Theoretical Studies on a Two Strain Model of Drug Resistance:

Understand, Predict and Control the Emergence of Drug Resistance.

by

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ABSTRACT

Infectious diseases are a leading cause of death worldwide. With the development of drugs, vaccines and antibiotics, it was believed that for the first time in human history diseases would no longer be a major cause of mortality. Newly emerging diseases, re-emerging diseases and the emergence of microorganisms resistant to existing treatment have forced us to re-evaluate our optimistic perspective. In this study, a simple mathematical framework for super-infection is considered in order to explore the transmission dynamics of drug-resistance. Through its theoretical analysis, we identify the conditions necessary for the coexistence between sensitive strains and drug-resistant strains. Farther, in order to investigate the effectiveness of control measures, the model is extended so as to include vaccination and treatment. The impact that these preventive and control measures may have on its disease dynamics is evaluated. Theoretical results being confirmed via numerical simulations.

Our theoretical results on two-strain drug-resistance models are applied in the context of Malaria, antimalarial drugs, and the administration of a possible partially effective vaccine. The objective is to develop a monitoring epidemiological framework that help evaluate the impact of antimalarial drugs and partially-effective vaccine in reducing the disease burden at the population level.

Optimal control theory is applied in the context of this framework in order to assess the impact of time dependent cost-effective treatment efforts. It is shown that cost-effective combinations of treatment efforts depend on the population size, cost of implementing treatment controls, and the parameters of the model. We use these results to identify optimal control strategies for several scenarios.

DEDICATION

To my husband Daniel M. Romero, my daughter Ylani A. Romero and my mom Maria Medina.

ACKNOWLEDGEMENTS

Though my name is printed on the cover of this thesis, the work ”I” does not appear within its chapters. I do this to pay tribute o the myriad contributions of my advisors, and committee members, and the support of my family and friends.

Carlos and Xiaohong, this Dissertation would have never been written if not for your help, you guys are my advisors, friends, mentors and role models. Dr. Carlos Castillo-Chavez, thank you for helping me and encouraging me through out this long process. Dr. Xiaohong Wang, my dearest friend, your guidance and support were a crucial ingredient in making this journey possible. Thanks for all the patience and encouragements through out this long journey. Many thanks also to Dr. Erika T. Camacho and Dr. Stephen Wirkus for all the wonderful and insightful feedback and accepting to be part of my committee.

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Chapter 1

INTRODUCTION

Infectious diseases such as Tuberculosis, Malaria, Influenza, etc, are the leading cause of death world wide. With the development of drugs, vaccines, and antibiotics, some diseases would now be reduced from major causes of mortality to relatively minor incovenieces. However, newly emerging diseases (e.g. AIDS, hantavirus pulmonary syndrome, SARS) and re-ermerging diseases (e.g. malaria, pertussis, tuberculosis) often involving drug-resistant variants, continue to challenge epidemiologist. Further, the emergence of microorganisms resistant to existing treatment pose a serious threat to human health [32]. The recent outbreaks of multidrug-resistant *Mycobacterium tuberculosis* [35] provide but one example. In order to avoid a return to the era of untreatable infections, a detailed understanding of the relationship between antibiotic use and the spread of antibiotic resistance is essential.

Mathematical models have become important tools in analyzing the spread and control of infectious diseases. The work of Kermack and McKendrick, published in 1927 [37], had a major influence on the way we model contagion. Kermack and McKendrick introduced a compartmental *SIR* model, where the host population is categorized by infection status as susceptible S, infectious I, and recovered R. The *classic SIR* model provides a basis for understanding more complex epidemiology disease contagion processes.

The classic infectious disease model provides a simple yet quite powerful representation of disease outbreak dynamics. Naturally, quite often modeling extensions are required. For example, most pathogens have evolved into multiple variants. Hence, the importance of studying the competition (interference or direct) between variants is important. For example, dengue appears in multiple variant and in four major serotypes [33]. Further, infection involving serotypes in a particular order

may lead the hosts experiencing haemorrhagic fever, which often results in death [33]. Dengue models with several serotypes have been considered in ([24], [27], and references therein). The virus that causes influenza, a highly mutable virus, has prompted scientists to derive epidemic models where infected individuals are tied in to particular virus phenotypes [45]. Multi-strain influenza models have been introduced to study their joint dynamics under crossimmunity([1], [46], [14], [15], [57], [58], [59]). Also epidemic models which investigate multistrain interactions are found in [10] and conclude that competitive exclusion is the ultimate outcome. Other models explore the competitive exclusion and coexistence of strains in diseases like gonorrhea and other sexually transmitted diseases [16], [17]. Models have also been developed to study the dynamics of tuberculosis re-emergence and the spread of drug-resistant strains [7], [13], [26] [18] .

Mathematical modeling can provide insight into the mechanisms that allows a strain that would normally be excluded to coexist with a competitively dominant strain. These mechanisms have been studied in the literature [1], [14], [15], [19], [48], [56]. Some of the mechanisms that have been identified to promote coexistence of pathogen variants are super-infection (one of the strains takes over a host infected with another strain) [43], [48], [56] [19], [51], co-infection (a host can be infected with two strains for a prolonged period of time) [49], cross-immunity (infection with one strain in part protects against infection with another after recovery from the first) [14], [15], [24], and mutation (one of the strains mutates into the other) [13], [26], [45].

This work focuses on understanding the competitive dynamics between drug resistant strains and sensitive strains. A simple epidemic framework is built that puts two strains, a drug sensitive and a drug resistant strain, into (interference) competition and considers the case, in particular where the resistant strain can infect individuals already infected by the sensitive strain. The aim of this work is to understand, predict and control the emergence of a drug-resistant strains.

The theoretical framework developed in this study is applied to a simplified version that mimics the transmission dynamics of drug-resistant Malaria. Malaria is a mosquito-borne infection caused by protozoa of the genus plasmodium. The parasites are transmitted by the bite of infected female mosquitos. Mosquitos become infected by feeding on the blood of infected people, and the parasites then undergo another phase of reproduction in the infected mosquito. Clinical symptoms such as fever, pains, and sweats may develop a few days after the infected mosquito bite [2].

In many parts of Africa, where malaria has long been endemic, treatment and control have become increasingly difficult due to the spread of drug-resistant malaria parasites strains [4], [72]. Drugs such as chloroquine, nivaquine, quinine, and fansidar have been used for treatment [2], [5]. It is estimated that 267 million people are presently infected, with 107 million clinical cases annually; the number of countries affected is estimated to be 103 [72]. The emergence of malaria parasite of drug-resistant strains has become a global health challenge.

In Chapter 2, a basic two-strain epidemic model with super-infection is introduced. Through the analyses of this model, we identify the necessary conditions for the coexistence between sensitive and drug-resistant strains.

In Chapter 3, the impact of two distinct control and prevention measures on disease transmission of sensitive and drug resistant strains is explored. The effect of introducing on the transmission dynamics of the two-strain model is studied, taking into account the possibility of various levels of compliance. The impact of vaccination as a preventative control measure is also studied. Theoretical results are illustrated using numerical simulations.

In Chapter 4, we illustrate earlier theoretical results in the context of Malaria. In over-simplified setting, the model considers a region of the world where Malaria is endemic. For example, the model assumes that we are dealing with a structure that

resembles the current Malaria disease conditions in sub-Saharan Africa. Focusing on an endemic region, allows for the assumption that the vector population is at steady-state and hence, it can be treated as a constant parameter, making it possible to omit the vector dynamics over our time-scale of interest. Selective numerical simulations are used to highlight the impact of implementing preventive and control measures while assessing their effect on Malaria prevalence, mortality reduction, and the reproductive number $\mathscr{R}_0$.

The implementation of optimal control strategies involving antimalarial treatment and vaccination can reduce significantly the number of cases of Malaria. Control measures must be carefully distributed specially in resource-limited situations. In Chapter 5, we apply optimal control to the model with interventions and evaluate the impact of antimalarial treatment and vaccination on spread of Malaria. Three control strategies involving antimalarial treatment and vaccination are tested under the ”unlimited” resource assumption. We conclude that the implementation of antimalarial treatment at the start of the outbreak tends to reduce the magnitude of the outbreak peak. The optimal strategy is the implementation of both control measures starting at the onset of the outbreak.

Chapter 2

DYNAMICS OF A TWO STRAIN MODEL OF DRUG RESISTANCE

It is well known that the emergence of drug resistant strains in infectious diseases such as tuberculosis (TB), malaria, and HIV among others, pose a threat to both developed and under-developed countries. Until recently, antibiotic discovery has kept ahead of microbial resistance, but the recent outbreaks of drug-resistant infections have prompted headlines in both the mainstream and the scientific press [6].

Most diseases are produced by a spectrum of closely related pathogens rather than by a single strain. In drug-resistance, an analogous phenomenon to superinfection (Nowak and May [56], May and Nowak [48] and Castillo-Chavez and Velasco-Hernandez [19]) occurs. One strain invades the host population, produces a brief period of temporary immunity to other strains but when the immunity is lost, the host becomes susceptible to reinfection with another strain. Under this condition, one important theoretical problem that we address here is that of the coexistence of drug-sensitive and drug-resistant strains, or the eventual extinction of one of them. A similar problem has been theoretically explore by several authors [43], [11], [44], [16].

The numerous published results discussing the problem of coexistence in pathogen-host interactions. Levin and Pimentel [43] constructed a mathematical *SI* model where the population in the absence of disease grows exponentially. Two strains with different virulences compete with each other. The most virulent strain can 'takeover' hosts already infected with the less virulent strain. With these assumptions a globally stable equilibrium is possible where both strains may coexist. The stability of the positive equilibrium is only guaranteed for certain range of values of superinfection. Outside this range once of the boundary equilibria is asymptotically stable.

Bremermann and Thieme [11] postulate a competitive exclusion principle in an *SIR* epidemic in a population with variable size. Several strains compete for a single host population. The pathogens differ on their virulence. In this model virulence is a strictly convex function of the transmission rate implying that the evolution of virulence leads to a transmission rate that maximizes the basic reproductive number of the pathogen [11].

Castillo-Chavez et al [44] find, for a *SIS* two-sex model with variable population size, that competitive exclusion is the norm: the strain with the highest reproductive number persists in both host types. Mena-Lorca, Velasco-Hernandez and Castillo-Chavez [51] studied the effect of variable population, virulence and density-dependent population regulation. Concluding that variable population size can reduce the area of parameter space on which coexistence is possible. Castillo-Chavez and Velasco-Hernandez [19], perform a qualitative analysis of three host pathogen system and show that the pathogen's competitive exclusion depends heavily on the population dynamics of host population. In this model, coexistence is feasible only in a certain window of parameter space.

In this model, we relax the assumption that the contact rate is a function of virulence, hence virulence becoming the growth regulatory factor. We adopt the Susceptible-Infective-Susceptible (SIS) framework and extend it to describe the competition between two types of strains: sensitive and resistant to drugs. We expand the SIS model by allowing hosts to be superinfected by a second strain, which may possibly lead to the coexistence of sensitive and drug-resistant strains even within the same patient. Sensitive and drug-resistant can indeed coexist in the same population and in fact, epidemiology models with superinfection have shown that coesxitence of many strains is possible and in particular the coexistence of strains with considerable differences of transmission success [56], [48], [19], [51].

2.1 Mathematical Model

In this section, we introduce a two strain epidemic model with super-infection. We consider a population whose size at time t is given by $N(t)$ whose demography is regulated by assumed constant birth/recruitment rate Λ and a constant natural per-capita mortality rate μ. The population is divided into the following epidemiological classes: Susceptible, Infected with sensitive strain and Infected with resistant strain. The susceptible population $S(t)$, which can be infected by the drug-sensitive strain at a the per-capita and per-infective rate β_1; and the drug-sensitive colonized class $I_s(t)$. Individuals in class I_s are assumed to recover at a rate α_1, returning to the susceptible class. Susceptibles can also become infected by the drug-resistant strain at the per-capita and per-infective rate β_2; drug-resistant individuals move to the class I_r. Drug-resistant strain infected individuals recover at a per-capita rate α_2, returning to the susceptible class.

This simple epidemic model incorporates the process of superinfection, where an already infected host can be infected by another parasite strain. We assume individuals infected with the drug-resistant strain can come into contact with infectious individuals colonized by the drug-sensitive strain and become reinfected with the first strain. In our approach, superinfection means that a more virulent (fit) parasite can infect and 'take over' a host that is already infected by a less virulent parasite strain. We also do not consider the possibility that a particular host is infected by more than one parasite strain at any given time [48], [56], [19]. We assume that more virulent strain can out compete the less virulent strain on the level of intra-host competition. The transmission coefficient in the case of super-infection is δ where δ is the coefficient of reduction or enhancement of infection at reinfection. In particular, if $\delta > 1$ then reinfection is more likely than the regular infection while if $0 < \delta < 1$ then reinfection is less likely than the regular infection. If $\delta = 0$ there is no super-infection.

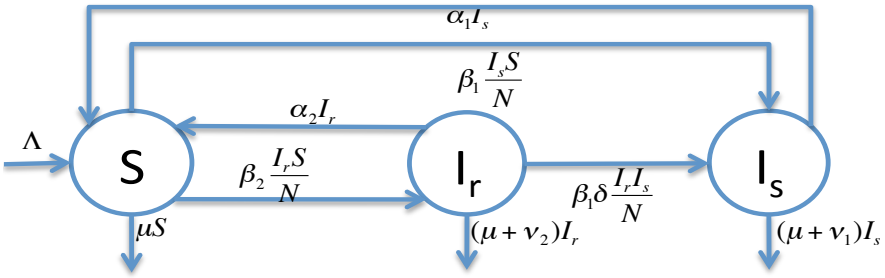

Figure 2.1: Representation of the two strain model with superinfection

The basic two-strain model with superinfection is therefore given by the system of differential equations, and takes the following form:

$$\begin{aligned} \dot{S} &= \Lambda - \beta_1 \frac{SI_s}{N} - \beta_2 \frac{SI_r}{N} - \mu S + \alpha_1 I_s + \alpha_2 I_r \\ \dot{I}_s &= \beta_1 \frac{SI_s}{N} + \beta_1 \delta \frac{I_s I_r}{N} - (\mu + \nu_1) I_s - \alpha_1 I_s \\ \dot{I}_r &= \beta_2 \frac{SI_r}{N} - \beta_1 \delta \frac{I_s I_r}{N} - (\mu + \nu_2) I_r - \alpha_2 I_r \end{aligned} \tag{2.1}$$

where

$$N(t) = S(t) + I_s(t) + I_r(t)$$

Table 2.1: Description and units for model variable and parameters.

Variable	Description [Units]
$S(t)$	susceptible individuals [individuals]
$I_s(t)$	drug-sensitive colonized individuals [individuals]
$I_r(t)$	drug-resistant colonized individuals [individuals]
Parameters	Description [Units]
Λ	recruitment/birth rate [individuals/unit time]
μ	natural death rate [1/unit time]
β_1	drug-sensitive effective contact rate [1/unit time]
β_2	drug-resistant effective contact rate [1/unit time]
α_1	natural drug-sensitive infection rate [1/unit time]
α_2	natural drug-resistant infection rate [1/unit time]
ν_1	disease-induced drug-sensitive mortality rate [1/unit time]
ν_2	disease-induced drug-resistant mortality rate [1/unit time]
δ	fitness cost [N/A]

2.2 Equilibria and stability

For this basic model 2.1, there exists a domain where the system of equations is epidemiologically and mathematically well-posed. We define this domain System, $\mathbb{S}$, as:

$$\mathbb{S} := \{(S, I_s, I_r) \in (\mathbb{R}_0^+)^3\}$$

This domain, $\mathbb{S}$, is valid epidemiologically as populations S, I_s, and I_r are all nonnegative. We use the notation $f^{'}$ to denote $\frac{df}{dt}$

Theorem 1 *Assuming that the initial conditions lie in $\mathbb{S}$, the system of equations for the basic model (2.1) has a unique solution that exists and remains in $\mathbb{S}$ for all time $t \geq 0$.*

Proof The right hand side of the system of equations (2.1) is continuous with continuous partial derivatives in $\mathbb{S}$. It remains to show that $\mathbb{S}$ is forward-invariant. We can see from (2.1) that if $S = 0$, then $S^{'} \geq 0$; if $I_s = 0$, then $I_s^{'} \geq 0$; and if $I_r = 0$, then $I_r^{'} \geq 0$. Therefore, none of the obits can leave $\mathbb{S}$ and a unique solution exists for all time □

Basic reproduction number, $\mathscr{R}_0$

We calculate the basic reproduction number, $\mathscr{R}_0$, using the next generation operator approach, as found in van den Driessche and Watmough [70]. Hence, it is important to distinguish new infections from all other class transitions in the population. The infected classes are I_s and I_r. We can write system (2.1) in the form

$$\dot{X} = f(X) \Leftrightarrow \dot{X} = \mathscr{F}(X) - \mathscr{V}(X) = \mathscr{F}(X) - (\mathscr{V}^-(X) - \mathscr{V}^+(X)),$$

where $X = (I_s, I_r, S)$, $\mathscr{F}$ is the rate of appearance of new infections in each class; $\mathscr{V}^+$ is the rate of transfer into each class by all other means and $\mathscr{V}^-$ is the rate of transfer

out of each class. Specifically,

$$\mathscr{F} \equiv \left(\beta_1 \frac{SI_s}{N} + \beta_1 \delta \frac{I_s I_r}{N}, \beta_2 \frac{SI_r}{N}\right)^T$$

and the disease-free equilibrium is $X_0 \equiv (0,0,\frac{\Lambda}{\mu})$. The matrices $\mathrm{D}\mathscr{F}(X_0)$ and $\mathrm{D}\mathscr{V}(X_0)$ can be partitioned as

$$D\mathscr{F}(X_0) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix}, D\mathscr{V}(X_0) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix}$$

where F and V correspond to the derivatives of $\mathscr{F}$ and $\mathscr{V}$ with respect to the infected classes. Specifically, we have that

$$F = \begin{bmatrix} \beta_1 & 0 \\ 0 & \beta_2 \end{bmatrix}, V = \begin{bmatrix} (\mu + \alpha_1 + \nu_1) & 0 \\ 0 & (\mu + \alpha_2 + \nu_2) \end{bmatrix}$$

The basic reproduction number is defined as the spectral radius (dominant eigenvalue) of the next generation matrix, FD^{-1}:

$$\mathscr{R}_0 = max\{R_s, R_r\}$$

where R_s and R_r are the two eigenvalues:

$$R_s = \frac{\beta_1}{\mu + \nu_1 + \alpha_1} \tag{2.2}$$

$$R_r = \frac{\beta_2}{\mu + \nu_2 + \alpha_2} \tag{2.3}$$

We interpret R_s and R_r as the average number of secondary cases that an infectious individual (with sensitive or resistant strain, respectively) would generate in a totally susceptible host population. It follows then that if $\mathscr{R}_0 > 1$, then the disease is able to invade the host population. Otherwise, if $\mathscr{R}_0 \leq 1$ the virus eventually disappears from the host population (local result).

Equilibria points

We are interested in the conditions that guarantee the permanence of drug-resistance as an endemic disease. There are, in our model, two boundary equilibria (where only

one strain is present), and the coexistence equilibrium. In the following section we analyze the equilibrium. Its existence is determined by the relative magnitude of the basic reproductive number of each strain. After that, we present the numerical results that characterize the stability of the equilibria points.

The system of differential equations has one disease-free equilibrium, $E_0 = (\frac{\Lambda}{\mu}, 0, 0)$ and three endemic equilibria of the form $E_s = (S^*, I_s^*, 0)$, $E_r = (S^*, 0, I_r^*)$, and $E_c = (S^*, I_s^*, I_r^*)$, corresponding, respectively, to states where only sensitive strains, or resistant strains, or both types of strains are present.

The bifurcation diagrams in Figures 2.2 and Figure 2.3 divides the (R_s, R_r) space into distinct regions as characterized by the long-term epidemiological outcomes, each corresponding to a stable steady state of the system: disease eradication (DFE), persistence of only drug-resistant strain, persistence of only drug-sensitive strain, or coexistence i.e., persistence of both drug-sensitive and drug-resistant strains. In Figure 2.2 we can see the corresponding stability regions for $\delta = 0$ (absence of superinfection) and $\delta = 0.8$. This figure illustrates the idea that superinfecetion makes coexistence possible [56], [48], [19], [51], [11]. Figure 2.3, shows the long-term behavior of two strain model with superinfection when we change δ. Notably, the resistant-strain only region decreases as the transmission coefficient in the case of superinfection δ increases.

Stability of the disease-free equilibrium

The stability properties of the disease-free equilibrium (trivial equilibrium) E_0, corresponding to the threshold condition for endemicity are given in Theorem 2.

Theorem 2 *Consider the quantities R_s, and R_r, given in $(2.3) - (2.3)$. The disease-free equilibrium E_0 of system (2.1) is locally asymptotically stable, if $R_0 < 1$, i.e., if $R_s < 1$ and $R_r < 1$, and it is unstable for $\mathscr{R}_0 > 1$.*

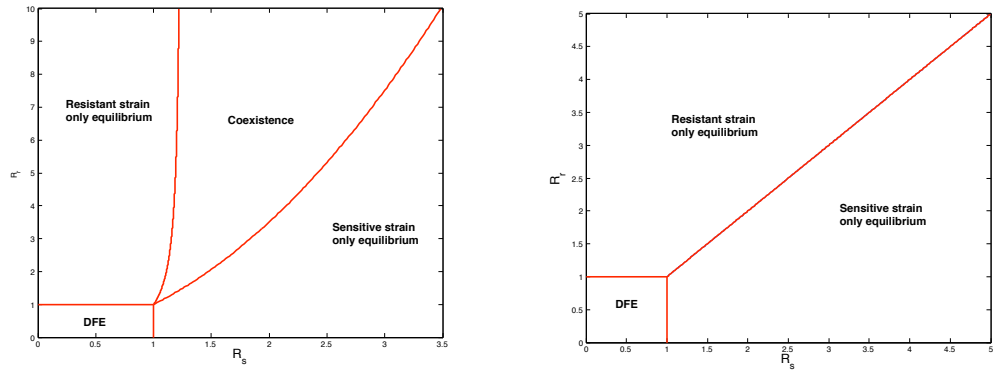

Figure 2.2: Bifurcation diagram: long-term epidemiological outcome of the (R_s, R_r) space. The parameter values are as follows: $\mu = 0.01$, $\nu_1 = 0.6$, $\nu_2 = 0.65$, $\alpha_1 = 0.03$, and $\alpha_2 = 0.02$. Figure to the left has $\delta = 0.8$ and figure to the right $\delta = 0$

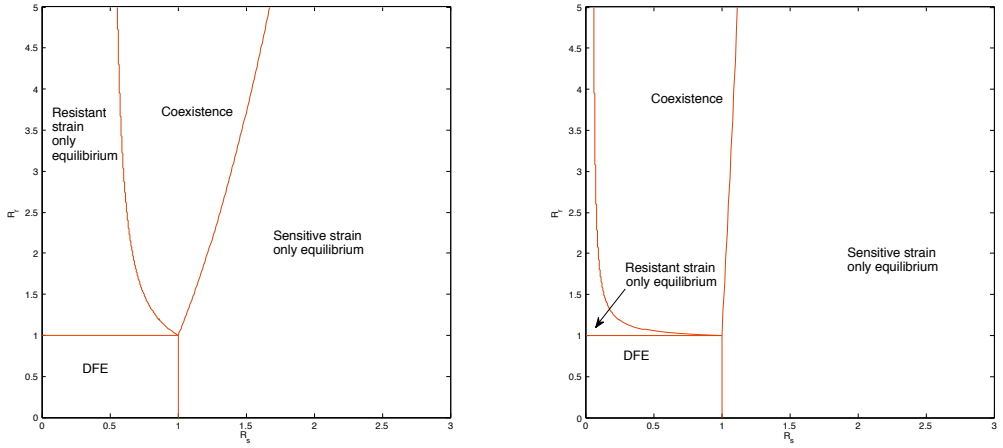

Figure 2.3: Bifurcation diagram: long-term epidemiological outcome of the (R_s, R_r) space. The parameter values are as follows: $\mu = 0.01$, $\nu_1 = 0.6$, $\nu_2 = 0.65$, $\alpha_1 = 0.03$, and $\alpha_2 = 0.02$. Figure to the left has $\delta = 2$ and figure to the right $\delta = 20$

Proof By Theorem 2 in van den Driessche and Watmough [70], it is sufficient to prove the following conditions:

- (A1) if $X \geq 0$, then $\mathscr{F}$, $\mathscr{V}^+$, $\mathscr{V}^- \geq 0$,
- (A2) if $X_i = 0$ then $\mathscr{V}_i^- = 0$ (where i refers to a vector component),
- (A3) $\mathscr{F}_i = 0$ for the components that correspond to uninfected classes,
- (A4) if X^* is a disease-free equilibrium then $\mathscr{F}_i(X^*) = 0$ and $\mathscr{V}_i^+(X^*) = 0$ for the components that correspond to uninfected classes

- (A5) if $\mathscr{F}$ is set to zero then all eigenvalues of $\mathrm{D}f(X_0)$ have negative real parts.

The verification of (A-1)-(A-4) are straightforward.

The Jacobian of f at X_0, with $\mathscr{F}$ set to zero, is

$$Df_{\mathscr{F}=0}(X_0) = \begin{bmatrix} -(\mu+\alpha_1+\nu_1) & 0 & 0 \\ 0 & -(\mu+\alpha_2+\nu_2) & 0 \\ -\beta_1+\alpha_1 & -\beta_2+\alpha_2 & -\mu \end{bmatrix}$$

The eigenvalues of the above matrix are $\lambda_1 = -(\mu+\alpha_1+\nu_1)$, $\lambda_2 = -(\mu+\alpha_2+\nu_2)$ and $\lambda_3 = -\mu$, all of which have negative real part and the result follows. □

Stability of boundary and coexistence equilibria

The system has three possible non-trivial equilibria, two boundary equilibria and a coexistence equilibrium. The boundary equilibria correspond to the presence of only one strain in the population, sensitive strain or resistant strain. The existence of the two boundary equilibria, where only sensitive strains or resistant strains persists, is given by the following theorems:

Theorem 3 *The system of differential equations (2.1) has one boundary equilibrium where the sensitive strain persists, $E_s = (S^*, I_s^*, I_r = 0)$, for $R_s > 1$*

Proof From the equations of the system (2.1) at equilibrium, we get a relation S, I_s, and I_r where

$$S = \frac{\Lambda - (\mu+\nu_1)I_s - (\mu+\nu_2)I_r}{\mu} = F(I_s, I_r)$$

Suppose that $I_r = 0$. If I_s is non-zero from the second equation in system (2.1) we get

$$[\beta_1 - (\mu+\nu_1+\alpha_1)]S - (\mu+\nu_1+\alpha_1)I_s = 0.$$

Equivalently, we can write this as follows:

$$[\beta_1 - (\mu + \nu_1 + \alpha_1)]F(I_s, 0) - (\mu + \nu_1 + \alpha_1)I_s = 0$$

Now, if we solve for I_s, we get

$$I_s = \frac{[\beta_1 - (\mu + \nu_1 + \alpha_1)]\frac{\Lambda}{\mu}}{[\beta_1 - (\mu + \nu_1 + \alpha_1)](\frac{\mu+\nu_1}{\mu}) + (\mu + \nu_1 + \alpha_1)}.$$

We observe that if $\beta_1 > (\mu + \nu_1 + \alpha_1) \iff R_s > 1$ and $I_s > 0$, that is, we have exactly one positive solution for I_s; while $\beta_1 \leq (\mu + \nu_1 + \alpha_1) \iff R_s \leq 1$, and $I_s \leq 0$, so there are no positive solutions for I_s. □

Theorem 4 *The system of differential equations (2.1) has one boundary equilibrium where the resistant strain persists, $E_r = (S^*, I_s = 0, I_r^*)$, for $R_r > 1$*

Proof From the equations of the system (2.1) at equilibrium, we get a relation S, I_s, and I_r where

$$S = \frac{\Lambda - (\mu + \nu_1)I_s - (\mu + \nu_2)I_r}{\mu} = F(I_s, I_r)$$

Suppose that $I_s = 0$. If I_r is non-zero from the third equation in system (2.1) we get

$$[\beta_2 - (\mu + \nu_2 + \alpha_2)]S + (\mu + \nu_2 + \alpha_2)I_r = 0.$$

We can write this as follows:

$$[\beta_2 - (\mu + \nu_2 + \alpha_2)]F(0, I_r) + (\mu + \nu_2 + \alpha_2)I_r = 0$$

Now, if we solve for I_r then we get

$$I_r = \frac{[\beta_2 - (\mu + \nu_2 + \alpha_2)]\frac{\Lambda}{\mu}}{[\beta_2 - (\mu + \nu_2 + \alpha_2)](\frac{\mu+\nu_2}{\mu}) + (\mu + \nu_2 + \alpha_2)}.$$

If $\beta_2 > (\mu + \nu_2 + \alpha_2) \iff R_r > 1$, then $I_r > 0$ and we have exactly one positive solution for I_r. If $\beta_2 \leq (\mu + \nu_2 + \alpha_2) \iff R_r \leq 1$, then $I_r \leq 0$, so there are no positive solutions for I_r. □

Two coexistence thresholds must be calculated: the first separates the region where only sensitive strains persist from the region of coexistence; the second marks the shift from coexistence to persistence of resistant strains alone.

In order to derive an expression for the region of stability of the boundary equilibria we measure the capacity of the strains to invade and persist in a population where either sensitive or resistant strains are at equilibrium. In the case where the sensitive strain is at equilibrium, in this context, $E_s = (S^*, I_s^*, 0)$ corresponds to an equilibrium free of resistant strain. In order to apply the methods in van den Driessche and Watmough [70], consider the case where the sensitive strain is at equilibrium and ask whether or not the resistant strain can invade.

The infected compartment is I_r. We can write system (2.1) as $X = (I_r, S, I_s)$ and

$$\mathscr{F} = \left(\beta_2 \frac{SI_r}{N}, S, 0\right)^T.$$

The disease (resistant strain)-free equilibrium is $(I_s, S, 0)$.

We can compute F and V that correspond to the derivatives at $X_0 = (0, \frac{\Lambda}{\mu}, 0)$ with respect to the infected classes of $\mathscr{F}$ and $\mathscr{V}$, respectively:

$$\begin{aligned} F &= \frac{\beta_2 S^2 + \beta_2 S I_s}{(S+I_s)^2} \\ &= \frac{\beta_2}{R_s}, \\ V &= (\mu + \nu_2 + \alpha_2) + \frac{\beta_1 \delta S I_s + \beta_1 \delta I_s^2}{(S+I_s)^2} \\ &= \frac{R_s(\mu + \nu_2 + \alpha_2) + \beta_1 \delta (R_s - 1)}{R_s} \end{aligned}$$

The basic reproduction number of the resistant strain in a population where sensitive strains are fixed is then the spectral radius of the next generation matrix, FV^{-1} [70]:

$$R_r(E_s) = \frac{\beta_2}{R_s(\mu + \alpha_2 + \nu_2) + \beta_1 \delta (R_s - 1)}$$

Similarly, applying the methods in van den Driessche and Watmough [70] once again, we find the basic reproduction number of the sensitive strains in a population where resistant strains are fixed:

$$R_s(E_r) = \frac{R_s}{R_r}[1 + \delta(R_r - 1)]$$

This formulation permits the derivation of a threshold condition for coexistence. Now equivalent to a threshold condition for resistant strain endemicity in a population where sensitive strains are at equilibrium, $R_r(E_s) = 1$: only sensitive strains persist for $R_r(E_s) < 1$, while for $R_r(E_s) > 1$ resistant strains can invade a population where sensitive strains are fixed, hence coexistence is possible. We also have a similar threshold condition for sensitive strain endemicity in a population where resistant strains are at equilibrium, $R_s(E_r) = 1$: only resistant strains persist for $R_s(E_r) < 1$, while for $R_s(E_r) > 1$ sensitive strains can invade a population where resistant strains are fixed, that is to say, coexistence is possible.

Theorem 5 and 6 below express these results in terms of stability for the equilibrium E_s and E_r.

Theorem 5 *If $R_s > 1$ the equilibrium E_s of the system of differential equations (2.1) is stable for $R_r(E_s) < 1$ and unstable for $R_r(E_s) > 1$.*

Proof By Theorem 2 in van den Driessche and Watmough [70], it is sufficient to prove conditions $(A1) - (A5)$. Once more, conditions $(A1) - (A4)$ are of trivial verification. To prove the remaining condition $(A5)$ we write the Jacobian of f at $X_0 = (\frac{\Lambda}{\mu}, 0, 0)$, with $\mathscr{F}$ set to zero, ordering coordinates as (S, I_s, I_r). Then, the Jacobian has the form

$$Df_{\mathscr{F}=0}(S^*, I_s^*, 0) = \begin{bmatrix} G_1 & G_2 \\ 0 & a \end{bmatrix}$$

where,

$$G_1 = \begin{bmatrix} \frac{-\beta_1 I_s^*}{S^*+I_s^*} + \frac{\beta_1 S^* I_s^*}{(S^*+I_s^*)^2} - \mu & \frac{-\beta_1 S^*}{S^*+I_s^*} + \frac{\beta_1 S^* I_s^*}{(S^*+I_s^*)^2} + \alpha_1 \\ \frac{\beta_1 I_s^*}{S^*+I_s^*} - \frac{\beta_1 S^* I_s^*}{(S^*+I_s^*)^2} & \frac{\beta_1 S^*}{S^*+I_s^*} - \frac{\beta_1 * S^* I_s^*}{(S^*+I_s^*)^2} - (\mu+\alpha_1+\nu_1) \end{bmatrix}$$

and

$$a = \frac{\beta_2 S^*}{S^*+I_s^*} - \frac{\beta_1 \delta I_s^*}{S^*+I_s^*} - (\mu+\alpha_2+\nu_2)$$

Therefore, the eigenvalues of the Jacobian are given by the eigenvalues of G_1 and a.

For G_1, the eigenvalues are the roots of the characteristic polynomial

$$p_1(\lambda) = \lambda^2 - b_1\lambda + b_0$$

where

$$\begin{aligned} -b_1 &= -(\beta_1 - (\alpha_1+\nu_1)), \\ b_0 &= [\beta_1 - (\mu+\alpha_1+\nu_1)][\beta_1\mu + \nu_1(\beta_1 - (\mu+\alpha_1+\nu_1))]. \end{aligned}$$

Now we must show that both $-b_1$ and b_0 are > 0.

We have the following,

$$\begin{aligned} -b_1 &= -(-\beta_1 + (\alpha_1+\nu_1)) \\ &= (\beta_1 - (\alpha_1+\nu_1)) + \mu - \mu \\ &= \mu + (\beta_1 - (\alpha_1+\nu_1+\mu)) \\ &> (\beta_1 - (\alpha_1+\nu_1+\mu)) \\ &> 0 \end{aligned}$$

since $R_s > 1$. Hence $-b_1 > 0$.

It is clear that $b_0 > 0$ since $R_s > 0$. Since $-b_1$ and b_0 are positive for all possible values of $R_s > 1$, then all eigenvalues of G_1 have negative real part.

For a, at equilibrium E_s, we get:

$$a = \frac{\beta_2}{R_s} - \frac{\beta_1\delta(R_s-1) + R_s(\mu+\alpha_2+\nu_2)}{R_s}$$

Now, we have that $a < 0$ for all the possible values of $\frac{\beta_2}{\beta_1\delta(R_s-1)+R_s(\mu+\alpha_2+\nu_2)} < 1$, *i.e.*, $R_r(E_s) < 1$, and $a \geq 0$ otherwise.

Hence, all the eigenvalues have negative real parts. Therefore if $R_s > 1$, then E_s is stable for $R_r(E_s) < 1$ and unstable otherwise. □

Theorem 6 *If $R_r > 1$ the equilibrium E_r of the system of differential equations (2.1) is stable for $R_s(E_r) < 1$ and unstable for $R_s(E_r) > 1$.*

Proof Once again, we apply Theorem 2 in van den Driessche and Watmough [70], and it is sufficient to prove conditions $(A1)-(A5)$. Once more, conditions $(A1)-(A4)$ are of trivial verification. To prove the remaining condition $(A5)$ we write the Jacobian of f at $X_0 = (\frac{\Lambda}{\mu}, 0, 0)$, with $\mathscr{F}$ set to zero, ordering coordinates as (S, I_r, I_s). Then, the Jacobian has the form

$$Df_{\mathscr{F}=0}(S^*, I_r^*, 0) = \begin{bmatrix} H_1 & H_2 \\ 0 & z \end{bmatrix}$$

where,

$$H_1 = \begin{bmatrix} \frac{-\beta_2 I_r^*}{S^*+I_r^*} + \frac{\beta_2 S^* I_r^*}{(S^*+I_r^*)^2} - \mu & \frac{-\beta_2 S^*}{S^*+I_r^*} + \frac{\beta_2 S^* I_r^*}{(S^*+I_r^*)^2} + \alpha_2 \\ \frac{\beta_2 I_r^*}{S^*+I_r^*} - \frac{\beta_2 S^* I_r^*}{(S^*+I_r^*)^2} & \frac{\beta_2 S^*}{S^*+I_r^*} - \frac{\beta_2 S^* I_r^*}{(S^*+I_r^*)^2} - (\mu+\alpha_2+\nu_2) \end{bmatrix}$$

and

$$z = \frac{\beta_1 S^*}{S^*+I_r^*} + \frac{\beta_1 \delta I_r^*}{S^*+I_r^*} - (\mu+\alpha_1+\nu_1)$$

Therefore, the eigenvalues of the Jacobian are given by the eigenvalues of H_1 and z. For H_1, the eigenvalues are the roots of the characteristic polynomial

$$p_2(\lambda) = \lambda^2 - c_1\lambda + c_0$$

where

$$\begin{aligned} -c_1 &= -(\beta_2 - (\alpha_2+\nu_2)), \\ c_0 &= [\beta_2 - (\mu+\alpha_2+\nu_2)][\beta_2\mu + \nu_2(\beta_2 - (\mu+\alpha_2+\nu_2))]. \end{aligned}$$

Now we must show that both $-c_1$ and c_0 are > 0.

So we have the following,

$$\begin{aligned} -c_1 &= -(-\beta_2 + (\alpha_2 + \nu_2)) \\ &= (\beta_2 - (\alpha_2 + \nu_2)) + \mu - \mu \\ &= \mu + (\beta_2 - (\alpha_2 + \nu_2 + \mu)) \\ &> (\beta_2 - (\alpha_2 + \nu_2 + \mu)) \\ &> 0 \end{aligned}$$

since $R_r > 1$. Hence $-c_1 > 0$.

It is clear that $c_0 > 0$ since $R_r > 0$. Since $-c_1$ and c_0 are positive for all possible values of $R_r > 1$, then all eigenvalues of H_1 have negative real part.

For z, at equilibrium E_r, we get:

$$z = \frac{\beta_1 + \beta_1 \delta (R_r - 1)}{R_r} - (\mu + \alpha_1 + \nu_1)$$

Now, we have that $z < 0$ for all the possible values of $\frac{R_s}{R_r}\big(1 + \delta(R_r - 1)\big) < 1$, *i.e.*, $R_s(E_r) < 1$, and $z \geq 0$ otherwise.

Hence, all the eigenvalues have negative real parts. Therefore, if $R_r > 1$, then E_r is stable for $R_s(E_r) < 1$ and unstable otherwise. □

The curves the define the coexistence region are given by the following relation: $R_r(E_s) = 1 \iff R_r = f(R_s)$

$$\begin{aligned} R_r(E_s) = 1 \iff R_r &= f(R_s) \\ &= R_s + \frac{\beta_1 \delta (R_s - 1)}{(\mu + \alpha_2 + \nu_2)} \end{aligned} \tag{2.4}$$

$$\begin{aligned} R_s(E_r) = 1 \iff R_s &= g(R_r) \\ &= \frac{R_r}{1 + \delta(R_r - 1)} \end{aligned} \tag{2.5}$$

Relations (2.4) and (2.5) reveals that persistence of drug-resistant strains and drug-sensitive strains depend on the superinfection process. Both expression have the superinfection parameter δ. In the case when superinfection is not considered, $\delta = 0$, reveal that persistence of only drug-resistant strains is possible when $R_r > R_s$ and persistence of only drug-sensitive strains is possible for $R_s > R_r$. Coexistence is not governed solely by the invasion capacities of each strain (R_s and R_r) but also by the ability of sensitive strains to overcome the superinfection pressure exerted by resistant strain and vice-versa. Numerical results support that above the curve defined by f and below the curve defined by g, in the (R_s, R_r)- space both types of strains will persists, thus allowing coexistence.

2.3 Fitness cost

A question that comes up over and over is may we expect drug resistant strains to be less transmissible than the drug sensitive strains? To explore the epidemiological consequences of resistance cost we fix the relative transmission coefficient, $\gamma = \frac{\beta_2}{\beta_1}$, and explore the system behavior by varying a parameter β such that

$$\beta_1 \equiv \beta, \beta_2 \equiv \gamma\beta$$

As such, $\gamma < 1$ means that the resistant strains have lower transmissibility than the sensitive. Despite being less likely, the possibility $\gamma > 1$ is also considered since this topic is still an open discussion among many scientists [21], [29]. Figure 2.3 shows the bifurcation diagrams obtained for various values of γ. When $\gamma = 0.5$ (dashed line) for both low values and high values of β_1 lead to only sensitive strains persisting in the population, which is the ideal situation since this is considered "best case scenario" since the sensitive strain is treatable. For $\gamma = 1.5$ (dotted line), β_1 and β_2 line in all the regions, hence for really low values of β_1 lead to disease free region, and as β_1 increases, we observe a transition to region where resistant strain persists, followed by coexistence and finally the region where the sensitive strains persist.

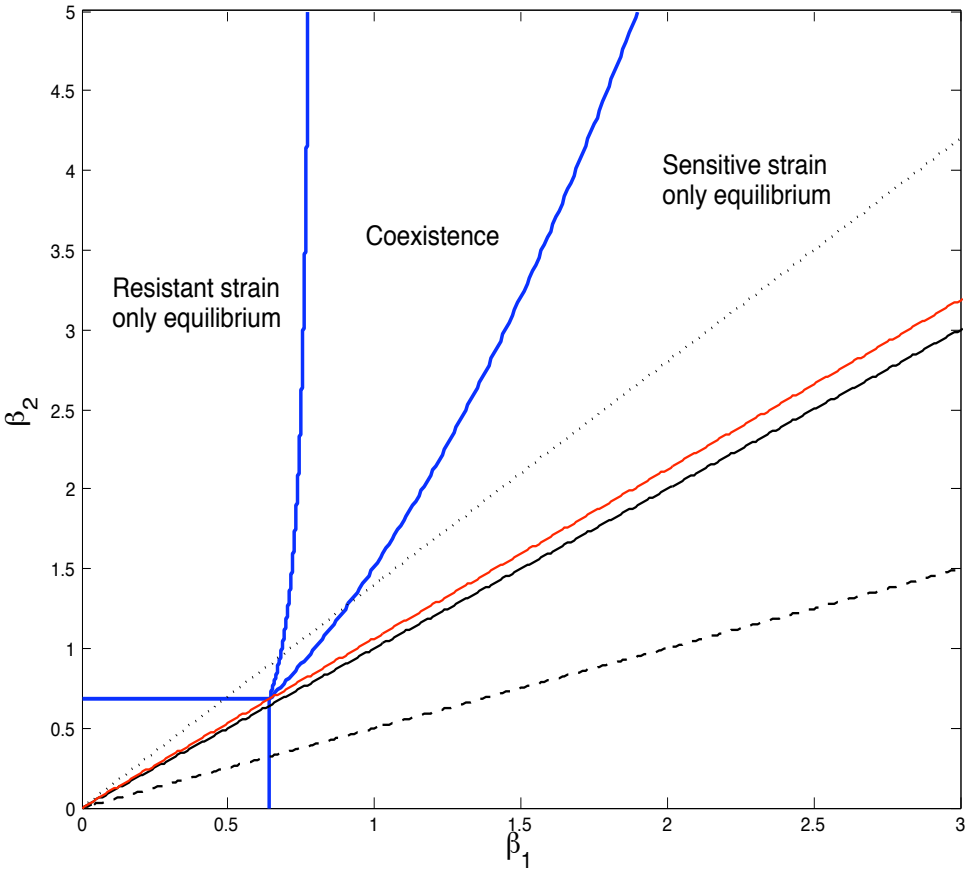

Figure 2.4: Decreased transmission plotted in the (β_1, β_2)-space. Bifurcation diagram where the straight lines correspond to $\beta_1 = \gamma\beta_2$ for different values of γ. $\gamma = 1.5$ dotted line, $\gamma = 1$ solid line, $\gamma = 0.5$ dashed line. The red line correspond to the critical value of γ.

We derive a critical value for γ below which a reduction in the overall transmission can open the possibility where the sensitive strains persist :

$$\gamma_c = \frac{\mu + \nu_2 + \alpha_2}{\mu + \nu_1 + \alpha_1}$$

The critical value can be used to compare the impact of different control measures.

In the case illustrated by $\gamma = 1.5$, as the transmission coefficient, β, increases the system evolves from dominance of the resistant strains to coexistence, and finally dominance of the sensitive strains. This can be interpreted as follows. The minimal transmissibility above which sensitive strains can be sustained in the population where

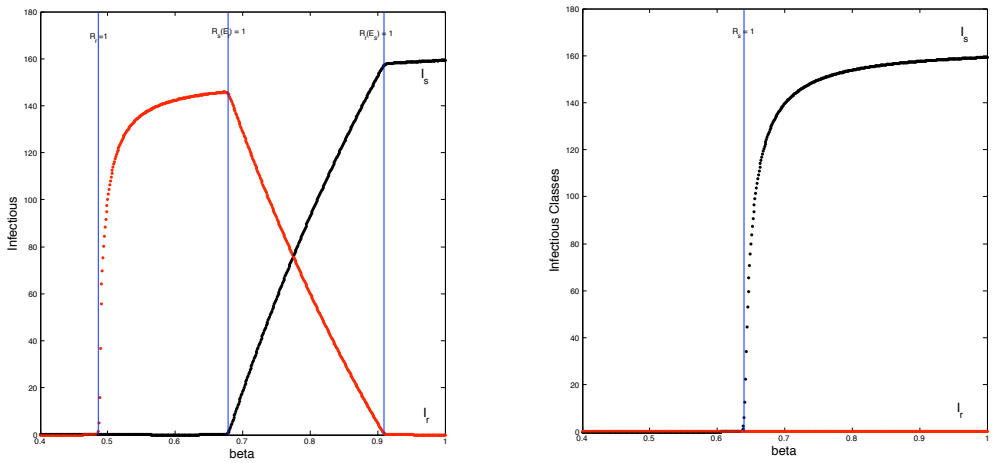

Figure 2.5: Equilibrium curves, the figure to the left is for $\gamma = 1.5$ with vertical blue lines marking the epidemic threshold of resistant strains and the super-infection threshold of sensitive strains. The figure to the right is for $\gamma = 0.5$ with vertical blue lines marking the epidemic threshold of sensitive strains.

resistant strains are endemic, is given by the condition $R_s(E_r) = 1$. This marks a threshold in transmission above which superinfection of resistant by sensitive strains occurs. This superinfection threshold is marked in Fig 2.5. Below the threshold, sensitive strains are outcompeted by the resistant due to a higher transmission coefficient of the latter (recall that $\gamma > 1$)

For the case where $\gamma = 0.5$, the system evolves to dominance of the sensitive strain. Recall that $\gamma = 0.5$ is below the critical value for γ. It is important to remark that as long as the value of γ is kept equal to or below the critical value defined earlier, the long term epidemiological outcome of the resistant strain will always be kept at zero. Hence it will not pose a threat to the population.

Chapter 3

TWO STRAIN MODEL WITH DRUG RESISTANCE AND INTERVENTIONS

In this chapter, the impact of two distinct control and prevention measures on disease transmission of sensitive and resistant strains is studied. Treatment is an important control measure, and its impact on the spread of diseases has been widely studied. However, the benefit of treatment can be compromised if drug-resistant strains arise, especially when treatment regimen is not completed. In this chapter, we develop a mathematical model to explore the impact of treatment on the transmission dynamics of sensitive and drug-resistant strains. A mathematical model that explores the impact of vaccination as a preventative control measure in the dynamics of drug-sensitive strains and drug-resistant strains is also formulated. We analytically find an expression for a critical vaccination rate which will contain the resistant strain and allow for the sensitive strain to prevail.

3.1 Two strain model with treatment

We extend the simple two strain model by including a treatment class and vital dynamics (recruitment and mortality). The new model allows us to study the effect of treatment on the prevalence of both drug-sensitive and drug-resistant strains. Mathematical properties of the model system are analytically studied. It is shown that the system has three possible equilibrium points, a disease free equilibrium, a drug-resistant only equilibrium, and an endemic equilibrium at which both strains are present. A detailed analysis of stability is conducted, which shows that the dynamic behaviors of the system are determined by the quantity $R_s(E_r)$.

Formulation of the model

In this section, we introduce a drug-resistance two strain epidemic model with super-infection and treatment. We consider a population $N(t)$ whose demography is

regulated by a constant birth/recruitment rate Λ and a natural mortality rate μ. The susceptible population $S(t)$ can be infected by the drug-sensitive strain at a transmission rate β_1 and go the drug-sensitive colonized class $I_s(t)$. The infected individuals in class I_s naturally recover at a rate α_1 and return to the susceptible class. Infected individuals with the sensitive strain can naturally die at a rate μ or a disease-induced death at a rate ν_1. Alternatively, susceptibles can be infected by the drug-resistant strain at a transmission rate β_2, in which case they go to the class I_r. Infected individuals with the drug-resistant strain naturally recover at a rate α_2, and upon recovery return to the susceptible class. Individuals in this class can either die of natural causes at a rate μ or disease-induced death at a rate ν_2. One assumption is that those infected with the drug-resistant strain can come into contact with infectious individuals colonized by the drug-sensitive strain and become reinfected with the sensitive strain. This process is referred to as *super-infection*. The transmission coefficient in the case of super-infection is $\beta_1\delta$ where δ is the coefficient of reduction or enhancement of infection at reinfection. In particular, if $\delta > 1$ then reinfection is more likely than the regular infection while if $0 < \delta < 1$ then reinfection is less likely than the regular infection. If $\delta = 0$ there is no super-infection.

This model captures two different ways of getting infected with the resistant strain; one is as a primary infection and the other is acquired resistance. Drug resistant cases may emerge when individuals are infected with a resistant strain (primary resistance) or as a result of treatment failure (acquired resistance). The model introduces a new class, the recovered class R, treatment is administered to the individuals colonized by the sensitive strain and as a result, some recovered and others acquired resistance through failing to comply to the medication guidelines. It is assumed that a fraction of infectious individuals colonized with drug-sensitive strain (I_s) progress into the drug-resistant class (I_r) due to treatment failure at a rate of $(1-s)\sigma$, where s is the probability of compliance and σ is the treatment rate. These

correspond to cases of acquired resistance. Another portion of individuals colonized with the drug-sensitive strain finish the treatment regime and move to the recovered class at a rate of σ.

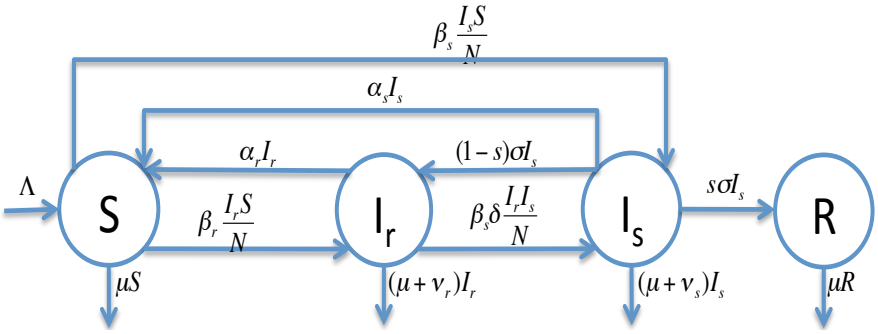

Figure 3.1: Representation of the model super-infection with treatment

$$
\begin{aligned}
\dot{S} &= \Lambda - \beta_1 \frac{SI_s}{N} - \beta_2 \frac{SI_r}{N} - \mu S + \alpha_1 I_s + \alpha_2 I_r \qquad (3.1)\\
\dot{I_s} &= \beta_1 \frac{SI_s}{N} + \beta_1 \delta \frac{I_s I_r}{N} - (\mu + \nu_1) I_s - \alpha_1 I_s - \sigma I_s \\
\dot{I_r} &= \beta_2 \frac{SI_r}{N} + (1-s)\sigma I_s - \beta_1 \delta \frac{I_s I_r}{N} - (\mu + \nu_2) I_r - \alpha_2 I_r \\
\dot{R} &= s\sigma I_s - \mu R
\end{aligned}
$$

Equilibria and stability

For system (3.1), the simplex

$$\mathbb{S} := \{(S, I_s, I_r, R) \in (\mathbb{R}_0^+)^4\}$$

is a positively invariant set, and thus we restrict the study of the solutions of the system to $\mathbb{S}$. By the fundamental theory of ODE's, we know that (3.1) defines a dynamical system on $\mathbb{S}$ as uniqueness, global existence and continuous dependence of solutions on initial data is guaranteed when initial values are in $\mathbb{S}$.

Table 3.1: Description and units for model variable and parameters.

Variable	Description [Units]
$S(t)$	susceptible individuals [individuals]
$I_s(t)$	drug-sensitive colonized individuals [individuals]
$I_r(t)$	drug-resistant colonized individuals [individuals]
R	recovered 'uncolonized' individuals [individuals]
Parameters	Description [Units]
Λ	recruitment/birth rate [individuals/unit time]
μ	natural death rate [1/unit time]
β_1	drug-sensitive effective contact rate [1/unit time]
β_2	drug-resistant effective contact rate [1/unit time]
α_1	natural drug-sensitive infection rate [1/unit time]
α_2	natural drug-resistant infection rate [1/unit time]
ν_1	disease-induced drug-sensitive mortality rate [1/unit time]
ν_2	disease-induced drug-resistant mortality rate [1/unit time]
δ	fitness cost [N/A]
σ	treatment rate[1/unit time]
s	probability of compliance [N/A]

Basic reproduction number, $\mathscr{R}_0$

We now calculate the basic reproduction number, $\mathscr{R}_0$ using the next generation approach. $\mathscr{R}_0$ is defined as the dominant eigenvalue of the next generation matrix,

$$\mathscr{R}_0 = max\{R_s, R_r\}$$

where R_s and R_r are the following two eigenvalues:

$$R_s = \frac{\beta_1}{\mu + \nu_1 + \alpha_1 + \sigma} \tag{3.2}$$

$$R_r = \frac{\beta_2}{\mu + \nu_2 + \alpha_2} \tag{3.3}$$

Steady states

System (3.1) has one disease-free equilibrium, $E_0 = (\frac{\Lambda}{\mu}, 0, 0, 0)$ and two endemic equilibria of the form $E_r = (S^*, 0, I_r^*, 0)$ and $E_{rs} = (S^*, I_s^*, I_r^*, R^*)$, corresponding,

respectively, to the states were only resistant strains, or both types of strains are present.

The bifurcation diagram in Figures 3.2, 3.3, and 3.4 divides the (R_s, R_r)-space into distinct regions as characterised by the long-term epidemiological outcomes, each corresponding to a steady state of the system: disease eradication (DFE), persistence of only drug-resistant strain or coexistence i.e., persistence of both drug-sensitive and drug-resistant strains.

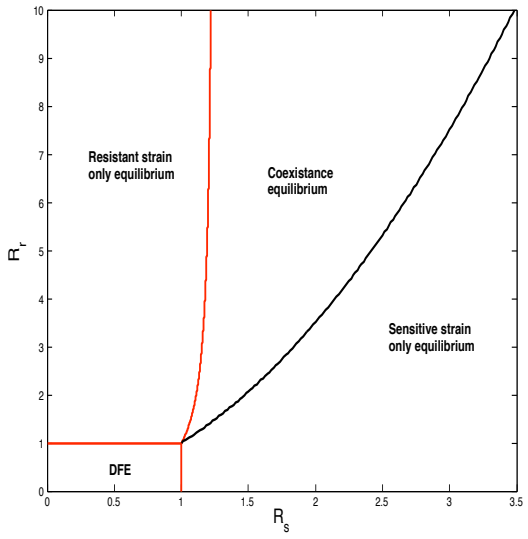

Figure 3.2: Long-term epidemiological outcome of the (R_s, R_r) space. The parameter values are as follows: $\mu = 0.01$, $\nu_1 = 0.6$, $\nu_2 = 0.65$, $\alpha_1 = 0.03$, $\alpha_2 = 0.02$, and $\delta = 0.8$. $\sigma = 0$ and β_1 and β_2 vary.

Note that, infectious cases with sensitive strains give rise to new cases of resistant strains at rate $(1-s)\sigma > 0$, due to acquisition of resistance through treatment failure. It is, therefore, not possible to have an equilibrium where only sensitive strains are present. Figure 3.3 illustrates the long-term epidemiological outcome when the treatment rate (σ) is positive. In this case, only three outcomes are possible, disease free equilibrium, drug-resistant strain only, and coexistence. In particular, this result can be compared to the analysis of Castillo-Chavez and Feng [13]. However, the drug-senstive strain only equilibrium exists in the limit case $\sigma = 0$, which corresponds

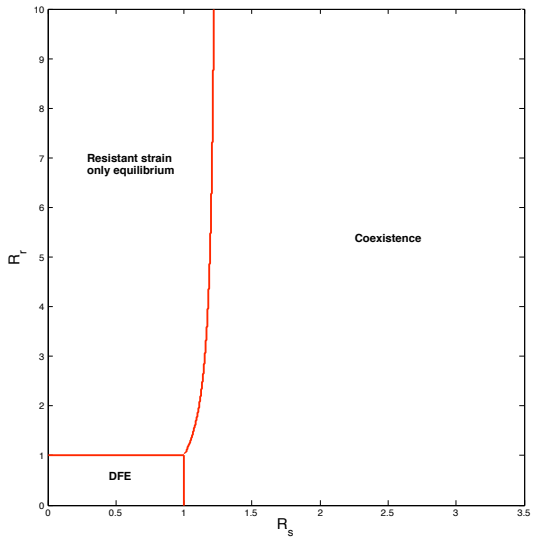

Figure 3.3: Long-term epidemiological outcome of the (R_s, R_r) space. The parameter values are as follows: $\mu = 0.01$, $\nu_1 = 0.6$, $\nu_2 = 0.65$, $\alpha_1 = 0.03$, $\alpha_2 = 0.02$, and $\delta = 0.8$. $\sigma = 0.2$ and β_1 and β_2 vary.

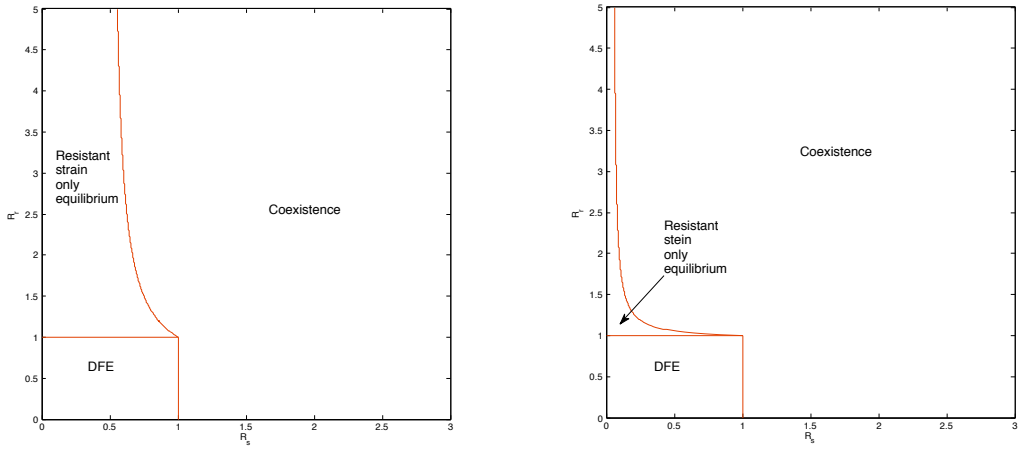

Figure 3.4: Long-term epidemiological outcome of the (R_s, R_r) space. The parameter values are as follows: $\mu = 0.01$, $\nu_1 = 0.6$, $\nu_2 = 0.65$, $\alpha_1 = 0.03$, $\alpha_2 = 0.02$, $\sigma = 0.2$, β_1 and β_2 vary. Figure to the left $\delta = 2$, and figure to the right $\delta = 20$.

to no acquired resistance. The resulting equilibrium has the form $E_s = (S^*, I_s^*, 0, 0)$ and in Figure 3.2 we can see the corresponding stability region (marked as sensitive strain only equilibrium). We explore this limit case in more detail in chapter 2 (two strain model of drug-resistance with super-infection). In Figure 3.4, we explore the effect of the superinfection term (δ) on the long-term epidemiological outcome. We

observe that as δ increases, the region where of the drug-resistant equilibrium only becomes smaller.

Stability of disease-free equilibrium

The stability properties of the disease-free equilibrium (trivial equilibrium) E_0, correspond to the threshold conditions for endemicity are given by Theorem 7, stated and proved below.

Theorem 7 *Consider the quantities R_s and R_r given in (3.2) -(3.3). The disease-free equilibrium E_0 of system (3.1) is locally asymptotically stable, if $\mathscr{R}_0 < 1$ i.e., if $R_s < 1$ and $R_r < 1$, and it is unstable for $\mathscr{R}_0 > 1$.*

Proof By Theorem 2 in van den Driessche and Watmough [70], it is sufficient to prove conditions:

- (A1) if $X \geq 0$, then $\mathscr{F}$, $\mathscr{V}^+$, $\mathscr{V}^- \geq 0$,
- (A2) if $X_i = 0$ then $\mathscr{V}_i^- = 0$ (where i refers to a vector component),
- (A3) $\mathscr{F}_i = 0$ for the components that correspond to uninfected classes,
- (A4) if X^* is a disease-free equilibrium then $\mathscr{F}_i(X^*) = 0$ and $\mathscr{V}_i^+(X^*) = 0$ for the components that correspond to uninfected classes
- (A5) if $\mathscr{F}$ is set to zero then all eigenvalues of $\mathrm{D}f(X_0)$ have negative real parts.

The verification of (A-1)-(A-4) are straightforward. The Jacobian of f at X_0 with $\mathscr{F}$ set to zero, is

$$Df_{\mathscr{F}=0}(X_0) = \begin{bmatrix} -(\mu+\alpha_1+\nu_1+\sigma) & 0 & 0 & 0 \\ 0 & -(\mu+\alpha_2+\nu_2) & 0 & 0 \\ -\beta_1+\alpha_1 & -\beta_2+\alpha_2 & -\mu & 0 \\ s\sigma & 0 & 0 & -\mu \end{bmatrix}$$

The eigenvalues of the above matrix are $\lambda_1 = -(\mu + \alpha_1 + \nu_1 + \sigma)$,
$\lambda_2 = -(\mu + \alpha_2 + \nu_2)$, $\lambda_3 = -\mu$, and $\lambda_4 = -\mu$, all of which have negative real part and the result follows $\square$.

Numerical results suggest that the disease-free equilibrium is in fact globally asymptotically stable for $\mathscr{R}_0 < 1$.

Stability of boundary and coexistence equilibria

The existence of an equilibrium for which only resistant strains persist is given by Theorem 8, stated and proved below.

Theorem 8 *System (3.1) has exactly one non-trivial boundary equilibrium,* $E_r = (S^*, 0, I_r^*, 0)$ *for* $R_r > 1$.

Proof From the equations of the system (3.1) at equilibrium, we get a relation for S, I_s, and I_r where

$$S = \frac{\Lambda - (\mu + \nu_1 + s\sigma)I_s - (\mu + \nu_2)I_r}{\mu} = F(I_s, I_r).$$

Suppose that $I_s = 0$. If I_r is non-zero from the third equation in system (3.1) we get

$$(\mu + \nu_2 + \alpha_2)S + (\mu + \nu_2 + \alpha_2)I_r = 0.$$

We can write this as follows:

$$(\mu + \nu_2 + \alpha_2)F(0, I_r) + (\mu + \nu_2 + \alpha_2)I_r = 0$$

Now, if we solve for I_r then we get

$$I_r = \frac{[\beta_2 - (\mu + \nu_2 + \alpha_2)]\frac{\Lambda}{\mu}}{[\beta_2 - (\mu + \nu_2 + \alpha_2)](\frac{\mu+\nu_2}{\mu}) + (\mu + \nu_2 + \alpha_2)}.$$

If $\beta_2 > (\mu + \nu_2 + \alpha_2) \iff R_r > 1$, then $I_r > 0$ and we have exactly one positive solution for I_r. If $\beta_2 \leq (\mu + \nu_2 + \alpha_2) \iff R_r \leq 1$, then $I_r \leq 0$, so there are no positive solutions for the I_r. $\square$

In order to derive an expression for the region of stability of the boundary equilibrium we measure the capacity of sensitive strains to invade and persist in a population where the resistant strain is at equilibrium. In this context, $E_r = (S^*, 0, I_r^*, 0)$ corresponds to an equilibrium free of sensitive strains. Applying the methods in van den Driessche and Watmough [70], once again we find the basic reproduction number of the sensitive strains in a population where resistant strains are fixed,

$$R_s(E_r) = \frac{R_s}{R_r}[1 + \delta(R_r - 1)].$$

The formalism permits the derivation of a threshold condition for coexistence, now equivalent to a threshold condition for sensitive strains endemicity in a population where resistant strains are at equilibrium, $R_s(E_r) = 1$: only the resistant strain persists for $R_s(E_r) < 1$, while for $R_s(E_r) > 1$ sensitive strains can invade a population where resistant strains are fixed, which implies that coexistence is possible.

Theorem 9 *If $R_r > 1$ the equilibrium E_r of system (3.1) is stable for $R_s(E_r) < 1$ and unstable for $R_s(E_r) > 1$.*

Proof Once again, we apply Theorem 2 in van den Driessche and Watmough [70], and it is sufficient to prove conditions $(A1) - (A5)$. Once more, conditions $(A1) - (A4)$ are of trivial verification. To prove the remaining condition $(A5)$ we write the Jacobian of f at $X_0 = (S^*, I_r^*, 0, 0)$, with $\mathscr{F}$ set to zero, ordering coordinates as (S, I_r, I_s, R). Then, the Jacobian has the form

$$Df_{\mathscr{F}=0}(S^*, I_r^*, 0, 0) = \begin{bmatrix} H_1 & H_2 \\ 0 & H_3 \end{bmatrix}$$

where,

$$H_1 = \begin{bmatrix} \frac{-\beta_2 I_r^*}{S^*+I_r^*} + \frac{\beta_2 S^* I_r^*}{(S^*+I_r^*)^2} - \mu & \frac{-\beta_2 S^*}{S^*+I_r^*} + \frac{\beta_2 S^* I_r^*}{(S^*+I_r^*)^2} + \alpha_2 \\ \frac{\beta_2 I_r^*}{S^*+I_r^*} - \frac{\beta_2 S^* I_r^*}{(S^*+I_r^*)^2} & \frac{\beta_2 S^*}{S^*+I_r^*} - \frac{\beta_2 S^* I_r^*}{(S^*+I_r^*)^2} - (\mu + \alpha_2 + \nu_2) \end{bmatrix}$$

and

$$H_3 = \begin{bmatrix} \frac{\beta_1 S^*}{S^*+I_r^*} + \frac{\beta_1 \delta I_r^*}{S^*+I_r^*} - (\mu+\alpha_1+\nu_1+s\sigma) & 0 \\ \sigma & -\mu \end{bmatrix}$$

Therefore, the eigenvalues of the Jacobian are given by the eigenvalues of H_1 and H_3.

For H_1, the eigenvalues are the roots of the characteristic polynomial

$$p_2(\lambda) = \lambda^2 - c_1\lambda + c_0$$

where

$$\begin{aligned} -c_1 &= -(\beta_2 - (\alpha_2+\nu_2)), \\ c_0 &= [\beta_2 - (\mu+\alpha_2+\nu_2)][\beta_2\mu + \nu_2(\beta_2 - (\mu+\alpha_2+\nu_2))]. \end{aligned}$$

Now we must show that both $-c_1$ and c_0 are > 0.

So,

$$\begin{aligned} -c_1 &= -(-\beta_2 + (\alpha_2+\nu_2)) \\ &= (\beta_2 - (\alpha_2+\nu_2)) + \mu - \mu \\ &= \mu + (\beta_2 - (\alpha_2+\nu_2+\mu)) \\ &> (\beta_2 - (\alpha_2+\nu_2+\mu)) \\ &> 0 \end{aligned}$$

since $R_r > 1$. Hence $-c_1 > 0$.

It is clear that $c_0 > 0$ since $R_r > 0$. Since $-c_1$ and c_0 are positive for all possible values of $R_r > 1$, then all eigenvalues of H_1 have negative real part. For H_3, at equilibrium E_r, the eigenvalues are

$$\begin{aligned} \lambda_1 &= -\mu \\ \lambda_2 &= \frac{\beta_1 + \beta_1\delta(R_r-1)}{R_r} - (\mu+\alpha_1+\nu_1+\sigma). \end{aligned}$$

Now, we have that $\lambda_1 < 0$ and $\lambda_2 < 0$ for all the possible values of $\frac{R_s}{R_r}\big(1+\delta(R_r-1)\big) < 1$, *i.e.*, $R_s(E_r) < 1$.

Hence, all the eigenvalues have negative real parts. Therefore, if $R_r > 1$, then E_r is stable for $R_s(E_r) < 1$ and unstable otherwise. □

The curve that defines the coexistence region is given by the following relation:

$$R_s(E_r) = 1 \iff R_s = g(R_r) = \frac{R_r}{1+\delta(R_r-1)} \tag{3.4}$$

Numerical results support that below the curve defined by g, in the (R_s, R_r)-space both types of strains will persist, thus giving coexistence.

3.2 Two strain model with vaccination dynamics

We extend the simple two strain model by including a vaccinated class and vital dynamics (recruitment and mortality). The new model allows us to study the effect of vaccination on the prevalence of both drug-sensitive and drug-resistant strains. Mathematical properties of the model system are analytically studied. It is shown that the system has three possible equilibrium points including an endemic equilibrium at which both strains are present. A detailed analysis of stability is conducted, which shows that the dynamic behaviors of the system are determined by two quantities, $R_s(E_r)$ and $R_r(E_s)$.

Model formulation

Vaccination is most effective against those viruses or bacteria that have little tendency to vary antigenically [5], [31]. The presence of multiple variants of the pathogen has a very significant impact on vaccination. Typically vaccines contain one or several strains called *vaccine strains*.

In this section, we introduce a vaccinated class and include vital dynamics. As the main purpose of this model is to look at the interaction between vaccination and different strains. Note, the main purpose of this model is to look at the effect of

vaccination only on the dynamics of the two strains, hence we exclude treatment from the model. Let N denote the total number of the population which is divided into four subclasses: susceptible (S), vaccinated (V), infected with drug sensitive strain (I_s), and infected with drug resistant strain (I_r). Assume that there is a constant recruitment rate Λ (into the susceptible class), and a per capital natural death rate μ. A transition diagram between these epidemic classes is shown in Fig. 3.5. Susceptible individuals are vaccinated at per-capita rate η and the immunity wanes at per-capita rate ω. β_1 and β_2 represent the rates at which a susceptible individual becomes infected with the drug sensitive and drug resistant strains, respectively. In this model, we also consider the possibility of natural recovery, hence α_1 and α_2 represent the natural recovery rates, and assume that $\alpha_1 > \alpha_2$. We also assume that those infected with the drug-resistant strain can come into contact with infectious individuals colonized by the drug-sensitive strain and become reinfected with the first strain. This process is referred to as *super-infection*. The transmission coefficient in case of super-infection is $\beta_1\delta$ where δ is the coefficient of reduction or enhancement of infection at reinfection. In particular, if $\delta > 1$ then reinfection is more likely than the regular infection while if $0 < \delta < 1$ then reinfection is less likely than the regular infection. If $\delta = 0$ there is no super-infection.

Based on the transition diagram in Figure 3.5, the model is described by the following system of differential equations:

$$\begin{aligned}
\dot{S} &= \Lambda - \beta_1 \frac{SI_s}{N} - \beta_2 \frac{SI_r}{N} + \omega V + \alpha_1 I_s + \alpha_2 I_r - \mu S - \eta S \qquad (3.5)\\
\dot{V} &= \eta S - \omega V - \mu V\\
\dot{I}_s &= \beta_1 \frac{SI_s}{N} + \beta_1 \delta \frac{I_s I_r}{N} - \alpha_1 I_s - \mu I_s\\
\dot{I}_r &= \beta_2 \frac{SI_r}{N} - \beta_1 \delta \frac{I_s I_r}{N} - \alpha_2 I_r - \mu I_r
\end{aligned}$$

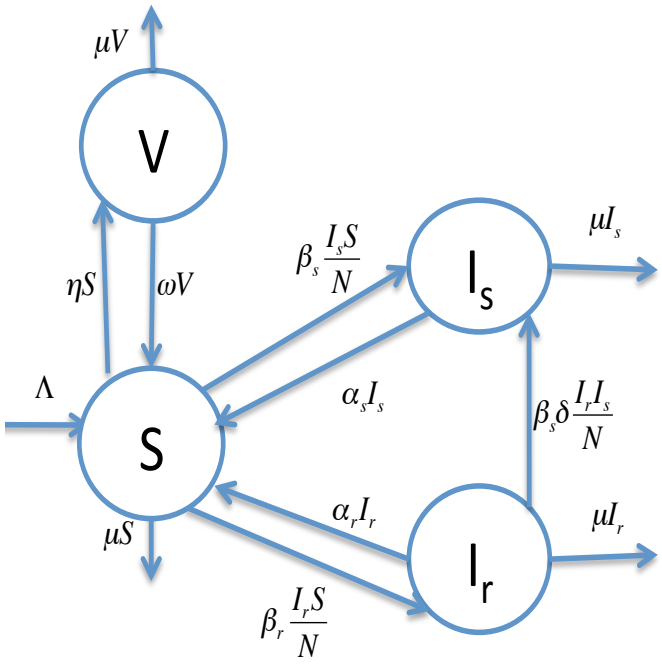

Figure 3.5: Representation of the model super-infection with vaccination

where

$$N = S + V + I_s + I_r$$

.

Equilibria and stability

For system (3.5), note that the total population size N satisfies the equation

$$\dot{N} = \Lambda - \mu N$$

and that $N(t) \to \frac{\Lambda}{\mu}$ as $t \to +\infty$, we know that the biologically feasible region

$$\Gamma = \{(S,V,I_s,I_r) : 0 \leq S,V,I_s,I_r,\ \ S+V+I_s+I_r \leq \frac{\Lambda}{\mu}\}$$

is positively invariant for the system (3.5). Therefore, in what follows, we consider only solutions with initial conditions inside the region Γ, in which the usual existence, uniqueness of the solutions and continuous dependence of solutions results hold.

Table 3.2: Description and units for model variable and parameters.

Variable	Description [Units]
$S(t)$	susceptible individuals [individuals]
$I_s(t)$	drug-sensitive colonized individuals [individuals]
$I_r(t)$	drug-resistant colonized individuals [individuals]
V	vaccinated individuals [individuals]
Parameters	Description [Units]
Λ	recruitment/birth rate [individuals/unit time]
μ	natural death rate [1/unit time]
β_1	drug-sensitive effective contact rate [1/unit time]
β_2	drug-resistant effective contact rate [1/unit time]
α_1	natural drug-sensitive recovery rate [1/unit time]
α_2	natural drug-resistant recovery rate [1/unit time]
δ	fitness cost [N/A]
η	rate at which susceptible individuals are vaccinates [1/unit time]
$\frac{1}{\omega}$	average time of losing vaccine-induced immunity [1/unit time]

The system (3.5) always has the disease-free equilibrium (DFE) $E_0 = (S^0, V^0, 0, 0)$, where

$$S^0 = \frac{\omega+\mu}{\omega+\mu+\eta}N^0, \qquad V^0 = \frac{\eta}{\omega+\mu+\eta}N^0, \qquad N^0 = \frac{\Lambda}{\mu}$$

represent the numbers of susceptible, vaccinated, and total populations, respectively, in the absence of infection. The existence of other equilibria are determined by the two quantities, R_s and R_r, given by

$$R_s = \frac{\beta_1(\mu+\omega)}{(\mu+\alpha_1)(\mu+\omega+\eta)} \tag{3.6}$$

$$R_r = \frac{\beta_2(\mu+\omega)}{(\mu+\alpha_2)(\mu+\omega+\eta)} \tag{3.7}$$

The biological interpretations of these quantities are as follows. Notice that $(\mu+\omega)/(\mu+\omega+\eta)$ is the fraction of the population that is susceptible. Thus, R_s represents the number of secondary sensitive cases produced by a typical sensitive case during the period of infection in a population where vaccination is implemented. Similarly, R_r represents the number of secondary drug resistant cases produced by a typical resistant case, *i.e.*, the control reproduction number of the resistant strain,

during the period of infection in a population where the fraction of susceptibles is $(\mu+\omega)/(\mu+\omega+\eta)$.

Steady states

The system of differential equations has one disease-free equilibrium, $E_0 = (S^*, V^*, 0, 0)$ and three endemic equilibria of the form $E_s = (S^*, V^*, I_s^*, 0)$, $E_r = (S^*, V^*, 0, I_r^*)$, and $E_c = (S^*, V^*, I_s^*, I_r^*)$, corresponding, respectively, to states where only sensitive strains, or resistant strains, or both types of strains are present.

The bifurcation diagram in Figures 3.6, 3.7, and 3.8 divides the (R_s, R_r) space into several regions as characterized by the long-term epidemiological outcomes, each corresponding to a stable steady state of the system: disease eradication (E_0), persistence of only drug-resistant strain (E_r), persistence of only drug-sensitive strain (E_s), or coexistence, i.e., persistence of both drug-sensitive and drug-resistant strains (E_c). Figures 3.6 and 3.7 illustrate the effect of the superinfection parameter δ. When $\delta = 0$, no superinfection, only three equilibria are plausible: DFE, sensitive strain only equilibrium and resistant strain only equilibrium. When superinfection is included in the model, δ positive, reveals that coexistence is now possible. Figure 3.8 considers two different values of δ and illustrates how the long-term epidemiological outcome changes as δ increases. The diagram shows that as δ increases, the region where the resistant strain is at equilibrium becomes smaller, making both the coexistence region and the sensitive strain only equilibrium region bigger.

Stability of the disease-free equilibrium

The stability properties of the disease-free equilibrium (trivial equilibrium) E_0, corresponding to the threshold condition for endemicity are given in Theorem 10.

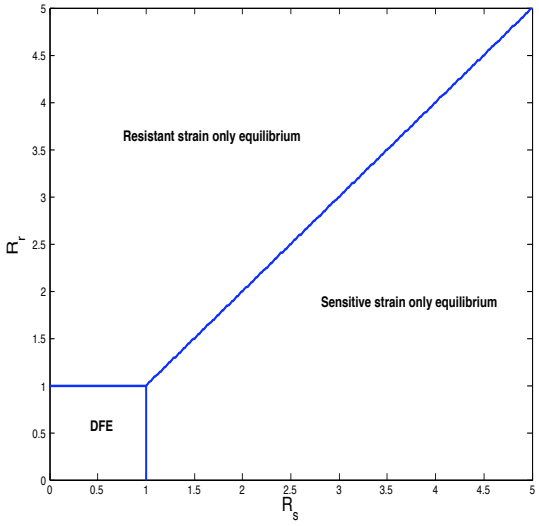

Figure 3.6: Long-term epidemiological outcome of the (R_s, R_r) space. The parameter values are as follows: $\mu = 0.01$, $\omega = 0.3$, $\eta = 0.5$, $\alpha_1 = 0.03$, and $\alpha_2 = 0.02$. $\delta = 0$ and β_1 and β_2 vary.

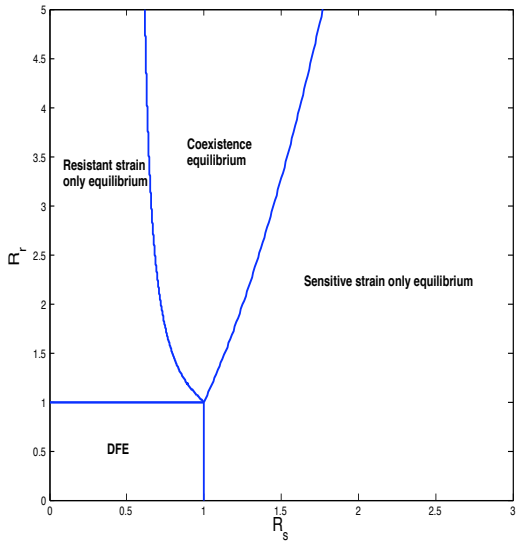

Figure 3.7: Long-term epidemiological outcome of the (R_s, R_r) space. The parameter values are as follows: $\mu = 0.01$, $\omega = 0.3$, $\eta = 0.5$, $\alpha_1 = 0.03$, and $\alpha_2 = 0.02$. $\delta = 0.8$ and β_1 and β_2 vary.

Theorem 10 *Consider the quantities R_s and R_r given in (3.6)-(3.7). The disease-free equilibrium E_0 of system (3.3) is locally asymptotically stable, if $R_0 < 1$, i.e., if $R_s < 1$ and $R_r < 1$, and it is unstable for $R_0 > 1$.*

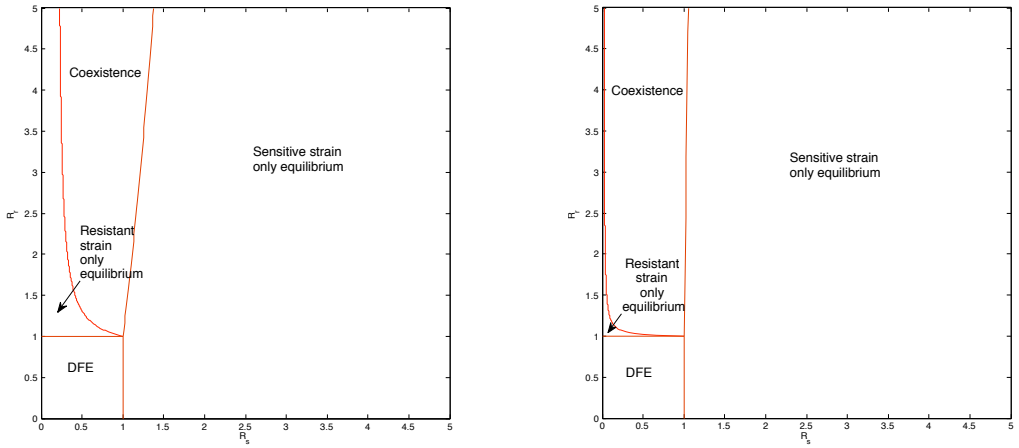

Figure 3.8: Long-term epidemiological outcome of the (R_s, R_r) space. The parameter values are as follows: $\mu = 0.01$, $\omega = 0.3$, $\eta = 0.5$, $\alpha_1 = 0.03$, and $\alpha_2 = 0.02$, β_1 and β_2 vary. Figure to the left $\delta = 2$, and figure to the right $\delta = 20$.

Proof By Theorem 2 in van den Driessche and Watmough [70], it is sufficient to prove conditions:

- (A1) if $X \geq 0$, then $\mathscr{F}$, $\mathscr{V}^+$, $\mathscr{V}^- \geq 0$,
- (A2) if $X_i = 0$ then $\mathscr{V}_i^- = 0$ (where i refers to a vector component),
- (A3) $\mathscr{F}_i = 0$ for the components that correspond to uninfected classes,
- (A4) if X^* is a disease-free equilibrium then $\mathscr{F}_i(X^*) = 0$ and $\mathscr{V}_i^+(X^*) = 0$ for the components that correspond to uninfected classes
- (A5) if $\mathscr{F}$ is set to zero then all eigenvalues of $\mathrm{D}f(X_0)$ have negative real parts.

The verification of (A-1)-(A-4) are straightforward.

The Jacobian of f at X_0 with $\mathscr{F}$ set to zero, is

$$Df_{\mathscr{F}=0}(X_0) = \begin{bmatrix} -(\mu+\alpha_1) & 0 & 0 & 0 \\ 0 & -(\mu+\alpha_2) & 0 & 0 \\ -\beta_1+\alpha_1 & -\beta_2+\alpha_2 & -\mu & 0 \\ 0 & 0 & \eta & -(\omega+\mu) \end{bmatrix}$$

The eigenvalues of the above matrix are $\lambda_1 = -(\mu+\alpha_1)$, $\lambda_2 = -(\mu+\alpha_2)$, $\lambda_3 = -\mu$, and $\lambda_4 = -(\omega+\mu)$ all of which have negative real part and the result follows. □

Stability of boundary and coexistence equilibria

The system has three non-trivial equilibria corresponding to the presence of each type of strains alone and coexistence. The existence of equilibria of the first two, only sensitive strains or resistant strains persists, is given by the following theorems:

Theorem 11 *The system of differential equations (3.5) has one boundary equilibrium where the sensitive strain persists, $E_s = (S^*, V^*, I_s^*, I_r = 0)$, for $R_s > 1$*

Proof From the equations of the system (3.5) at equilibrium, we get a relation S, I_s, and I_r where

$$S = \frac{(\Lambda - \mu I_s - \mu I_r)(\omega+\mu)}{\mu(\mu+\eta+\omega)} = F(I_s, I_r)$$

Suppose that $I_r = 0$. If I_s is non-zero from the second equation in system (3.5) we get

$$\left[\frac{\beta_1(\omega+\mu) - (\mu+\alpha_1)(\mu+\omega+\eta)}{(\omega+\mu)}\right] S - (\mu+\alpha_1) I_s = 0.$$

We can write this as follows:

$$\left[\frac{\beta_1(\omega+\mu) - (\mu+\alpha_1)(\mu+\omega+\eta)}{(\omega+\mu)}\right] F(I_s, 0) - (\mu+\alpha_1) I_s = 0$$

Now, if we solve for I_s we then get

$$I_s = \frac{[\beta_1(\omega+\mu) - (\mu+\alpha_1)(\mu+\omega+\eta)]\frac{\Lambda}{\mu}}{\beta_1(\mu+\omega)}.$$

If $\beta_1(\omega+\mu) > (\mu+\alpha_1)(\mu+\omega+\eta) \iff R_s > 1$, then $I_s > 0$ and we have exactly one positive solution for I_s.

If $\beta_1(\omega+\mu) < (\mu+\alpha_1)(\mu+\omega+\eta) \iff R_s \leq 1$, then $I_s \leq 0$, so there are no positive solutions for the I_s. □

Theorem 12 *The system of differential equations (3.5) has one boundary equilibrium where the resistant strain persists, $E_r = (S^*, V^*, I_s = 0, I_r^*)$, for $R_r > 1$*

Proof From the equations of the system (3.5) at equilibrium, we get a relation S, I_s, and I_r where

$$S = \frac{(\Lambda - \mu I_s - \mu I_r)(\omega + \mu)}{\mu(\mu + \eta + \omega)} = F(I_s, I_r).$$

Suppose that $I_s = 0$. If I_r is non-zero from the third equation in system (3.5) we get

$$\left[\frac{\beta_2(\omega+\mu) - (\mu+\alpha_2)(\mu+\omega+\eta)}{(\omega+\mu)}\right] S - (\mu+\alpha_2) I_r = 0.$$

We can write this as follows:

$$\left[\frac{\beta_2(\omega+\mu) - (\mu+\alpha_2)(\mu+\omega+\eta)}{(\omega+\mu)}\right] F(0, I_r) - (\mu+\alpha_2) I_r = 0$$

Now, if we solve for I_r we then get

$$I_r = \frac{[\beta_2(\omega+\mu) - (\mu+\alpha_2)(\mu+\omega+\eta)]\frac{\Lambda}{\mu}}{\beta_2(\mu+\omega)}.$$

If $\beta_2(\omega+\mu) > (\mu+\alpha_2)(\mu+\omega+\eta) \iff R_r > 1$, then $I_r > 0$ and we have exactly one positive solution for I_r.

If $\beta_2(\omega+\mu) < (\mu+\alpha_2)(\mu+\omega+\eta) \iff R_r \leq 1$, then $I_r \leq 0$, so there are no positive solutions for the I_r. □

Two coexistence thresholds must be calculated: the first separates the region where only sensitive strains persist from the region of coexistence; the second marks the shift from coexistence to persistence of resistant strains alone.

In order to derive an expression for the region of stability of the boundary equilibria we measure the capacity of the strains to invade and persist in a population where either sensitive or resistant strains are at equilibrium. In the case where the sensitive strain is at equilibrium, in this context, $E_s = (S^*, V^*, I_s^*, 0)$ corresponds to an equilibrium free of resistant strain.

In order to apply the methods in van den Driessche and Watmough [70], consider the case when only the resistant strain is transmissible, in a population where

the sensitive strain is at equilibrium. The infected compartment is I_r. We can write system (3.5) as $X = (I_r, S, V, I_s)$ and

$$\mathscr{F} = \left(\beta_2 \frac{SI_r}{N}, S, V, 0\right)^T.$$

The disease (resistant strain)-free equilibrium is $X_0 = (I_s, S, V, 0)$.

We can compute derivatives at X_0 with respect to the infected classes of $\mathscr{F}$ and $\mathscr{V}$, respectively:

$$\begin{aligned} D\mathscr{F}_{I_r} &= \frac{\beta_2 S^2 + \beta_2 SV + \beta_2 SI_s}{(S+V+I_s)^2} \\ &= \frac{\beta_2(\mu+\alpha_1)}{\beta_1}, \\ D\mathscr{V}_{I_r} &= (\mu+\alpha_2) + \frac{\beta_1\delta SI_s + \beta_1\delta VI_s + \beta_1\delta I_s^2}{(S+V+I_s)^2} \\ &= \frac{R_s(\mu+\alpha_2) + \beta_1\delta(R_s-1)}{R_s} \end{aligned}$$

The basic reproduction number of the resistant strain in a population where sensitive strains are fixed is then the spectral radius of the next generation matrix:

$$R_r(E_s) = \frac{R_r(\alpha_2+\mu)}{R_s(\mu+\alpha_2) + \beta_1\delta(R_s-1)}$$

Similarly, we find the capacity of the sensitive strains to invade and persist in a population where the resistant strains are fixed. $E_r = (S^*, V^*, 0, I_r^*)$ corresponds to an equilibrium free of sensitive strain. Following van den Driessche and Watmough [70], we write the system of differential equations of our model (3.5) as $X = (I_r, S, V, I_s)$ and

$$\mathscr{F} = \left(\beta_1 \frac{SI_s}{N} + \beta_1\delta \frac{I_sI_r}{N}, S, V, 0\right)^T.$$

The disease (sensitive strain)-free equilibrium is $(I_r, S, V, 0)$.

As before, we compute the derivative at X_0 with respect to the infected classes of $\mathscr{F}$ and $\mathscr{V}$, respectively:

$$\begin{aligned} D\mathscr{F}_{I_s} &= \frac{\beta_1 S^2 + \beta_1 SV + \beta_1 SI_r + \beta_1 \delta SI_r + \beta_1 \delta I_r V + \beta_1 \delta I_r^2}{(S+V+I_s)^2} \\ &= \frac{R_s(\mu+\alpha_1) + \beta_1 \delta (R_r - 1)}{R_r}, \\ D\mathscr{V}_{I_s} &= (\mu + \alpha_1) \end{aligned}$$

The basic reproduction number of the sensitive strains in a population where resistant strains are fixed, is given by the spectral radius of the next generation matrix:

$$R_s(E_r) = \frac{R_s}{R_r} + \frac{\beta_1 \delta (R_r - 1)}{R_r(\alpha_1 + \mu)}$$

This formulation permits the derivation of a threshold condition for coexistence. Now equivalent to a threshold condition for resistant strain endemicity in a population where sensitive strains are at equilibrium, $R_r(E_s) = 1$: only sensitive strains persist for $R_r(E_s) < 1$, while for $R_r(E_s) > 1$ resistant strains can invade a population where sensitive strains are fixed, hence coexistence is possible. We also have a similar threshold condition for sensitive strain endemicity in a population where resistant strains are at equilibrium, $R_s(E_r) = 1$: only resistant strains persist for $R_s(E_r) < 1$, while for $R_s(E_r) > 1$ sensitive strains can invade a population where resistant strains are fixed, that is to say coexistence is possible.

Theorem 13, and 14 below express these results in terms of stability for the equilibrium E_s and E_r.

Theorem 13 *If $R_s > 1$ the equilibrium E_s of the system of differential equations is stable for $R_r(E_s) < 1$ and unstable for $R_r(E_s) > 1$.*

Proof By Theorem 2 in van den Driessche and Watmough [70], it is sufficient to prove conditions $(A1) - (A5)$. Once more, conditions $(A1) - (A4)$ are of trivial verification.

To prove the remaining condition $(A5)$ we write the Jacobian of f at X_0, with $\mathscr{F}$ set to zero, ordering coordinates as (S,V,I_s,I_r). Then, the Jacobian has the form

$$Df_{\mathscr{F}=0}(S^*,V^*,I_s^*,0) = \begin{bmatrix} G_1 & G_2 \\ 0 & a \end{bmatrix}$$

where,

$$G_1 = \begin{bmatrix} x-(\mu+\eta) & \frac{\beta_1 S^* I_s^*}{(S^*+V^*+I_s^*)^2}+\omega & y+\alpha_1 \\ \eta & -(\omega+\mu) & 0 \\ -x & \frac{-\beta_1 S^* I_s^*}{(S^*+V^*+I_s^*)^2} & -y-(\mu+\alpha_1) \end{bmatrix}$$

where,

$$\begin{aligned} x &= \frac{-\beta_1 I_s^*}{(S^*+V^*+I_s^*)}+\frac{\beta_1 S^* I_s^*}{(S^*+V^*+I_s^*)^2} \\ y &= \frac{-\beta_1 S^*}{(S^*+V^*+I_s^*)}+\frac{\beta_1 S^* I_s^*}{(S^*+V^*+I_s^*)^2} \end{aligned}$$

and

$$a = \frac{\beta_2 S^*}{(S^*+V^*+I_s^*)}-\frac{\beta_1 \delta I_s^*}{(S^*+V^*+I_s^*)}-(\mu+\alpha_2)$$

Therefore, the eigenvalues of the Jacobian are given by the eigenvalues of G_1 and a.

For G_1, the eigenvalues are $-\mu$ and the roots of the characteristic polynomial

$$p_1(\lambda) = \lambda^2 - b_1\lambda + b_0$$

where

$$\begin{aligned} -b_1 &= -\Big[\frac{-\beta_1(\omega+\mu)-\omega(\eta+\mu+\omega)+\alpha_1(\eta+\mu+\omega)}{(\omega+\mu)}\Big], \\ b_0 &= \beta_1(\omega+\mu)-(\eta+\mu+\omega)(\mu+\alpha_1). \end{aligned}$$

Now we must show that both $-b_1$ and b_0 are > 0.

So,

$$\begin{aligned}
-b_1 &= -\Big[\frac{-\beta_1(\omega+\mu)-\omega(\eta+\mu+\omega)+\alpha_1(\eta+\mu+\omega)}{(\omega+\mu)}\Big] \\
&= \frac{\beta_1(\omega+\mu)+\omega(\eta+\mu+\omega)-\alpha_1(\eta+\mu+\omega)+\omega(\eta+\mu-\omega)-\omega(\eta+\mu+\omega)}{(\omega+\mu)} \\
&= \frac{\beta_1(\omega+\mu)-(\alpha_1+\omega)(\eta+\mu+\omega)+2\omega(\eta+\mu-\omega)}{(\omega+\mu)} \\
&> \frac{\beta_1(\omega+\mu)-(\alpha_1+\omega)(\eta+\mu+\omega)}{(\omega+\mu)} \\
&> 0
\end{aligned}$$

since $R_s > 1$. Hence $-b_1 > 0$.

It is clear that $b_0 > 0$ since $R_s > 0$. Since $-b_1$ and b_0 are positive for all possible values of $R_s > 1$, then all eigenvalues of G_1 have negative real part.

For a, at equilibrium E_s, we get:

$$a = \frac{R_r(\mu+\alpha_2)}{R_s} - \frac{\beta_1\delta(R_s-1)+(\mu+\alpha_2)R_s}{R_s}$$

Now, we have that $a < 0$ for all the possible values of $\frac{R_r(\mu+\alpha_2)}{\beta_1\delta(R_s-1)+(\mu+\alpha_2)R_s} < 1$, *i.e.*, $R_r(E_s) < 1$, and $a \geq 0$ otherwise.

Hence, all the eigenvalues have negative real parts. Therefore if $R_s > 1$, then E_s is stable for $R_r(E_s) < 1$ and unstable otherwise. □

Theorem 14 *If $R_r > 1$ the equilibrium E_r of the system of differential equations is stable for $R_s(E_r) < 1$ and unstable for $R_s(E_r) > 1$.*

Proof Once again, we apply Theorem 2 in van den Driessche and Watmough [70], and it is sufficient to prove conditions $(A1)-(A5)$. Once more, conditions $(A1)-(A4)$ are of trivial verification. To prove the remaining condition $(A5)$ we write the Jacobian of f at X_0, with $\mathscr{F}$ set to zero, ordering coordinates as (S,V,I_r,I_s). Then, the Jacobian has the form

$$Df_{\mathscr{F}=0}(S^*,V^*,I_r^*,0) = \begin{bmatrix} H_1 & H_2 \\ 0 & z \end{bmatrix}$$

where,

$$H_1 = \begin{bmatrix} u-(\mu+\eta) & \frac{\beta_2 S^* I_r^*}{(S^*+V^*+I_r^*)^2}+\omega & v+\alpha_2 \\ \eta & -(\omega+\mu) & 0 \\ -u & \frac{-\beta_2 S^* I_r^*}{(S^*+V^*+I_r^*)^2} & -v-(\mu+\alpha_2) \end{bmatrix}$$

where,

$$\begin{aligned} u &= \frac{-\beta_2 I_r^*}{(S^*+V^*+I_r^*)}+\frac{\beta_2 S^* I_r^*}{(S^*+V^*+I_r^*)^2} \\ v &= \frac{-\beta_2 S^*}{(S^*+V^*+I_r^*)}+\frac{\beta_2 S^* I_r^*}{(S^*+V^*+I_r^*)^2} \end{aligned}$$

and

$$z = \frac{\beta_1 S^*}{(S^*+V^*+I_r^*)}+\frac{\beta_1 \delta I_r^*}{(S^*+V^*+I_r^*)}-(\mu+\alpha_1)$$

Therefore, the eigenvalues of the Jacobian are given by the eigenvalues of H_1 and z.

For H_1, the eigenvalues are $-\mu$ and the roots of the characteristic polynomial

$$p_2(\lambda) = \lambda^2 - c_1\lambda + c_0$$

where

$$\begin{aligned} -c_1 &= -\Big[\frac{-\beta_2(\omega+\mu)-\omega(\eta+\mu+\omega)+\alpha_2(\eta+\mu+\omega)}{(\omega+\mu)}\Big], \\ c_0 &= \beta_2(\omega+\mu)-(\eta+\mu+\omega)(\mu+\alpha_2). \end{aligned}$$

Now we must show that both $-c_1$ and c_0 are > 0.

So,

$$\begin{aligned} -c_1 &= -\Big[\frac{-\beta_2(\omega+\mu)-\omega(\eta+\mu+\omega)+\alpha_2(\eta+\mu+\omega)}{(\omega+\mu)}\Big] \\ &= \frac{\beta_2(\omega+\mu)+\omega(\eta+\mu+\omega)-\alpha_2(\eta+\mu+\omega)+\omega(\eta+\mu-\omega)-\omega(\eta+\mu+\omega)}{(\omega+\mu)} \\ &= \frac{\beta_2(\omega+\mu)-(\alpha_2+\omega)(\eta+\mu+\omega)+2\omega(\eta+\mu-\omega)}{(\omega+\mu)} \\ &> \frac{\beta_2(\omega+\mu)-(\alpha_2+\omega)(\eta+\mu+\omega)}{(\omega+\mu)} \\ &> 0 \end{aligned}$$

It is clear that $c_0 > 0$ since $R_r > 0$. Since $-c_1$ and c_0 are positive for all possible values of $R_r > 1$, then all eigenvalues of H_1 have negative real part.

For z, at equilibrium E_r, we get:

$$z = \frac{\beta_1(\mu+\alpha_2)}{\beta_2} + \frac{\beta_1\delta(R_r-1)}{R_r} - (\mu+\alpha_1)$$

Now, we have that $z < 0$ for all the possible values of $\frac{R_s}{R_r} + \frac{\beta_1\delta(R_r-1)}{R_r(\mu+\alpha_1)} < 1$, *i.e.*, $R_s(E_r) < 1$, and $z \geq 0$ otherwise.

Hence, all the eigenvalues have negative real parts. Therefore, if $R_r > 1$, then E_r is stable for $R_s(E_r) < 1$ and unstable otherwise. □

The curves the defines the coexistence region are given by the following relation: $R_r(E_s) = 1 \iff R_r = f(R_s)$

$$\begin{aligned} R_r(E_s) = 1 \iff R_r &= f(R_s) \\ &= \frac{\beta_1\delta(R_s-1)+R_s(\alpha_2+\mu)}{(\mu+\alpha_2)} \end{aligned} \tag{3.8}$$

$$\begin{aligned} R_s(E_r) = 1 \iff R_s &= g(R_r) \\ &= R_r - \frac{\beta_1\delta(R_r-1)}{(\alpha_1+\mu)} \end{aligned} \tag{3.9}$$

Numerical results support that above the curve defined by f and below the curve defined by g, in the (R_s, R_r)- space both types of strains will persist, thus giving coexistence.

Critical Vaccination Rate

All that is required for the incidence of an infectious disease to go into decline is that each case should generate, on average, less than one other case. The number of secondary infections caused by one infectious individual is often referred to as the effective reproductive number and denoted R. Epidemics often peak and go into decline as R falls below 1 because the pool of susceptible individuals has been

temporarily exhausted. For the trajectory of incidence to remain on a downward course until the agent is eradicated requires that the effective reproductive rate should remain below 1, even when the number of susceptible individuals is at its maximum. $R_{0\eta}$, the basic reproductive number under vaccination is the number of secondary cases caused by one primary case introduced into a population in which the vaccination rate is given by η. For a vaccine that takes into account the loss of protection, *i.e.*, $\omega > 0$ in (3.5)

$$R_{0\eta} = \frac{\mu + \omega}{\mu + \eta + \omega} R_0$$

Note that when $\omega = 0$, denotes the case of a perfect vaccine that confers life-long protection.

The critical vaccination rate that will achieve eradication, η_c, is that for which the basic reproductive number under vaccination is just equal to 1. This yields:

$$\eta_c = \mu(R_0 - 1) + \omega(R_0 - 1)$$

Since $R_0 = max\{R_s, R_r\}$ then $\eta_c = max\{\eta_{cs}, \eta_{cr}\}$, where

$$\eta_{cs} = \mu(R_s - 1) + \omega(R_s - 1)$$

$$\eta_{cr} = \mu(R_r - 1) + \omega(R_r - 1)$$

Figure 3.9 illustrates the critical vaccination rate for any given natural death rate. Hence, if the model is capturing the dynamics for a disease in a region like Southern Africa, where the life expectancy is 40 years, ($\mu = 0.025$), then we can conclude that if the vaccination rate is above 0.125, then the sensitive strain will prevail.

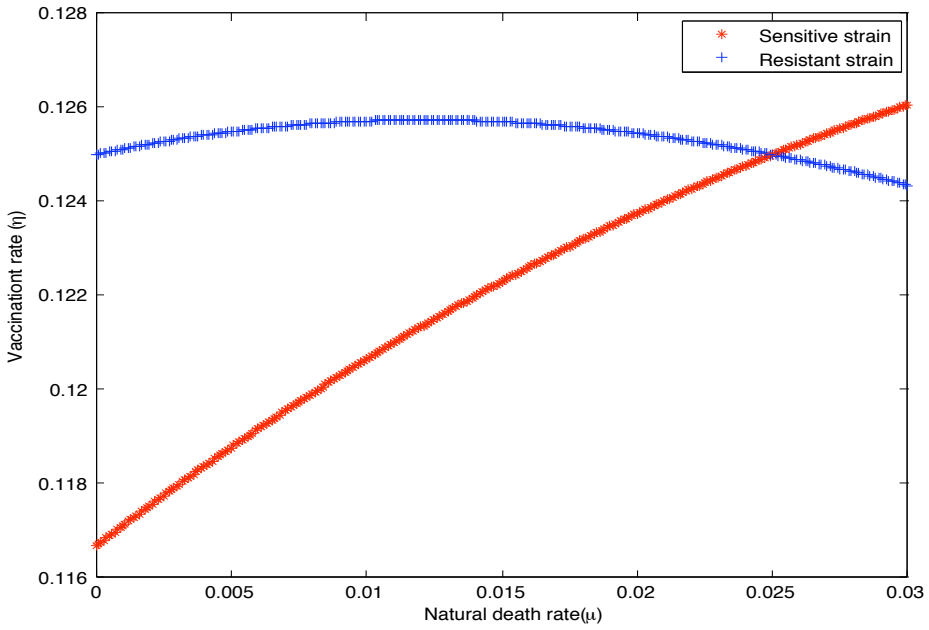

Figure 3.9: The figure shows the required vaccination rate to eradicate the resistant strain for a given the natural death rate. $\beta_1 = 0.65$, $\beta_2 = 0.45$, $\alpha_1 = 0.3$, $\alpha_2 = 0.2$, $\omega = 0.1$, μ varies and η also varies.

3.3 Numerical Simulations

The following initial conditions are assumed for the simulations, $S(0) = \frac{\Lambda}{\mu}$, $V(0) = 10$, $I_s(0) = 10$, $I_r(0) = 1$ and $T(0) = 1$. Simulations were run for different sets of initial conditions and the qualitative form of the solution were similar.

The model (3.1) is simulated using the parameters in Table 3.3 (unless otherwise stated) to illustrate some of the theoretical results established in this chapter. The competitive exclusion property of the model is illustrated by considering the case when $R_s > 1$ and $R_r > 1$. First of all, it can be shown that, in such a case,

(i) $R_s > R_r$ (for the stability of E_c) corresponds to

$$1 < \frac{R_s}{R_r}[1 - \delta(R_r - 1)] \equiv \mathscr{A}$$

Table 3.3: Parameter values for models 3.1 and 3.5

Param.	Description (value/year)	Approx.	Ref.
Λ	birth rate	variable	
μ	natural death rate	0.025	[62]
β_1	drug-sensitive effective contact rate	0.75	[55]
β_2	drug-resistant effective contact rate	0.75	[55]
α_1	natural drug-sensitive recovery rate	0.00078	[34]
α_2	natural drug-resistant recovery rate	0.00078	[34]
ν_1	disease induced mortality rate	0.0014	[12]
ν_2	disease induced mortality rate	0.0014	[12]
σ	treatment rate	variable	
s	probability of compliance	variable	
δ	fitness cost	variable	
η	vaccination rate	variable	
ω	loss of vaccine-induced immunity	0.5	Assumed

(ii) $R_r > R_s$ (for the stability of E_r) implies that

$$1 > \mathscr{A}$$

The above calculations allow us to investigate the competitive exclusion principle by simulating the model with various parameter values. Simulating the model using the parameters in Table 3.3 with $\tau_r = 0.2$, $\delta = 0.4$, $\sigma = 0.2$ and $s = 0.5$ (so that $R_s = 3.5411$ and $R_r = 3.0864$) shows convergence to the coexistence equilibrium (Fig. 3.10).

Using the same parameter values above but with $\delta = 0.2$ (so that $R_s = 1.7705$ and $R_r = 2.1605$), the solution profile converges to the resistant strain only equilibrium (Fig. 3.11). It should be noted that, in this case, the drug-sensitive strain dies out even though $R_s > 1$, provided that the condition $R_r > R_s$ holds. Thus, these simulations suggest that the result of Theorem 3 can be extended to the case $R_s > 1$.

Recall that for the treatment model, R_s given in (3.2), depends on the treatment

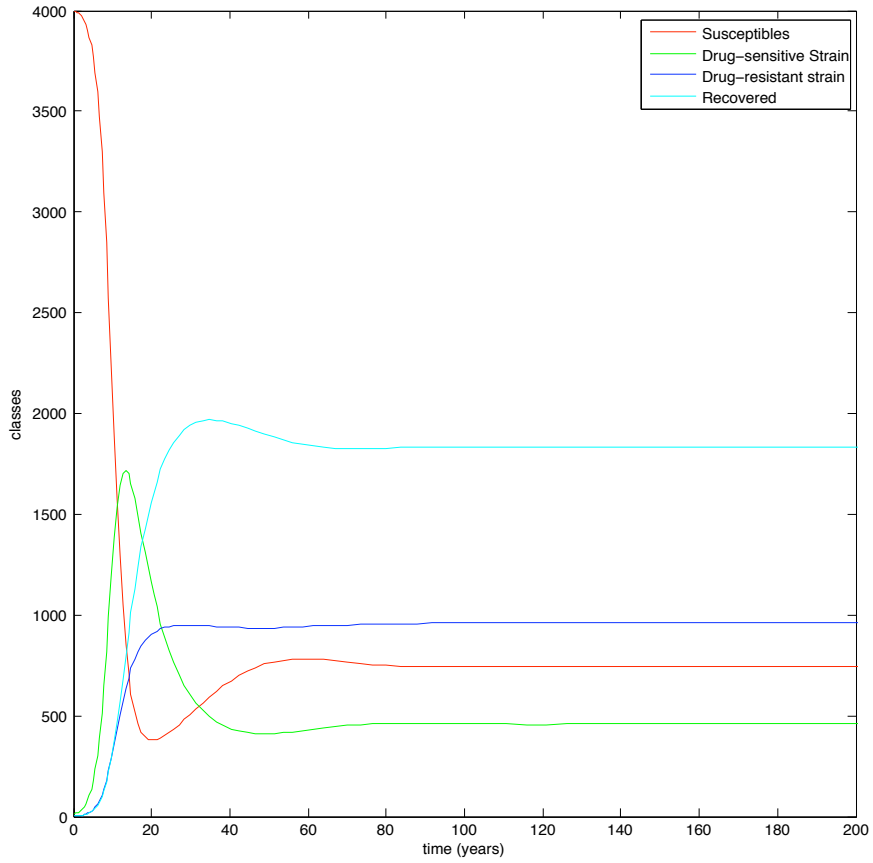

Figure 3.10: Simulations of the model with treatment (3.1). The figure depicts the temporal course of the classes for the case when $R_s > R_r$. Parameter values used are: $\tau_r = 0.2$, $\delta = 0.4$, $\sigma = 0.2$ and $s = 0.5$, $\Lambda = 100$, and the rest are as in Table 3.3. In this case $R_s = 3.5411$ and $R_r = 3.0864$

rate σ. Hence, the effect of drug treatment (σ) is monitored by noting,

$$\frac{\partial \mathscr{A}}{\partial \sigma} = -\frac{R_s}{R_r}\frac{[1+\delta(R_r-1)]}{(\mu+\nu_1+\alpha_1+\sigma)}$$

Thus, $\mathscr{A}$ is decreasing function of σ. Therefore, increasing treatment could lead to a scenario where $1 > \mathscr{A}$, so that $R_r > R_s$. In which case, the resistant strain could displace the drug-sensitive strain. This result is illustrate in Fig 3.12, where simulations are carried out with varying values of σ and the other parameter values chosen so that $R_r = 3.0864$, and R_s varies.

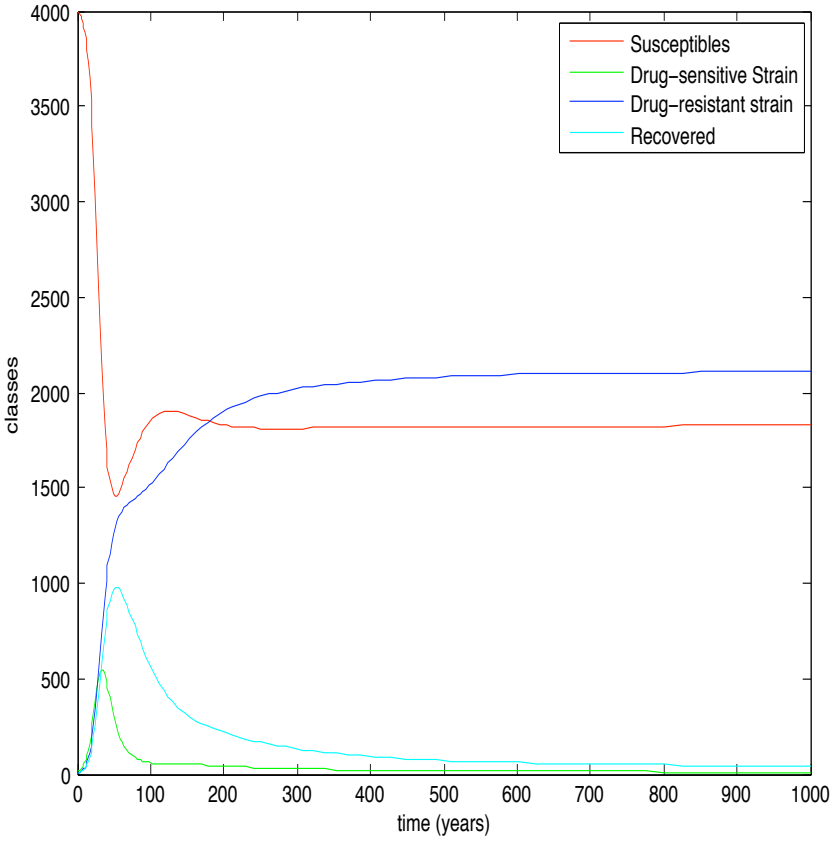

Figure 3.11: Simulations of the model with treatment (3.1). The figure depicts the temporal course of the classes for the case when $R_r > R_s$. Parameter values used are: $\tau_r = 0.2$, $\delta = 0.4$, $\sigma = 0.2$ and $s = 0.5$, $\Lambda = 100$, and the rest are as in Table 3.3. In this case $R_s = 1.7705$ and $R_r = 2.1605$

Numerical Simulations: Vaccination Model

The model (3.5) is simulated using the parameters in Table 3.3 (unless otherwise stated) to illustrate some of the theoretical results established in this chapter. The competitive exclusion property of the model is illustrated by considering the case when both $R_s > 1$ and $R_r > 1$. First of all, it can be shown that in such a case,

(i) the stability of E_s corresponds to,

$$R_r < R_s + \frac{\beta_1 \delta (R_s - 1)}{(\alpha_2 + \mu)} \equiv \mathscr{B}$$

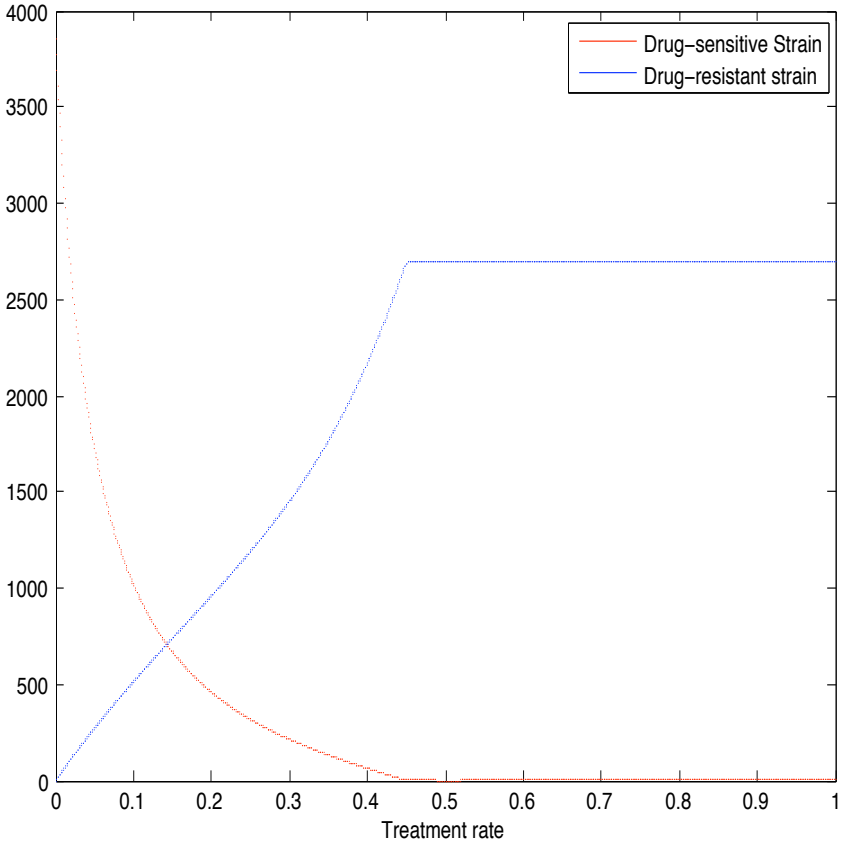

Figure 3.12: Simulations of the model with treatment (3.1). The figure depicts the long term dynamics for varying treatment rate. For values of σ (treatment rate), coexistence is achieved and as the treatment rate increases, it leads to drug-resistant only equilibrium. Parameter values used are: $\tau_r = 0.2$, $\delta = 0.4$, and $s = 0.5$, $\Lambda = 100$, and the rest are as in Table 3.3. In this case R_s varies and $R_r = 3.0864$

(ii) the stability of E_r corresponds to

$$R_s < \frac{R_r(\mu+\omega)}{(\mu+\omega)+\delta(R_r-1)(\mu+\omega+\eta)} \equiv \mathscr{C}$$

(iii) the stability of E_c corresponds to

$$R_r > \mathscr{B}$$

$$R_s > \mathscr{C}$$

The above calculations allow us to investigate the competitive exclusion principle by simulating the model with varying parameters. Simulating the model

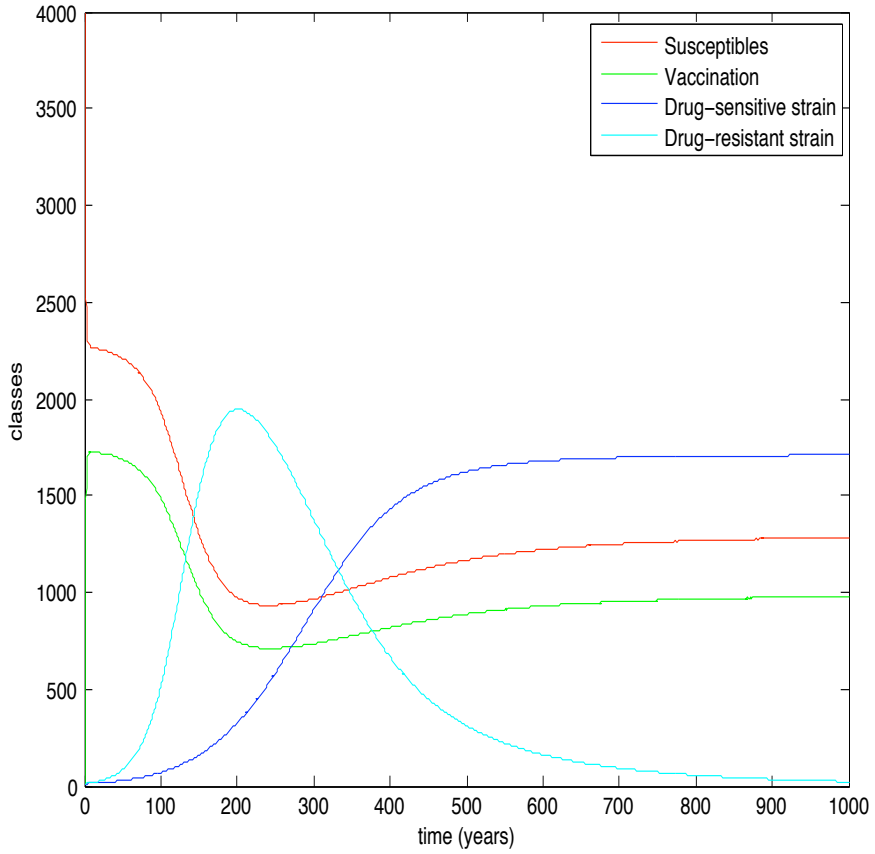

Figure 3.13: Simulations of the model with treatment (3.5). The figure depicts the temporal course of the classes for the case when $R_r < \mathscr{B}$. Parameter values used are: $\tau_r = 0.3$, $\delta = 0.5$ and $\eta = 0.4$, and the rest are as in Table 3.3. In this case For values of σ (treatment rate), coexistence is achieved and as the treatment rate increases, it leads to drug-resistant only equilibrium. Parameter values used are: $\tau_r = 0.2$, $\delta = 0.4$, and $s = 0.5$, $\Lambda = 100$, and the rest are as in Table 3.3. In this case $R_s = 1.7613$, $R_r = 2.6419$

using parameters in Table 3.3 with $\tau_r = 0.3$, $\delta = 0.5$ and $\eta = 0.4$ so that $R_s = 1.7613$, $R_r = 2.6419$, and $\mathscr{B} = 2.942$ (which implies that $R_r < \mathscr{B}$) shows convergence to the drug-sensitive strain (Fig 3.13). Thus, the drug-sensitive strain out competes the drug-resistant strain even though $R_s < R_r$

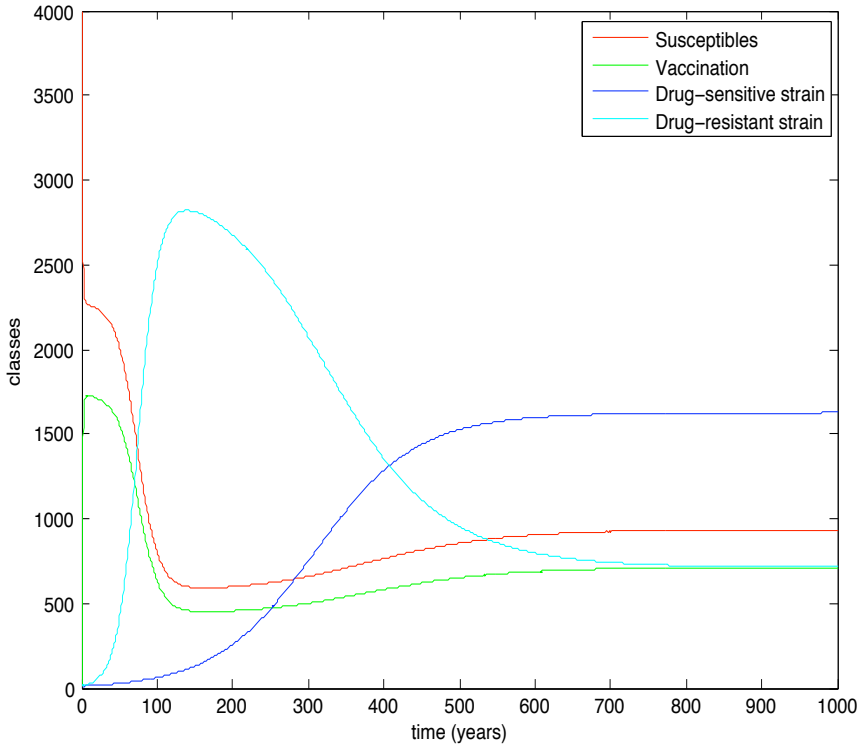

Figure 3.14: Simulations of the model with treatment (3.5). The figure depicts the temporal course of the classes for the case when $R_r > \mathscr{B}$ and $R_s > \mathscr{C}$. Parameter values used are: $\tau_r = 0.45$, $\delta = 0.5$ and $\eta = 0.4$, $\Lambda = 100$, and the rest are as in Table 3.3. In this case $R_s = 1.7613$ and $R_r = 3.968$

Using the same parameters as above but with $\tau_r = 0.45$ which implies that $R_s = 1.7613$ and $R_r = 3.968$, $\mathscr{B} = 1.3468$ and $\mathscr{C} = 1.6045$, gives $R_r > \mathscr{B}$ and $R_s > \mathscr{C}$. Hence the solution profile converges to the coexistence of both the drug-sensitive strain and the drug-resistant strain (Fig 3.14). To illustrate the competitive exclusion principle showing the convergence to the drug-resistant strain, the same parameters were used but with $\tau_r = .27$, thus $R_s = 1.7613$, $R_r = 2.377$ and $\mathscr{C} = 1.9502$ (Fig. 3.15).

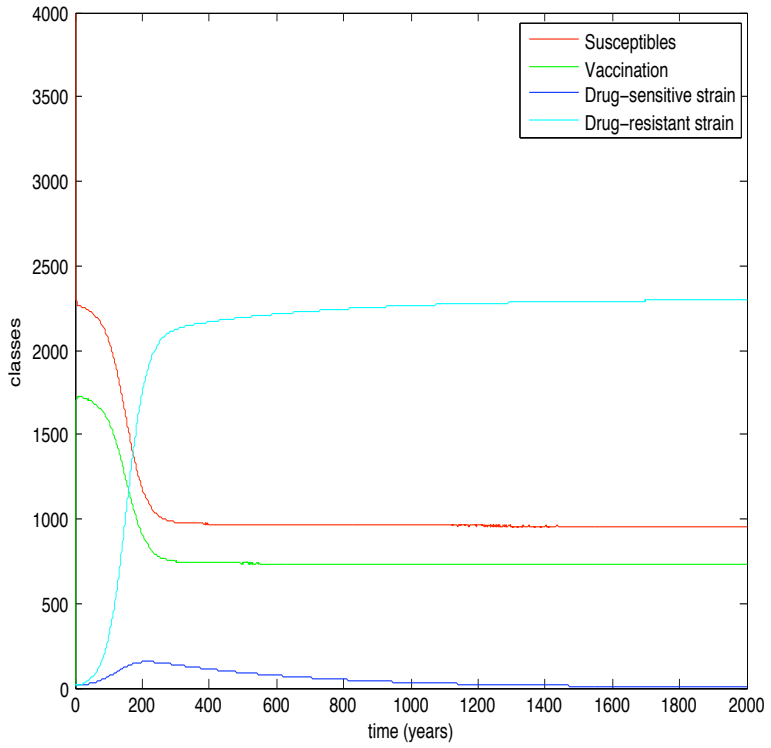

Figure 3.15: Simulations of the model with treatment (3.5). The figure depicts the temporal course of the classes for the case when $R_s < \mathscr{C}$. Parameter values used are: $\tau_r = 0.27$, $\delta = 0.5$ and $\eta = 0.4$, $\Lambda = 100$, and the rest are as in Table 3.3. In this case $R_s = 1.7613$, $R_r = 2.377$

The effect of vaccination on the emergence of drug-resistant strains (η) is plotted in Fig. 3.16. The vaccination rate is varied and the long term dynamics of the drug-sensitive strain and drug-resistant strain are noted. The plot shows that for low rates of vaccination, the drug-sensitive strain out competes the drug-resistant strain, resulting in the drug-sensitive equilibrium. As the vaccination rate increases, the dynamics of the model promote the coexistence of both the drug-senstive and the drug-resistant strain. Followed by the competitive exclusion of the drug-senstive strain which leads to the equilibrium where the drug-resistant is stable. Its interesting to note, that high vaccination rates, lead to the extinction of both the drug-sensitive and the drug-resistnat strains, leading to an equilibrium free of the disease.

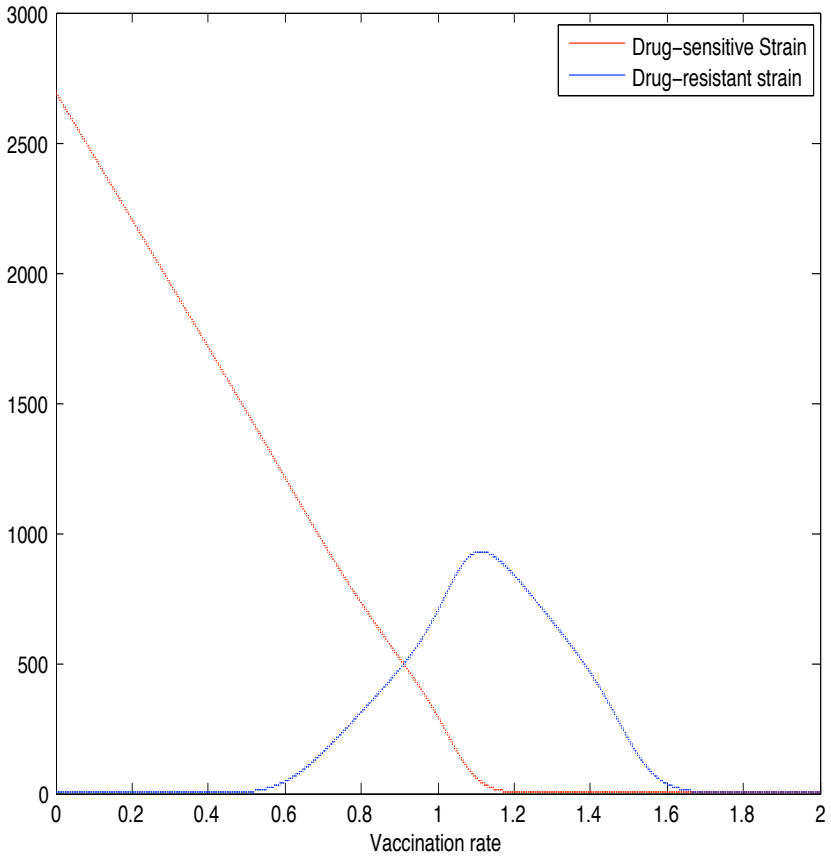

Figure 3.16: Simulations of the model with treatment (3.5). The figure depicts the long term dynamics for varying vaccination rate. For values of η (vaccination rate), all three equilibria are achieved: drug-sensitive only, coexistence, drug-resistant only, and as vaccination rate increases, it leads to DFE. Parameter values used are: $\tau_r = 0.27$, $\delta = 0.4$, $\Lambda = 100$, and the rest are as in Table 3.3. In this case R_s and R_r vary.

Chapter 4

EPIDEMIOLOGICAL MODELS FOR THE SPREAD OF ANTI-MALARIAL RESISTANCE

Malaria remains a major cause of mortality and morbidity in the tropical and subtropical areas of the world. According to World Health Organization, around 30% of the global population is at constant risk of infection, with sub-Saharan Africa being the worst affected region [73]. Malaria has also recently been identified as a candidate for global eradication. Despite the effort aimed at eradicating malaria globally, the disease continues to be a major cause of morbidity and mortality in the tropical and sub-tropical regions of the world, with some parts of Africa being the most affected [72]. Malaria accounts for 300 million cases and over a million fatalities globally every year (World Health Organization Expert Committee on Malaria, [73], and such burden is expected to significantly increase.

Malaria infection is caused by the protozoan *Plasmodium*, and transmitted to humans by *Anopheles* mosquitoes, after taking a blood meal from humans. Four species of the parasite, (*P. falciparum*, *P. vivax*, *P. ovale*, and *P. malarie*) infect humans. These species differ in geographical distribution, microscopic appearance, and clinical features such as potential of infection, potential for severe disease and ability to cause relapses. Of the four species, *P. falciparum* is the most virulent, and potentially deadly to humans.

Although numerous control strategies, such as mosquito-reduction strategies, personal protection, and treatment exists, it is unlikely that a single strategy would be applicable to all nations and epidemiological situations. Further, global changes in weather, together with changes in demographics structures, development of resistance to antimalarial drugs, and the absence of an effective vaccine, constitute additional challenges in the global effort to effectively control the malaria parasite. Thus,

antimalaria control strategies need to be designed for the specific environment in which they will be used taking into account the available resources.

Although there is currently no effective anti-malaria vaccine available for use in humans, a number of candidate vaccines are under development and/or undergoing various stages of clinical trials [22], [31], [52], [64]. For the most part, some of these vaccines are designed to target the liver stages (pre-erythrocytic stages) of the parasite to reduce the changes of a human being infected, while others are designed to target the asexual blood stages (erythocytic stage) of the parasite, to reduce disease severity and risk of death during infection [22], [31], [64], [71]. In addition, there are other vaccines that are designed to target the sexual stages of the parasite to prevent its transmission to a mosquito vector and ultimately to another human [22], [64]. An ideal vaccine should be cheap, extremely safe, induce life long immunity, be active against all types of the *plasmodiun falciparum* parasite, and result in substantial interruption of the malaria life cycle through vaccine-induced responses. Unfortunately, this remains a daunting and impossible task. Consequently, the current strategies for malaria vaccine development are focused on achieving more modest goals of reducing the risk of infection and reducing the transformation of the sexual staged gametocytes to gametes in the mosquito [71]. In fact, efforts for vaccine development against the pre-erythrocytic and the erythrocytic stages have focused on strategies aiming at a 50% or more efficacy rate [71], which are considered as a sizeable scale implementation by many public-health officials [71]. Thus, it is instructive to design models for assessing the potential impact of a future anti-malaria vaccine. Such a vaccine is expected to be imperfect and may possess some important therapeutic characteristics such as, blocking infection (at some efficacy level), reducing transmissibility in breakthrough infection, slowing onset of symptoms, slowing mortality rate and accelerating the rate.

4.1 A model for anti-malarial resistance transmission

The model assumes that the population of humans is subdivided into three classes. Assume $S(t)$ be the density of susceptible human population, $V(t)$ be the density of vaccinated human population, $I_s(t)$ be the density of infected with sensitive strain of malaria human population, $I_r(t)$ to be the density of infected with anti-malarial resistance human population and $R(t)$ to be the density of the recovered population. Since we are interested in long term dynamics, the model does not include any latent or exposed classes. In this model we assume that hosts can be superinfected by a second parasite, which leads to a mixture of sensitive and resistant parasites in the same patient. We further assume that sensitive and resistant parasites develop independently within their host.

The susceptible population is increased by the recruitment of individuals (assumed susceptible) into the population (at a rate Λ) and decreased by natural death at a rate μ. The susceptible population is further decreased by the administration of a malaria vaccine (at a rate η). In the presence of the disease, susceptible population also increases by the loss of infection-acquired immunity by individuals who recovered from malaria (at the rates α_s and α_r for individuals infected with the sensitive and resistant strain, respectively). It is assumed that infection-acquired immunity is higher for sensitive strain population then for the resistant strain population ($\alpha_s > \alpha_r$). The susceptible population if further increased by the loss or vaccine immunity (at a rate ω). The vaccinated population is generated by the administration of malaria vaccine to susceptible individuals (at a rate η) and diminished by the loss of acquired vaccine immunity (at a rate ω), and natural death (at a rate μ). The infected population with sensitive strain is generated by the infection of susceptible individuals with sensitive strain and diminished by natural death (at the rate μ), natural recovery (at a rate α_s), disease induced mortality (at a rate ν_s) and

administration of antimalarial drugs (at a rate σ). The infected population with resistant strain is generated by the infection of susceptible individuals with resistant strain and diminished by natural death (at the rate μ), natural recovery (at a rate α_r), and disease induced mortality (at a rate ν_r). The infected population with resistant strain is further increased by acquired resistant due to failure to comply with antimalarial drugs regimen (at a rate $(1-s)\sigma$), where s is the probability of compliance. The recovered population is generated by the treatment of the population infected with the sensitive strain who complied with the antimalarial drugs regimen and hence cleared the infection (at a rate $s\sigma$). It is decreased by the natural death (at a rate μ).

The susceptible population is further decreased by infection acquired via mosquito bites from female vectors carrying either the wild or the resistant strain. The infection rate of humans ($\lambda_s(t)$ and $\lambda_r(t)$) is dependent on the biting rate of mosquitoes, the transmission probability per bite, and the proportion of infected mosquitoes in the population. The force of infection, ($\lambda_s(t)$ and $\lambda_r(t)$), depends on the density of mosquitoes and hence varies between regions. Since our study focuses on understanding the dynamics of resistant malaria in Sub-Saharan Africa, a region where Malaria is endemic and hence of high transmission, it is reasonable to exclude the vector dynamics and assume that the proportion of infected humans is a good estimate for the force of infection [67], [2]. Then the force of infection for sub-Saharan Africa is given by

$$\lambda_s(t) = \frac{p_s(t)I_s}{N} \text{ and } \lambda_r(t) = \frac{p_r(t)I_r}{N}$$

where $p_s(t)$ and $p_r(t)$, is the transmission probability at time t of the sensitive strain and resistant strain, respectively. For now, it is assume to be constant for all t.

The governing equations for the transmission of the disease in the presence of demographic parameters, and preventive and control measures are

$$\begin{aligned}
\dot{S} &= \Lambda - \lambda_s(t)\frac{S}{N} - \lambda_r(t)\frac{S}{N} - \mu S - \eta S + \omega V + \alpha_s I_s + \alpha_r I_r \qquad (4.1)\\
\dot{V} &= \eta S - \omega V - \mu V\\
\dot{I}_s &= \lambda_s(t)\frac{S}{N} + \lambda_s(t)\delta\frac{I_r}{N} - (\mu + \nu_s)I_s - \alpha_s I_s - \sigma I_s\\
\dot{I}_r &= \lambda_r(t)\frac{S}{N} + (1-s)\sigma I_s - \lambda_s(t)\delta\frac{I_r}{N} - (\mu + \nu_r)I_r - \alpha_r I_r\\
\dot{R} &= s\sigma I_s - \mu R
\end{aligned}$$

where $\lambda_s(t)$=$\frac{p_s(t)I_s}{N}$ and $\lambda_r(t)$= $\frac{p_r(t)I_r}{N}$. Since the study focuses on modeling the disease dynamics of Malaria in sub-Saharan Africa, where Malaria is considered to be endemic, the dynamics of the vector population are negligible. Entomological studies have shown that is reasonable to estimate the force of infection in high transmission areas as $\lambda = -ln(1-\frac{I}{N})$ [67][2]. Hence the force of infection can be considered proportional to the infected population. Therefore, this study we assume that the vector population does not fluctuate and can be treated as a constant population proportional to the infected humans Therefore, $p_s(t)$ is proportional to the population to the sensitive strain population and $p_r(t)$ is proportional to the resistant strain population.

4.2 Parameter values

We compile a reasonable set of baseline values for the parameters in the model for areas of high transmission ($\mathscr{R}_0$ = 5.0).

Baseline parameter values

We show baseline values and ranges in Table 4.1. We include for areas of low transmission. We also describe our reasons for using these values and the references, where available. We estimate parameter values from published studies and

country-wide data. For human population in our model, we consider villages, small towns, or small regions. We assume high transmission occurs in parts of Africa, more specifically in sub-Saharan Africa. We use two significant figures of accuracy for all parameters.

Table 4.1: Parameters values for Malaria disease dynamics in sub-Saharan Africa of 4.1

Parameter	Baseline value	Range	Reference
η	0.00273 $Days^{-1}$	0.00136986 - 0.3	Assumed
α_s	0.005 $Days^{-1}$		[25][23][63]
α_r	0.005 $Days^{-1}$		[25][23][63]
ν_s	0.000082079 $Days^{-1}$		[3]
ν_r	0.000082079 $Days^{-1}$		[3]
σ	0.04 $Days^{-1}$	0.0035 - 0.4	Assumed
δ		0 -1	Assumed
s		0 -1	Assumed
ω	0.000548 $Days^{-1}$	0.0055 - 0.00027397	Assumed
μ	0.025 $years^{-1}$		[20]

Population data for humans

Table 4.2 shows the life expectancy and birth rate estimates for the year 2010 for some African countries with areas of high malaria transmission. Using this data we assume a birth rate of 40 births per year per 1000 people so Λ = 40/365.25/1000. We set the values of $\mu = 6.8x10^{-5}$, which corresponds to, in the absence of malaria, a life expectancy of 40 years.

To determine the range of these parameters, we allow the birth rate to vary from 10 births per 1000 people per year to 50 births per 1000 people per year. We allow μ to vary so that the minimum removal rate corresponds to a life expectancy of 80 years and the maximum removal rate corresponds to a life expectancy of 30 years. The exact value of μ, for a given life expectancy, would depend on the values of the birth rate.

Table 4.2: Demographic data for countries with areas of high levels of malaria transmission. The unit for life expectancy is years and the unit for the birth rate is total births per 1000 people per year.

Country	Life Expectancy	Birth Rate	Reference
Bostwana	33.87	23.33	CIA (2005) [20]
Congo, DR	49.35	44.38	CIA (2005) [20]
Kenya	47.99	40.13	CIA (2005) [20]
Malawi	36.97	43.95	CIA (2005) [20])
Zambia	39.7	41.38	CIA (2005) [20]

Data for ν_s and ν_r

The value of the disease-induced death rate varied considerably across different regions, depending on the diagnosis and treatment facilities available. Arudo *et al*. (2003) [3] give the mortality rate for malaria for children under 5 years old in Asembo (a region in western Kenya) as 32.9 deaths per year per 1000 children. Although this data is only for children and for all children (not only those that are infectious), we use it as an estimate for the per capita disease-induced death rate. This assumption is reasonable because in areas of high malaria transmission like Asembo, almost all children suffer from clinical malaria and most adults do not contract clinical malaria. We assume that the range of ν_s and ν_r can vary from no disease-induced deaths to 150 deaths per year per 1000 infected people.

Data for α_s and α_r

The model assumes that people infected with sensitive strain and resistant strain clear at a constant per-capita rate, α_s and α_r, respectively. The waiting time to clear a simple infection is an important parameter. Estimates of the waiting time to clear an infection come from several different sources. One important source was data from the malaria therapy of neurosyphilis patients, which estimated an average duration of 220 days [25]. The 200-day waiting time was also consistent with an older study in Puerto

Rico [23], and with recent studies that compared models and estimated waiting time to clear infections of 150 days in northern Ghana [63]. We assume that the range of α_s and α_r can vary from 150 days to naturally clear the infection to 220 day, with $\alpha_s > \alpha_r$

4.3 Simulations of the anti-malarial resistance model with interventions

Further simulations of the anti-malarial resistance model (4.1) are performed, using a reasonable set of parameter values that are in line with the literature on malaria transmission, transmission intensity as shown in Table 4.1 (unless otherwise states), are carried out in this section. Since there are currently no effective anti-malaria vaccines, the vaccine-related parameters of the malaria model are assumed (making them as biologically feasible and realistic as possible). The impact of preventive and control measures on the disease dynamics of sensitive and drug-resistant strains is evaluated by depicting a plot of the prevalence as a function of time in Fig. 4.1. It follows from Fig. 4.1 that the number of infections is reduced dramatically if both the preventive (vaccination) and control (treatment) measures are implemented in a population where Malaria is at an endemic state. The impact of these measures is not significant in the number of Malaria cases until after the about 1.5 years. The major impact on reducing Malaria prevalence is observed when both vaccination and treatment are implemented in the population. However, after roughly 13, the reduction in Malaria prevalence when only treatment is implemented as a control measure is comparable to one where both preventive and control measures are implemented. It is important to note that for this specific scenario the vaccine induced immunity is set to 3 years and the vaccination rate is assumed to be 300 people per year per 1000 people.

The impact of the vaccination program is assessed by depicting contour plots of the reproduction number in the presence of vaccination as a function of the vaccine induced immunity (ω) and vaccination rate (η) in Fig. 4.2. It is shown that for relatively low values of the basic reproduction number (R_0), such as $R_0 = 1.5$,

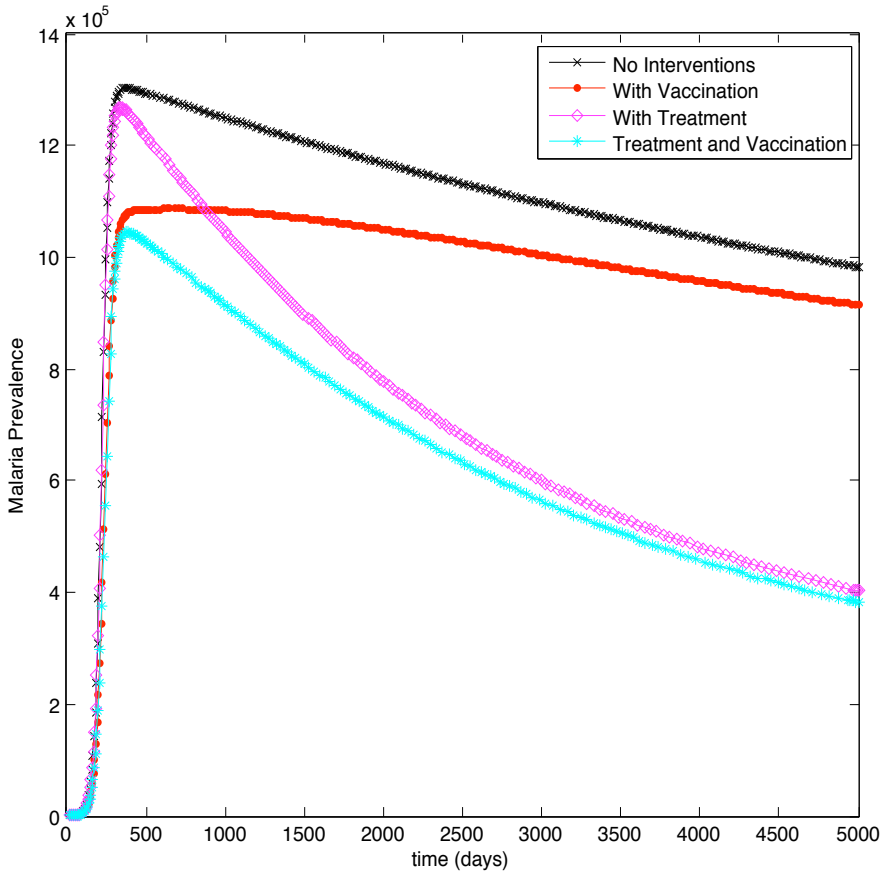

Figure 4.1: Simulations of the model Malaria model (4.1) assessing the impact of interventions. Malaria prevalence is defined as the number of individuals infected with the sensitive strain of Malaria and resistant stain. The parameter values are: treatment rate(σ) is 200 people per year per 1000 people, vaccination rate (η) is 300 people per year per 1000 people and the vaccine immunity (ω) is assumed to be 3 years. The rest of the parameter values are as in Table 4.1.

increasing the vaccine induced immunity and increasing the vaccination rate can lead to disease elimination (since, such levels of vaccine induced immunity and vaccination rate will result in $R_0 < 1$; which may lead to disease elimination) On the other hand, if the associated reproduction number is relatively high (*e.g.*, $R_0 = 5.5$), the most effective way to reduce or eliminate the disease. The greatest impact would be increasing the vaccine induced immunity. Increasing the vaccination rate alone will not help reduce the disease. The treatment rate (σ) assumed for this simulation is 300 people per year per 1000 people. Increasing the treatment rate affects the value of R_0

but it does not affect the qualitative behavior of R_0.

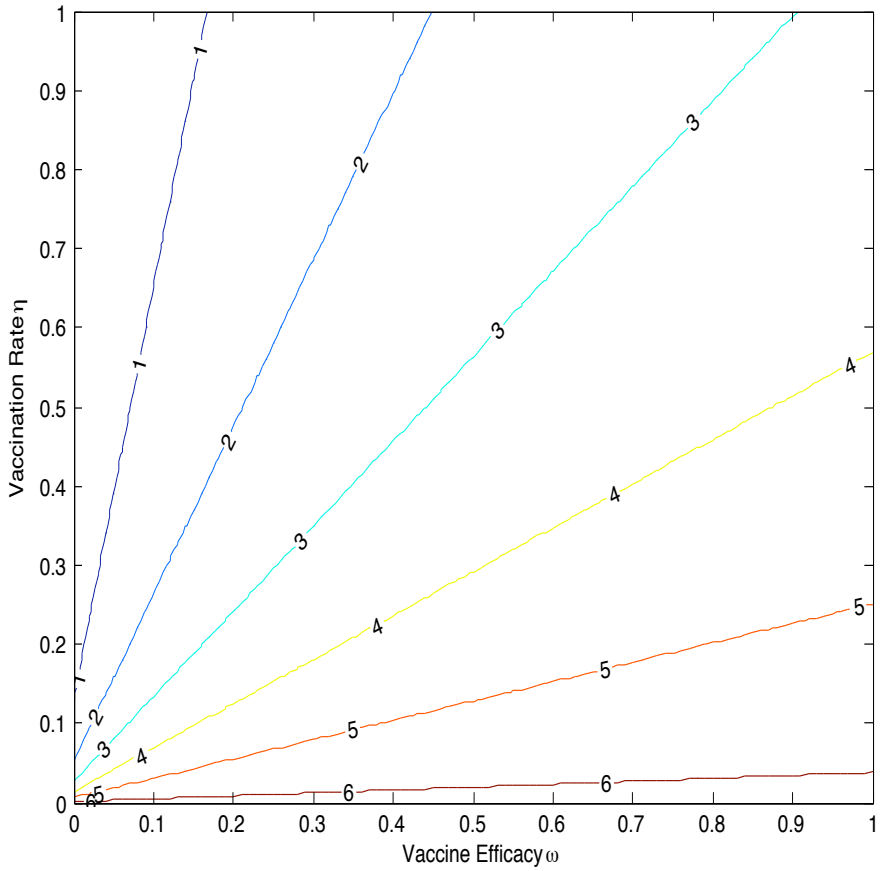

Figure 4.2: Simulations of the Malaria model (4.1) showing contour plots of the R_0 as a function of the vaccination rate (η) and vaccine-induced immunity (ω). The treatment rate (σ) is assumed to be 200 people per year per 1000 people. All other parameters as in Table 4.1

The effect of varying the values of treatment rate (σ) on the basic reproduction number (R_0) are illustrated in Fig. 4.3. Two different scenarios are depicted on this plot, one where a vaccination regimen is not implemented in the population, hence only treatment is used a control measure to reduce Malaria prevalence. In the other scenario, an established vaccination regimen is implemented in the population, with a vaccination rate (η) of 300 people per year per 1000 people and a vaccine induced immunity (ω) of three years. The plot shows that for low values of treatment rate, less than roughly 200 people per year per 1000 people, the value of R_0 drops significantly.

If treatment rate is increased, treating more than 200 per year per 1000 people, will have no effect on the value of R_0. At that point, increasing the vaccination rate (η) and increasing the vaccine induced immunity (ω) will further lower the R_0.

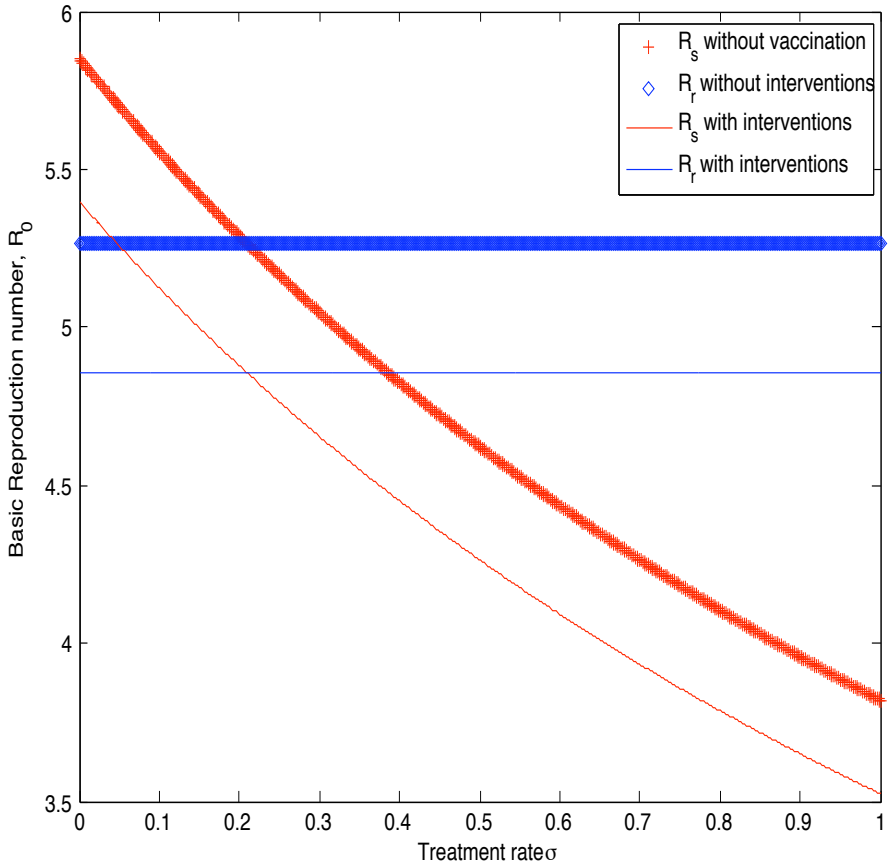

Figure 4.3: Simulation of the Malaria model (4.1) showing R_0 as a function of treatment rate (σ). The figure shows two curves, blue curve is for R_0 without vaccination and the red curve is for R_0 with vaccination. The figure depicts the impact of treatment rate (σ) on R_0. All other parameters as in Table 4.1

The impact of the preventive measure (vaccination) and control measure (treatment) are assessed by depicting a plot of the total population size with respect to time under various scenarios, Fig 4.4. The first scenario is a population where Malaria is endemic however no measures have been implemented. In this case, the population size is the lowest. The second scenario is a population where a vaccination regimen is implemented as a attempt to reduce the Malaria prevalence. In this scenario, the

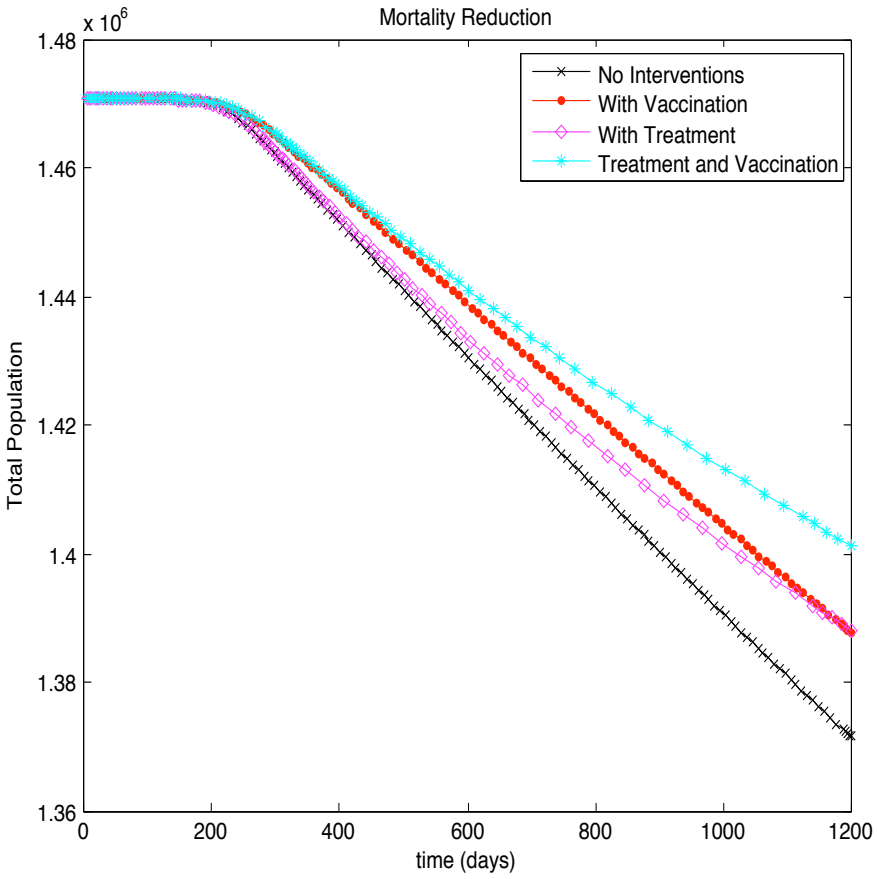

Figure 4.4: Simulation of the Malaria model (4.1) showing the impact the intervention measures have on the total population size. The plot illustrates that a control strategy for Malaria that includes both vaccination and treatment will save the most lives. The parameter values are: treatment rate(σ) is 200 people per year per 1000 people, vaccination rate (η) is 300 people per year per 1000 people and the vaccine immunity (ω) is assumed to be 3 years. The rest of the parameter values are as in Table 4.1.

population size increases. Similarly, a population where Malaria is endemic and treatment is the only control measure implemented will also increase the population size. It is interesting to note that the impact of the implementations is not noticeable until after almost a year. Also, at during the first years, vaccination has a larger population size, hence a lower mortality rate. However, after the third year, both of the measures, vaccination and treatment, have the same population size. The last scenario, is the implementation of both the preventive and control measures. It is clear that this scenarios produces the least mortality rate, hence the largest population size.

However, for the first year and a half, the population size is the same as a population where only vaccination is implemented.

Chapter 5

OPTIMAL CONTROL OF DRUG-RESISTANT MALARIA MODEL WITH TREATMENT AND VACCINATION

5.1 Introduction

Presently, the strategy for controlling Malaria consists of the use of drugs for early treatment of the disease, managing severe and difficult cases, and prophylactic use in vulnerable population, such as pregnant women. Chloroquine is still the preferred therapy for Malaria, but the startling rise in resistance in eastern and southern Africa demands that sulfodoxine-pyrimethamine replaces chloroquine. Despite the efforts to eradicate Malaria, it continues to affect a vast majority of the population. However, new hope is now set on the possible availability of a safe and effective vaccine against Malaria. Various candidate vaccines targeting different stages of the parasite are in pre-clinicaland clinical development [5].

In this section, we formulate an optimal control problem of the Malaria model with interventions, in order to study the best strategies to eradicate the epidemic.

5.2 Optimal control analysis

For the optimal control problem, we consider the following equations:

$$\begin{aligned}
\dot{S} &= \mu N - \beta_s \frac{SI_s}{N} - \beta_r \frac{SI_r}{N} - \mu S - u_2(t)S + \omega V + \alpha_s I_s + \alpha_r I_r \qquad (5.1)\\
\dot{V} &= u_2(t)S - \omega V - \mu V\\
\dot{I}_s &= \beta_s \frac{SI_s}{N} + \beta_s \delta \frac{I_s I_r}{N} - (\mu + \nu_s)I_s - \alpha_s I_s - \sigma I_s\\
\dot{I}_r &= \beta_r \frac{SI_r}{N} + (1 - u_1(t))\sigma I_s - \beta_s \delta \frac{I_s I_r}{N} - (\mu + \nu_r)I_r - \alpha_r I_r\\
\dot{R} &= u_1(t)\sigma I_s - \mu R
\end{aligned}$$

The model represents the dynamics for increasing vaccination, waning of vaccine and treatment rates.

Table 5.1: Variables and parameters explanations

Variable/Parameter	Explanation
S	Susceptible individuals
V	Vaccinated individuals
I_s	Infected and infectious with sensitive strain
I_s	Infected and infectious with resistant strain
R	Recovered individuals
N	Total population ($N = S + V + I_s + I_r + R$)
Λ	Rate at which new recruits enter the population
η	Rate at which susceptible individuals are vaccinated
β_s	Effective contract rate for sensitive strain
β_r	Effective contract rate for resistant strain
α_s	Natural drug-sensitive recovery rate
α_r	Natural drug-resistant recovery rate
ν_s	Disease induced mortality rate for sensitive strain
ν_r	Disease induced mortality rate for resistant strain
σ	Treatment rate
δ	Fitness cost for resistant strain
ω	Rate at which the vaccine based immunity wanes
μ	Natural death rate for each class

We use the following control variables: $u_1(t)$ to measure the effectiveness of treatment and $u_2(t)$ which measures the effectiveness of vaccination. The effectiveness of the vaccine could be linked to the way it is administered, how early or late is the vaccine given. Also, the choice of a risk group could save help save the cost: Should it be administered to the entire population or only a specific targeted group. How early treatment starts after a positive diagnosis, could be crucial to the effectiveness of the treatment strategy and hence the effectiveness of the drug. One question to be answered is: will there be optimal values for $u_1(t)$, and $u_2(t)$ that improves (maximizes) the efficacy of vaccine and minimizes the cost, the side effects of the drug usage and the total number of infected population within a given community?

The control problem involves a model in which the number of individuals with resistant strain Malaria and the cost of applying controls on vaccination and treatment rates $u_1(t)$, and $u_2(t)$, respectively, are minimized subject to the differential equations

in model 5.1. Our objective functional is defined as:

$$J(u_1,u_2)=\int_0^{t_f}\left[I_r+\frac{B_1}{2}u_1^2(t)+\frac{B_2}{2}u_2^2(t)\right]dt \tag{5.2}$$

where t_f if the final time and the coefficients, B_1 and B_2 are balancing cost factors. This performance specification involves minimizing the number of individuals with resistant strain Malaria, as well as the cost for applying controls on treatment $(u_1(t))$, and vaccination $(u_2(t))$, in individuals with Malaria. The costs can include finds needed to control implementation, hospitalization and lost of many hours of work due to illness. Using the results of Lukes [47] an optimal control, $u_1^*(t)$ and $u_2^*(t)$, exists such that

$$J(u_1^*(t),u_2^*(t))=\min\{J(u_1(t),u_2(t))|u_1(t),u_2(t)\in\mathscr{U}\} \tag{5.3}$$

where $\mathscr{U}=\{(u_1(t),u_2(t))|(u_1(t),u_2(t))$ measurable,
$a_i\leq(u_1(t),u_2(t))\leq b_i,i=1,2,a_i=0,b_i=0t\in[0,t_f]\}$ is the control set.

The necessary conditions that an optimal control must satisfy come from the Pontryagin's Maximum Principle [61]. This principle converts the system of differential equations 5.1 and 5.2 into a problem of minimizing pointwise a Hamiltonian H, with respect to $(u_1(t),u_2(t))$. First we formulate the Hamiltonian from the cost functional 5.2 and the governing dynamics 5.1 to obtain the optimality conditions.

$$\begin{aligned}H &= I_r+\frac{B_1}{2}u_1^2(t)+\frac{B_2}{2}u_2^2(t)+\lambda_1(\mu N-\beta_1\frac{SI_s}{N}-\beta_2\frac{SI_r}{N}-\mu S-u_2(t)S \\ &\quad +\omega V+\alpha_1 I_s+\alpha_2 I_r)+\lambda_2(u_2(t)S-\omega V-\mu V)+\lambda_3(\beta_1\frac{SI_s}{N}+\beta_1\delta\frac{I_sI_r}{N} \\ &\quad -(\mu+\nu_1)I_s-\alpha_1 I_s-\sigma I_s)+\lambda_4(\beta_2\frac{SI_r}{N}+(1-u_1(t))\sigma I_s-\beta_1\delta\frac{I_sI_r}{N} \\ &\quad -(\mu+\nu_2)I_r-\alpha_2 I_r)+\lambda_5(u_1(t)\sigma I_s-\mu R)\end{aligned} \tag{5.4}$$

where the λ_1, λ_2, λ_3, λ_4, and λ_5 are the associated adjoints for the states S,V,I_s,I_r,R. The system of equations is found by taking the appropriate partial derivatives of the Hamiltonian 5.4 with respect to the associated state variable.

Theorem 15 *There exists an optimal control u_1^*, u_2^* and corresponding solution, S^*, V^*, I_s^*, I_r^*, and R^* of the corresponding state system* 5.1*, that minimizes $J(u_1,u_2)$ over $\mathscr{U}$. Furthermore, there exists adjoint functions, $\lambda_1(t),\ldots,\lambda_5(t)$, such that*

$$\begin{aligned}
\dot{\lambda_1} &= \lambda_1(\beta_1\frac{I_s}{N}+\beta_2\frac{I_r}{N}+\mu+u_2(t))-\lambda_2(u_2(t))-\lambda_3(\beta_1\frac{I_s}{N}-\lambda_4(\beta_2\frac{I_r}{N}) \quad (5.5)\\
\dot{\lambda_2} &= -\lambda_1\omega+\lambda_2(\omega+\mu)\\
\dot{\lambda_3} &= \lambda_1(\beta_1\frac{S}{N}-\alpha_1)-\lambda_3(\beta_1\frac{S}{N}+\beta_1\delta\frac{I_r}{N}-(\mu+\alpha_1+\sigma))\\
&\quad -\lambda_4((1-u_1(t))\sigma-\beta_1\delta\frac{I_r}{N})-\lambda_5u_1(t)\sigma\\
\dot{\lambda_4} &= \lambda_1(\beta_2\frac{S}{N}-\alpha_2)-\lambda_3(\beta_1\delta\frac{I_s}{N})-\lambda_4(\beta_2\frac{S}{N}-\beta_1\delta\frac{I_s}{N}-(\mu+\alpha_2))\\
\dot{\lambda_5} &= \lambda_5\mu
\end{aligned}$$

with transversality conditions

$$\lambda_i(t_f)=0, i=1,\ldots,5$$

and $N=S^*+V^*+I_s^*+I_r^*+R^*$. The following characterization holds

$$u_1^*=\min(\max(a_1,\frac{1}{B_1}\sigma I_s^*(\lambda_4-\lambda_5),b_1). \quad (5.6)$$

and

$$u_2^*=\min(\max(a_2,\frac{1}{B_2}S^*(\lambda_1-\lambda_2),b_2). \quad (5.7)$$

Proof Corollary 4.1 of [28] gives the existence of an optimal control pair due to the convexity of integrand of J with respect to u_1 and u_2, a *priori* boundedness of the state solutions, and the *Lipschitz* property of the state system with respect to the state variables. Applying Pontryagin's Maximum Principle, we obtain

$$\frac{d\lambda_1}{dt}=-\frac{\partial H}{\partial S},\lambda_1(t_f)=0 \quad (5.8)$$

$$\vdots$$

$$\frac{d\lambda_5}{dt}=-\frac{\partial H}{\partial R},\lambda_4(t_f)=0$$

evaluated at the optimal control pair and corresponding states, which results in the stated adjoint system 5.8, [36]. By considering the optimality condition,

$$\frac{\partial H}{\partial u_1} = 0$$

and solving for u_1^* and u_2^*, subject to the constraints, the characterization 5.6 and 5.7 can be derived. To illustrate the characterization of u_1^*, we have

$$\frac{\partial H}{\partial u_1} = B_1 u_1 + I_s^*(\lambda_5 - \lambda_4) = 0$$

at u_1^* on the set $\{t | a_1 < u_1^*(t) < b_1\}$. On this set,

$$u_1^* = \frac{1}{B_1} I_s^*(\lambda_4 - \lambda_5)$$

Taking into account the bounds on u_1^*, we obtain the characterization of u_1^* in 5.6 Similarly, the characterization of u_2^*, is obtained from

$$\frac{\partial H}{\partial u_2} = B_2 u_2 + S(\lambda_2 - \lambda_1) = 0$$

at u_2^* on the set $\{t | a_2 < u_2^*(t) < b_2\}$. On this set,

$$u_2^* = \frac{1}{B_2} S^*(\lambda_1 - \lambda_2)$$

Taking into account the bounds on u_2^*, we obtain the characterization of u_2^* in 5.7□

Next, we discuss the numerical solutions of the optimality system and the corresponding results of varying the optimal controls $u_1(t)$ and $u_2(t)$, some parameter choices, and the interpretations from various cases using the baseline parameter values in Table 5.2. Due to lack of some data, parameter values are assumed within realistic ranges for a typical scenario in a rural community for the purpose of illustration. The units where applicable are *per days*.

Table 5.2: Parameters values used in the optimal control simulations of 5.1

Parameter	Baseline value	Range	Reference
Λ	0.041 *Humans* x $Days^{-1}$	0.0027 - 0.27	[20]
η	0.00273 $Days^{-1}$	0.00136986 - 0.3	Assumed
β_s	11.04 $years^{-1}$	0.12 - 43.97	[2]
β_r	9.25 $years^{-1}$	0.12 - 43.97	[2]
α_s	0.005 $Days^{-1}$		[25][23][63]
α_r	0.005 $Days^{-1}$		[25][23][63]
ν_s	0.000082079 $Days^{-1}$		[3]
ν_r	0.000082079 $Days^{-1}$		[3]
σ	0.04 $Days^{-1}$	0.0035 - 0.4	Assumed
δ		0 -1	Assumed
ω	0.000548 $Days^{-1}$	0.0055 - 0.00027397	Assumed
μ	0.025 $years^{-1}$		[20]

Table 5.3: Computational parameters

Computational Parameters	Symbol	Value
Final time	t_f	100 days
Timestep duration	d_t	0.01 days
Upper bound for controls		0.95
Lower bound for controls		0.05
Initial population size	N(0)	12, 918,000
Initial susceptible individuals	S(0)	N(0)
Initial vaccinated individuals	V(0)	1000
Initial sensitive strain infected individuals	$I_s(0)$	N(0)*0.035
Initial resistant strain infected individuals	$I_r(0)$	N(0) * 0.015
Initial recovered individuals	$R(0)$	1000

5.3 Numerical Simulations

Numerical solutions to the optimality system comprising of the state equations 5.1 and adjoint equations 5.2 are carried out using MatLab and using parameters in Table 5.2 together with the following weight factors and initial conditions: $B_1 = 50$, $B_2 = 50$, $N(0) = 12,918,000$, $S(0) = 12,918,000$ $V(0) = 1000$, $I_s(0) = N(0) * 0.035$, $I_r(0) = N(0) * 0.015$, and $R(0) = 1000$. The algorithm is the forward-backward

scheme: starting with an initial guess for the optimal controls u_1 and u_2, the state variables are then solved forward in time from the dynamics in 5.1 using a Runge-Kutta method of the fourth order. Then, those state variables and initial guess for u_1 and u_2 are used to solve the adjoint equations 5.5 backward in time with given final conditions 5.6 and 5.7, again employing a fourth order Runge-Kutta method. The controls u_1 and u_2 are updated and used to solve the state and then the adjoint system. This iterative process terminates when current state, adjoint, and control values converge significantly [41].

For the figures presented here, there is no set relationship between the weight factor B_2 associated with control u_2 and B_1 which is associated with control u_1 because vaccination for Malaria is not currently available, hence there is no reference as to the cost pertaining the application of the Malaria vaccine. Therefore, we explore several scenarios between the relationship of the weight factor B_2 associated with control u_2 and B_1 which is associated with control u_1. Other epidemiological and numerical parameters are presented in table 5.1 and 5.2, respectively.

Three different control strategies are explored. This approach can be use to test various options. Here, however, we only look at the following three alternative:

- Strategy 1: Anti-malarial treatment control on sensitive strain infectious cases (control $u_1(t)$ alone)
- Strategy 2: Vaccination control on susceptible individuals (control $u_2(t)$ alone)
- Strategy 3: Anti-malarial treatment control on sensitive strain infectious cases and vaccination control on susceptible individuals (controls $u_1(t)$ and $u_2(t)$)

We evaluate the impact of optimal anti-Malarial treatment and vaccination for the dynamics of resistant Malaria under distinct values of transmissibility as measured by the reproductive number $\mathscr{R}_0$ and under the assumption that we have an unlimited

supply of anti-Malarial treatment and vaccination. The graphs of the two computed optimal controls under strategies 1, 2, and 3 are shown in Fig. 5.1 (the parameter values used are provided in Table 5.2 with $\mathscr{R}_0 = 1.78$. In the absence of control and preventive interventions, both sensitive strain Malaria and resistant strain Malaria persist in the population, with the sensitive strain malaria dominating the population. In Fig. 5.1, we can compare the impact of each strategy on the epidemic state variables in the absence of control when $\mathscr{R}_0 = 1.78$. These graphs show the daily number of cases in each class under no controls and under Strategies 1, 2, and 3. The black solid epidemic curves (under no interventions) are shown to highlight the differences from those generated via the implementation of optimal strategies. Strategy 3, which is the use of both vaccination and treatment (blue solid line), shows significant reduction (roughly 90% reduction when compared to the no interventions scenario). On the other hand, implementing only treatment, generated a reduction of about 10% and Strategy 2, vaccination only generated a reduction of roughly 80%. Optimal strategies for Strategy 1 and Strategy 3 demand the implementation of intensive efforts for the duration of the outbreak, while Strategy 2 requires half effort for the duration of the outbreak. The use of a single optimal control does not have a significant impact comparatively speaking, that is, the use of both strategies is more efficient.

Fig. 5.2 explores the case where both sensitive Malaria and resistant Malaria persist in the population, however the resistant strain Malaria is most prevalent of the two. Similarly to the previous scenario, the case when both Strategies are implemented simultaneously yields the best results.

In general, high reproduction numbers imply high epidemic peaks. In the two strain epidemic model, high values of $\mathscr{R}_0$ can occur in two different scenarios, one where the sensitive strain out-competes the resistant strain, hence a population where only the sensitive strain persists. The second scenario takes place when the resistant strain is the one that out-competes the sensitive strain and persists in the population.

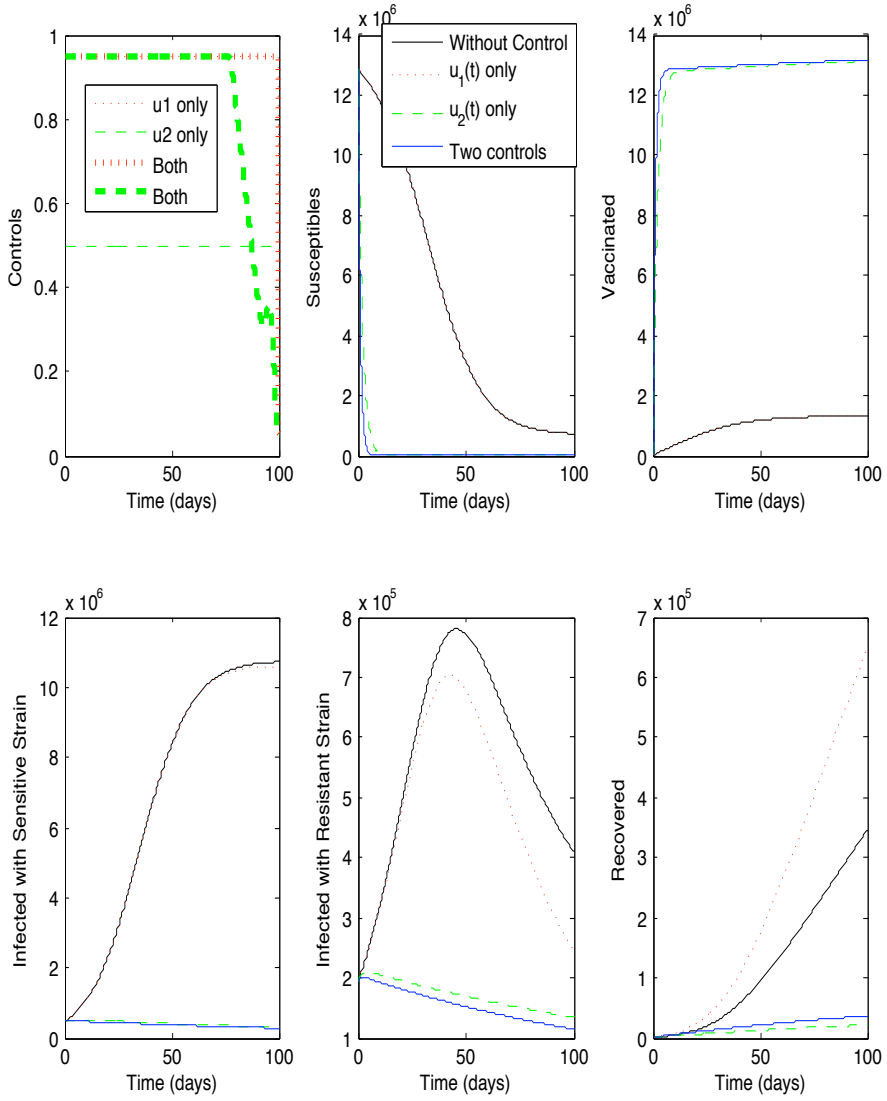

Figure 5.1: The figures shows optimal control functions as a function of time computed for Strategy 1, 2, and 3. The figure also shows the daily number of cases in each state class under no controls, and those generated with Strategies 1, 2, and 3. Optimal Strategy 3, implementing both control efforts, shows significant reductions in all state solutions. Parameter values used are $\delta = 0.3$, and $\sigma = .001$, all other parameter values are given in Table 5.2. The weight factors associated with each control are $B_1 = 50$ and $B_2 = 100$. $R_s = 1.7823$ and $R_r = 1.277$ which results in a $\mathscr{R}_0 = 1.7823$

Fig. 5.3 depicts the scenario where the competitive exclusion favors the sensitive strain, hence becoming endemic in the population and Fig 5.4 illustrates the opposite scenario, where the competitive exclusion favors the resistant strain. In both scenarios, the implementation of Strategy 3, where both controls are implemented

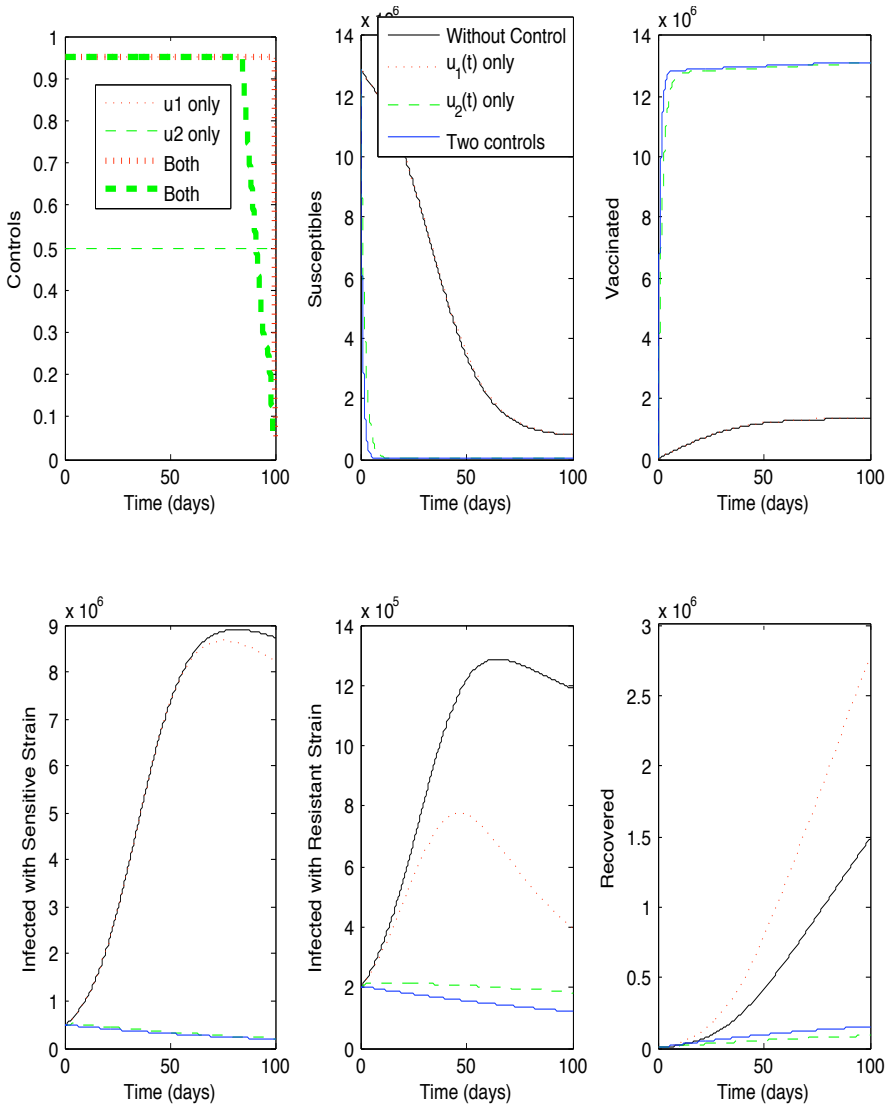

Figure 5.2: The figures shows optimal control functions as a function of time computed for Strategy 1, 2, and 3. The figure also shows the daily number of cases in each state class under no controls, and those generated with Strategies 1, 2, and 3. Optimal Strategy 3, implementing both control efforts, shows significant reductions in all state solutions. Parameter values used are $\delta = 0.3$, and $\sigma = .005$, $\omega = 0.000391$; all other parameter values are given in Table 5.2. The weight factors associated with each control are $B_1 = 50$ and $B_2 = 100$. $R_s = 1.3981$ and $R_r = 1.6533$ which results in a $\mathscr{R}_0 = 1.6533$

simultaneously throughout the course of the epidemic, results in a decrease of the daily number of resistant strain cases of roughly 80% to 90%. In Fig. 5.3, no interventions produces the highest peak (solid black curve), followed by Strategy 1 where only a control on anti-malarial treatment administration is implemented (dotted

red line). The next best scenario is Strategy 2, where only the vaccination control is implemented (dashed green line). This case can be handled optimally through the implementation of an initial full effort followed by a sharp effort reduction towards the end of the epidemic. The weight factors associated with each control are $B_1 = 50$ and $B_2 = 50$. In Fig. 5.4, the number of daily resistant strain cases is the lowest when a combination of controls is implemented, Strategy 3. Strategy 1, effort in treatment implementation, produces the next second least daily number of infected resistant strain. Hence, if the population is in a scenario where the resistant strain is endemic and there are limited resources, the best scenario would be to implement Strategy 1, put all the effort in the anti-malarial treatment. The $\mathscr{R}_0 = 3.768$ and the weight factors associated with this simulations are $B_1 = 50$ and $B_2 = 50$.

The impact of optimal Strategies 1-3, in terms of the cumulative number of resistant strain cases as a function of $\mathscr{R}_0$ is presented in Fig 5.5. The black star curve corresponds to the no interventions case. Strategy 1 (red circle curve) generates higher reductions than Strategy 2 corresponds to the green diamond curved, that is the use of anti-malarial treatment for reduction of resistant strain malaria can be more effective than the use of vaccination in the unlimited resources case. Combined control strategy (Strategy 3) generates significant reduction in resistant malaria cases when compared to those generated via the use of a single control.

Sensitivity Analyses

The sensitivity of the weight constants on controls (B_1 and B_2), has been assessed via extensive simulations. Figs. 5.6 - 5.11 provide a glance at the impact of varying the weight constants in terms of the epidemic curve for the resistant strain malaria. The case of no interventions versus the scenarios generated when controls are in place are illustrated. The three selected strategies are compared using distinct values of the weight factors. The role of the weight constants for all three strategies is explored, the

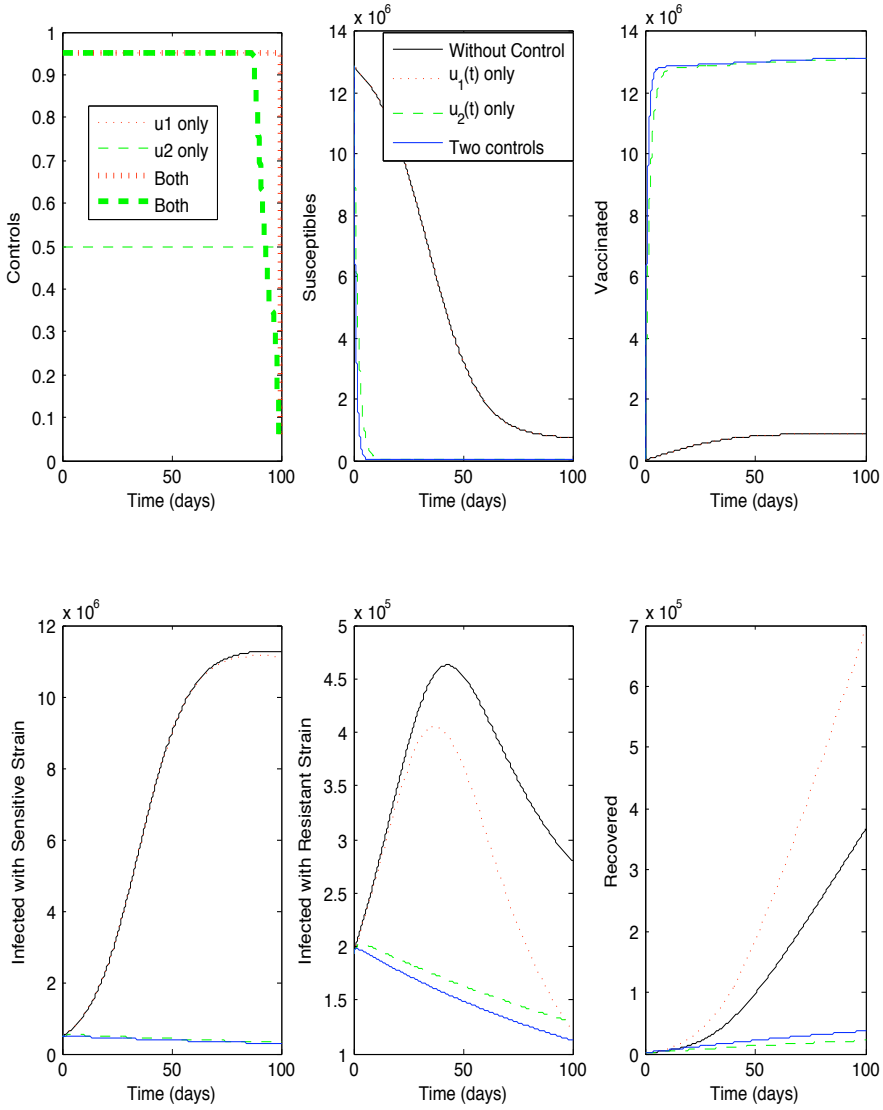

Figure 5.3: The figures shows optimal control functions as a function of time computed for Strategy 1, 2, and 3. The figure also shows the daily number of cases in each state class under no controls, and those generated with Strategies 1, 2, and 3. Optimal Strategy 3, implementing both control efforts, shows significant reductions in all state solutions. Parameter values used are $\delta = 0.3$, and $\sigma = .001$ $\eta = 0.001826$; all other parameter values are given in Table 5.2. The weight factors associated with each control are $B_1 = 50$ and $B_2 = 50$. $R_s = 4.1005$ and $R_r = 1.9587$ which results in a $\mathscr{R}_0 = 4.1005$

outcome however, turned out no to be too sensitive to large variations in these weights. The focus of this study is on the role of relative costs as the exact costs are not always known, hence the weights factors range from 10 to 1500.

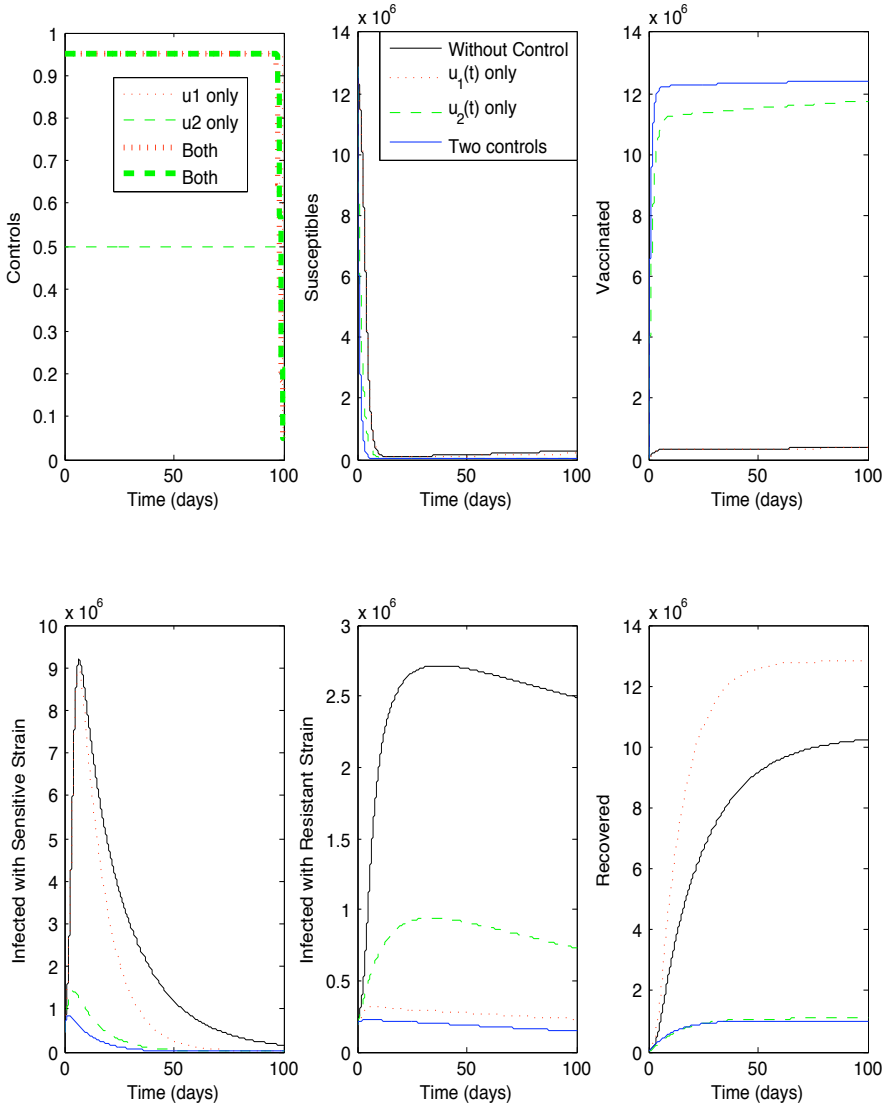

Figure 5.4: The figures shows optimal control functions as a function of time computed for Strategy 1, 2, and 3. The figure also shows the daily number of cases in each state class under no controls, and those generated with Strategies 1, 2, and 3. Optimal Strategy 3, implementing both control efforts, shows significant reductions in all state solutions. Parameter values used are $\delta = 0.2$, and $\sigma = .09$ $\eta = 0.00667$ and $\omega = 0.000913$; all other parameter values are given in Table 5.2. The weight factors associated with each control are $B_1 = 50$ and $B_2 = 50$. $R_s = 1.3484$ and $R_r = 3.769$ which results in a $\mathscr{R}_0 = 3.769$

In Fig. 5.6 and Fig. 5.7, the case were the two strains, sensitive and resistant, coexists in the population, in one the sensitive strain dominates and the other the resistant strain dominates, respectively. In these two simulations we explore the

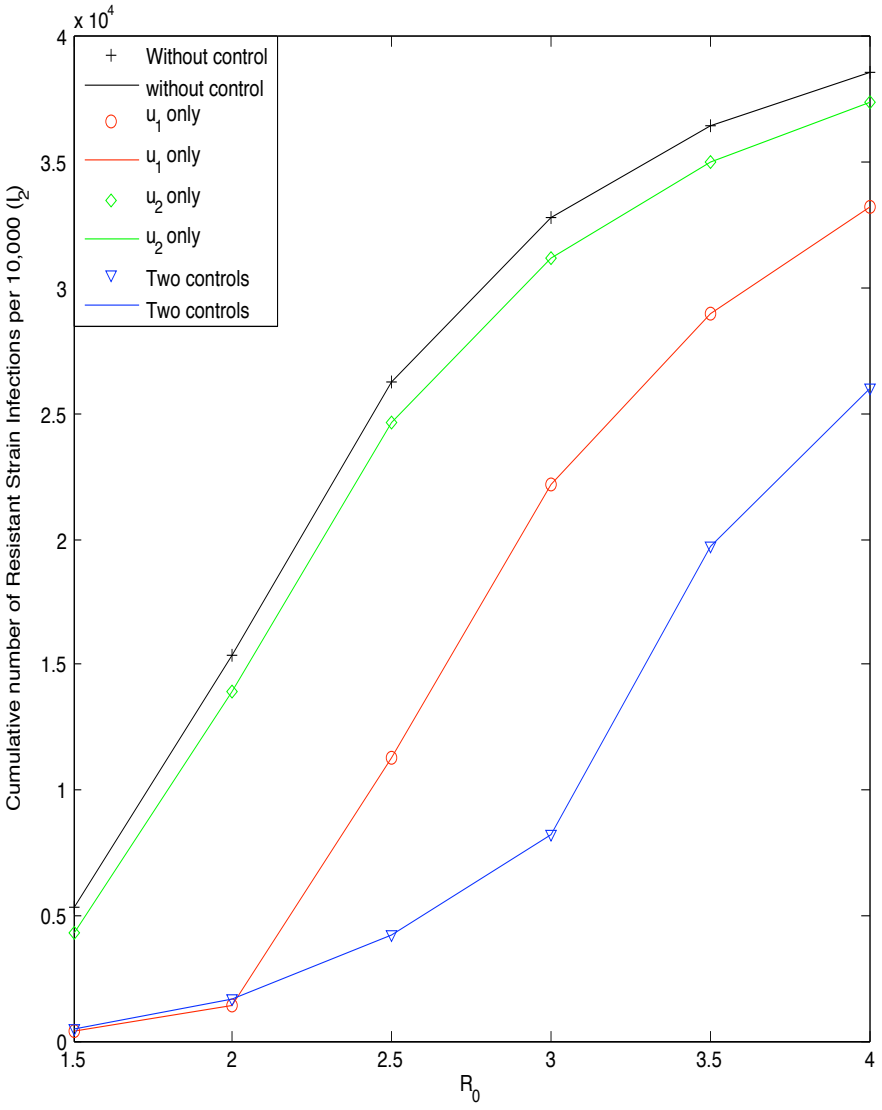

Figure 5.5: The cumulative number of resistant strain cases under no control and under Strategies 1-3 as a function of $\mathscr{R}_0$. Strategy 3, generates a significant reduction in the cumulative number of resistant Malaria cases.

scenario where the weight constants are relatively low and equal ($B_1 = B_2 = 50$), and one where one is 30 times bigger than the other ($B_1 = 50$ and $B_2 = 1500$; $B_1 = 1500$ and $B_2 = 50$). In all of these three scenarios for the case where sensitive strain dominates in the population, the combination optimal strategy has the biggest impact on the reduction of resistant strain cases. Looking at the control efficacy needed for each of these scenarios, we note that in the case where both are equal and relatively

low, full control effort is needed from the start of the epidemic of both of the controls, $u_1(t)$ and $u_2(t)$, with a sharp decrease of the vaccine effort towards the end of the epidemic. In the scenario where the cost associated with vaccination, B_2, is 30 times higher than the cost associated with treatment, B_1, $u_2(t)$ has a slight decrease long before the epidemic ends. In the last case, where the cost associated with treatment B_1 is 30 times higher than the cost associated with B_2, full treatment effort is necessary throughout the epidemic in order to reduce the number of resistant Malaria. In the case where resistant malaria dominates in the population, the case where the cost associated with vaccination B_2 is 30 times higher than the cost associated with the treatment B_2, produces and interesting behavior in the control effort. Full effort of both controls is required for the first few days of the epidemic, followed by a slight drop in effort of the vaccination rate until half way through the epidemic, when the effort for vaccination must be increased again, and finally decreased one last time towards the end of the epidemic. This interesting behavior is probably due to the fact that the cost associated with B_2 is so high that full effort is only optimal for the start of the epidemic, and not for the on-course of it.

In Fig. 5.8 and Fig. 5.9, we explore the scenario where both of the costs associated with each of the controls are kept the same, but increased from case to case. We explore the values of $B_1 = B_2 = 10$, $B_1 = B_2 = 100$ and $B_1 = B_2 = 250$. In all three cases for both coexistence scenarios, the curves of the efforts require full effort at the start of the epidemic and decrease accordingly depending on the cost. For all the cases, no matter the weight associated with treatment, full effort of treatment is required for the length of the epidemic.

The objective of optimal control strategies explored so far has been to reduce the number of daily cases of resistant strain Malaria, ignoring the outcome of the sensitive strain Malaria. In Fig. 5.12 - 5.16, we explore the case where the objective of the optimal control is to minimize the number of infections, both sensitive and

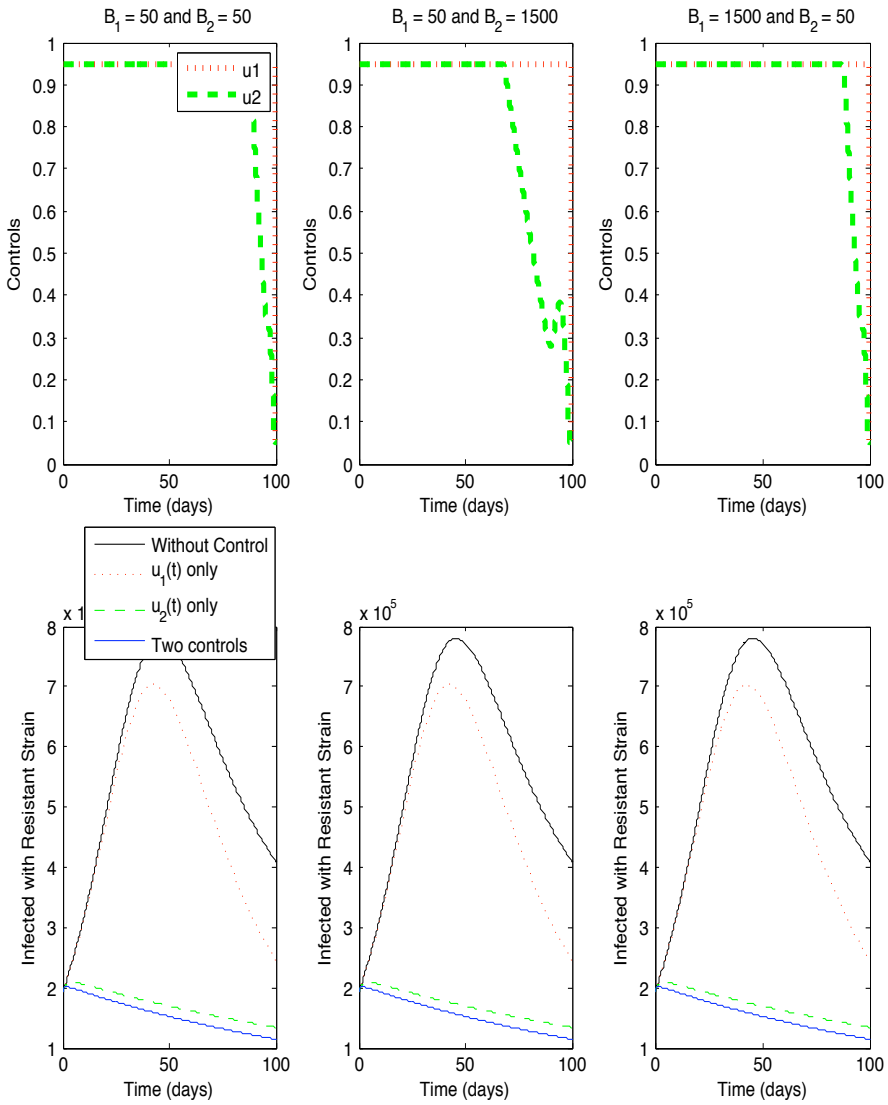

Figure 5.6: The daily number of resistant malaria cases are plotted for three different values scenarios of weight constants. The general curves of the control efforts are very similar with slight changes in the time when the reduction of effort associated with vaccination is reduced. The epidemiological curves illustrate a scenario where both strains coexist in the population and the sensitive strain dominates. $R_s = 1.7823$ and $R_r = 1.277$. We illustrate the scenario where the costs are not the same and differ by a factor of 30.

resistant Malaria, by exploring the impact of different weight factors. Fig. 5.12 and Fig. 5.13, illustrate the case of competitive exclusion with the sensitive strain surviving in the population. In Fig. 5.12, we explore different weight factors and we conclude that implementing both control strategies simultaneously results in a

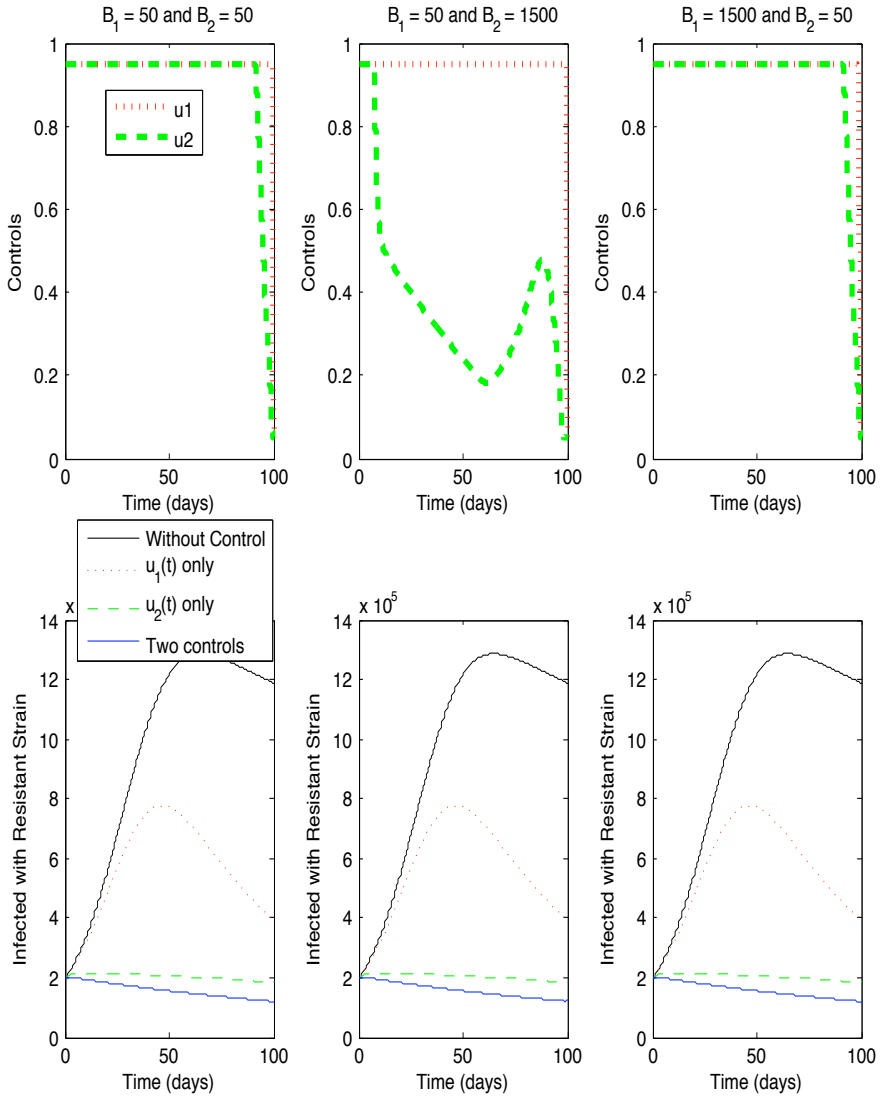

Figure 5.7: The daily number of resistant malaria cases are plotted for three different values scenarios of weight constants. The general curves of the control efforts are very similar with slight changes in the time when the reduction of effort associated with vaccination is reduced. The epidemiological curves illustrate a scenario where both strains coexist in the population and the resistant strain dominates. $R_s = 1.3981$ and $R_r = 1.6533$. We illustrate the scenario where the costs are not the same and differ by a factor of 30.

reduction of infected cases. Full effort must be employed since the onset of the epidemic and stay through out the entire epidemic if both of the weight factors are low and equal. For the case where the B_1 is 10 times bigger than B_2, we see a reduction in effort of the treatment control versus when B_2 is 10 times bigger than B_1, a reduction

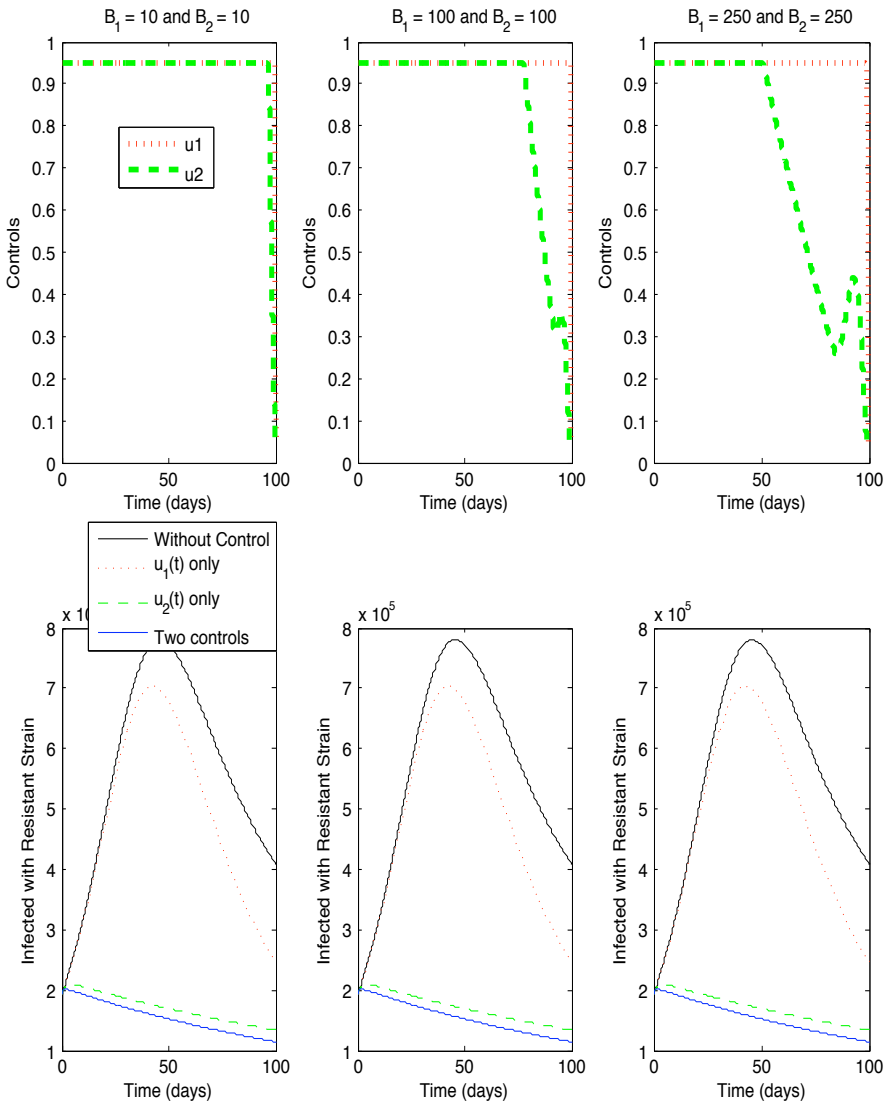

Figure 5.8: The daily number of resistant malaria cases are plotted for three different values scenarios of weight constants. The general curves of the control efforts are very similar with slight changes in the time when the reduction of effort associated with vaccination is reduced. The epidemiological curves illustrate a scenario where both strains coexist in the population and the sensitive strain dominates. $R_s = 1.7823$ and $R_r = 1.277$. We consider the case where the costs associated with vaccination and treatment are both the same but change in value.

in effort of the vaccination control is required towards the end of the epidemic. In Fig. 5.13, we explore the case where both of the weight factors are equal but they increase, $B_1 = B_2 = 10$, $B_1 = B_2 = 500$, $B_1 = B_2 = 1000$. In this case, full treatment efforts are required for the duration of the epidemic. However, if the weight factor associated

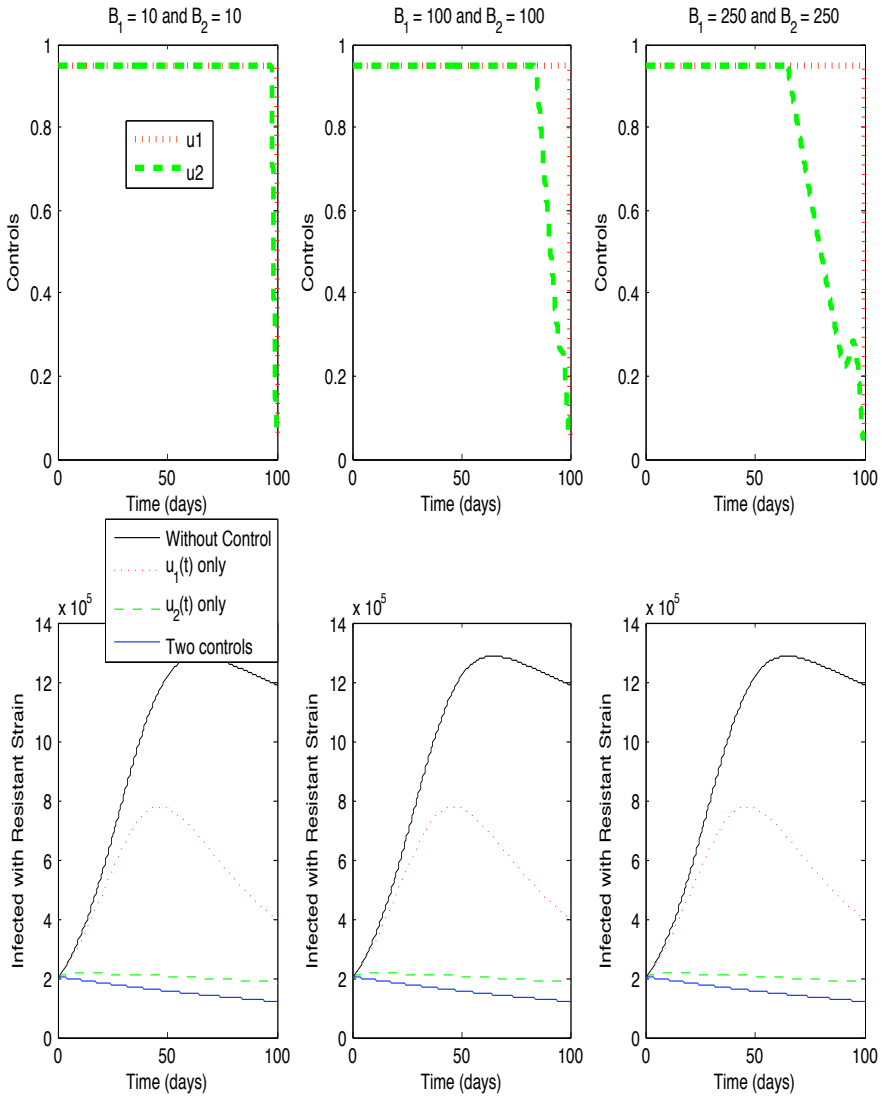

Figure 5.9: The daily number of resistant malaria cases are plotted for three different values scenarios of weight constants. The general curves of the control efforts are very similar with slight changes in the time when the reduction of effort associated with vaccination is reduced. The epidemiological curves illustrate a scenario where both strains coexist in the population and the resistant strain dominates. $R_s = 1.3981$ and $R_r = 1.6533$. We consider the case where the costs associated with vaccination and treatment are both the same but change in value.

with the vaccination efforts is low, (*i.e.* 10) then full vaccination effort is required through out the course of the epidemic. As the weight factor increases, the vaccination effort must be decreased before the end of the epidemic, depending on the value of the weight factor. Similar behavior is observed in Fig. 5.14 and Fig. 5.15 where the we

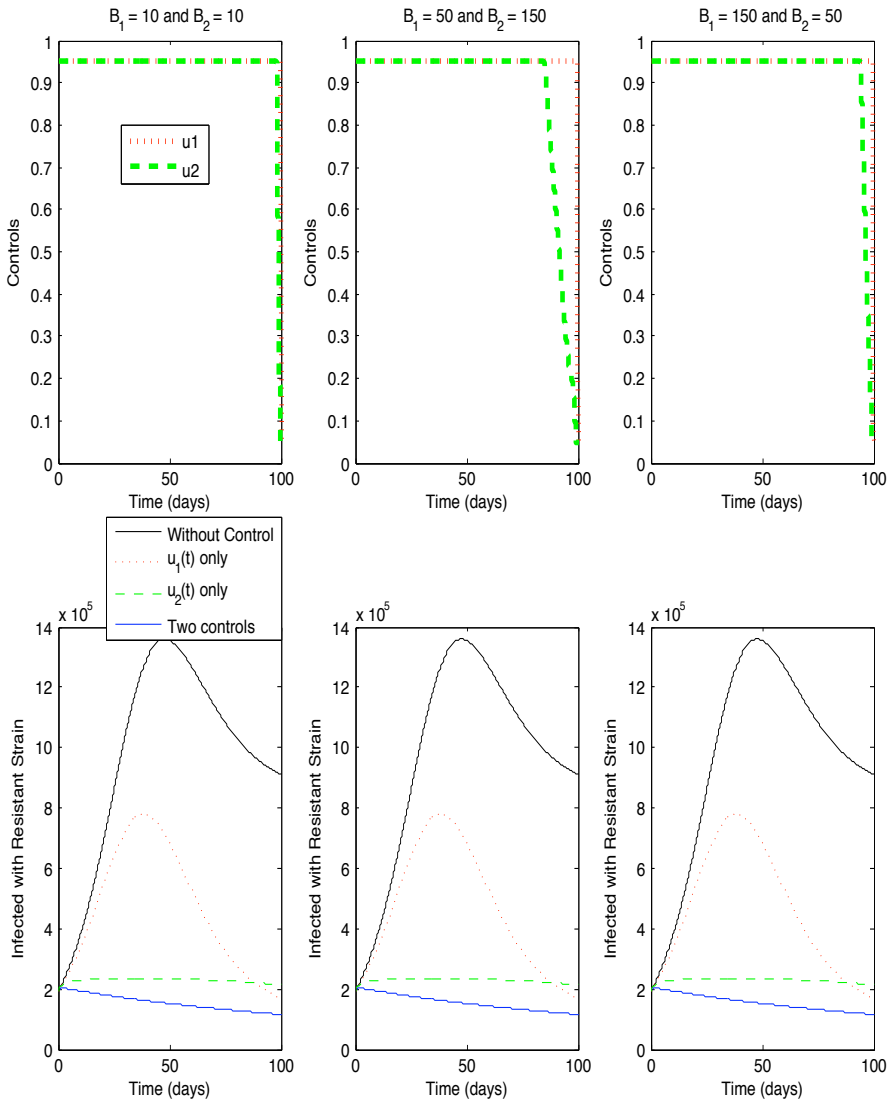

Figure 5.10: The daily number of resistant malaria cases are plotted for three different values scenarios of weight constants. The general curves of the control efforts are very similar with slight changes in the time when the reduction of effort associated with vaccination is reduced. The epidemiological curves illustrate a scenario where resistant strain out-competes the sensitive strain. Resistant out-compete: $R_s = 2.3068$ and $R_r = 4.7501$. We illustrate the scenario where the costs are not the same and differ by a factor of 3.

illustrate a scenario where the resistant strain outcompetes the sensitive strain and becomes endemic in the population. In this scenario, implementing both control at full effort for most of the length of the epidemic will yield in a significant reduction in the daily number of Malaria cases. In Fig. 5.16, we explore the case where both strains

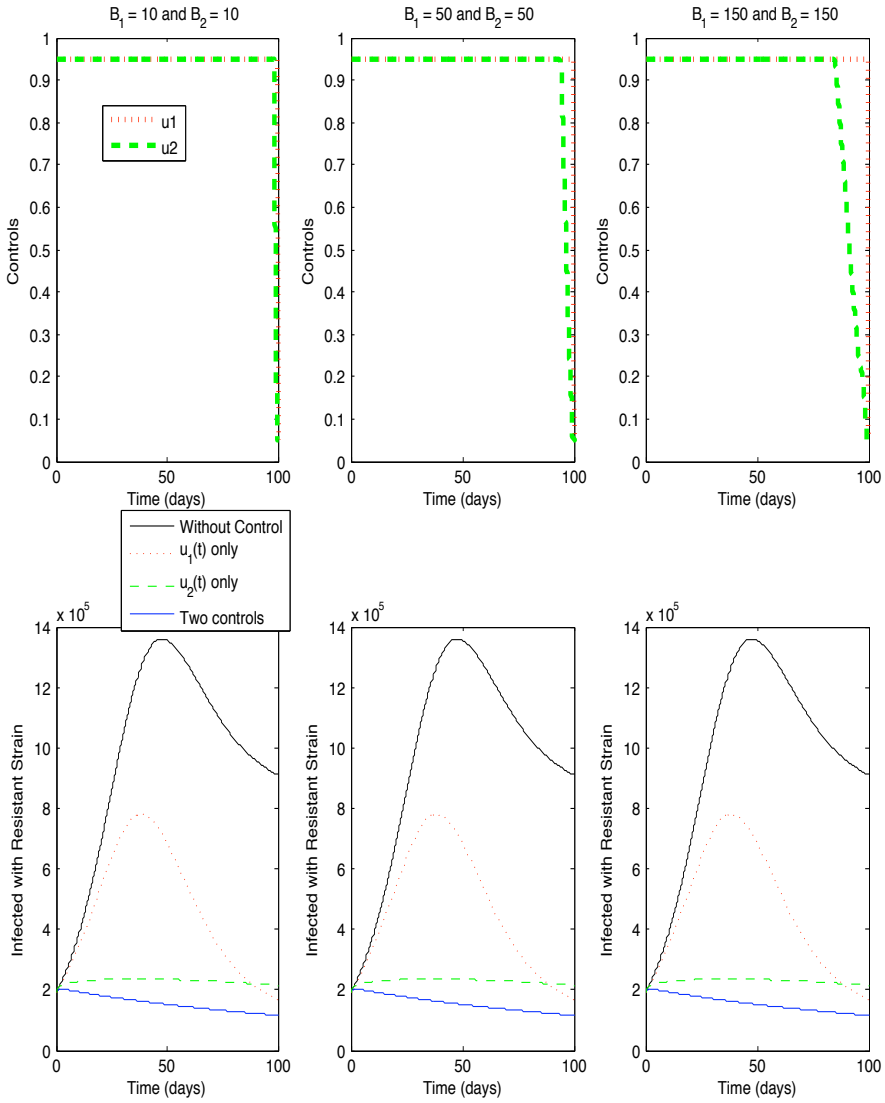

Figure 5.11: The daily number of resistant malaria cases are plotted for three different values scenarios of weight constants. The general curves of the control efforts are very similar with slight changes in the time when the reduction of effort associated with vaccination is reduced. The epidemiological curves illustrate a scenario where resistant strain out-competes the sensitive strain. Resistant out-compete: $R_s = 2.3068$ and $R_r = 4.7501$. We consider the case where the costs associated with vaccination and treatment are both the same but change in value.

are present in the population. In this scenario, full control effort for both vaccination and treatment is necessary in the case where $B_1 = B_2 = 10$ and where B_1 is 100 times bigger than B_2. However, in the case where B_2 is 100 times bigger than B_1, then full vaccination effort is only required for the first half of the epidemic, followed by a

steady drop in effort. That is due to the weight associated with the effort for vaccination.

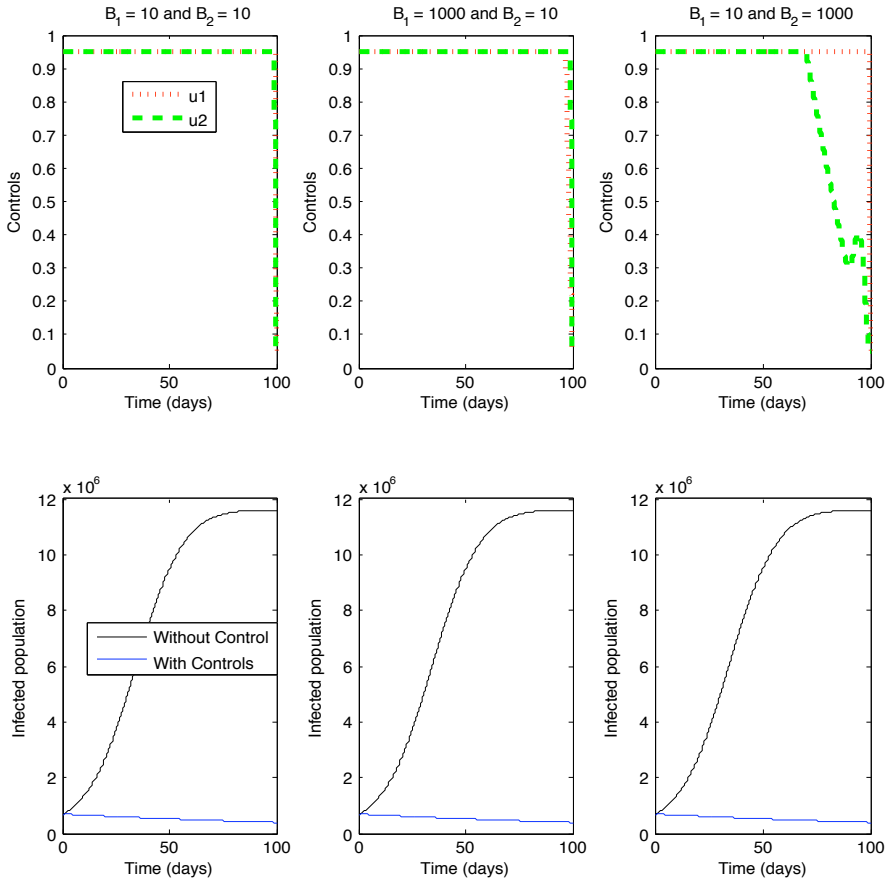

Figure 5.12: The daily number of malaria cases are plotted for three different values scenarios of weight constants. The general curves of the control efforts are very similar with slight changes in the time when the reduction of effort associated with vaccination is reduced. The epidemiological curves illustrate a scenario where sensitive strain outcompetes the resistant strain and is endemic in the population. We illustrate the scenario where the costs are not the same and differ by a factor of 100.

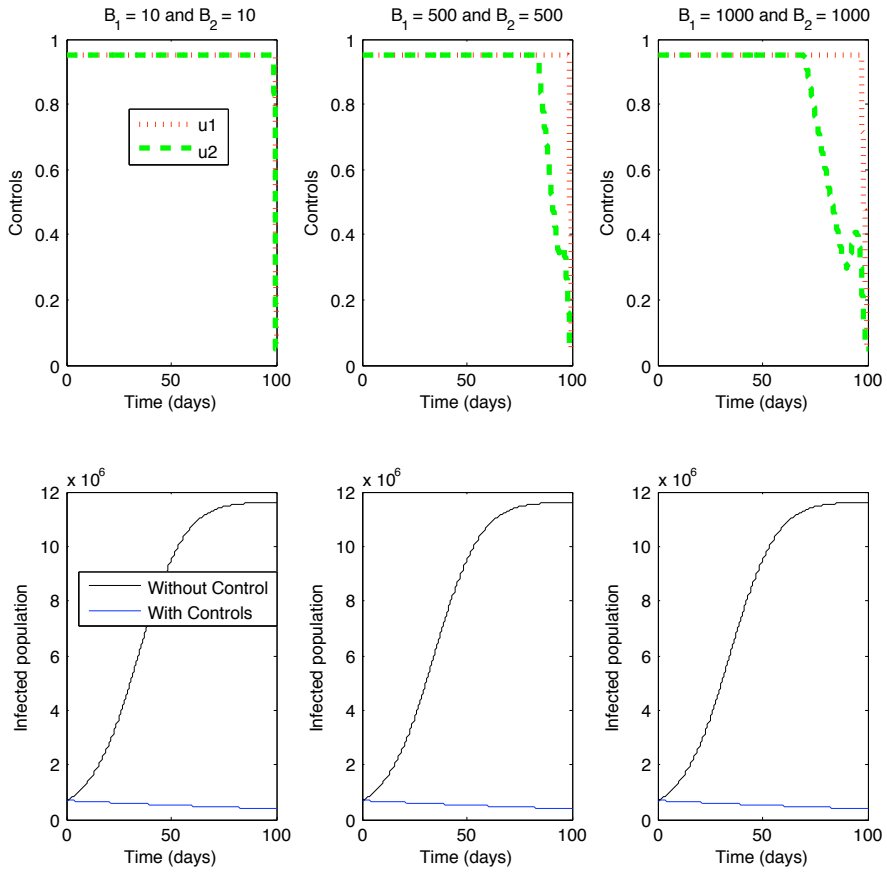

Figure 5.13: The daily number of malaria cases are plotted for three different values scenarios of weight constants. The general curves of the control efforts are very similar with slight changes in the time when the reduction of effort associated with vaccination is reduced. The epidemiological curves illustrate a scenario where sensitive strain is endemic in the population. We consider the case where the costs associated with vaccination and treatment are both the same but change in value.

5.4 Conclusions

Estimating the reproductive number, $\mathscr{R}_0$, is the first step in the process of assessing the potential impact of control interventions. However, optimal control theory is another tool that allows for a more detailed assessment of when and how much effort should be put each of the control measures in order to minimize a targeted objective. In the scenarios illustrated here, the best, most optimal strategy, is one that includes both control efforts, treatment and vaccination. Both of these efforts must be implemented

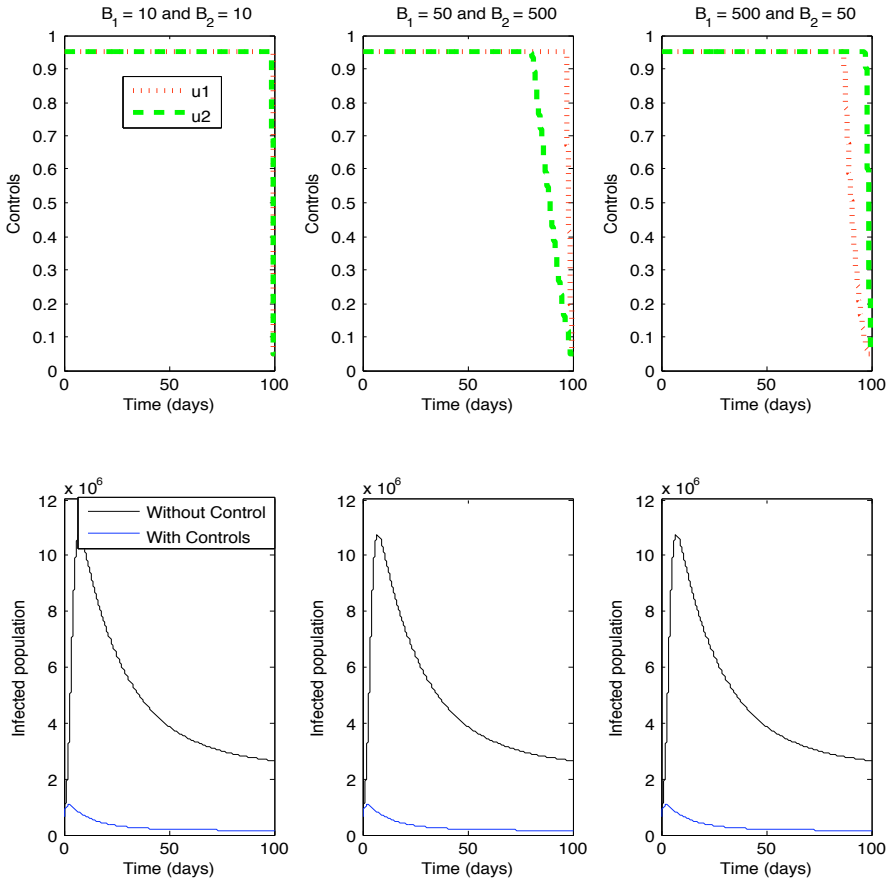

Figure 5.14: The daily number of malaria cases are plotted for three different values scenarios of weight constants. The general curves of the control efforts are very similar with slight changes in the time when the reduction of effort associated with vaccination is reduced. The epidemiological curves illustrate a scenario where resistant strain outcompetes the sensitive strain and is endemic in the population. We illustrate the scenario where the costs are not the same and differ by a factor of 10.

at full capacity at the onset of the epidemic, regardless of the weight factors associated with each. Treatment efforts must be fully implemented through out the course of the epidemic, regardless of the weight associated with the control and regardless whether resistant Malaria is endemic in the population, sensitive Malaria, or both of the strains are present in the population. However, full vaccination effort is not needed for the course entire course of the epidemic. The reduction in vaccination effort is sensitive to the weight effort associated with it.

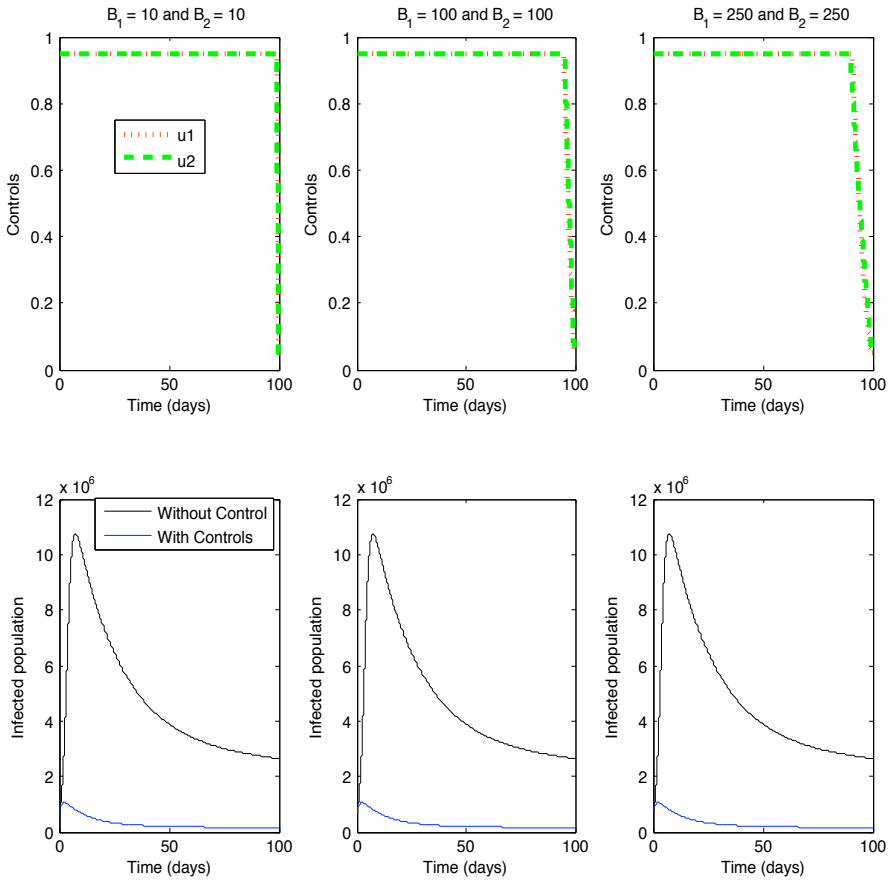

Figure 5.15: The daily number of malaria cases are plotted for three different values scenarios of weight constants. The general curves of the control efforts are very similar with slight changes in the time when the reduction of effort associated with vaccination is reduced. The epidemiological curves illustrate a scenario where resistant strain is endemic in the population. We consider the case where the costs associated with vaccination and treatment are both the same but change in value

Finally, our analysis assumes that control can be implemented very fast, which may somehow be unrealistic because in most situations, it will take a while before an active control program can be implemented, even on a small population, and even when preparations were made before introduction of the infection. Similarly, the assumption that we have limited resources, may be unrealistic. Hence putting constraints on the supply and running the optimal control may yield different results and is worth investigating further.

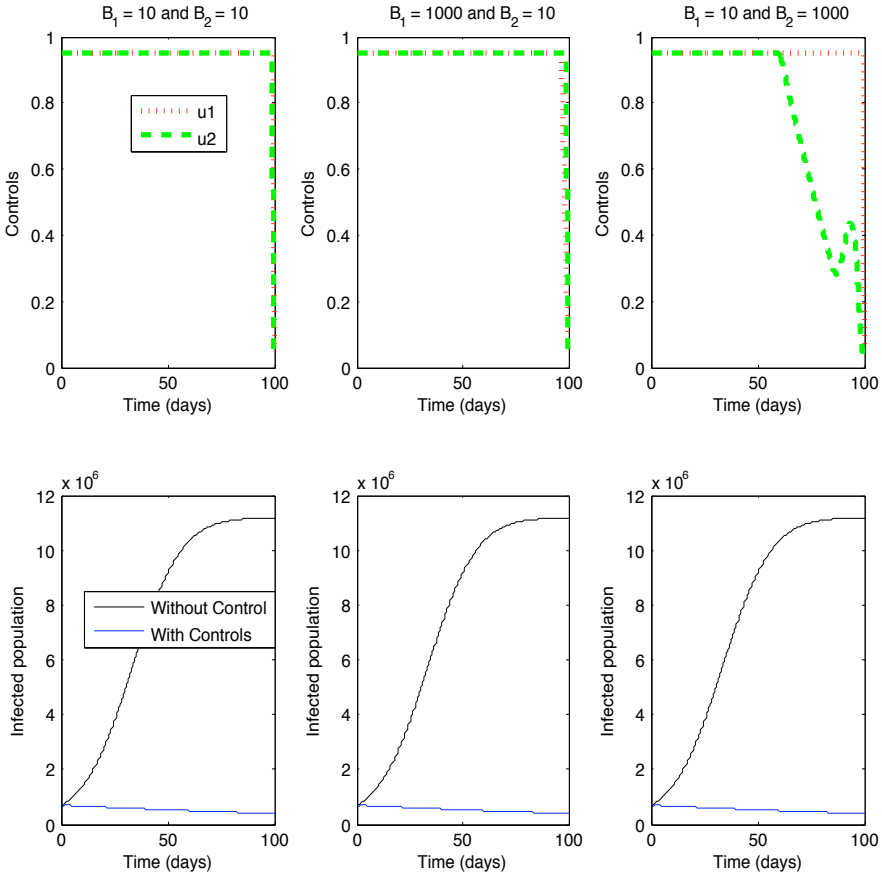

Figure 5.16: The daily number of malaria cases are plotted for three different values scenarios of weight constants. The general curves of the control efforts are very similar with slight changes in the time when the reduction of effort associated with vaccination is reduced. The epidemiological curves illustrate a scenario where both strains of Malaria are present in the population, coexistence. We illustrate the scenario where the costs are not the same and differ by a factor of 100.

Chapter 6

CONCLUSIONS

This study presents a simple deterministic model of the transmission dynamics of two strain, sensitive strain and drug-resistant strain, with superinfection. The model allows for the assessment of the role of super-infection on disease spread. The simple model is extended to incorporate a preventive measure (vaccination) and a control measure (treatment). Rigorous mathematical analyses are carried out to gain insights into qualitative dynamics of the three models.

The expressions for the reproduction numbers, R_s and R_r of the sensitive and drug-resistant strains, respectively, are given in the terms of the model parameters. The study shows that the spread of the disease can be effectively controlled in a population if $\mathscr{R}_0 = max(R_r, R_s)$ less than unity. If $\mathscr{R}_0 > 1$, the two strains can coexists when $R_s = R_r$ ¿1 holds. In this case, there is a continuum of coexistence equilibria and depending on the initial conditions (the initial number of state variables of the model), the infected populations will evolve to one of them. The model predicts competitive exclusion when $R_s \neq R_r$, where the strain with the higher reproduction number eventually displaces the other. The threshold determining which strain will dominate depends on the fitness of the resistant strain, and the infection period. For the models that include the intervention measure, the threshold also depends on the treatment rate, the vaccination rate and the vaccine induced immunity.

When resistance development due to transmission occurs, both strains coexist if $R_s > 1$ and $R_s > R_r$. In such a case, increasing the transmission rate of the sensitive strain induces an indirect impact on resistance development by increasing the number infected cases. Furthermore, resistance can emerge and persist without primary transmission of the resistant strain. On the other hand, if $R_r > 1$ and $R_r > R_s$, the resistant strain displaces the sensitive strain, and the prevalence of the resistance strain

is higher than that of the case when the two strains co-exists. When the rate of resistance development increases, the transmission rate of the sensitive strain decreases, and the likelihood of displacing this sensitive strain by the resistant strain increases. Numerical simulation indicate that when both strains coexist, the endemic value of the resistant strain decreases as the rate of resistance development increases, probably due to the fact that, in this case, transmission of the resistant strain depends mainly on the number of individuals infected with the sensitive strain, and the number decreases with increasing the rate of resistance development.

A model that incorporates both the preventive measure and the control measure (vaccination and treatment) is studied numerically using parameter values the disease transmission dynamics of Malaria in sub-Saharan Africa. It is shown numerically, that the best strategy for controlling the drug-resistant strain cases of Malaria, is to implement both measures simultaneously. In order to perform a more in depth analysis of the appropriate control strategies, we performed an optimal control analysis. We consider three scenarios, one where only treatment is administered, one where only vaccination is administered and the third that incorporates both vaccination and treament. We conclude, that the best, most optimal strategy, is one that includes both control efforts, treatment and vaccination. Both of these efforts must be implemented at full capacity at the onset of the epidemic, regardless of the weight factors associated with each.

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