & 0 & -k_3 \\ 0 & -L & 0 & \alpha_r & 0 & 0 & 0 & 0 & k_3 \\ 0 & 0 & k_4 & k_5 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -N & 0 & 0 & 0 & 0 & 0 \\ 0 & k_6 & 0 & 0 & -k_7 & 0 & 0 & 0 & 0 \\ 0 & 0 & k_8 & 0 & 0 & -k_7 & 0 & 0 & 0 \\ 0 & 0 & 0 & k_9 & 0 & 0 & -k_7 & 0 & 0 \\ 0 & -k_{10} & 0 & -k_{11} & 0 & 0 & 0 & -k_{12} & 0 \\ 0 & k_{10} & 0 & k_{11} & 0 & 0 & 0 & 0 & -k_{12} \end{pmatrix}$$

where,

$k_1 = r$, $k_2 = r\theta_2$, $k_3 = ab$, $k_4 = r - M$, $k_5 = r\theta_2 + \alpha_m$, $k_6 = \eta_m + t_1$, $k_7 = \mu_h + \beta$, $k_8 = \eta_r + t_2$, $k_9 = \eta_{mr} + t_3$, $k_{10} = ac$, $k_{11} = ac\theta_1$, $k_{12} = \mu_v + q$, $N = (\alpha_3 + \eta_{mr} + \alpha_r + \alpha_m + t_3 + \mu_h)$. Now, we will calculate the right eigenvector of the Jacobian J_2.

Let it be denoted by $w = [w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9]^T$. After calculation, we get,

$$\begin{aligned} -\mu_h w_1 - k_1 w_3 - k_2 w_4 + \beta w_5 + \beta w_6 + \beta w_7 - k_3 w_9 &= 0 \\ -L w_2 + \alpha_r w_4 + k_3 w_9 &= 0 \\ k_4 w_3 + k_5 w_4 &= 0 \\ -N w_4 &= 0 \\ k_6 w_2 - k_7 w_5 &= 0 \\ k_8 w_3 - k_7 w_6 &= 0 \\ k_9 w_4 - k_7 w_7 &= 0 \\ -k_{10} w_2 - k_{11} w_4 - k_{12} w_8 &= 0 \\ k_{10} w_2 + k_{11} w_4 - k_{12} w_9 &= 0. \end{aligned} \tag{4.13}$$

From above set of equations (4.13), we get,

$w_1 = \frac{w_2}{\mu_h}(\frac{\beta k_6}{k_7} - \frac{k_3 k_{10}}{k_{12}})$, $w_2 = w_2$, $w_3 = w_4 = 0$, $w_5 = \frac{k_6 w_2}{k_7}$, $w_6 = w_7 = 0$, $w_8 = -\frac{k_{10} w_2}{k_{12}}$, $w_9 = \frac{k_{10} w_2}{k_{12}}$.

Let us suppose that left eigenvector of Jacobian J_2 associated with zero eigenvalue is denoted by

$v = [v_1,\ v_2,\ v_3,\ v_4,\ v_5,\ v_6,\ v_7,\ v_8,\ v_9]^T$.

After calculation, we get,

$$\begin{aligned}
-\mu_h v_1 &= 0\\
-Lv_2 + K_6 v_5 - k_{10} v_8 + k_{10} v_9 &= 0\\
-k_1 v_1 + k_4 v_3 + k_8 v_6 &= 0\\
-k_2 v_1 + \alpha_2 v_2 + k_5 v_3 - N v_4 + k_9 v_7 - k_{11} v_8 + k_{11} v_9 &= 0\\
\beta v_1 - k_7 v_5 &= 0\\
\beta v_1 - k_7 v_6 &= 0\\
\beta v_1 - k_7 v_7 &= 0\\
-k_{12} v_8 &= 0\\
-k_3 v_1 + k_3 v_2 - k_{12} v_9 &= 0.
\end{aligned} \tag{4.14}$$

Here $L = \eta_m + t_1 + \alpha_1 + \mu_h$, $M = \eta_r + t_2 + \alpha_2 + \mu_h$ and $N = \eta_{mr} + t_3 + \alpha_m + \alpha_r + \alpha_3 + \mu_h$. Solving the above equations in (4.14), we get, $v_1 = 0, v_2 = v_2, v_3 = 0, v_4 = \frac{v_2}{N}(\alpha_r + \frac{Lk_{11}}{k_{10}}), v_5 = v_6 = v_7 = v_8 = 0,\ v_9 = \frac{Lv_2}{k_{10}}$, where v_2 can be calculated satisfying the condition for eigenvectors v and w such that $v.w = 1$. The coefficients l and m are defined in the equations given below :

$$l = \sum_{k=i=j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(s_h^0, 0, 0, 0, 0, 0, 0, s_v^0, 0) \tag{4.15}$$

$$m = \sum_{k=i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial b^*}(s_h^0, 0, 0, 0, 0, 0, 0, s_v^0, 0). \tag{4.16}$$

Here, $f_i's$ denote the right hand side of the equations (4.12). Considering the system (4.12) and taking into account only non-zero components of v, it is calculated that:

$$l = \frac{v_2 w_2^2 k_{10} a b^* a_0}{\mu_h k_{12}},\ m = a v_2 w_9,$$

where

$$a_0 = \frac{\beta k_9}{k_7} - \frac{k_3 k_{10}}{k_{12}}. \tag{4.17}$$

Since, the coefficient m is always positive. Therefore, the bifurcation of the system (4.12) at $b = b^*$ is dependent on value of l. From the equation (4.17), it can be clearly seen that $l > 0$ iff $a_0 > 0$, that is, $\frac{\beta k_9}{k_7} > \frac{k_3 k_{10}}{k_{12}}$. Hence, for $l > 0$, the system exhibits backward bifurcation and for $l < 0$, it undergoes forward bifurcation at disease-free equilibrium at $R_0 = 1$. □

4.5.4 Sensitivity Analysis

In this section, the sensitivity analysis is done. With the aid of this, we can identify those parameters having greater influence on R_0. The technique used by [72] have been applied. Sensitivity index of a function R_0 with respect to any parameter say p is defined as

$$\Upsilon_p^{R_0} = \frac{\partial R_0}{\partial p} \frac{p}{R_0}.$$

Since, $R_0 = max\left[R_{0m}, R_{0r}\right]$, we have performed the sensitivity analysis for both R_{0r} and R_{0m} separately. Positive value of sensitivity index means that corresponding to a hike in given parameter, there will be increase in the value of basic reproduction number. On the other side, a negative value of sensitivity index implies that an increase in the parameter value will reflect in the form of diminishing value of basic reproduction number. From the table 4.2, it has been observed that the parameters r, a, b and c have huge effect in spreading the disease. If their values are increased, there is rise in basic reproduction number provided other parameters are fixed. This can be clearly verified as the parameters a, b, c and r are the rates of transmission of disease. So, increase in the values of these will definitely increase the basic reproduction number and which in turn increases the

TABLE 4.2: Table for Sensitivity Indices.

Symbol	**Sensitivity index**
R_{0r}	Basic reproduction number for rotavirus-only model
r	1.0000
μ_h	-1.0002
η_r	-0.4543
t_2	-0.4998
α_2	-0.0004
R_{0m}	Basic reproduction number for malaria-only model
a	1.0000
b	0.5000
c	0.5000
μ_h	-0.5000
μ_v	-0.0001
q	-0.0001
η_m	-0.2498
t_1	-0.2498
α_1	-0.2498

*Table for Sensitivity indices

spread of these diseases. The parameters having negative sensitivity indices like η_m, η_r, t_1, t_2 and q will diminish the value of basic reproduction number if their values are increased thereby controlling the disease. This is biologically true that increase in recovery naturally or by treatment will control the spread of disease along with the increased usage of insecticide.

4.6 Numerical Simulation and Discussion

We simulate the model (4.1) for different values of treatment in each case. Here, four types of control strategies are applied: (1) malaria-treatment for malaria infected (2) rotavirus treatment for rotavirus infected (3) malaria-rotavirus treatment for co-infected (4) insecticide treatment for vectors (5) all treatments combined.

4.6.1 Table for Parameter Values for the Co-infection Model

TABLE 4.3: Table for Parameters for the Co-infection Model.

Parameters	**Description**	**Value**	**Source**
a	Average number of bites from mosquito to human	4×10^{-1}	[167]
b	Transmission rate of malaria from infected mosquito to human	0.83333 day^{-1}	[72]
c	Transmission rate of malaria from infected human to mosquito	7.2×10^{-2} day^{-1}	[168]
β	Rate at which human recovered from co-infection transfer to susceptible class (S_h)	0.0027 day^{-1}	[149]
μ_h	Natural mortality rate of humans	2.537×10^{-5} day^{-1}	[169]
μ_v	Natural mortality rate of mosquitoes	4×10^{-5} day^{-1}	[170]
η_m	Natural recovery rate from malaria	0.5 day^{-1}	[171]
η_r	Natural recovery rate from rotavirus	0.5 day^{-1}	Assumed
η_{mr}	Natural recovery rate from malaria-rotavirus co-infection	5.75×10^{-4} day^{-1}	Assumed
t_1	Effective treatment control for malaria	0.5 day^{-1}	Assumed
t_2	Effective treatment control for rotavirus	0.5 day^{-1}	Assumed
t_3	Effective treatment control for malaria-rotavirus co-infection	0.5 day^{-1}	Assumed
α_1	Disease death due to malaria	4.49312×10^{-4} day^{-1}	[172]
α_2	Disease death due to rotavirus	4.466×10^{-4} day^{-1}	[173]
α_3	Disease death due to malaria-rotavirus co-infection	5.0×10^{-2} day^{-1}	Assumed
q	Mortality rate of mosquitoes due to insecticide	0.2 day^{-1}	Assumed

*Table for Values of Parameters.

Discussion on Insecticide Treatment

Figures 4.1 and 4.2 shows the impact of insecticide in eradicating co-infection in the population. It is verified that co-infection decreases sharply as we apply all the treatments and it takes longer if we apply insecticide treatment only on vector compartment. It can seen in Figure 4.1 that it takes 40 days for the infection to die out with only insecticide treatment where as it takes only 10 days for the infection to vanish with all treatments as seen in Figure 4.2.

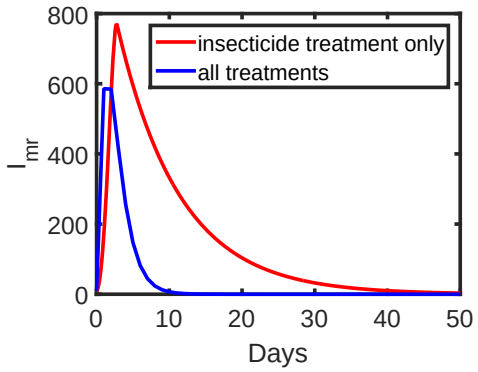

FIGURE 4.1: Simulation results for co-infected population I_{mr} under the effect of insecticide treatment.

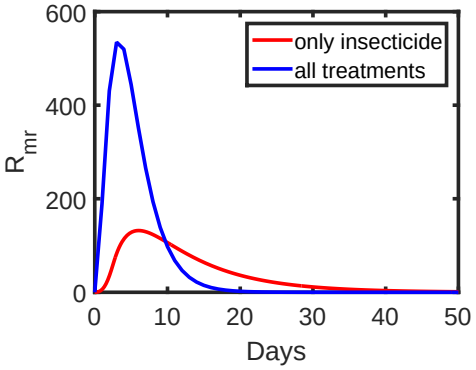

FIGURE 4.2: Simulation results for recovered from both malaria and rotavirus I_{mr} under the effect of insecticide treatment.

Discussion on Malaria Treatment and Rotavirus Treatment

Similarly, in Figure 4.3, it can be seen that with malaria treatment only, the co-infection dies out in around 40 days while it takes around 10 days with all treatments for the same to happen. Also, it is evident from the Figure 4.4 that the recovered population is high when all the treatments are given. Similarly, it is apparent from Figure 4.5 that co-infection dies out in 10 days with all treatments whereas it takes about 30 days with rotavirus treatment only. Also, it is clear from the Figure 4.6 that the recovered population is at its peak when all the treatments are given.

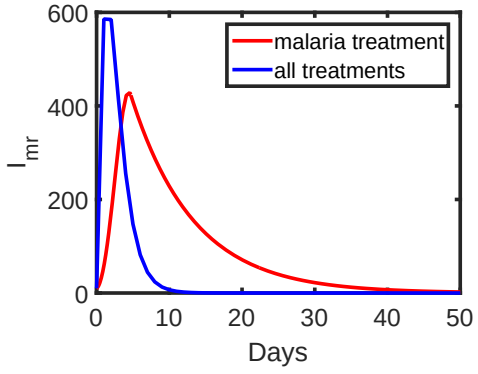

FIGURE 4.3: Simulation results for co-infected population I_{mr} under the effect of malaria treatment only.

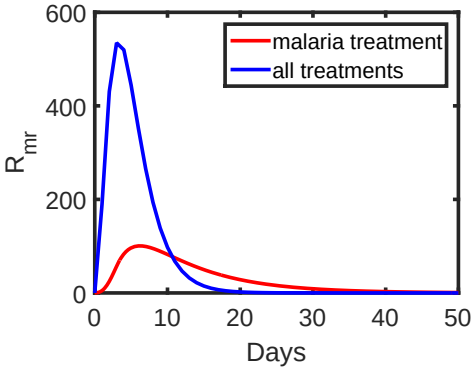

FIGURE 4.4: Simulation results for recovered from both malaria and rotavirus R_{mr} under the effect of malaria treatment only.

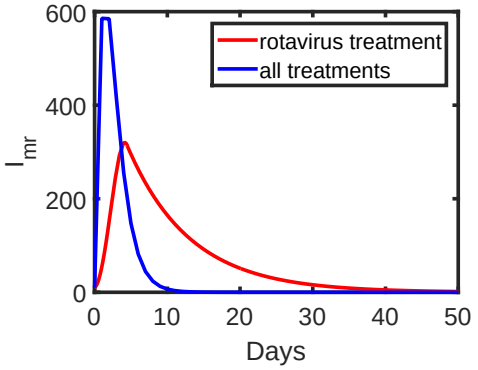

FIGURE 4.5: Simulation results for co-infected population I_{mr} under the effect of rotavirus treatment only.

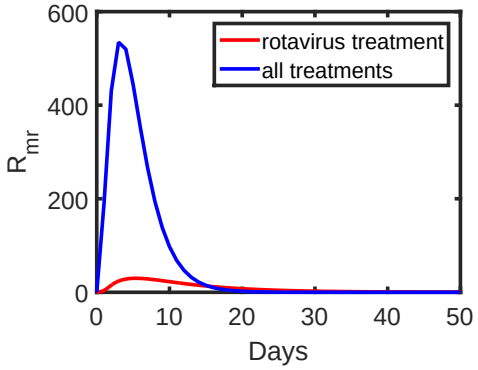

FIGURE 4.6: Simulation results for recovered from both malaria and rotavirus R_{mr} under the effect of rotavirus treatment only.

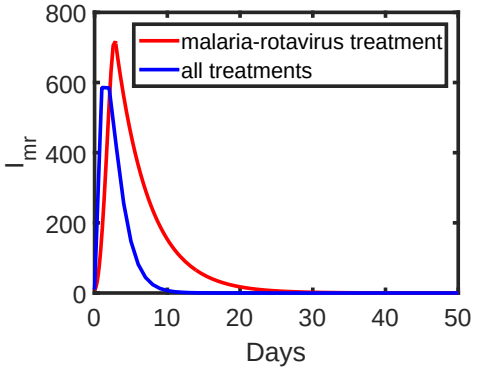

FIGURE 4.7: Simulation results for co-infected population I_{mr} under the effect of malaria-rotavirus treatment only.

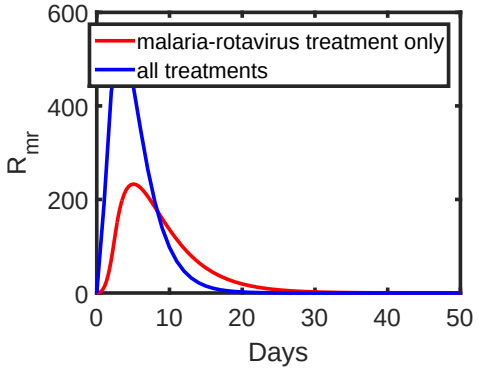

FIGURE 4.8: Simulation results for recovered from both malaria and rotavirus R_{mr} under effect of malaria-rotavirus treatment only.

Discussion on Malaria-Rotavirus Treatment

It can be seen in Figure 4.7 that co-infection dies off in 10 days with all treatment effects where as it takes 20 days for the disease to terminate with malaria-rotavirus treatment. Figure 4.8 shows that all treatments have better effect on disease progression in comparison with malaria-rotavirus treatment.

Comparison of Values of Malaria-Rotavirus Treatment

We simulated the system for various values of treatments and studied the co-infected and recovered population. It is being seen in the Figures 4.9 and 4.10 that increase in the value of t_3, that is, malaria-rotavirus treatment decreases the number of days in which co-infection dies off and it also reduces the amplitude of co-infection.

Comparison of Values of Rotavirus Treatment

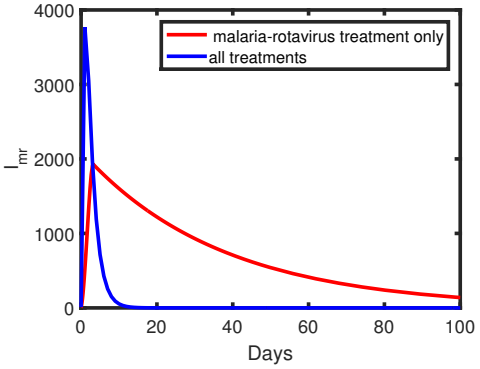

FIGURE 4.9: Simulation results for co-infected population I_{mr} with $t_3 = 0.01$.

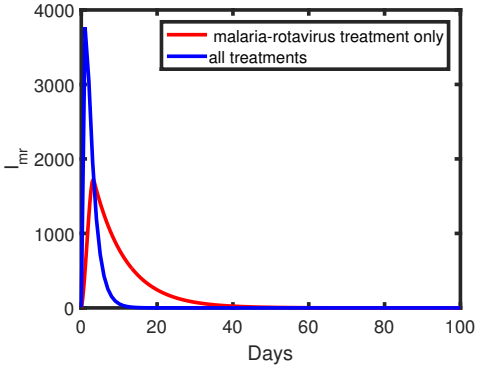

FIGURE 4.10: Simulation results for co-infected population I_{mr} with $t_3 = 0.1$.

We simulated the system for variety of values of rotavirus treatment and then malaria treatment. Figures 4.11 and 4.12 shows the effect of increasing the value of treatments for rotavirus i.e. t_2 in decreasing the co-infection.

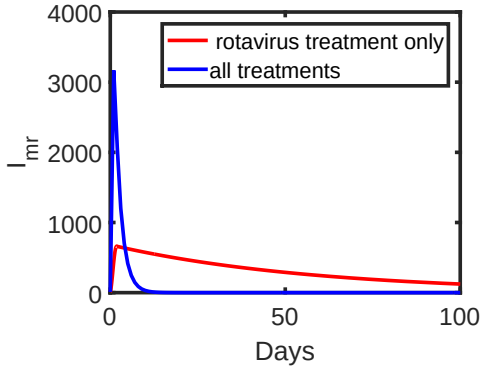

FIGURE 4.11: Simulation results for co-infected population I_{mr} with $t_2 = 0.1$.

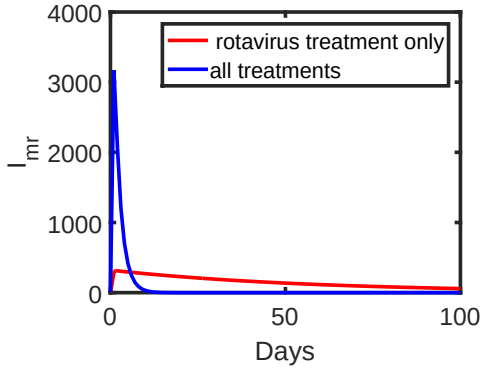

FIGURE 4.12: Simulation results for co-infected population I_{mr} with $t_2 = 0.5$.

Comparison of Values of Malaria Treatment

Figures 4.13 and 4.14 shows the effect of increasing the value of treatments for malaria on co-infection.

Discussion on Collective Impact of Various Treatments

Figure 4.15 shows the collective impact of different treatments for all the susceptible population and Figure 4.16 shows the collective impact of different treatments on co-infected population. It is evident that all treatments have better results than any other treatment. When we compare malaria-rotavirus treatment with

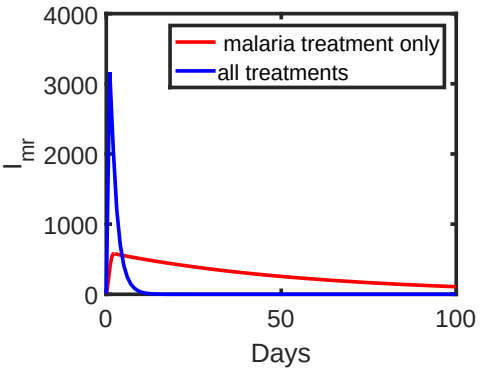

FIGURE 4.13: Simulation results for co-infected population I_{mr} with $t_1 = 1$.

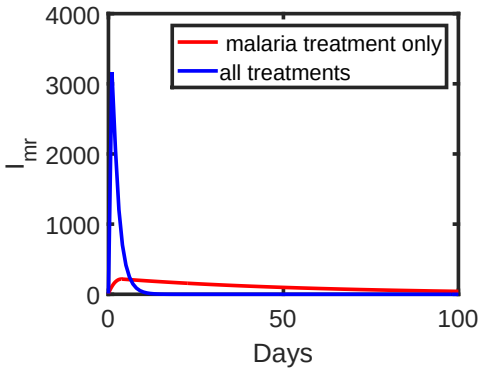

FIGURE 4.14: Simulation results for co-infected population I_{mr} with $t_1 = 10$.

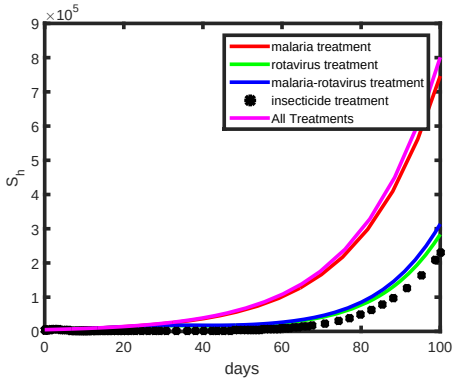

FIGURE 4.15: Simulation results for susceptible population S_h under the effect of different treatments.

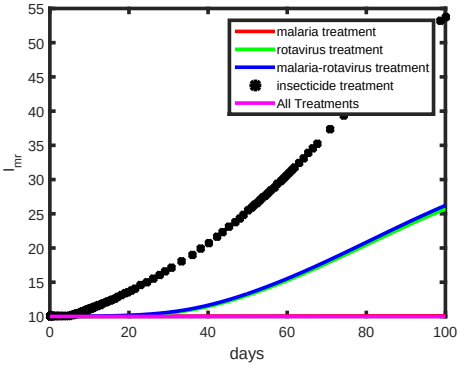

FIGURE 4.16: Simulation results for co-infected population I_{mr} under the effect of different treatments.

all treatments, the results are better with all treatments which means that the additional treatment factor of insecticide gives additional control on disease transmission. In vector borne diseases, vector control helps in eradicating the disease. As a result, it can be interpreted that vector control is a major factor in controlling the co-infection along with other control strategies in reduction of co-infected individuals.

4.7 Conclusion

A compartmental model for transmission of malaria and rotavirus is formulated and studied for various control measures/treatments. The effect of various control strategies namely treatment for humans infected with rotavirus, treatment for humans infected with malaria, treatment for humans co-infected with malaria-rotavirus and insecticide control for mosquito population is studied. Since, the results are based on theoretical and numerical analysis, they offer some very important insights about the dynamics of diseases. The underlying relationship of two diseases under different control scenario is quite clear from the analysis.

Firstly, we studied single disease models and performed the disease-free stability analysis. It is found that the dynamics of disease is determined by threshold value R_{0r} and R_{0m} in case of rotavirus and malaria respectively. According to analysis, disease-free equilibrium is locally asymptotically stable as well as globally asymptotically stable for rotavirus-only model and malaria-only model if $R_{0r} < 1$ and $R_{0m} < 1$ respectively. We derived the basic reproduction number for co-infection model $R_{mr} = max\{R_{0r}, R_{0m}\}$. Sensitivity analysis of the model indicates that the parameters a, b and c have positive value creating great influence on the spread of malaria whereas the basic reproduction number of rotavirus-only model is most sensitive to r. Bifurcation analysis of the full co-infection model is done. The full co-infection model is found to be globally asymptotically unstable at disease-free equilibrium. It is evident that single control measure takes longer to control or eradicate the infection from the system. It is observed that only insecticide treatment also takes longer to control the infection in human population. It is clear that when all treatments namely malaria-rotavirus treatment and insecticide treatment to mosquitoes are applied collectively, the infection dies out in much lesser time. This means that the combined strategy saves more accumulative cases of co-infection than any other strategy of treatment. Altogether, we can say that the study indicates that the possibility of controlling the co-infection of rotavirus

and malaria using effective strategies for treatment/controls for both the diseases is bright.

Chapter 5

Analysis of Mathematical Model of an Infectious Disease with Incubation Period as Delay in Control

5.1 Introduction

A very important aspect of disease transmission is incubation period. Incubation period of a communicable or an infectious disease is time from exposure to infection and its symptoms onset [174]. Incubation period is the delay in terms of time by the human system in showing symptoms after being exposed to microorganisms. It is very important to know the incubation period of a disease as it helps in investigation about the cause as well as source of infection. It also helps in another way that from the incubation period, the date of infection can be calculated which can help health officials to set the periods of quarantine and control the possible epidemic without help of vaccine or treatment [175–177]. As the potentially exposed person can be isolated for a period longer than the incubation period to contain its movement. Many antiviral medications are effective only if given before or instantly after symptoms onset. Incubation period distribution also helps

in hypothesis testing that whether the outbreak of an infectious disease has ended or not.

Based on the literature reviewed by [178], the incubation period of nine respiratory virus have been found. For example, for adenovirus, the median value of incubation period is 5.3 days (95% CI $9.8 - 6.3$). It is 4.0 days for SARS coronavirus, 1.4 days for influenzas A (95% CI $1.3 - 1.5$), 4.4 days ($3.9 - 4.9$ at 95% level of confidence) for syncytial virus related to respiratory system, 9.25 days for measles (95% CI $11.8 - 13.3$) and so on. It is also used in epidemiological studies by estimating the time of exposure when a outbreak at some particular time is there. For example, in case of food poisoning on a large scale, the identification of source of infection is done [174]. In ecological studies, the determination of adaptive strategy by a parasite in case of vivax malaria can be done by the knowledge of incubation period thereby helping in understanding the evolution relevant to the seasonal pressure [179]. The prediction of disease control greatly depends upon the assumption made in model formulation. Epidemic models with delay can predict result which can be very complicated dynamical patterns and in many cases destabilises the system leading to periodic solutions ([180], [181]). Various researchers have worked in the field to explore different aspects of incubation period. For example, a model for infectious disease hepatitis B virus with latent period, incubation period and control strategies was studied for different strategies [182]. In the work, it was emphasised that it is important to incorporate incubation period because when virus infects a healthy liver, it may take 6 weeks to 6 months from infection to the incidence of disease. Further, for typhoid infection, it was observed that the incubation period vary extensively according to the available reports by [183]. It is of significant interest that reports by WHO and CDC ([184], [185]) mention that its incubation period ranges from $3 - 60$ days and $3 - 30$ days respectively. Although, the value of the mean incubation period investigated by [183] was found to be 9.6 days. In a similar kind of research, it was found that the mean value of period of incubation for the infection of measles is 12.5 days with range $8.1 - 9.8$ (at 95% Confidence interval). This has been based

on five observational studies, where 5% of cases develop symptoms before 8.9 days (95% CI) whereas 95% before 17.7 days (95% CI $16.1 - 19.2$) after exposure to infection [186]. Similarly, the incubation period of yellow fever lies between $3 - 6$ days [57]. Various researchers have contributed by calculating the incubation period of corona virus by various methods. For example, the mean incubation period of COVID-19 was concluded to be 3.2 days with range $2.8 - 3.7$ (at 95% level of confidence) for human coronavirus [187].

Further, it is quite interesting to know that the period of incubation for several diseases is higher as compared to others. For example, hantavirus, listeriosis, Crimean-Congo hemorrhagic fever and many more. Crimean-Congo hemorrhagic fever classifies to be a part of infectious disease with high incubation period with maximum value 50 days as observed clinically [188]. Further, it has been observed that sometimes disease have longer incubation period than expected as in case quoted in [189], the incubation period of measles was 23 days. Taking the research to the next level is work done by [190]. It was found that in a recent emergence of confirmed case of monkeypox, the incubation period is around 21 days which indicates that the quarantine period should be planned accordingly. It is of great interest to know that other than incubation period, delay can be modelled in many different forms ([191], [192]). For example, cholera being a water borne disease, for control of infection, there should be a sampling of contaminated water from various sources in order to see how much disinfectant is required. As there is time lag between sampling and application of disinfectants. Further, in case of tuberculosis, control can be achieved by quick identification of TB infected cases and thereby reducing the delays in identification of TB cases [193]. Similarly, malaria parasite may take days or months in the liver of a human to grow whereas in the mosquito, it takes 10 days or so before it can be injected to a host [194]. In the work done by [195] maturation delay along with latent period of disease has been incorporated for childhood disease. Further, the disease dynamics have been shown to be immensely affected by the critical value of delays. Taking the work done in model with delay in [196], latent period of infection and control strategy

in the form of media awareness has been incorporated.

Being relevant to control and prevention of the disease, it is quite helpful in analysing the results of the mathematical model. The information of incubation period will be useful in making control strategies for tackling the disease transmission and ultimately controlling the epidemic. Underestimation of the incubation period can make an individual to release early from quarantine while overestimation of it can have financial and psychological effects on the individual. Quite complicated models have been formulated earlier to calculate incubation period of a disease. This is an attempt to formulate a simple model that fit majority of infectious diseases. Here, in the light of previous work done, a model has been formulated with discrete time delay. Here, the delay incorporated in the system is the time that is required for exposed human being to be infectious.

5.2 The Mathematical Model

In the upcoming section, formulation, the description, parameters in the formation of model and finally the model in the concluding form in terms of ordinary differential equations is stated. In this work, it is being assumed that the total population of humans is stratified into different classes named susceptible, exposed, infected and recovered denoted by $S_h(t)$, $E_h(t)$, $I_h(t)$ and $R_h(t)$ respectively. Also, here we assume that the susceptible or completely naive category increases by birth or immigration with rate Λ. With the assumption that the human gets infected with infection rate b when exposed to the virus, thereby the $bS_h(t)I_h(t)$ term represents interaction of susceptible class with infected class. Let c denotes the rate at which humans transits to infected compartment from exposed compartment. The time lag in the mathematical model is included in exposed compartment in the term $E_h(t-\tau)$. Here, delay incorporated in the model denotes the time necessary for the exposed human to be infectious and starts showing symptoms, that is, incubation period. Exposed humans move to recovery class naturally at a rate γ. It has been assumed that an exposed individual can have ability to naturally recover

thereby adding the term $\gamma E_h(t)$ in the recovery class. Infected persons are reduced by disease deaths at a rate α, thereby reducing the infected compartment by the term $\alpha I_h(t)$. Here, we assume that an individual having weak immunity catches virus easily, thereby die natural death which justifies the natural death in case of infected individual. Here, r is the rate at which infected recover. They recover thereby term $rI_h(t)$ is added in the recovered class. Here d_1, d_2, d_3 and d_4 are the natural mortality rates of susceptible persons, exposed persons, infectious persons and persons who have recovered.

5.2.1 Governing Equations

With the assumptions mentioned above, a mathematical model for an infectious disease by incorporating incubation period in the exposed class has been formulated. The model in its final form is stated under:

$$\begin{aligned}
\dot{S_h}(t) &= \Lambda - bS_h(t)I_h(t) - d_1S_h(t),\\
\dot{E_h}(t) &= bS_h(t)I_h(t) - cE_h(t-\tau) - \gamma E_h(t) - d_2E_h(t),\\
\dot{I_h}(t) &= cE_h(t-\tau) - (\alpha + d_3 + r)I_h(t),\\
\dot{R_h}(t) &= \gamma E_h(t) + rI_h(t) - d_4R_h(t).
\end{aligned} \tag{5.1}$$

Here, $S_h(0) > 0$, $E_h(0) > 0$, $I_h(0) > 0$, $R_h(0) > 0$.

Here, the expression for $N_h(t)$ can be achieved by adding above equations.

$$N_h(t) = S_h(t) + E_h(t) + I_h(t) + R_h(t).$$

5.2.2 Parameter Description

The parameters in the equations (5.1) are described in the tabular format which is given below:

TABLE 5.1: Table for Parameters in the Model with Delay in an Infectious Disease.

Parameters	Description	Units
Λ	Rate of birth or rate of immigration	day^{-1}
c	Rate at which exposed individuals transfer to infected compartment	day^{-1}
b	Transmission rate of disease	per person per day
γ	Rate at which exposed individuals recover naturally	day^{-1}
α	Disease induced death rate of infectious population	day^{-1}
d_1	Natural mortality rate of susceptible individuals	day^{-1}
d_2	Natural mortality rate of exposed individuals	day^{-1}
d_3	Natural mortality rate of infectious individuals	day^{-1}
d_4	Natural mortality rate of recovered individuals	day^{-1}
N_h	Total human population	-
r	Recovery rate of infectious individuals	day^{-1}

5.3 Dynamic Behaviour of the Model

The dynamics of the disease is analysed by determining various aspects associated with the model like positivity, bounds, stability at equilibrium points etc.

5.3.1 Positivity and Boundedness of Solutions

In the upcoming part, we will check the boundedness and positivity of the solutions of the model represented by (5.1). Assuming that the parameters taken in the model are non-negative since the model is based on human dynamics. Now, we know that

$$\begin{aligned} N_h(t) &= S_h(t) + E_h(t) + I_h(t) + R_h(t), \\ &= \Lambda - \alpha I_h(t) - d_1 S_h(t) - d_2 E_h(t) - d_3 I_h(t) - d_4 R_h(t), \\ &\leq \Lambda - a_1 N_h(t), \end{aligned}$$

here a_1= minimum of $\{d_1, d_2, \alpha + d_3, d_4\}$.

Therefore, $N_h(t)$ is proved to be bounded and hence, $S_h(t), E_h(t), I_h(t)$ and $R_h(t)$ are all bounded.

Now, for positive solution of the system (5.1). Consider, $C([-\tau, 0], R_+^4)$ be space of continuous functions which maps $[-\tau, 0]$ with R_+^4 and this space is a Banach space. By the fundamental theory of functional differential equations, it is neccessary to prove that $\exists$ a solution (unique) $(S_h(t), E_h(t), I_h(t), R_h(t))$ for the system under study with $(S_h(0), E_h(0), I_h(0), R_h(0)) \in$ C. Since, we are dealing with human epidemiology, it is assumed that $\exists$ a unique solution of (5.1) which satisfies

$$S_h(\eta) = \phi_1(\eta), E_h(\eta) = \phi_2(\eta), I_h(\eta) = \phi_3(\eta), R_h(\eta) = \phi_4(\eta),$$

where $\phi_i(0) > 0$ and $\eta \in [-\tau, 0]$, $\phi_i(\eta) \in C([-\tau, 0], R_+^4)$ for all i varying from $1, 2, 3$ and 4.

Theorem 5.1. *The solutions of the model consisting of equations* (5.1) *show positivity* $\forall\ t \geq 0$.

Proof. From first equation of the model (5.1),

$$\begin{aligned} \dot{S_h}(t) &= \Lambda - bS_h(t)I_h(t) - d_1S_h(t), \\ &\geq -bS_h(t) - d_1S_h(t). \end{aligned}$$

Which implies, $S_h(t) \geq S_h(0)e^{-(b+d_1)t}$.

Hence, we get $S_h(t) \geq 0$ as $t \to \infty$.

Taking second equation of the model (5.1),

$$\begin{aligned} \dot{E_h}(t) &= bS_h(t)I_h(t) - cE_h(t-\tau) - d_2E_h(t) - \gamma E_h(t), \\ &\geq -cE_h(t-\tau) - d_2E_h(t) - \gamma E_h(t). \end{aligned}$$

Which implies, $E_h(t) \geq E_h(0)e^{-(c+d_2+\gamma)t}$.

$E_h(t) \geq 0$, as $t \to \infty$.

In the similar manner, it can be proved that, $I_h(t) \geq I_h(0)e^{-(\alpha+d_3+r)t}$, which implies $I_h(t) \geq 0$ as time approaches infinity.

and it is be verified that $R_h(t) \geq 0$ as time approaches infinity.

Hence, $S_h(t), E_h(t), I_h(t), R_h(t)$ are non-negative for all $t \geq 0$. □

To proceed further and see the system dynamics corresponding to different scenarios, analysis of the model to see its stability will be done.

5.4 Model Analysis

In the upcoming section, possible steady states and evaluation of R_0 for the model (5.1) is done.

5.4.1 Existence and Evaluation of Possible Equilibrium states

Now, in the direction to obtain all the possible equilibria for the model given by (5.1), we will solve the equations for solutions by equating to zero the growth rates of all the state variables. The model (5.1) possesses two equilibria namely disease-free and endemic equilibrium.

Disease-free steady state is calculated as $E_0(S_0, 0, 0, 0)$, with $S_0 = \frac{\Lambda}{d_1}$ and

disease endemic state is denoted as $E_1(S_1, E_1, I_1, R_1)$.

5.4.2 Threshold Parameter: Basic Reproduction Number

We will evaluate the threshold value R_0 by next generation matrix [93]. The infected compartments have been divided in two matrices F i.e. transmission matrix and V i.e. transition matrix, where F, V are:

$$F = \begin{pmatrix} 0 & bS_0 \\ 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} -(c + d_2 + \gamma) & 0 \\ c & -(\alpha + d_3 + r) \end{pmatrix}$$

Yielding FV^{-1},

$$FV^{-1} = \begin{pmatrix} \frac{bcS_0}{PQ} & \frac{bS_0}{Q} \\ 0 & 0 \end{pmatrix}$$

Here, $P = c + d_2 + \gamma$ and $Q = \alpha + d_3 + r$.

The spectral radius for FV^{-1} is given under:

$$\rho(FV^{-1}) = \frac{\Lambda bc}{d_1 PQ}.$$

Applying the formula in [73],

$$R_0 = \rho(FV^{-1}) = \frac{\Lambda bc}{d_1(c + d_2 + \gamma)(\alpha + d_3 + r)}$$

Now, as we have the expression for R_0, the endemic equilibrium $E_1(S_1, E_1, I_1, R_1)$ can be presented as: $S_1 = \frac{PQ}{bc}, E_1 = \frac{Qd_1(R_0-1)}{bc}, I_1 = \frac{d_1(R_0-1)}{b}, R_1 = \frac{d_1(r+\frac{\gamma Q}{c})(R_0-1)}{bd_4}$

Now, local stability at equilibria for both the cases for $\tau = 0$ along with $\tau > 0$ is done to explore the dynamics of system.

5.4.3 Local Stability Analysis for $\tau = 0$

Now, we will check the behaviour of given model at both the equilibrium points for $\tau = 0$. First, stability at disease-free equilibrium is discussed.

5.4.3.1 Stability Analysis at E_0

At E_0 and $\tau = 0$ the analysis is stated as:

Theorem 5.2. *The disease-free equilibrium (E_0) exists stably for $R_0 < 1$ whereas it shows instability if $R_0 > 1$.*

Proof. The local stability at E_0 is checked through calculation of the eigenvalues of Jacobian. The Jacobian for the system (5.1) is presented here

$$J_0 = \begin{pmatrix} -bI_h - d_1 & 0 & -bS_h & 0 \\ bI_h & -P & bS_h & 0 \\ 0 & c & -Q & 0 \\ 0 & \gamma & r & -d_4 \end{pmatrix}$$

At $E_0(\frac{\Lambda}{d_1}, 0, 0, 0)$

$$J_0 = \begin{pmatrix} -d_1 & 0 & \frac{-b\Lambda}{d_1} & 0 \\ 0 & -P & \frac{b\Lambda}{d_1} & 0 \\ 0 & c & -Q & 0 \\ 0 & \gamma & r & -d_4 \end{pmatrix}$$

The eigenvalues obtained are $\lambda = -d_1, -d_4$. The remaining eigenvalues can be calculated from the equation

$$\lambda^2 + (P+Q)\lambda + PQ - \frac{bc\Lambda}{d_1} = 0.$$

This can be rewritten in the form $\lambda^2 + a_1\lambda + a_2 = 0$, here $a_1 = P+Q, a_2 = PQ - \frac{bc\Lambda}{d_1}$. Applying Routh-Hurwitz theorem, characteristic equation has negative eigenvalues if the following holds $a_1 > 0$ and $a_2 > 0$.

It is evident that $a_1 > 0$ definitely and $a_2 > 0$ if the following holds

$$PQ > \frac{bc\Lambda}{d_1}.$$

From this, it can be interpreted that $R_0 < 1$.

Therefore, the infection-free equilibrium E_0 is LAS provided $R_0 < 1$. □

5.4.3.2 Stability Analysis at E_1

Here, we will check the local stability conditions at E_1.

Theorem 5.3. *The disease-endemic equilibrium E_1 shall be locally asymptotically stable provided $R_0 < 1$ and sustains condition of being unstable under $R_0 > 1$.*

Proof. For the system of equations represented by (5.1), we shall check the local stability at E_1 by calculating the eigenvalues through Jacobian at E_1. The Jacobian J_1 for given system is presented by

$$J_1 = \begin{pmatrix} -bI_1 - d_1 & 0 & -bS_1 & 0 \\ bI_1 & -P & bS_1 & 0 \\ 0 & c & -Q & 0 \\ 0 & \gamma & r & -d_4 \end{pmatrix}$$

One eigenvalue is $\lambda = -d_4$ and the remaining eigenvalues are obtained from the equation:

$$\lambda^3 + k_1\lambda^2 + k_2\lambda + k_3 = 0,$$

here

$k_1 = P + Q + bI_1 + d_1, k_2 = PQ - bcS_1 + (P + Q)bI_1 + d_1(P + Q)$ and

$k_3 = bI_1PQ + PQd_1 - d_1bcS_1$.

Applying Routh-Hurwitz theorem, the eigenvalues of the system should be negative. This implies that endemic equilibrium point E_1 will be locally stable if the condition given below satisfies:

$k_1 > 0, k_2 > 0, k_3 > 0, k_1k_2 - k_3 > 0$. □

In the forthcoming section, the local stability at both equilibria for $\tau > 0$ will be done.

5.4.4 Local Stability Analysis for $\tau > 0$

Now, we will analyse the model (5.1) for $\tau > 0$. Here, the conditions for stability and hopf-bifurcation at E_1 will be advancing. Linearizing system (5.1) about E_1, we get,

$$J_2 = \begin{pmatrix} -bI_1 - d_1 & 0 & -bS_1 & 0 \\ bI_1 & -ce^{-\tau\lambda} - d_2 - \gamma & bS_1 & 0 \\ 0 & ce^{-\tau\lambda} & -Q & 0 \\ 0 & \gamma & r & -d_4 \end{pmatrix}$$

We get one eigenvalue as $\lambda = -d_4$ and the other eigenvalues can be evaluated from characteristic equation:

$$\lambda^3 + p_1\lambda^2 + p_2\lambda + p_3 + e^{-\tau\lambda}[q_1\lambda^2 + q_2\lambda + q_3] = 0. \tag{5.2}$$

Where, $p_1 = Q + d_1 + d_2 + \gamma + d_1(R_0 - 1)$, $p_2 = (d_2 + \gamma)[Q + d_2 + d_1(R_0 - 1)] + d_1Q$,
$p_3 = Q(d_2 + \gamma)d_1R_0$, $q_1 = c$, $q_2 = c(Q - \frac{PQ}{c} + d_1R_0)$,
$q_3 = d_1R_0Q(c - P) + PQd_1(R_0 - 1)$.
Now, the local stability conditions can be presented in the theorem form given below:

Theorem 5.4. *The infected state of system (5.1) under study is LAS provided $R_0 > 1$ with $\tau \geq 0$.*

Proof. When $\tau > 0$, we rewrite the characteristic equation (5.2) in the form

$$G(\lambda) + e^{-\tau\lambda}H(\lambda) = 0,$$

here $G(\lambda) = \lambda^3 + p_1\lambda^2 + p_2\lambda + p_3$ and $H(\lambda) = q_1\lambda^2 + q_2\lambda + q_3$.

To show the phenomenon of hopf-bifurcation, we prove that equation (5.2) possess a pair of purely imaginary roots. After substituting $\lambda = \iota\omega$ in equation (5.2) and segregating real and imaginary parts, the transcendental equations are:

$$\begin{aligned} p_3 - p_1\omega^2 &= (q_1\omega^2 - q_3)\cos(\tau\omega) - q_2\omega\sin(\tau\omega), \\ \omega^3 - p_2\omega &= (q_1\omega^2 - q_3)\sin(\tau\omega) + q_2\omega\cos(\tau\omega). \end{aligned} \tag{5.3}$$

Squaring and adding equations in (5.3), we get,

$$\omega^6 + l_1\omega^4 + l_2\omega^2 + l_3 = 0, \tag{5.4}$$

here $l_1 = p_1^2 - 2p_2 - q_1^2, l_2 = p_2^2 - 2p_1p_3 - q_2^2 + 2q_1q_3, l_3 = p_3^2 - q_3^2$,
substituting $\omega^2 = \rho$ in (5.4), we arrive at

$$\rho^3 + l_1\rho^2 + l_2\rho + l_3 = 0. \tag{5.5}$$

Now, if coefficients in equation (5.5), i.e. l_1, l_2, l_3 satisfies the Routh-Hurwitz condition, then the equation (5.5) will not have any real root which is positive. In that case, we shall not have any non-negative value of the parameter ω which satisfies equation (5.4).

Therefore, we can conclude that if coefficients l_1, l_2 and l_3 in the equation numbered as (5.5) satisfies Routh-Hurwitz theorem, then the disease endemic equilibrium E_1 of (5.1) is LAS if $\tau > 0$ provided it is stable when $\tau = 0$. □

Let us suppose the other way around that l_1, l_2 and l_3 in the equation (5.5) does not satisfy criteria given by Routh-Hurwitz. Let us suppose $l_3 < 0$, which gives:

$$p_3^2 - q_3^2 < 0. \tag{5.6}$$

Now, if the condition given by (5.6) holds, then (5.5) has all non-negative roots along with that the equation (5.4) will have imaginary root with real part zero

denoted by $\iota\omega_0$. From equations in (5.3), τ_0 for this value of ω_0 is given by

$$\tau_0 = \frac{1}{\omega_0}\arccos\frac{(q_2\omega_0^2)(p_2-\omega_0^2)+(p_3-p_1\omega_0^2)(q_1\omega_0^2-q_3)}{(q_2^2\omega_0^2)+(q_1\omega_0^2-q_3)^2}+\frac{2\pi k}{\omega_0}, \tag{5.7}$$

here $k = 1, 2, 3, ...$

Applying Butler's lemma [197], we can state that the model shows stability at E_1 for $\tau < \tau_0$.

Now, we will cross check if hopf-bifurcation is there as τ transits from τ to τ_0. For the phenomenon named hopf bifurcation to happen, transversality condition should be satisfied, which is given under:

$$sign\{\frac{d}{d\tau}Re(\lambda)\}_{\omega=\omega_0} > 0,$$

where sign is signum function. Differentiating (5.2) with respect to τ,

$$[(3\lambda^2+2p_1\lambda+p_2)+e^{-\lambda\tau}(2q_1\lambda+q_2)]\frac{d\lambda}{d\tau}-e^{-\lambda\tau}(\lambda+\tau\frac{d\lambda}{d\tau})(q_1\lambda^2+q_2\lambda+q_3)=0,$$

$$\begin{aligned}\left(\frac{d\lambda}{d\tau}\right)^{-1} &= \frac{3\lambda^2+2p_1\lambda+p_2}{(q_1\lambda^2+q_2\lambda+q_3)(\lambda e^{-\lambda\tau})}+\frac{2q_1\lambda+q_2}{\lambda(q_1\lambda^2+q_2\lambda+q_3)}-\frac{\tau}{\lambda},\\ &= \frac{3\lambda^2+2p_1\lambda+p_2}{-\lambda(\lambda^3+p_1\lambda^2+p_2\lambda+p_3)}+\frac{2q_1\lambda+q_2}{\lambda(q_1\lambda^2+q_2\lambda+q_3}-\frac{\tau}{\lambda},\\ &= \frac{2\lambda^3+p_1\lambda^2-p_3}{-\lambda^2(\lambda^3+p_1\lambda^2+p_2\lambda+p_3)}+\frac{q_1\lambda^2-q_3}{\lambda^2(q_1\lambda^2+q_2\lambda+q_3)}-\frac{\tau}{\lambda}.\end{aligned}$$

When $\lambda = \iota\omega_0$,

$$sign\{(\frac{d(Re(\lambda))}{d\tau})\} = sign\{Re(\frac{d\lambda}{d\tau})^{-1}\},$$
$$= \frac{1}{\omega_0^2} sign\{Re(\frac{p_1\omega_0^2 + p_3 + 2\iota\omega_0^3}{(p_1\omega_0^2 - p_3) + \iota(\omega_0^3 - p_2\omega_0)}) + (\frac{q_1\omega_0^2 + q_3}{(q_3 - q_1\omega_0^2) + q_2\iota\omega_0})\},$$
$$= \frac{1}{\omega_0^2} sign\{Re(\frac{2\omega_0^6 + (p_1^2 - 2p_2)\omega_0^4 - p_3^2}{(p_1\omega_0^2 - p_3)^2 + (\omega_0^3 - p_2\omega_0)}) + \frac{(q_1\omega_0^2 + q_3)(q_3 - q_1\omega_0^2)}{(q_3 - q_1\omega_0^2)^2 + (q_2^2\omega_0^2)}\},$$
$$= \frac{1}{\omega_0^2} sign\{\frac{2\omega_0^6 + (p_1^2 - 2p_2 - q_1^2)\omega_0^4 + (q_3^2 - p_3^2)}{(q_3 - q_1\omega_0^2)^2 + q_2^2\omega_0^2}\}.$$

Now, when condition (5.6) satisfies, we have, $sign\{\frac{d}{d\lambda}Re(\tau)\}_{\omega=\omega_0} > 0$.

The above proven is stated in the theorem form given under:

Theorem 5.5. *If the condition $p_3^2 - q_3^2 < 0$ satisfies, where $p_3 = Q(\mu_2 + \omega)\mu_1 R_0$, $q_3 = \mu_1 R_0 Q(\eta - P) + PQ\mu_1(R_0 - 1)$, then the infectious state E_1 of system under study stabilizes if $\tau < \tau_0$ and is not stable if $\tau > \tau_0$. Hopf-Bifurcation criteria is justified creating cyclic solutions when τ transits through the value τ_0, that is, Hopf-Bifurcation is achieved at $\tau = \tau_0$.*

5.5 Numerical Examples and Discussion

To substanciate the results proven analytically for the system of equations (5.1), numerical simulation has been done. The initial conditions and parameter values considered are given as $S_h(0) = 700$, $E_h(0) = 300$, $110(0) = 50$ and $R_h(0) = 4$. We simulated the model (5.1) keeping $\Lambda = 4$, $d_1 = d_2 = d_3 = 0.0000948, d_4 = 0.0099, \gamma = 0.05, \alpha = 0.01$ fixed and keep varying r = 0.09, b = 0.001 and c = 0.09. The local asymptotic stability for infection-free equilibrium for $\tau = 0$, b = 0.0001, c = 0.05 and $r = 0.09$ is shown in Figure 5.1. The value of R_0 is found to be 0.2031. Further, the asymptotic stability for disease endemic equilibrium for parameters $\tau = 0$, r = 0.05, b = 0.001 and c = 0.1 can be seen in Figure 5.2. The value of R_0 is found to be 2.9062. It can be interpreted that as we increase the values of parameters affecting the disease transmission, namely b and c the value

of R_0 increases from less than one to greater than one. This in turn implies that by controlling the transmission associated factors, disease can be controlled.

Discussion on Switch of Stability

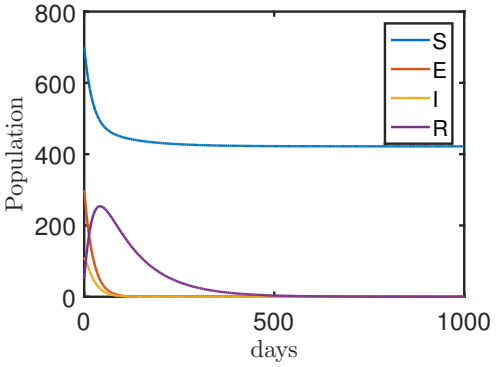

FIGURE 5.1: Simulation results for $\Lambda = 4$, b $= 0.0001$, c $= 0.1$, $d_1 = d_2 = d_3 = 0.0000948, d_4 = 0.0099, \gamma = 0.05, \alpha = 0.01$, r $= 0.09$ and $R_0 = 0.2031 < 1$.

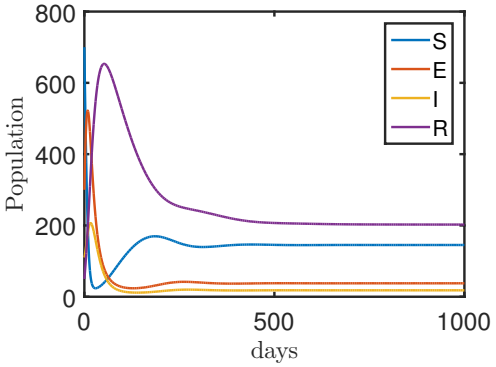

FIGURE 5.2: Simulation results for $\Lambda = 4$, b $= 0.001$, c $= 0.09$, $d_1 = d_2 = d_3 = 0.0000948, d_4 = 0.0099, \gamma = 0.05, \alpha = 0.01$, r $= 0.2$ and $R_0 = 2.9062 > 1$.

In the present work, it is being observed that as the value of incubation period (τ) is increased from 19.4 to 19.7 while all other model parameters are fixed as given above, the system looses its stability transforming stable solutions to oscillatory solutions. Here, the endemic equilibrium is unstable and hopf bifurcation occurs for $\tau = 19.7 > 19.5$ as shown in 5.3. Again, the system is asymptotically stable $\tau = 19.4 < 19.5$ as can be seen in 5.4.

Discussion on Value of Incubation Period

Since, the value of incubation period plays a vital role in disease dynamics. It is worth calculating to control the disease. The critical value of τ is found to be 19.5. This work has been supported by [2] in which the value of incubation period of a virus named hantavirus is $7 - 39$ days with median value 18 days. It is caused by infected rodents and humans can get infected by inhaling rodent urine, saliva or feces. This has also been validated as the incubation period of an infection named listeriosis may vary from $3 - 70$ days [3]. Here, the system is asymptotically stable $\tau = 19.4 < 19.5$ as can be seen in Figures 5.5 and 5.7. The switch in stability for $\tau = 19.7 > 19.5$ is seen in phase portrait given in Figures 5.6 and 5.8.

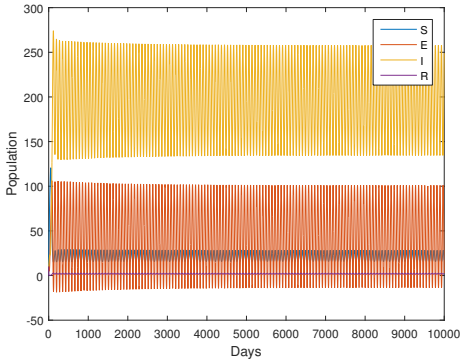

FIGURE 5.3: Simulation results for $\tau = 19.7$ showing periodic solutions. The endemic equilibrium is unstable for $\Lambda = 4$, b $= 0.001$, c $= 0.09$, $d_1 = d_2 = d_3 = 0.0000948, d_4 = 0.0099, \gamma = 0.05, \alpha = 0.01$ and r $= 0.2$, $\tau = 19.7 > 19.5$.

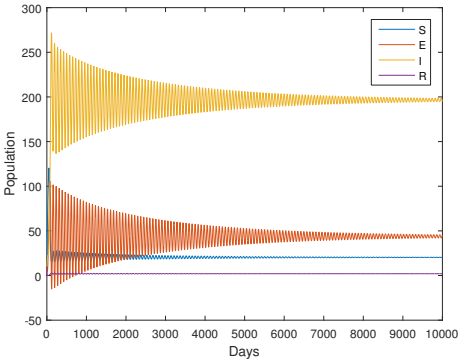

FIGURE 5.4: Simulation results for $\tau = 19.4$ showing asymptotic stability. The endemic equilibrium is stable for $\Lambda = 4$, b $= 0.001$, c $= 0.09$, $d_1 = d_2 = d_3 = 0.0000948, d_4 = 0.0099, \gamma = 0.05, \alpha = 0.01$ and r $= 0.2$, $\tau = 19.4 < 19.5$.

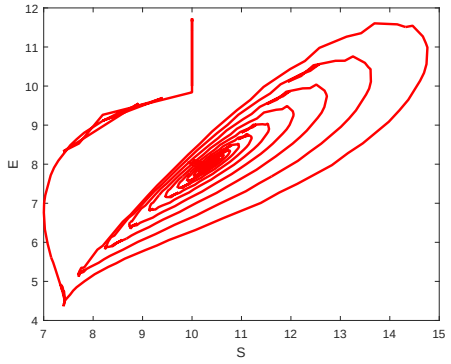

FIGURE 5.5: Simulation results for phase plane graphs of $S_h(t)$ and $E_h(t)$ for $\tau = 19.4$ showing it to be asymptotic stable.

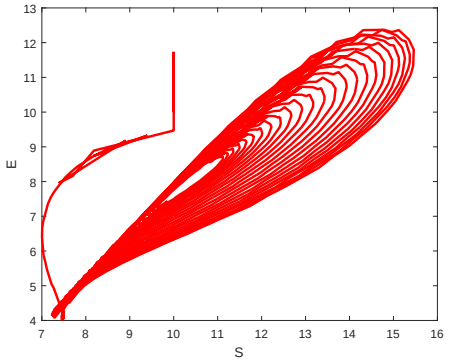

FIGURE 5.6: Simulation results for phase plane graphs of $S_h(t)$ and $E_h(t)$ for $\tau = 19.7$ showing phenomenon of hopf bifurcation.

Discussion on Transmission Rate

Transmission rate of an infectious disease plays a dominant role in dynamics of disease. We varied transmission parameter b and it can be seen in Figures 5.9 and 5.10, that disease dies off in around 150 days for $b = 0.001$ and when transmission rate is decreased to $b = 0.0001$, it takes around 100 days for disease to die off.

Thus, it is concluded in this work that the cumulative effect of transmission of disease and incubation period of disease greatly affects the dynamics of disease. Thus, it is imperative that for disease to be under control, transmission of disease should be controlled. Further, the value of incubation period of a disease needs to

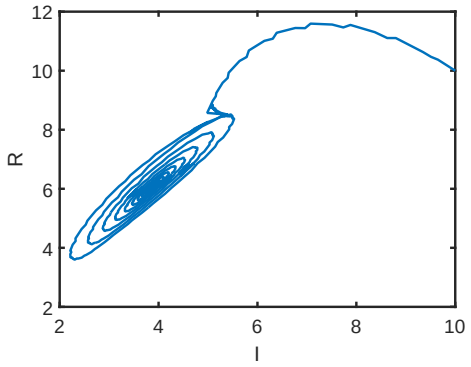

FIGURE 5.7: Simulation results for phase plane graphs of $I_h(t)$ and $R_h(t)$ for $\tau = 19.4$ showing it to be asymptotic stable.

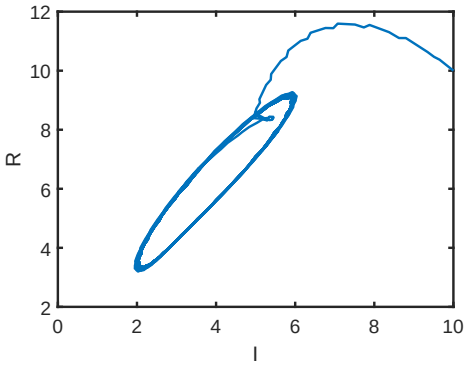

FIGURE 5.8: Simulation results for phase plane graphs of $I_h(t)$ and $R_h(t)$ for $\tau = 19.7$ showing the phenomenon of hopf bifurcation.

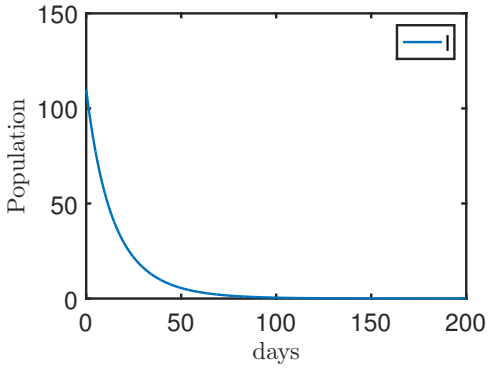

FIGURE 5.9: Simulation results for infected class for $b = 0.001$, $R_0 = 6.585$.

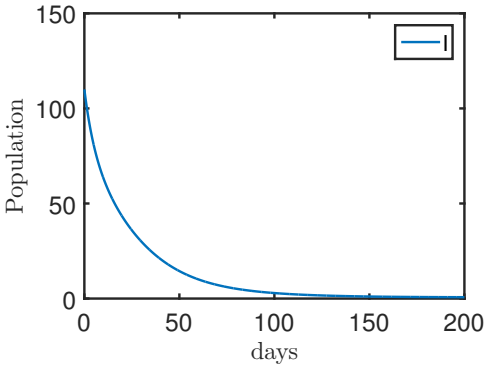

FIGURE 5.10: Simulation results for infected class for $b = 0.0001$, $R_0 = 0.6585$.

be monitored so that treatment can be given in time, otherwise with increase in infection and not monitoring incubation periods, situation of epidemic can occur.

5.6 Conclusion

A non-linear mathematical model for infectious diseases is proposed. Since, the incubation period of a disease plays very important role in disease dynamics. It can guide policy makers and officials of health department to make policies to control an emerging disease. The model incorporates incubation period in its formulation in the form of delay. The conditions of local stability for the equilibrium points have been investigated. Further, it is found that infection-free equilibrium is locally

stable when $R_0 < 1$. Also, the endemic equilibrium is LAS for certain conditions including $\tau < \tau_0$, where τ_0 is the critical value of τ. It was also observed that phenomenon of hopf-bifurcation is there which leads to periodic solutions for $\tau \geq \tau_0$. Further investigation leads us to the fact that transmission parameter plays a significant role in disease spread. Furthermore, while analysing the model, it was observed that infection can be managed or curbed provided particular level of recovery rate and incubation period is administered failing which can lead to epidemic. Analytic results have been supported by numerical examples.

Chapter 6

Conclusion and Future Scope

In the upcoming chapter, important results corresponding to the objectives proposed have been summarised. Moreover, suggestions for further research, recommendations and future scope in the area of work done in the thesis are discussed.

6.1 Conclusion

The work explores the contemporary use of mathematical models in analyzing the control of epidemic in a community, region or a nation. The proposed models are very appropriate in solving the problems surging from infectious diseases and can be applicable for creating awareness among community and to control the infections caused by various viruses creeping in the population. The aim is to control the disease by making the policy makers of the nation aware through the results obtained from the models. In this way, it starts a discourse among people making them aware by designing health policies, control strategies and various health related programmes. All mathematical models are proposed to make real world problems understandable and control measures that help in better prediction of future problems.

In all the models proposed, the population has been divided into various compartments which are mutually exclusive. There is instantaneous movement of

individuals in all the models except in the model in last chapter, where there is delay in movement from one compartment to another.

In chapter 2, we proposed and analyzed model for yellow fever with different control strategies namely vaccination and insect repellent creams/sprays. This work can be helpful in making appropriate health policies.

Secondly, in chapter 3, two infectious diseases are studied to investigate the effect of control measures on both human and mosquito population. Firstly, a mathematical model for yellow fever has been proposed and analysed with awareness through media as a control strategy. This will help people become aware about the infectious disease which can help them in decisions regarding travelling to various destinations, controlling mosquito population and this aware class of people can help the society to cope up with the crisis. In the same chapter, a model for the disease chikungunya is proposed with multiple control measures to study its impact on both humans and mosquito population.

In chapter 4, co-infection of rotavirus and malaria is studied. The model proposed is studied for association of control of one disease and the other. The model is studied for its stability, bifurcation, direction of bifurcation and sensitivity indices have been calculated to notice the impact of parameters on the basic reproduction number. The normalized forward sensitivity indices help in determining the sensitivity of parameters in the model responsible for the transmission of disease and its prevalence.

In chapter 5, a mathematical model is studied for an infectious disease by incorporating incubation period of a disease as a control measure. The incubation period of a disease can help in the formation of policies regarding health to decide the quarantine periods for exposed individuals to control the disease transmission. The existence of hopf-bifurcation is seen for some threshold value of delay.

The models are analyzed with the help of various tools like stability theories for dynamical systems, bifurcation theory (wherever applicable), next generation matrix. The performance of stability analysis for disease-free equilibrium and disease

endemic equilibrium using Routh-Hurwitz criteria and calculation of basic reproduction number is done. It is observed that for all the systems, the disease-free equilibrium is locally asymptotically stable provided $R_0 < 1$ and is not stable provided $R_0 > 1$. Numerical simulation is done using MATLAB to produce and support the analytic results graphically.

6.2 Applications and Future scope

The work in the thesis has been devoted to investigate the effect of control measures in the transmission of infectious diseases. The said work has been processed by using mathematical models, that is, by considering the whole system of population in the form of ordinary differential equations. Further, the effect of the said control measures has been investigated by incorporating them in the equations as parameters. Since, infectious diseases invade the human population since ages and still affect us with the strains that are unknown. Therefore, the work can be beneficial to a variety of diseases with relevant variation. Keeping this in mind and as seen in the literature survey done in the work, it can be well considered that this work can be extended in many ways in which the human population can better cope up with the crisis of these infectious diseases.

In the work done in chapter 2, insect repellent has been used as precautionary measure. The waning effect of insect repellent creams can be added in the model as it wanes off after some time.

In the work done in chapter 3, two infectious diseases are studied. One is Yellow fever and the other is chikungunya. For yellow fever transmission, the awareness through media has been used as a control measure to fight the epidemic. The usage of these awareness programmes definitely delay the progression of the epidemic but not prevent it all together. This is particularly important in humid weathers that support mosquito growth. There is a great scope of adding various mosquito control tools for extra benefit. For the dynamics of chikungunya, we are dealing with a vector-host model with various control measures. This kind of model can

be considered for other vector-host models like Dengue, West Nile virus, Zika virus by changing the parameters to relevant ones.
In all, the work is done on control of the infectious diseases. So, there are many factors that can be considered to extend the work. A few of them has been mentioned here.

- The change in climate and seasonal variation which is cause of fluctuating disease burden can also be considered.
- Delay in treatment response, latent period of infection can also be considered in the work wherever applicable.
- Since, mortality rate is associated with infectious diseases in general and its value keeps on changing depending on different factors. One of the great way is to consider some vaccination campaign evaluations in future.
- The models can also be applied for particular classes like immuno-deficient individuals whose immunity is compromised due some health related issues. This can be done by considering immunity as one of the factors to study.
- In the disease dynamics, one of the practical problems is lack of experimental data for validation of the model proposed. Some experiments can be conducted for evaluation of model parameters in future.

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