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A SIMULATION MODEL OF
ANTIMALARIAL DRUG
RESISTANCE



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Abstract

Malaria ranks among the world's most important tropical parasitic diseases with world prevalence figures between 350 and 550 million clinical cases per annum. [WHO, 2008a] Treatment and prevention of malaria places a considerable burden on struggling economies where the disease is rampant. Research in malaria does not stop as the change in response to antimalarial drug treatment requires the development of new drugs and innovation in the use of old drugs. This thesis focused on building a model of the spread of resistance to Sulfadoxine/Pyrimethamine (SP) in a setting where both SP and SP in artemisinin-based combination therapy (ACT) are the first line therapies for malaria. The model itself is suitable to any low transmission setting where antimalarial drug resistance exists but the country of choice in this modeling exercise was Mozambique. The model was calibrated using parameters specific to the malaria situation in Mozambique. This model was intended to be used to aid decision making in countries where antimalarial drug resistance exists to help prevent resistance spreading to such an extent that drugs lose their usefulness in curing malaria.

The modeling technique of choice was differential equation modeling; a simulation technique that falls under the System Dynamics banner in the Operations Research armamentarium. It is a technique that allowed the modeling of stocks and flows that represent different stages or groupings in the disease process and the rate of movement between these stages respectively. The base model that was built allowed infected individuals to become infectious, to be treated with SP or ACT and to be sensitive to or fail treatment. Individuals were allowed a period of temporary immunity where they would not be reinfected until the residual SP had been eliminated from their bloodstream. The base model was then further developed to include the pharmacokinetic properties of SP where individuals were allowed to be reinfected with certain strains of infection given the level of residual drug in their bloodstream after their current infection had been cleared.

The models used in this thesis were built with idea of expanding on previous models and using available data to improve parameter estimates. The model at its core is similar to the resistance model used in Koella and Antia [2003] where differential equation modeling was used to monitor a population as it became infected with a sensitive or resistant infection and then

recovered. The inclusion in the model of the PK component was derived from Prudhomme-O'Meara et al. [2006] where individuals could be reinfected depending on the residual drug in their bloodstream. Rather than modeling simply sensitive and resistant infections, mutations categories were used as was the case in Watkins et al. [2005] population genetics model. The use of mutation categories allowed one to use parameters specific to these categories rather than the sensitive/resistant stratification and this is particularly relevant in Mozambique where all mutation categories still exhibit some degree of sensitivity to treatment i.e. total resistance has not yet developed for any particular mutation category. The last adaptation of the model was to use gametocyte information directly to determine human infectiousness rather than through using a gametocyte switching rate (constant multiplier used to convert parasite density to gametocyte density) as was done in Pongtavornpinyo [2006].

The models developed in this thesis found that the existing vector control and drug policy in Mozambique had the major effect of decreasing total prevalence of malaria by approximately 70% in the 11 year period. The distribution of Res3 (presence of DHFR triple) and Res5 (presence of DHFR triple and DHPS double) infections changed over the 11 year period with Res3 infections initially increasing and then decreasing while Res5 infections started low and increased to overtake Res3 infections. The timing of the change in this composition of infection corresponds with the introduction of ACT and thus it appears that the use of ACT prompted the increased prevalence of quintuple parasites over DHFR triple and sensitive parasites. The total number of failures decreased substantially after the introduction of ACT to 17% of its previous level. The results of the base model corresponded with the observed data from the SEACAT study in terms of the magnitude and the trends of the impact of the change to ACT policy, but underestimated the impact of the vector control strategies compared to rapid effect noted in Sharp et al. [2007]. The Scenario testing of the base model showed that vector control is an effective strategy to reduce prevalence and that it is sensitive to the time at which the control is started as it decreased prevalence very gradually. The Scenario testing of the base model also showed that the introduction of ACT in Mozambique had a greater impact on reducing prevalence and that the start time of the ACT strategy did not decrease the effect on prevalence though earlier start times decreased the total number of resistance cases. The ratio of Res5 to Res3 infections increased faster when ACT was the treatment policy than

when SP was the policy. Thus higher values of this ratio are associated with ACT being the treatment strategy in place. Thus differential equation modeling is an effective modeling tool to capture the spread of disease and to test the effects of policy interventions as it allows one to assess these effects on populations and averages out individual-level intricacies to better inform policy decisions.

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Nomenclature

ACPR	Adequate Clinical and Parasitological Response
ACT	Artemisinin-based Combination Therapy
AMFM	Affordable Medicines Facility for Malaria
BSE	Bovine Spongiform Encephalopathy
CDA	Chlorproguanil-Dapsone-Artesunate
CIA	Central Intelligence Agency
DDT	Dichloro-Diphenyl-Trichloroethane
DHFR	Dihydrofolate Reductase
DHPS	Dihydropteroate Synthase
EIR	Entomological Inoculation Rate
ETF	Early Treatment Failure
IPT	Intermittent Preventive Treatment
IRS	Indoor Residual Spraying
ITN	Insecticide Treated Nets
LSDI	Lubombo Spatial Development Initiative
LTF	Late Treatment Failure
MMV	Medicines of Malaria Vision
MVI	Malaria Vaccination Initiative

OR	Operations Research
ORSSA	Operations Research Society of South Africa
PoC	Period of Chemoprophylaxis
RBM	Roll Back Malaria
SDS	System Dynamics Society
SEACAT	South East African Combination Antimalarial Therapy
SIS	Susceptible-Infected-Susceptible
SP	Sulfadoxine Pyrimethamine
UTL	Useful Therapeutic Life
WHO	World Health Organisation

Chapter 1

Operations Research in Development

1.1 Introduction

Malaria ranks among the world's most important tropical parasitic diseases with world prevalence figures between 350 and 550 million clinical cases per annum. [WHO, 2008a] Treatment and prevention of malaria places a considerable burden on struggling economies where the disease is rampant. Malaria is a disease that warrants research and understanding from epidemiological, economic, social and political perspectives. Studies have been conducted that look into the effects of drug use, mosquito control, parasite development and the economic burden of malaria. Research in malaria does not stop as the change in response to antimalarial drug treatment requires the development of new drugs and innovation in the use of old drugs.

This thesis focuses on building a model of the spread of resistance to Sulfadoxine/Pyrimethamine (SP) in a setting where both SP and SP in artemisinin-based combination therapy (ACT) are the first line therapies for malaria. The model looks at the spread (and not the emergence) of resistance taking into account the pharmacokinetic properties of the drugs in question as well as selection properties of the SP-resistant strain of infection. The model itself is suitable to any low transmission setting where antimalarial drug resistance exists but the country of choice in this modeling exercise is Mozambique. The model will be run using parameters specific to the malaria situation in Mozambique and the model outputs will be compared with data from Mozambique. This model is intended to be used to

aid decision making in countries where antimalarial drug resistance exists to help prevent resistance spreading to such an extent that drugs lose their usefulness in curing malaria.

The modeling methodology used and the purpose for which this model is created fall under the umbrella of System dynamics in the Operations Research armamentarium. As such, it is necessary to understand the nature of Operations Research to better understand the usefulness of the model.

1.2 Operations Research in Development

This section serves to provide a brief description of Operations Research and its contribution to the Health sector. Particular focus will be given to the area of Systems Dynamics and its contribution to Health and disease modeling.

1.2.1 Overview

Operations Research has its origins with Lord Blackett in World War II, arising through the need to solve important real complex problems. [Fildes, 2000] The best definition of Operations Research is perhaps a description of its many and varied tools and methodologies. Operations Research is a multi-disciplinary approach to problem-solving and decision-making in issues concerning world welfare like government, business, society, nature etc. It's tools and ideologies may be applied to problems big and small, important and less so. [ORSSA, 2008] Operations Research also takes a systemic view of problems by focusing on the bigger or overall problem thus attempting to include all aspects of a situation. Ultimately the objective of Operations Research is to understand the current situation, outline a possible better situation and enforce the change required to achieve it.

One of the major classifications within the field of Operations Research is that of Hard and Soft OR. The definition of the terms Hard and Soft within OR profession is not set in stone. In his paper 'A systems map of the Universe' in the early seventies, Peter Checkland described ". . . 'Hard' systems (to be) . . . characterised by easy to define objectives, clearly defined decision-taking procedures and quantitative measures of performance. At the other extreme are the 'soft' systems in which objectives are hard to define, decision-taking is uncertain, measures of performance are at best

qualitative and human behaviour is irrational.” [Checkland, 1972, pg 113] Checkland’s statement refers to a hard-soft divide in both the realms of application and the tools used by OR practitioners.[Taket and White, 1993]

Operations Research in Development is the application of Operations Research tools and ideologies to problems typical of the developing world. It is not a separate arm of OR but rather a focus on the application of OR tools in the social, political and economic milieu of developing countries. OR practitioners in developing countries often face problems with lack of data, lack of resources, lack of trained and experienced personnel etc and as result find it difficult to take pre-packaged solutions from industrialised countries and implement them in developing countries. Though practitioners of Operations Research in Development are constrained to work within these limits, the ideology of OR still allows one to understand problems systemically and systematically and use suitable qualitative and quantitative tools to bring improvement to otherwise unsolvable problems.

1.2.2 Operations Research in Development: Applications in Health

The contributions of Operations Research since its inception have been wide and far-reaching. Of particular concern here is the contribution of Operations Research in Development to problems in the Health sector.

In the last half century OR studies have been conducted in numerous areas of health including analysing queuing systems in clinics, simulation modeling of diseases, hospital systems, healthcare management and strategic planning. The OR tools and methodologies that have been used include hard techniques like discrete event simulation used to model disease [Caro, 2005], queuing theory in modeling patient flow [Hall, 2006], system dynamics in disease modeling [Flessa, 1999], and soft OR techniques like cognitive mapping in health provision planning [Blackham and Corless, 1992] and Ulrich’s critical heuristics in the use of patient involvement to improve mental health services. [Davies and Bensley, 2005] In particular the use of Systems Dynamics in disease modelling has made important contributions towards better understanding the epidemiology of diseases. Examples include the analysis of the HIV/Aids epidemic, bovine spongiform encephalopathy (BSE) in cattle and new variant Creutzfeldt-Jakob Disease in humans. [Dangerfield, 1999]

It is necessary to provide a more detailed overview of Systems Dynamics as it is the OR tool to be used in this thesis.

1.2.3 System Dynamics

System Dynamics is a methodology for understanding and managing complex systems. [SDS, 2008] It is based on the concept of everything is connected to everything else. The idea is to work with the big picture. System Dynamics involves developing computer simulation models to compare model behaviour with observed system behaviour. The value of System Dynamics is that the simulation model may be used to test the effects of different policies to enable better understanding of the ramifications policies will have should they be implemented. The structure of a system is characterised by feedback loops, stocks and flows and other non-linearities like boundary conditions. [Sterman, 2000] Movements between these stocks and flows are modeled through the use of difference or differential equations. This technique will be described in more detail in Chapter 3.

Mathematical models of diseases were initially forced to be non-complex owing to a lack of computing power. But now that computing power is easily available there is opportunity for complex models of stocks and flows through the use of Systems Dynamics. As Bailey [1977] said “ One extremely promising tool in the OR armamentarium is the approach implied by the term ‘system dynamics’ (and therefore malaria models based on system dynamics) could be of prime practical importance for the control of malaria..” [Bailey, 1977, pg 193] Thus System Dynamics is the tool and ideology of choice for the attempt presented in this thesis at modeling the malaria disease.

1.3 Overview

What follows is a literature review where characteristics of the malaria disease and disease modeling are presented as well as an overview of differential equation and other methodologies of malaria modeling. An overview of antimalarial policy interventions is also presented in Chapter 2. Chapter 3 presents a causal loop diagram of malaria transmission and control as well as an overview of System Dynamics. The model to be simulated is then discussed and built in Chapter 4; the results and model extensions are presented in Chapter 5. Scenario Testing of the policy interventions as well as

the discussion of these results within the framework provided in Chapter 3 are detailed in Chapter 6. This is followed by a discussion of the results and concluding remarks.

Chapter 2

Literature Review

2.1 Characteristics of Malaria

This section provides an overview of the malaria disease, discussing the burden the disease places on the world as well as the dynamics and epidemiological aspects of malaria.

2.1.1 Overview of Malaria

According to the World Health Organisation [WHO, 2008a], malaria ranks among the world's most important tropical parasitic diseases with world prevalence figures between 350 and 550 million clinical cases per annum. After AIDS and Tuberculosis, malaria kills more people than any other communicable disease. The estimated death toll is over 1.1 million people annually with the majority of deaths occurring in children under the age of five. [WHO, 2008a] Approximately 40% of the world's population is exposed to the malaria parasite with the majority of cases and deaths occurring in Africa. However as Figure 2.1 shows, other parts of world like Asia, Latin America, the Middle East and parts of Europe are also exposed to risk of malaria. [WHO, 2008b]

In 1998 the World Health Organisation in partnership with the United Nations Children's Fund, the United Nations Development Programme and the World Bank launched the Roll Back Malaria (RBM) Partnership. Through its partners, the RBM works to scale up country-level efforts at controlling malaria, providing a coordinated effort to ensure the optimal use of resources. [Partnership, 2008] Roll Back Malaria's vision is to uphold and work towards Target 8 in Goal 6 of the Millenium Development Goals i.e.

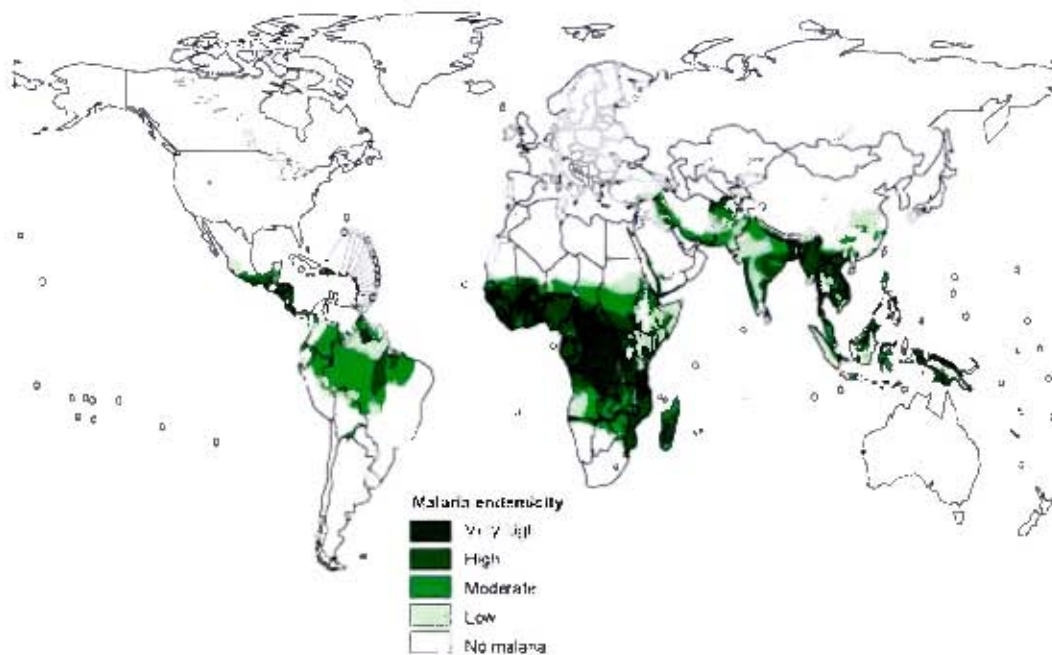


Figure 2.1: Global distribution of malaria transmission risk (2003) [WHO, 2005]

“...(to have) halted by 2015 and begun to reverse the incidence of malaria and other major diseases.” [WHO, 2008c]

2.1.2 Epidemiology of Malaria

Malaria, classified as an infectious disease is caused by a parasite belonging to the genus *Plasmodium*. There are many species of *Plasmodium*, four of which account for almost all human infections viz. *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. The majority of the infections in Africa can be attributed to *Plasmodium falciparum*; responsible for the most severe morbidity and mortality. [Greenwood et al., 2005] It is spread to humans through bites from the *Anopheles* mosquito. Figure 2.2 provides a detailed picture of the parasite’s development in the human body. The *Plasmodium* parasite requires both the human and the mosquito during its life cycle. A mosquito infected with the *Plasmodium* parasite injects cells called sporozoites into the human being through a bite. These sporozoites enter the human bloodstream and pass into the liver where they undergo asexual reproduction and

form merozoites. These merozoites enter the bloodstream and infect the red blood cells. Some merozoites rupture to form new merozoites and others develop sexual cells called male and female gametocytes. It is at this point that the human becomes infectious to mosquitoes. If a mosquito is to bite a human at this stage, gametocytes may pass into the mosquito and should they survive the incubation period in the mosquito, they will develop sporozoites and the transmission process continues. [Malaria Background Information]

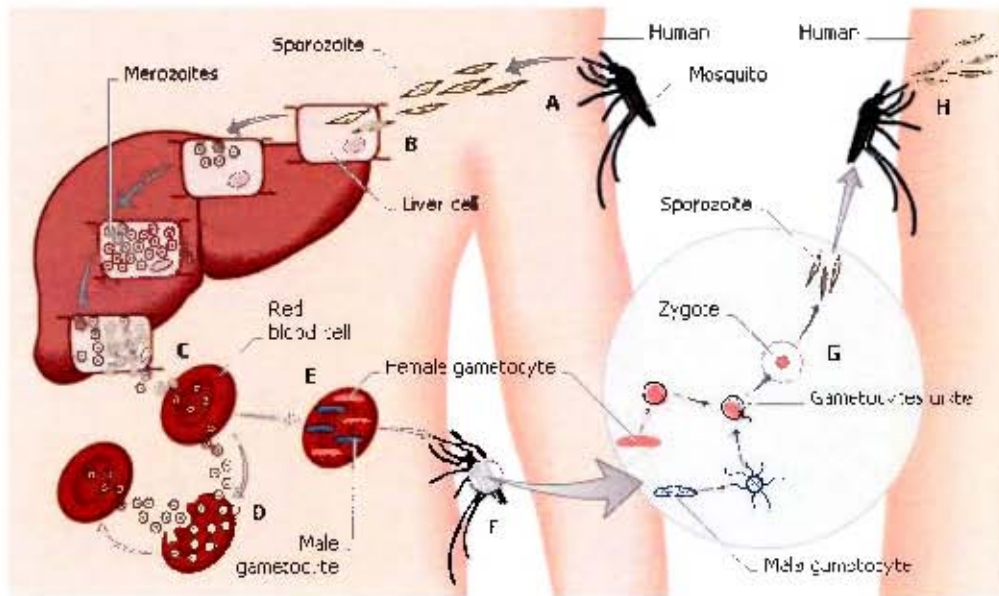


Figure 2.2: The Life Cycle of the Malaria Parasite (@msn.encarta.com)

2.1.3 The Development of Resistance

Antimalarial drugs are one of the main tools used to not only cure individual episodes of malaria but in doing so also decrease malaria transmission. However, effective treatment of malaria has been hampered by the development of resistance to drugs in use. This is discussed in more detail in Section 2.2. Resistance to antimalarial drugs emerges as a result of spontaneous gene amplification or mutations which affect the parasites receptiveness to the drug. In some cases, a single mutation may result in complete resistance to a drug (E.g. atovaquone) but generally a sequential accumulation of mutations is necessary to confer increasing levels of resistance. Mutations while

characterizing the emergence of resistance, do not guarantee its spread as there is no survival advantage to resistant mutations if the drug for which resistance has emerged is not in use. If the drug is in use, sensitive parasites will be inhibited by the drug and resistant mutants will be able to multiply resulting in the spread of resistance. [Yeung et al., 2004]

Parasites can be categorized into three stages: Res0 – the original wild-type parasite that is fully sensitive to the drug in use, Res1 – parasites that are less sensitive to the drug and though they are cleared at therapeutic levels of the drug, they may still persist at higher residual levels than the sensitive parasites. Res2 parasites display full resistance to the drug in use and cannot be cleared even at therapeutic levels of the drug. [Hastings et al., 2002]

Drug elimination half lives (the time taken for the drug concentration to decrease by half) also play a role in the development of resistance. The period of chemoprophylaxis (PoC) is the time in which residual drug levels in the bloodstream protect the host against re-infection. Drugs with long elimination half-lives, while advantageous for recovery of anaemia and in prevention of future episodes, also allow for the drug to remain in the hosts bloodstream at sub-therapeutic levels providing opportunity for the development of resistance. Research suggests that drugs with long elimination half-lives result in longer PoCs and hence increase the rate at which resistance evolves. [Hastings et al., 2002]

2.1.4 Immunity

Important to policy-makers is the body's own fighting mechanism of immunity to the malaria parasite. People living in areas of high transmission may develop immunity to malaria through increased exposure to malaria parasites. In the case of children, they are exposed to parasites early in life and exhibit relatively more severe symptoms than adults up till the age of five. As immunity develops however, symptoms become less severe and the number of parasites in the blood stream declines. This immunity results in the development of mechanisms in the human body that clear parasites and/or inhibit their replication. This immunity is acquired through increased exposure to the same strain of malaria. Should the immune person move to another area, this immunity will gradually be lost. [Cross, 2004]

Clinical immunity can be described as a decrease in the frequency and severity of clinical symptoms in hosts and this results in a decrease in the need for antimalarial drugs. Klein et al. [2008] cites studies that show that individuals who develop clinical immunity are less likely to display clinical symptoms and to infect mosquitoes due to a reduction in asexual parasites and gametocytes. However acquiring immunity does not mean that individuals are less likely to be infected.

2.1.5 R_0 - The Basic Reproductive Number

The degree of successful transmission of all infectious diseases can be measured by the Basic Reproductive Number. In the case of malaria, the life cycle of a malaria infection with its host and vector characteristics is captured by the basic reproductive number R_0 which describes the number of secondary malaria cases that result through the introduction of a single case in an uninfected population in the absence of treatment. [Macdonald, 1957, Anderson and May, 1980] It is used as a measure of transmission intensity. A basic form of the R_0 follows.

$$R_0 = \frac{ma^2b_1b_2e^{-\mu\tau}}{r\mu} \quad (2.1)$$

This form of R_0 applies for a basic model of transmission where humans are bitten by mosquitoes randomly, there is no acquired immunity and the host and vector populations are homogenous. R_0 as a measure of transmission can be understood intuitively through its parameters. Transmission is aided by a high density of mosquitoes (number of mosquitoes per human, m) that frequently bite (at a rate of a bites per day) highly susceptible humans (with the rate of acquiring infection, b_2) who become highly infectious (at a rate b_1). Transmission is hampered by a quicker host recovery time (r days) and mosquitoes with shorter lifespans (at a force of mortality of μ). Given that transmission requires two mosquito bites (one to pick up gametocytes and the other to inject sporozoites) the biting frequency is squared and $e^{-\mu\tau}$ represents the probability of survival of the mosquito for the duration of the parasite incubation period. [Koella, 1992] There needs to be at least one secondary case of malaria in order for infection to spread in the population i.e. $R_0 \geq 1$.

R_0 needs to be adapted for different transmission models of malaria. Hence different R_0 expressions will exist for resistant and sensitive strains of malaria relative to the basic R_0 expression. A reduction in the fitness of

a resistant parasite relative to that of a sensitive parasite can be defined as the cost of resistance. [Koella, 1998] This cost of resistance may be expressed in terms of any of the defining parameters in the R_0 expression. The competition between resistant and sensitive parasites will depend on (among other things) whether the R_0 expression for sensitive parasites is greater than that of resistant parasites as well as the proportion of the infected population that receives treatment.

Another measure of transmission is the EIR or entomological inoculation rate. It measures the number of infectious bites per person per day. As such it is calculated as the product of number of mosquito bites per hum (ma) and the proportion of mosquitoes infected with sporozoite-stage malaria parasites (s).

$$EIR = m \times a \times s \quad (2.2)$$

2.2 History of Antimalarial Interventions

The three main areas of policy intervention are the use of antimalarial drugs, vector control and vaccine development. Quinine has been used for treatment of malaria from as early as 1632 with primaquine and quinacrine emerging after the First World War. [Baird et al., 1996] Chloroquine became the antimalarial drug of choice in the 1940's with resistance emerging some 10-15 years later at independent focal points in the world. In Africa it was only in the late 1980's that countries began changing their national treatment policies from chloroquine to Sulfadoxine/Pyrimethamine (SP). [Talisuna et al., 2004] However, the long half life of SP has reduced its useful therapeutic life due to a higher probability of the selection of resistant strains of infection. [D'Alessandro and Buttiëns, 2001] Resistance to SP is widespread in Asia, South America and is spreading in Africa. As resistance develops to affordable drugs like chloroquine and SP, they are replaced with more costly drugs which is unsuitable to African health budgets where drugs constitute 90% of the malaria budget. Artemisinin-based drugs are currently the only drugs that remain effective. To protect these against the emergence of resistance, they should be administered in combination with other drugs. There is increasing acceptance that combining two or more drugs (preferably with an artemisinin derivative) will hamper resistance to individual constituent drugs. [Yeung et al., 2004] Such combinations are called artemisinin-based combination therapy (ACT). The downside of ACT is that it is relatively expensive and can be problematic to implement in terms of drug rollout and

patient adherence. There is growing discussion around the idea of introducing multiple first line ACT's in countries to delay and decrease the spread of drug resistance. Whether such strategies are affordable and implementable in resource-constrained African countries remains to be seen.

Vector Control has become the most generally effective measure of malaria control with the objective of reducing malaria morbidity and mortality through a reduction in malaria transmission. [WHO, 2006] This has occurred largely through the use of dichloro-diphenyl-trichloroethane (DDT) in indoor residual spraying but also through other avenues like the use of Insecticide treated nets. In Southern Africa indoor residual spraying has been used to great effect with marked reductions being seen in South Africa, Swaziland, Zimbabwe and southern Mozambique. In some cases certain species of vectors have been reduced to negligible levels.[Mabaso et al., 2004] Careful monitoring of the use of indoor residual spraying and insecticide treated nets is essential in order to detect the development of resistance to insecticides used. Trials of insecticide treated nets have shown a reduction in child mortality and episodes of malaria though problems with implementation exist in the need for re-treatment, the cost of nets and user-adherence. [Greenwood et al., 2005]

Vaccine development against falciparum and vivax malaria has progressed rapidly in recent years. The epidemiology of malaria through its various parasite stages and the ability of hosts to have simultaneous infections of different strains are some of the challenges facing vaccine developers. [MVI, 2008] Vaccines may be developed to counter different stages of a parasite's development in the host such as sporozoite development, gametocyte development etc. The development of transmission-blocking vaccines against Plasmodium falciparum and Plasmodium vivax are well on their way and phase I trials are taking place though it may be at least ten years before vaccines are available for widespread use. [Greenwood et al., 2005]

2.3 Antimalarial Treatment Strategies Conference: South Africa 2008

The Antimalarial Treatment Strategies Conference was held in Mpumalanga, South Africa in April 2008. Dr Francesca Little and I attended this five day gathering of representatives from all areas of malaria management including policy makers, members of international bodies like WHO and MMV, those

working in drug development, and disease modelers from around the world. The conference was a platform to discuss experiences of implemented drug treatment strategies, the proposal of new drug treatment strategies including the use of multiple first line treatments, and the multiple issues surrounding antimalarial drug development and rollout. These discussions were key to informing the contents of the System Dynamics model presented later. It was an excellent opportunity to meet experts involved in global malaria management and a privilege to attend.

2.4 Modeling Approaches to Malaria

This section serves to highlight different approaches to modelling malaria. There are two standard approaches to modelling resistance in malaria. The first and perhaps most popular is the epidemiological approach i.e. using differential equation models of stocks and flows tracking the host and/or the vector. These compartment models have been used to describe the epidemiological patterns of malaria like the relationship between high transmission and the development of immunity. [Koella and Antia, 2003] The second approach is a genetic modelling approach where the evolution of drug resistance is modelled directly through the parasite genotype.

Four models are presented here; three epidemiological models and one genetic-based model.

2.4.1 The Koella and Antia Model of Resistance

The models presented in Koella and Antia [2003] paper are based on extensions of the classical Macdonald-Ross model. Koella and Antia present an epidemiological model which focuses on malaria transmission and allows for differences in transmission between parasites infected with the sensitive and resistant strain of the disease. They present a number of models beginning with a basic SIR (Susceptible-Infected-Immune/Recovered), extending the basic model to include the spread of resistance and two further models incorporating super-infection and the spatial variability in treatment rates. The model of resistance is the focal point presented in Figure 2.3 where f represents the proportion of individuals who receive treatment. In Figure 2.3, sensitive infections are categorised as treated and untreated whereas resistant infections are not. This is because if one is infected with a drug-resistant parasite, it does not matter whether the individual is treated or not as they will fail treatment regardless.

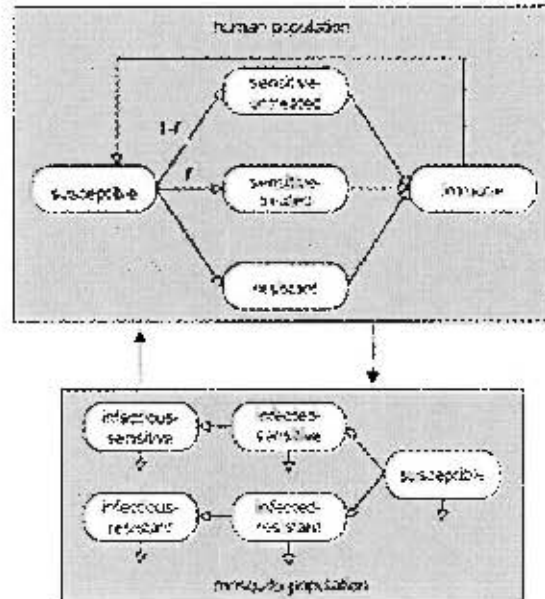


Figure 2.3: Malaria Dynamics in Koella and Antia [Koella and Antia, 2003]

Host and Vector Modeling

Here susceptible humans upon being infected are separated into categories depending on strain of the infection and whether one is treated or not. Individuals are then moved to the Immune stock at rates depending on their recovery time. In time, this immunity may be lost which returns individuals to the susceptible category.

The assumption underlying the spread of resistance is that there are only two strains of parasites viz. resistant and sensitive ones that exist in competition. Hence there is no focus on the degree of resistance that parasites have developed. In terms of immunity, the model takes into account acquired immunity and allows for immunity to depend on exposure to parasites. Figure 2.3 can be modelled through differential equations.

As described in Figure 2.3, there are two sets of dynamics that require modelling viz. the host population (humans) and the vector or mosquito population. The vector population is separated into compartments depend-

ing on the strains of infection they carry as well as the development of the parasite in the mosquito (infected or infectious). Movement between these groups may also be modelled through differential equations.

However, given that mosquito dynamics occur on a faster time scale than host dynamics, it can be assumed that the mosquito population is at equilibrium with respect to changes in the human population. [Koella and Antia, 2003] Thus the vector dynamics can be incorporated into the model through the basic transmission/inoculation rate h . In the model for the spread of resistance, this inoculation rate is different for parasites carrying the resistant and sensitive strains of malaria.

$$h_S = mb_S a^2 e^{-\mu\tau} \frac{y_S}{\mu + a(b_S y_S + b_R y_R)} \quad (2.3)$$

$$h_R = mb_R a^2 e^{-\mu\tau} \frac{y_R}{\mu + a(b_S y_S + b_R y_R)} \quad (2.4)$$

where m , a , μ and τ are as defined previously, y_S and y_R represent the proportion of drug-sensitive and drug-resistant infections respectively, and b_S and b_R are the probability of a bite leading to a drug-sensitive and drug-resistant infection respectively.

Use of the Koella and Antia Model

One of the main limitations of this model is how it deals with resistance in that it does not incorporate the different levels of resistance. Resistant parasites can be further categorised into partially and fully resistant parasites or by the accumulation of mutations of the relevant enzymes. By incorporating these categories one is able to extend the recovery process of the model by allowing for susceptibility to infection by different parasites depending on the residual drug level in the blood system. Further, one is able to track more effectively the differences in the spread of partially and fully resistant parasites. Thus to better understand the dynamics of resistance, it is necessary to model resistance in a more complex manner.

However, this model will be used as the base from which a more complex model will be built. More importantly, the form of the transmission rate or inoculation rate h will be used in the final model with adaptations for additional aspects to be included in the final model.

Similar to the Koella and Antia Model is an epidemiological model by Flessa [1999] that is framed in the System Dynamics terminology. The models presented in his paper simulate both the host and vector populations with the ultimate aim of setting up a series of models on which different policy interventions can be tested before implementation. As result the model incorporates various climatic conditions like precipitation and temperature, human migration and larvæ development. It also models human infectiousness; albeit indirectly rather than through gametocyte density. Given its goal of decision support, the model is focused on two small geographical regions of differing ecological and malarial conditions. This model differs little in structure from Koella and Antia [2003] save the explicit modeling of the Anopheles population which is assumed to be at equilibrium in Koella and Antia [2003]. Figure 2.4 depicts the model used in Flessa [1999].

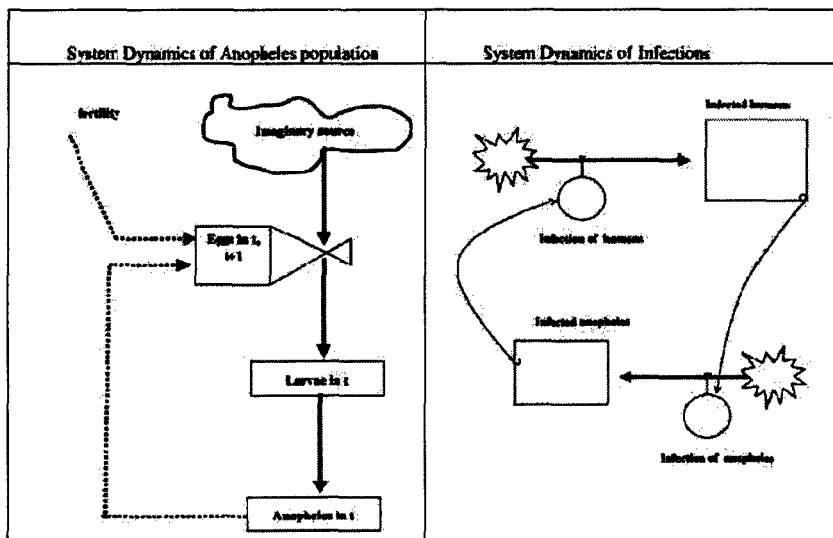


Figure 2.4: Malaria Dynamics in Flessa [1999]

The chief difference in this diagram compared to that of Koella and Antia [2003] is that stocks and flows are shown explicitly where as in Koella and Antia [2003] only the stocks are shown. Difference equations are used to represent changes in the stocks. As can be seen the vector population and the malaria infections are modeled as separate systems but are linked through the inoculation rate.

2.4.2 The Prudhomme O'Meara et al Model

The Prudhomme O'Meara et al model is an epidemiological model that focuses on assessing the spread of drug resistant malaria through the use of Intermittent Preventive Treatment (IPT). [Prudhomme-O'Meara et al., 2006] IPT can be described as the treatment of individuals with antimalarial drugs at regular time intervals with no consideration for the individual's infection status. Unlike the Koella and Antia model this model includes the pharmacokinetic properties of drugs in the bloodstream. By monitoring levels of drug elimination in the blood stream, the model takes into account one's susceptibility to parasites with varying degrees of resistance. Hence resistance is modelled at a higher level of complexity than was the case in Koella and Antia [2003].

The Human Dosing model

The Prudomme O'Meara et al human dosing model is presented in Figure 2.5.

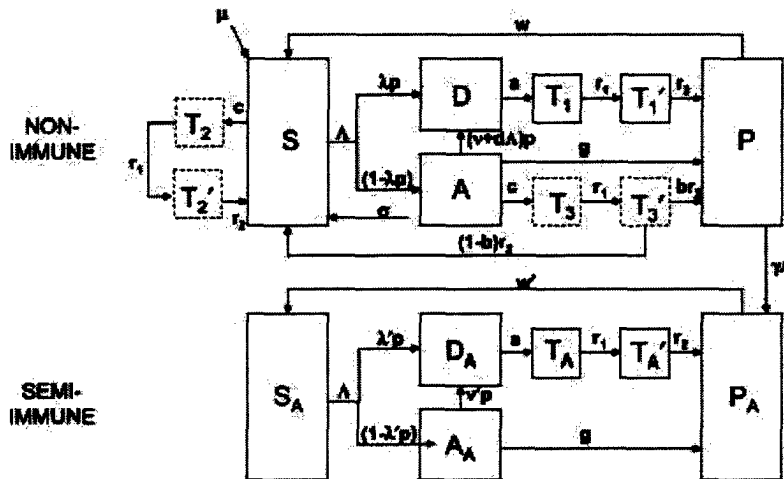


Figure 2.5: Malaria Dynamics in Prudhomme O'Meara et al [Prudhomme-O'Meara et al., 2006]

The human population is categorised into Non-immune and Semi-Immune. At birth, individuals are declared non-immune and after experiencing a se-

ries of infections and treatments and temporary immunity thereafter move into the semi-immune class of individuals. While the model focuses on IPT and immunity, of particular interest is the way in which drug levels are modeled. Upon being infected, treated individuals wait an average of 5 days between the onset of symptoms and the clearance of infection; a move illustrated by $D \rightarrow T_1$. Over a period of 15 days, the drug level in the individual's bloodstream decreases to level permissive to partially resistant parasites ($T_1 \rightarrow T'_1$) and over a further period of 37 days, the drug is fully eliminated from the individual's bloodstream and after a period of temporary immunity, the individual is once again susceptible to both sensitive and partially or fully resistant infections. ($T'_1 \rightarrow P \rightarrow S$)

Use of the Prudhomme O'Meara et al Model

The model handles the development of resistance and its interaction with immunity extensively. However, a key assumption is that resistant and sensitive parasites have the same Entomological inoculation rate (EIR). This assumption has not been shown to be robust as studies have been conducted that relate drug resistance to increased gametocyte production and possibly transmission. [Buckling et al., 1999, Puta and Manyando, 1997] Increased gametocyte production would in theory increase the infectiousness of humans to mosquitoes which could lead to an increased rate of transmission from mosquito to human. Hence the use of different EIR's for resistant and sensitive infections is another avenue of complexity to be modelled in this thesis.

Though the Prudhomme O'Meara et al model focussed mainly on IPT and immunity, the portrayal of the pharmacokinetic properties of the drug in use will be included in the final model of this thesis as an innovative way to model resistance and reinfection.

2.4.3 Wirichada Pongtavornpinyo's PhD Thesis

The main model presented by Pongtavornpinyo is an epidemiological model that seeks to include all the major aspects of malaria. Its comprehensive structure may be useful as a tool to predict the effect of treatment interventions and vector controls. [Pongtavornpinyo, 2006]

The Main Model

The structure and major inputs to the model are depicted in Figure 2.6.

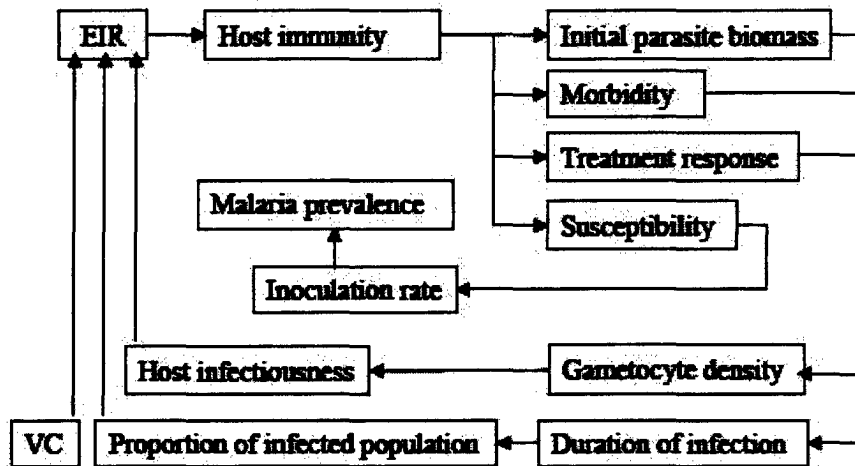


Figure 2.6: Malaria Dynamics in Pongtavornpinyo's main model [Pongtavornpinyo, 2006]

Figure 2.6 shows how the EIR is informed in the model through host, vector, parasite and drug characteristics. Host immunity impacts on initial parasite biomass, morbidity (manifestation of clinical symptoms), treatment response (cured, failure etc) and host susceptibility. Infections are characterised as drug-sensitive or drug-resistant. The degree of immunity and the treatment response impact on the duration of infection and the number of parasites is directly proportional to the number of gametocytes produced in each infection. Gametocyte density impacts directly on host infectiousness and duration of infections impacts directly on the proportion of infected population. Both of these aspects directly affect and update the EIR value in the model. Host susceptibility also impacts the inoculation rate which updates malaria prevalence figures. Vector characteristics captured through Vectorial Capacity (VC) also update the EIR.

Use of the Pongtavornpinyo Model

There are two major aspects in this complex model that are of relevance to this thesis. Firstly the number of gametocytes are calculated indirectly through a switch rate rendering them proportional to the number of asexual parasites. Gametocyte data is now available in some studies for Mozambique

which allows one to model gametocyte density directly. This new data will be used in this thesis. Secondly, resistance is assessed indirectly through clinical outcomes like early and late treatment failures etc. The next model provides a method to model resistance directly.

2.4.4 The Watkins et al Model

The paper by Watkins et al. [2005] describes an approach that aims to model the effect on the resistance selection processes of combinations of antifolate antimalarial drugs with artesunate and amodiaquine under various user-specific conditions. [Watkins et al., 2005] An output of the model is the estimated Useful Therapeutic Life (UTL) for combinations of drugs that have been modelled. This model differs from other models of resistance in that it is not an epidemiological model. Rather it is a population genetics model that models the genotypes and their mutations directly rather than through clinical outcomes.

The Model

The paper uses Sulfadoxine Pyrimethamine (SP) as a mono-therapy as the base case. Sulfadoxine inhibits dihydropteroate synthase (DHPS) while Pyrimethamine inhibits the dihydrofolate reductase (DHFR) enzyme. A sequential accumulation of mutations of the DHFR domain with mutations in the DHPS domain result in the development of resistance. The Watkins et al model considers only the mutations of the DHFR enzyme. The period of chemoprophylaxis (PoC) is the period in which the genotype cannot re-infect the host. This PoC is used to model the sequential accumulation of DHFR mutations. A host who has been treated with SP alone has a PoC of 52 days. The PoC values may differ for combinations of SP with other drugs like artesunate and amodiaquine.

The spread of antifolate resistance is modelled through a series of equations describing the fitness of the genotypes. These equations take account of the treatment proportion (x), the number of secondary infections (k), the proportion of hosts that were not treated in the PoC, the ability of the mutation to survive the SP treatment at therapeutic levels etc. These equations then allow the frequency of the DHFR mutations to be tracked over time thus modelling the evolution of resistance. The UTL as described above is a forecasted output of this model.

These equations can be used to model other combinations of antimalarial drugs as was done in the case of Chlorproguanil-dapsone (*LapdapTM*) and *LapdapTM*-artesunate combination (CDA).

The main conclusions from the Watkins et al study were that combination therapy should be deployed before any of the constituent drugs have been used as a mono-therapy in order to prolong its useful therapeutic life, short periods of mono-therapy of individual drugs can seriously shorten the UTL of their combination therapy and trying to rescue an already failing drug by combining it with a new drug is ultimately a fruitless exercise.

Use of the Watkins et al Model

One criticism of this model is the use of the DHFR enzyme only to detect resistance. More accurate measures of the emergence of resistance in patients can be made if both the DHFR and DHPS enzymes are used. Where data exists for both enzymes, it should be used to better understand the development of resistance. A very positive aspect of this model is the incorporation of the drug-specific period of chemoprophylaxis which allows one to model one's susceptibility to resistant infections directly for any drug or combination of drugs. Both the above aspects (the use of DHFR and DHPS enzymes as well as the period of chemoprophylaxis) of this population genetics model will be included in the models in this thesis as they allow one to model resistance directly rather than through clinical outcomes.

2.5 Conclusion

Both genetic based models and epidemiological models have their advantages and disadvantages. Epidemiological models can help establish patterns between aspects like transmission and immunity. They can also be used to assess the impact on transmission of various policy interventions like the effect of vector controls and change of drug policy. They can be used to model resistance as Koella and Antia have done. [Koella and Antia, 2003] However they ignore the population genetics aspect of resistance in malaria. Population genetics models on the other hand allow for more complex modelling of resistance but tend to ignore the epidemiological processes of malaria. Depending on the purpose of the model and the availability of information, one may choose the more suitable modelling approach.

Perhaps what is needed is a marriage of standard epidemiological models and population genetics models, as host and vector dynamics as well as the

genetic intricacies of resistance will be taken into account. [Koella and Antia, 2003] The model used in this thesis seeks to do this.

Chapter 3

A Systemic View of Malaria

This chapter seeks to present the different aspects of the malaria disease in a System Dynamics framework in order to facilitate an understanding of the interactions between role-players and forces at work.

3.1 System Behaviour and Causal Loop Diagrams

System Dynamics is the study of the behaviour of systems. In order to present the different aspects of malaria in the System Dynamics framework, an understanding of system structure is necessary. The behaviour of a system is characterised by its structure through feedback loops, stocks and flows and other non-linearities like boundary conditions. [Sterman, 2000] Most types of behaviour may be described by interactions between positive feedback and negative feedback. Positive feedback is behaviour in which the system responds to a change in the same direction as the change. It is thus an amplification of a change that has occurred in the system. Negative feedback is the opposite of positive feedback in that the system responds to a change in the opposite direction as the change. Thus it has a balancing effect on the system. Positive and negative feedback do not describe the desirability of the change (positive being good and negative being bad) but rather the direction of the impact of a change on the system.

Behaviour patterns include growth (exponential growth through positive or self-reinforcing feedback and S-shaped growth through both positive and negative feedbacks) and oscillation (behaviour in which the system constantly overshoots and undershoots the goal through time delays in the negative feedback process).

A causal loop diagram is a map that represents the structure of a system. It provides a view of all variable interactions and behaviour relevant to a system. Arrows in the diagram indicate the direction of causal influences. If two variables X and Y are connected by an arrow with a + sign, it can be interpreted as 'an increase in X will lead to an increase in Y'. Likewise if two variables are connected by an arrow with a - sign, it can be interpreted as 'an increase in X will lead to a decrease in Y'.

Before the causal map of malaria is presented it is necessary to first determine the key areas of control in malaria as shown in Figure 3.1. These key areas of control will be later unpacked in the causal map of malaria.

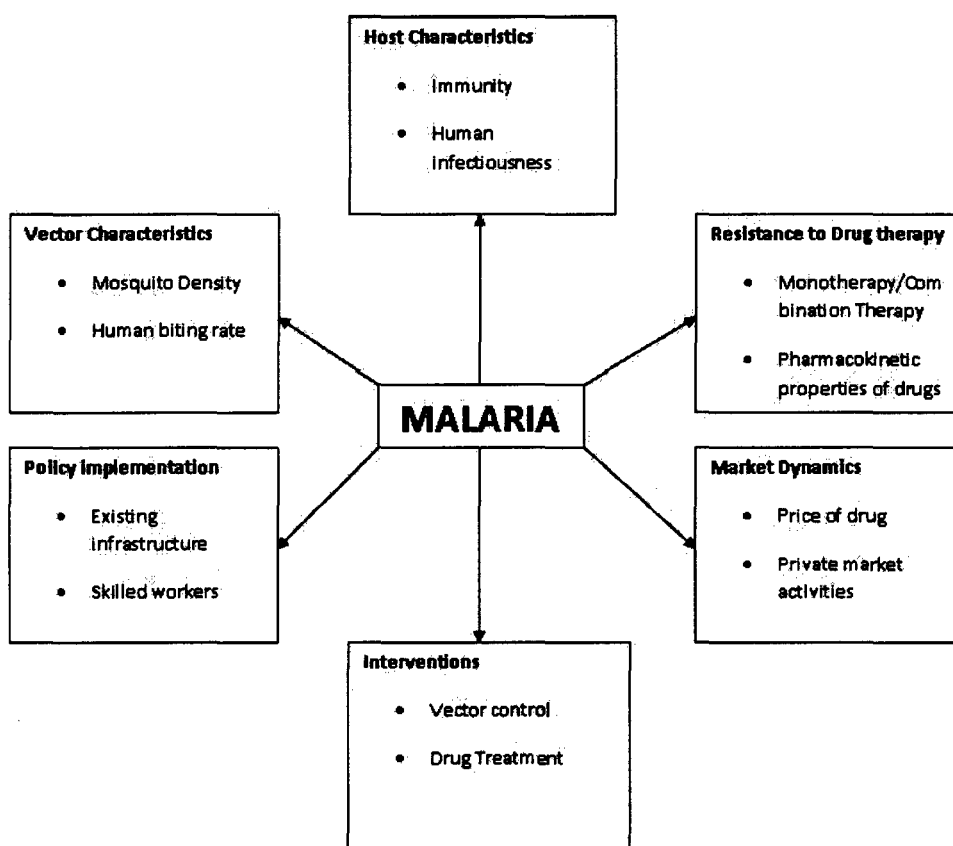
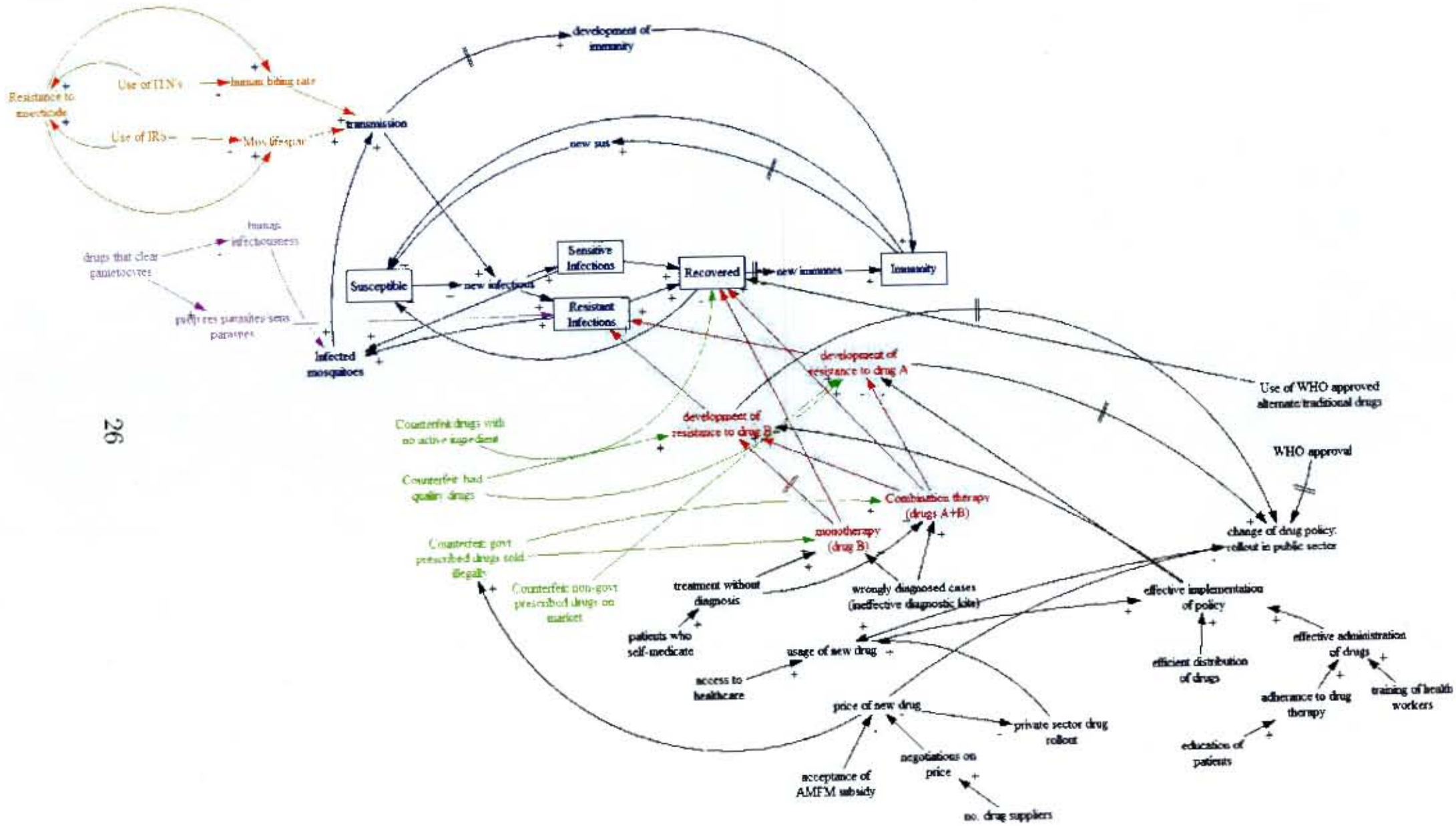


Figure 3.1: Key Areas of Control in Malaria

Moving clockwise from the left, there is the vector or mosquito compo-

Figure 3.2: A causal map of malaria transmission and control



be applicable to low transmission areas where individuals do not have the 'opportunity' to develop immunity.[Aron, 1988] The diagram also shows that

- An increase in the number of new infections leads with a time delay (reflected as two vertical lines in the arrow) to an increase in the development of immunity to positively impact the number of new immunes.
- Thus individuals may (through a series of previous infections) develop immunity.
- An increase in the number of immunes will lead to a decrease in the number of susceptibles.

This presents the first balancing effect that more infections through the development of immunity lead to fewer susceptibles. However, this immunity can also be lost though with a time delay resulting in another positive feedback loop increasing the susceptible pool once again.

The inclusion of mosquitoes in the transmission mechanism of malaria is vital and is hence included in the causal loop diagram.

- The more infections (resistant and sensitive) there are, the more humans there are to become infectious and infect mosquitoes.
- The greater the number of infected mosquitoes, the greater the number of infectious mosquitoes and this leads to an increase in the sensitive and resistant transmission or inoculation rates of malaria.

This is another positive feedback loop summarising the cycle of more infected humans leads to more infected mosquitoes who will go on to infect more humans. This transmission aspect of the model accounts for the interaction between mosquitoes, transmission rates and humans to assess the course of malaria if no intervention takes place. The only factor to deter the rapid spread of malaria is the development of immunity which itself takes time and previous infections and can be lost. Hence, some form of intervention is necessary to hinder the spread of disease.

3.2.2 Vector Control

The impact of vector control is depicted in orange and is presented in Figure 3.4.

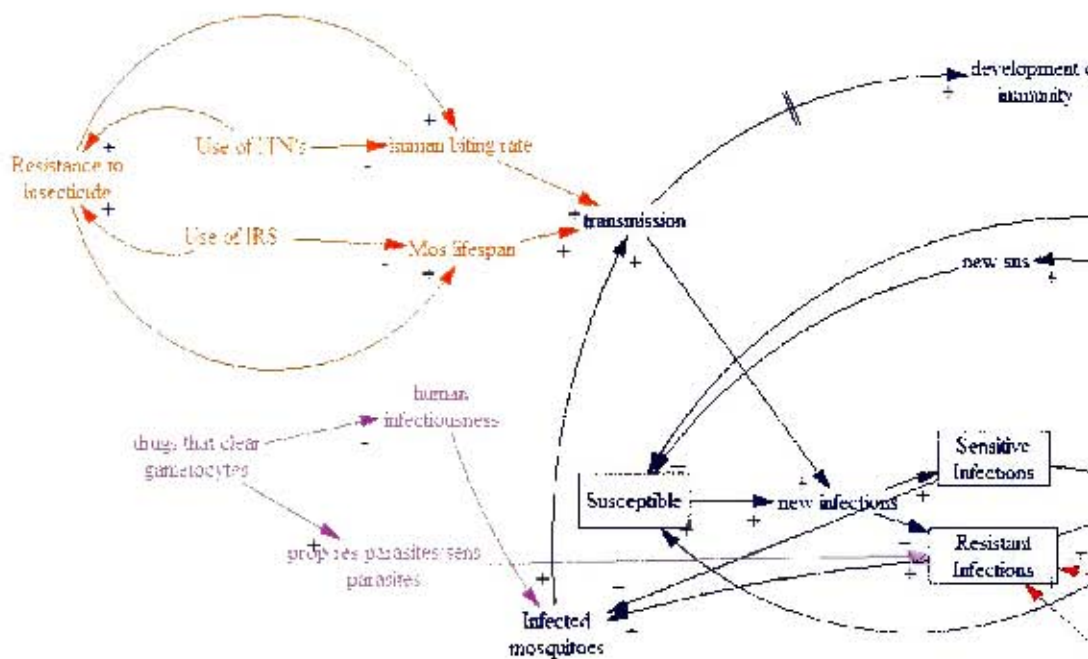


Figure 3.4: Causal Map: Vector Control and Eradication of malaria vs Eradication of resistance

One of the policies that have been used to great effect in many countries is that of vector control. Here, two major techniques are used to impact the transmission between mosquito and human viz. indoor residual spraying (IRS) and the deployment of insecticide treated bed-nets (ITN).

- An increase in the number of houses that are sprayed will lead to a shorter lifespan of mosquitoes
- This will lead to a decrease in the transmission rates of both sensitive and resistant infections.
- However, increased usage of spraying may lead to the development of resistance to the sprays which reverses the impact on the biting rate.

With regards to insecticide treated bed-nets

- An increase in the number of bed-nets will lead to a decrease in the number of bites on a human per annum.
- This will in turn decrease the resistant and sensitive transmission rates.
- Increased usage of ITNs may lead to the development of resistance to the insecticide which may reverse the impact on average mosquito lifespan.

The effect on the development of immunity is most noticeable here. A decrease in the number of bites which reduces transmission also leads in time to a decrease in the development of immunity and hence will decrease the pool of immune individuals. Only a simulation model will be able to determine which effect is stronger in the long run.

3.2.3 Eradication of malaria versus Eradication of Resistance

From Figure 3.4 one can see that

- An increase in the use of gametocyte-clearing antimalarial drugs would lead to a decrease in human infectiousness which would lead to a decrease in the number of infected mosquitoes.
- Through the transmission mechanism, fewer infected mosquitoes would lead to fewer infected humans and through time this could (in combination with vector control perhaps) lead to the eradication of malaria.
- However rolling out drugs that clear gametocytes would lead to an increase in the ratio of resistant parasites to sensitive parasites which would lead to increase in resistance. This is due to the preferential selection of resistant parasites over sensitive ones.

Hence in order to eliminate resistance, it is necessary to have parasites that are still sensitive to antimalarial drugs.

3.2.4 Antimalarial Drug Treatment

The impact of antimalarial drug treatment is depicted in red and is presented in Figure 3.5. It assumes two drugs with different half-lives where B is the existing mono-therapy and A is the new partner drug.

In the case of monotherapy with drug B,

- An increase in the proportion of monotherapy leads to an increase in the number of recoveries by initially curing infections.

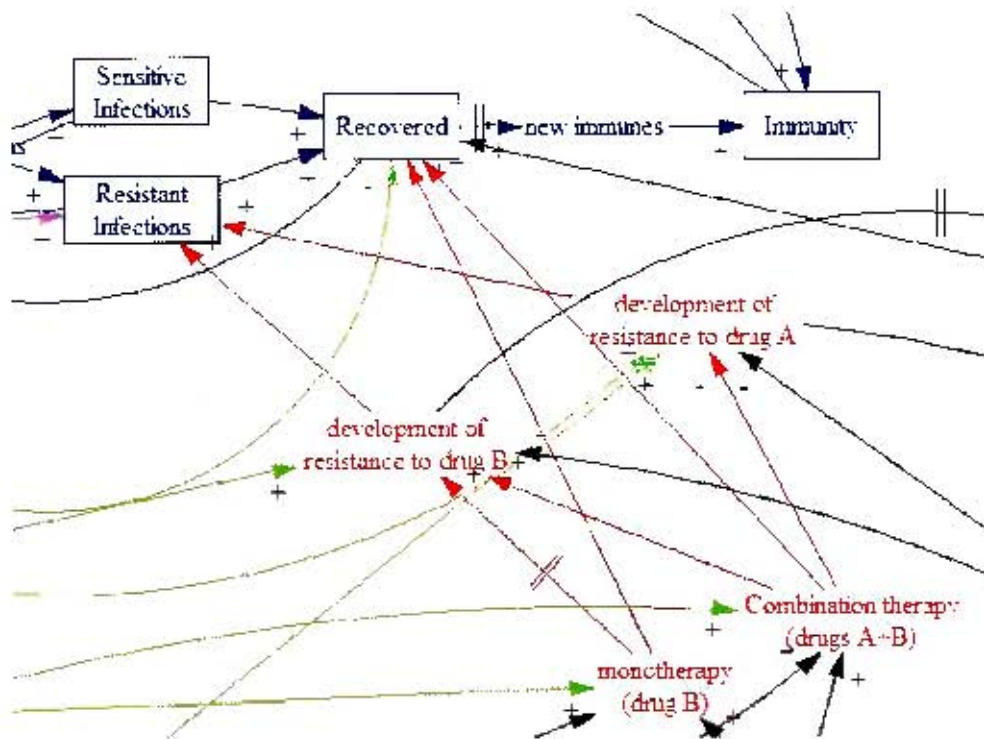


Figure 3.5: Causal Map: Antimalarial Drug Treatment

- However, in time it also leads to an increase in the development of resistance to drug B which leads to an increase in the number of resistant infections.

In the case of combination therapy with drugs A (new) and B (drug used for monotherapy), it must first be recognised that these drugs have different half lives. Once the drug with the shorter half life has been eliminated from the human's bloodstream the remaining drug is left unprotected until it too is eliminated from the bloodstream. In the scenario illustrated in Figure 3.5, the new drug A is assumed to have a shorter half life than the old drug B.

- An increase in the proportion of combination therapy used also leads to an increase in the number of recoveries by curing infections.
- It also leads to a decrease in the development of resistance to drug A since drug B protects drug A, and this in turn leads to a decrease in the number of resistant infections.

self-medicate, a drug that has no active ingredient and a drug that is allowed to be distributed but is of poor quality.

- If the correct drug is sold illegally to patients who self-medicate, it first increases drug treatment pressure.
- This may lead to an increase in the development of resistance to the drug as the patient is taking the drug like an intermittent preventive treatment rather than as a result of a diagnosis of malaria.
- Further an increase in the price of the desired drug may also lead to an increase in the number of drugs sold illegally owing to individuals not being able to afford the drugs at the market price.

Another type of counterfeit drug is drugs that are different to the government prescribed drugs. These drugs could be artemisinin-based administered as a mono-therapy. These drugs could be sold illegally on the black market (purchases of drugs from other countries who have changed treatment policies) or legally through the private sector. They have just been labelled as counterfeit because they are not government-prescribed.

- An increase of these drugs on the market may well lead to an increase in the development of resistance to the protected drug in combination therapy (drug A).

If a drug is given that has no active ingredient, then it does not cure the patient and the patient will need to go back to the medical facility and receive alternate medication. Hence an increase in the availability of this drug may lead to a decrease in the number of recoveries. This type of counterfeit drug does not impact resistance as there is no active ingredient in the patient's bloodstream. On the other hand, bad quality drugs are disastrous for controlling resistance as the drug may not be strong enough to clear sensitive parasites but stays in the bloodstream at sub-therapeutic levels for a longer period than a standard quality drug. Thus counterfeit drugs of this type will lead to an increase in the development of resistance of both drugs A and B if combination therapy is used (drug B is not strong enough to protect drug A) or just drug B if mono-therapy is used.

3.2.6 Policy and Policy Implementation

The impact of policy and policy implementation is depicted in black and is presented in Figure 3.7.

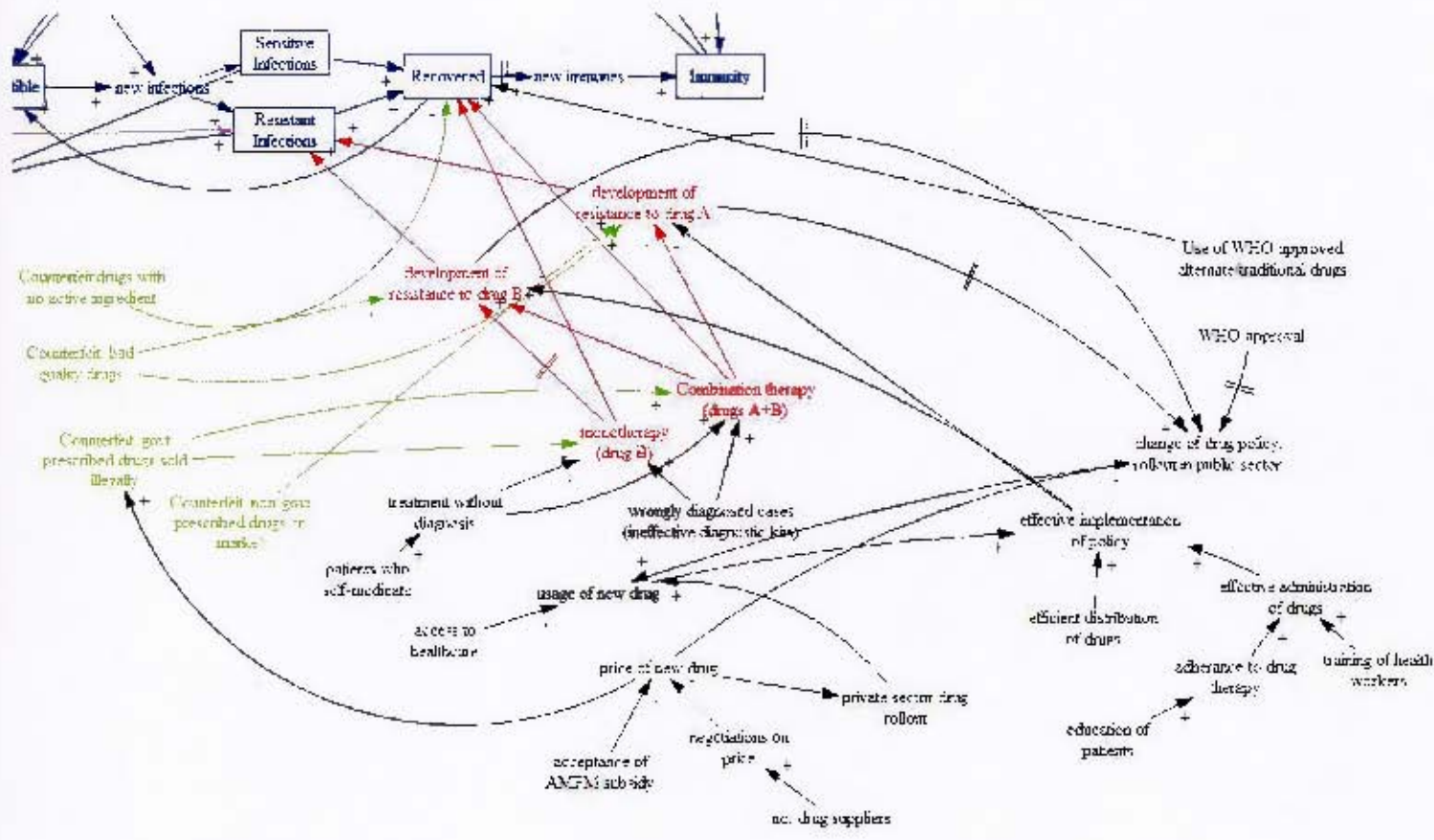


Figure 3.7: Causal Map: Policy and Policy Implementation

Policy is perhaps the most important aspect of this diagram as it is the control mechanism that can ultimately eradicate malaria. Along with the correct policy, policy implementation is vital as developing countries often lack the infrastructure to apply policies fully.

As resistance to drugs A and/or B develop, there will be a significant time delay before a change in national policy takes place. Contributing to this delay is the nod of approval from WHO for the new drug strategy. The price of the new drug also affects the number of drugs that will be rolled out by government.

- The more expensive a drug or set of drugs is, the less successful the roll out by government will be as many developing countries cannot

afford to purchase more expensive, yet more effective drugs.

Given that government has no control over what drugs are sold on the private sector, the roll-out of the new drug applies to public sector users only. Other mechanisms will need to be employed in order for the private sector to roll out the new drug as well. Hence,

- An increase in the number of drugs rolled out by government will lead to an increase in the number of users of the drug in the public sector.
- An increase in access to healthcare will also lead to increased usage of drug in the public sector.
- Increased usage of the drug leads to the effective implementation of the new policy
- An increase in training of health workers will lead to an increase in the effectiveness of the administration of the drugs.
- An increase in patient education about the new policy should also lead to an increase in adherence to drug therapy which in turn increases the effectiveness of the administration of the drugs.
- An increase in the efficiency of the distribution and administration of the drugs will both lead to an increase in the effectiveness of the implementation of the change in policy.
- The effective implementation will with a time delay lead to increasing the number of recoveries or cure rate of drug therapy.

However, no matter how good the implementation of the policy is, if adherence to the drug therapy is low, resistance will prevail as the drug levels in the blood stream will be at a sub-therapeutic level and this will fuel the development of resistance.

The private sector roll out of antimalarial drugs can also impact on the development of resistance to drugs deployed by the public sector. For example, selling 'counterfeit' pills that contain different active ingredients to that of government, like artemisinin-based drugs as a mono-therapy will be vital to the development and spread of resistance. The choice of drugs marketed by the private sector is influenced greatly by the price of the drugs.

- An increase in the price of the drug will lead to a decrease in the rollout of that drug by the private sector.

- An increase in the price of the drug may also lead to an increase in its availability on the illegal/black market
- If the new drug proposed by government is priced highly, its rollout to the private sector may be decreased and hence fewer private sector patients will use the drug which may decrease the effectiveness of implementation of the new policy.

This effect of price and the rollout of the new drug by the private sector will need to be understood in terms of the socio-economic status of the private sector market for antimalarial drugs. If the private sector serves the poor in a country, the effect described above may well occur. However, if the private sector serves those who are well-off, then these patients might be more prone to purchasing expensive drugs given the existence of medical aid programs.

The price of the new drug paid by the public and private sectors also needs to be understood in terms of the dynamics of the supply chain of antimalarial drugs.

- The greater the number of drug suppliers, the more bargaining power they will have and this may lead to an increase in the negotiation of prices which may serve to bring down the price of the drugs.
- Subsidies serve to reduce the price of the drug to be introduced by the public sector so that it will be selected by the private sector to be rolled out because of its reduced price.

One such subsidy that may serve in the favour of antimalarial policy is the AMFM (Affordable Medicines Facility for Malaria) subsidy. By reducing the price of the chosen drug/s this subsidy serves to align the interests of the public and private sector.

Not all drugs are prescribed after a diagnosis of malaria has been made. For example,

- An increase in the number of people who self-medicate leads to an increase in the roll-out of antimalarial drugs without diagnosis.
- This increases the proportion of monotherapy and combination therapy and may eventually lead to an increase in resistance to drug B.

Antimalarial drugs may be given to patients who display symptoms of malaria as the diagnostic kits take too much time or are too complicated for use. This may be the case in clinics that operate on a low budget and/or experience high patient volumes.

- An increase in the number of patients diagnosed incorrectly as having malaria leads to an increase in the proportions of monotherapy and combination therapy which can again fuel the development of resistance.

Other drugs in use are WHO-approved traditional/alternate antimalarial drugs, the use of which may increase the number of recoveries.

3.3 Conclusions

This causal map tries to depict the many inter-relationships between variables in the malaria system. Whether the model is used in a simulation or not, it provides helpful support as a decision-making tool as one is able to better grasp the interdependencies of aspects of malaria. Due to the complexity of this Causal map of malaria transmission and control and the associated difficulty to obtain estimates of the parameter inputs, the modeling attempt in this thesis focuses on a small part of the causal map i.e. the modeling of prevalence and antimalarial drug resistance with the impact of vector control and ACT. This modeling attempt will be done using a standard System Dynamics model of differential equations or epidemiological model as it is known in malaria research circles. Epidemiological modeling and System Dynamics modeling using differential equations are identical approaches that employ different terminology and nomenclature. Once the model of resistance has been run, its results will be interpreted within the framework of this causal map of malaria transmission and control to assess the reach of policies in place to combat malaria.

Chapter 4

Methodology

Having surveyed various resistance models in the literature, a model of resistance to antimalarial drugs will be built. The model will be built up from a simple Susceptible-Infected-Susceptible (SIS) model to the final complex model incorporating characteristics desirable for modelling resistance. A description and discussion of the parameters will follow thereafter.

4.1 Models of Drug Resistance

The model will be built first followed by a discussion on the model flows. Throughout this procedure, a number of stocks and flows are referred to by name. A description of these stocks and flows are provided in Tables 4.1 and 4.2 respectively. A description of the parameters used to inform the flows is provided in Table 4.9.

4.1.1 Model building

The most basic of disease models is an SIS model where a population is either susceptible or infected. There is no distinction of the type of infection one may have, whether an infected individual receives treatment or whether the infected individual has developed full or partial immunity to the infection. Such a model is depicted in Figure 4.1.

Here the stock entitled Susceptibles (Sus) represents the *proportion* of the population that is susceptible to the disease in question; in this case malaria and the stock entitled Infected (Inf) represents the proportion of the population that is infected with malaria. The arrows represent the rates of flow out of and into the stocks. The equations underlying Figure 4.1

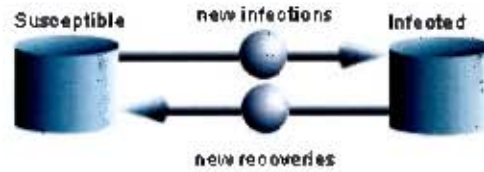


Figure 4.1: A Susceptible-Infected-Susceptible (SIS) model

follow:

$$\frac{dSus}{dt} = rInf - hSus \quad (4.1)$$

$$\frac{dInf}{dt} = hSus - rInf \quad (4.2)$$

where r is the rate of recovery and h is the rate of infection or inoculation rate. Depending on their form, these rates may be time-dependent. Details will not be given just yet on how rates such as r and h are derived. This will be discussed once the final model has been presented.

One can differentiate between different kinds of infection by separating the Infections stock into two or more stocks; each indicating a different kind of infection. Of specific interest is to differentiate between infections that display different degrees of resistance to the given treatment. Koella and Antia [2003] did this by dichotomising the Infections stock into Sensitive Infections and Resistant Infections stocks. One can differentiate further between degrees of resistance as illustrated in Figure 4.2.

Here infections have been separated into three categories viz. Sensitive, Partially resistant and Fully resistant infections. Resistance to a drug may either develop gradually as is the case with mefloquine resistance or in a stepwise manner from complete sensitivity through an accumulation of mutations as is the case with resistance to Pyrimethamine. [Hastings et al., 2002] The type of infection labelled Sensitive is the fully sensitive wild-type form of malaria that existed before drug treatment was applied. Partially resistant infections are less sensitive to the drug and can survive at higher residual drug levels. However, these infections may still be cleared at therapeutic doses of drugs. Fully resistant infections however are not significantly

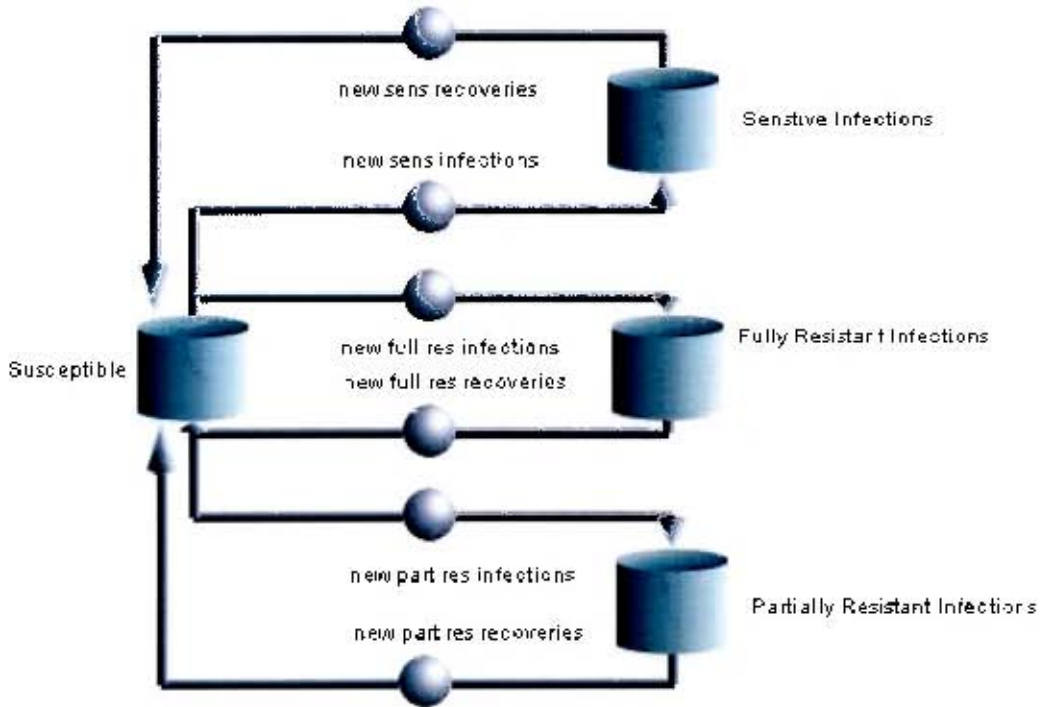


Figure 4.2: A basic model of resistance

affected by therapeutic levels of the drug. [Hastings et al., 2002] The equations underlying this extended SIS model follow. Sensitive infections are denoted as *Sens*, partially resistant infections as *PRes* and fully resistant infections as *FRes*. The only flows in this model are still transmission and recovery and separating infection strains in this manner allows one to incorporate different rates of transmission and recovery for each strain.

$$\frac{dSus}{dt} = r_{R0}Sens + r_{R1}PRes + r_{R2}FRes - (h_{R0} + h_{R1} + h_{R2})Sus \quad (4.3)$$

$$\frac{dSens}{dt} = h_{R0}Sus - r_{R0}Sens \quad (4.4)$$

$$\frac{dFRes}{dt} = h_{R2}Sus - r_{R2}FRes \quad (4.5)$$

$$\frac{dPRes}{dt} = h_{R1}Sus - r_{R1}PRes \quad (4.6)$$

In my model the drug in use to which resistance has developed is Sulfadoxine Pyrimethamine (SP). Resistance markers specific to the drug to which resistance has developed will be used to categorise infections. The use of genetic markers rather than clinical outcomes such as treatment failure allow one to directly incorporate the genetics of resistance development into the model as was suggested in the discussion of Watkins et al. [2005]. SEACAT data on Mozambique shows that total resistance to SP had not yet developed before the introduction of combination therapy though the resistance problem was substantial. [SEACAT, 2001] Thus rather than classifying infections according to sensitive, partial and full resistance, infections will be categorized according to whether they have zero, three or five resistant mutations. None of these infection categories exhibit total resistance to SP or total sensitivity to it. They do however represent an increasing degree of resistance. Labels for these categories will be Res0 (S), Res3 (R3) and Res5 (R5).

At this point in the model one may stratify populations in each compartment according to their age, whether they were treated or not and whether they were symptomatic or not. Given that this model will be adapted to suit the malaria situation in Mozambique where almost everyone who has malaria is treated, (see Section 4.2.1) it is not necessary to stratify populations according to the proportion treated. Further the low transmission setting in Mozambique inhibits the development of immunity against the parasite. Given that immunity may be associated with a decreased severity of clinical symptoms, malaria cases in Mozambique are generally symptomatic. [Klein et al., 2008] Thus it is also not necessary to stratify the population by the manifestation of clinical symptoms. However, temporary immunity will be included in the model.

At this point populations are still classified as either susceptible or infected. Given that immunity will not be included in the model, one may still add a recovered stock to allow for temporary immunity caused through the presence of drugs in the bloodstream. This was done in Koella and Antia [2003]. In order to return to the Susceptible stock, individuals must be susceptible to Res0, Res3 and Res5 infections. Thus after being infected, individuals are first moved to the Recovered stock as any residual drug in

the bloodstream that may restrict new infections will have to be eliminated before infected individuals are moved back to the susceptible stock. This is depicted in Figure 4.3 where additions to the previous model are shown in red.

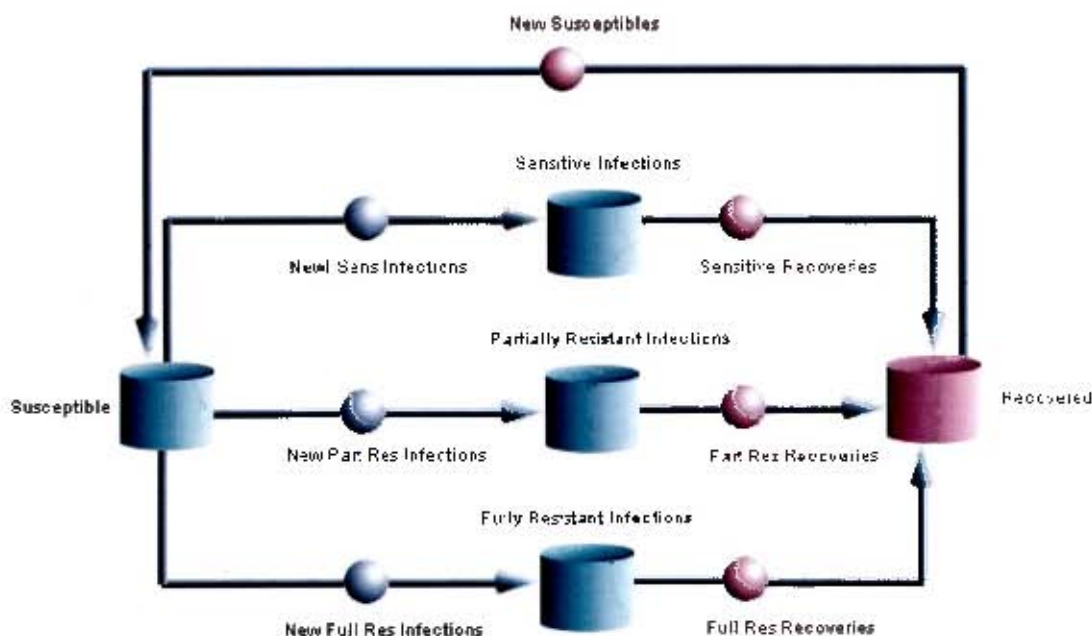


Figure 4.3: A model of resistance and recovery

Before the model is developed further it is necessary to chart an individual's progress through a malaria infection as is depicted in Figure 4.4.

A susceptible individual upon being infected with either a Res0, Res3 or Res5 infection immediately receives treatment. There are two treatment regimes under investigation in this model viz. SP and Artemisinin-based Combination Therapy (ACT). Individuals infected with malaria are not infectious to mosquitoes and hence are unable to transmit malaria parasites to susceptible mosquitoes unless the parasites have reached the sexual stage of gametocytes. Only when gametocytes are present are individuals infectious to mosquitoes. Not all individuals carry gametocytes and hence individuals may or may not be infectious. In this model becoming infectious depends in part on treatment outcome. Having received their treatment, the treatment

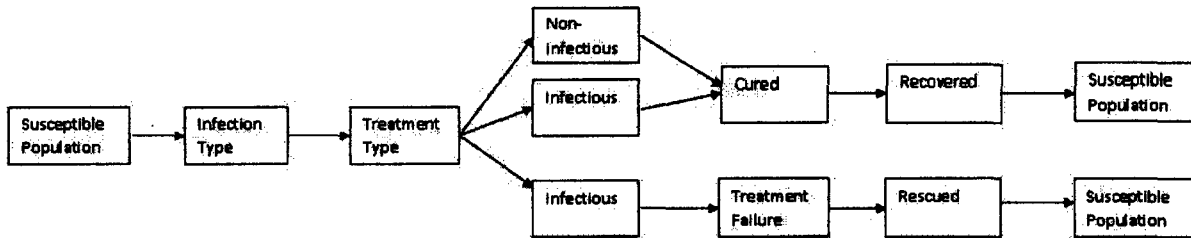


Figure 4.4: An individual's progress through a malaria infection

may either cure the infection or result in a treatment failure. For Res0, Res3 and Res5 infections, a proportion of these infections may be cleared with a therapeutic dose of SP or ACT and the rest of these infections may result in treatment failure. Sensitive infections may become infectious if gametocytes are present in the bloodstream. Other sensitive infections won't become infectious. Both these groups of sensitive infections then move to the Recovered stock where they experience temporary immunity due to the presence of residual drug in their bloodstream. Once this drug has been eliminated, they move to the Susceptible stock where they may be infected again with a Res0, Res3 or Res5 infection.

Treatment failures resulting from Res0, Res3 or Res5 infections may be Early Treatment Failures (ETF) or Late Treatment Failures (LTF). All treatment failures are assumed to be infectious in the model. Once treatment has failed, individuals are hospitalised and rescued with another drug such as quinine. Given that quinine has a very short half life, once the treatment regimen is over, the drug is completely eliminated from the bloodstream. [White, 1999]. Having been rescued, individuals move to back to the Susceptible stock. It is assumed that if those who fail treatment and are treated with quinine do not die of other causes, they will be rescued and cured.

We now proceed to add the different components depicted in Figure 4.4 step-wise into our model. Figure 4.5 depicts the inclusion of the infectious component of the model. Additions to the previous model are depicted in red. Here, upon being infected, individuals may become infectious. If they become infectious they are moved to stocks entitled *Infect.* where the

_ represents the strain of infection. Because the probability of becoming infectious and the rate of recovery are dependent on the strain of infection, it is necessary to have an infectious stock for each infection type. Similarly because the rates of recovery differ for each infection type, each infection type also has its own Recovery stock labelled *Rec_* where _ again represents the strain of infection. Those who do not become infectious, upon being infected are moved to a general recovery stock labelled *Rec* from which they gradually become susceptible again.

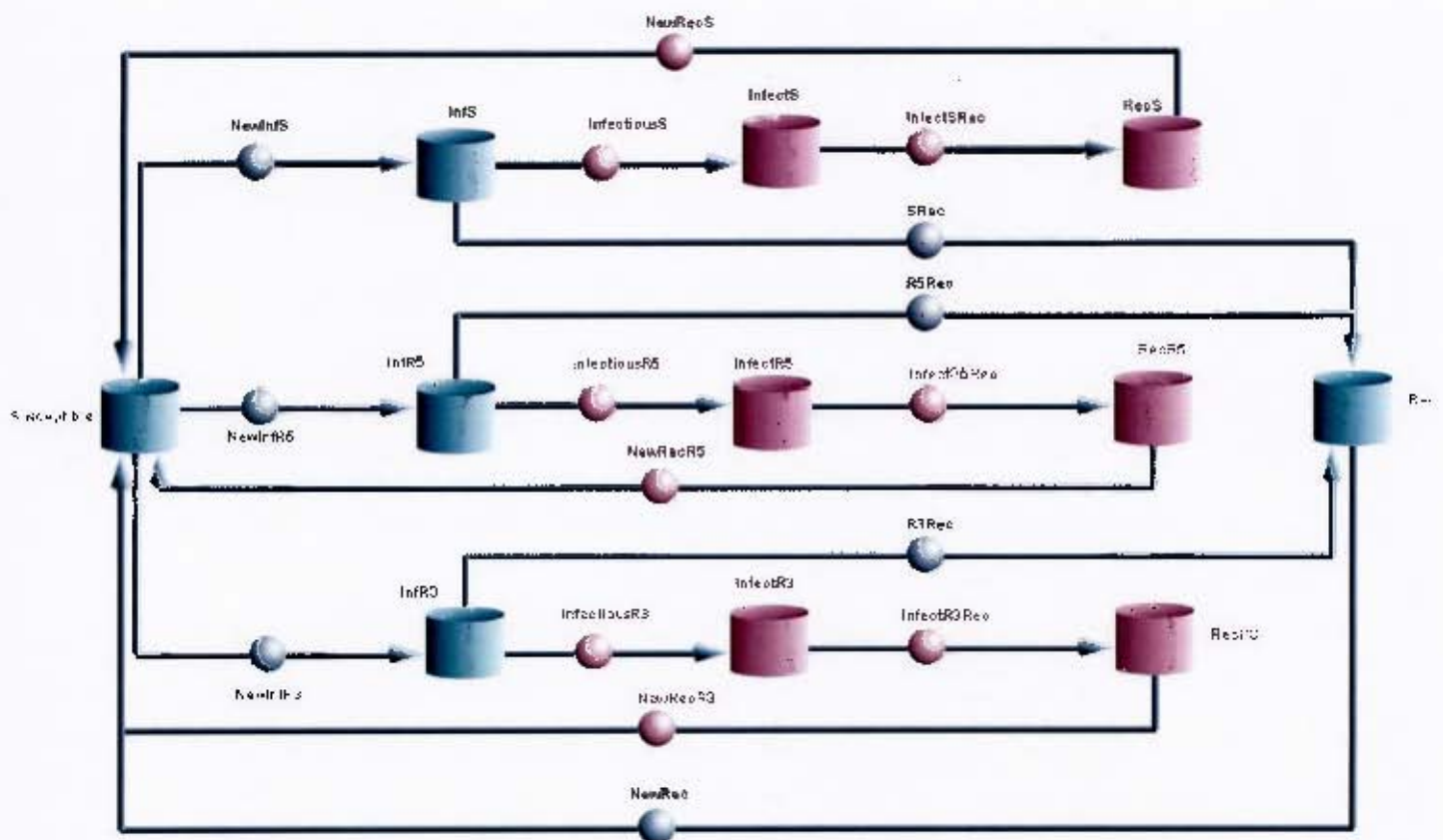


Figure 4.5: A model of resistance incorporating Infectiousness and Recovery

The equations for the model in Figure 4.5 follow. The equations are written in a different form to previous equations in that each term describes the movement between stocks. This method of writing equations will be used until the final model is presented where each term will be discussed

in detail. Consistent notation is used throughout the model where prefixes and suffixes of S , $R3$ and $R5$ describe the flow/stock for sensitive, Res3 and Res5 infections respectively.

$$\frac{dSus}{dt} = NewRecS + NewRecR5 + NewRecR3 + NewRec - NewInfS - NewInfR3 - NewInfR5 \quad (4.7)$$

$$\frac{dInfS}{dt} = NewInfS - InfectiousS - SRec \quad (4.8)$$

$$\frac{dInfR5}{dt} = NewInfR5 - InfectiousR5 - R5Rec \quad (4.9)$$

$$\frac{dInfR3}{dt} = NewInfR3 - InfectiousR3 - R3Rec \quad (4.10)$$

$$\frac{dInfectS}{dt} = InfectiousS - InfectSRec \quad (4.11)$$

$$\frac{dInfectR5}{dt} = InfectiousR5 - InfectR5Rec \quad (4.12)$$

$$\frac{dInfectR3}{dt} = InfectiousR3 - InfectR3Rec \quad (4.13)$$

$$\frac{dRecS}{dt} = InfectSRec - NewRecS \quad (4.14)$$

$$\frac{dRecR5}{dt} = InfectR5Rec - NewRecR5 \quad (4.15)$$

$$\frac{dRecR3}{dt} = InfectR3Rec - NewRecR3 \quad (4.16)$$

$$\frac{dRec}{dt} = SRec + R5Rec + R3Rec - NewRec \quad (4.17)$$

As resistance to SP emerged in Mozambique, there was a switch in drug treatment policy to artemisinin based combination therapy. Here artesunate was used in conjunction with SP. Thus there is now a need for stratification in the model according to the drug used for treatment. Such a model is presented in Figure 4.6. Additions to the previous model are depicted in red and those stocks and flows ending with 'A' refer to those treated with ACT.

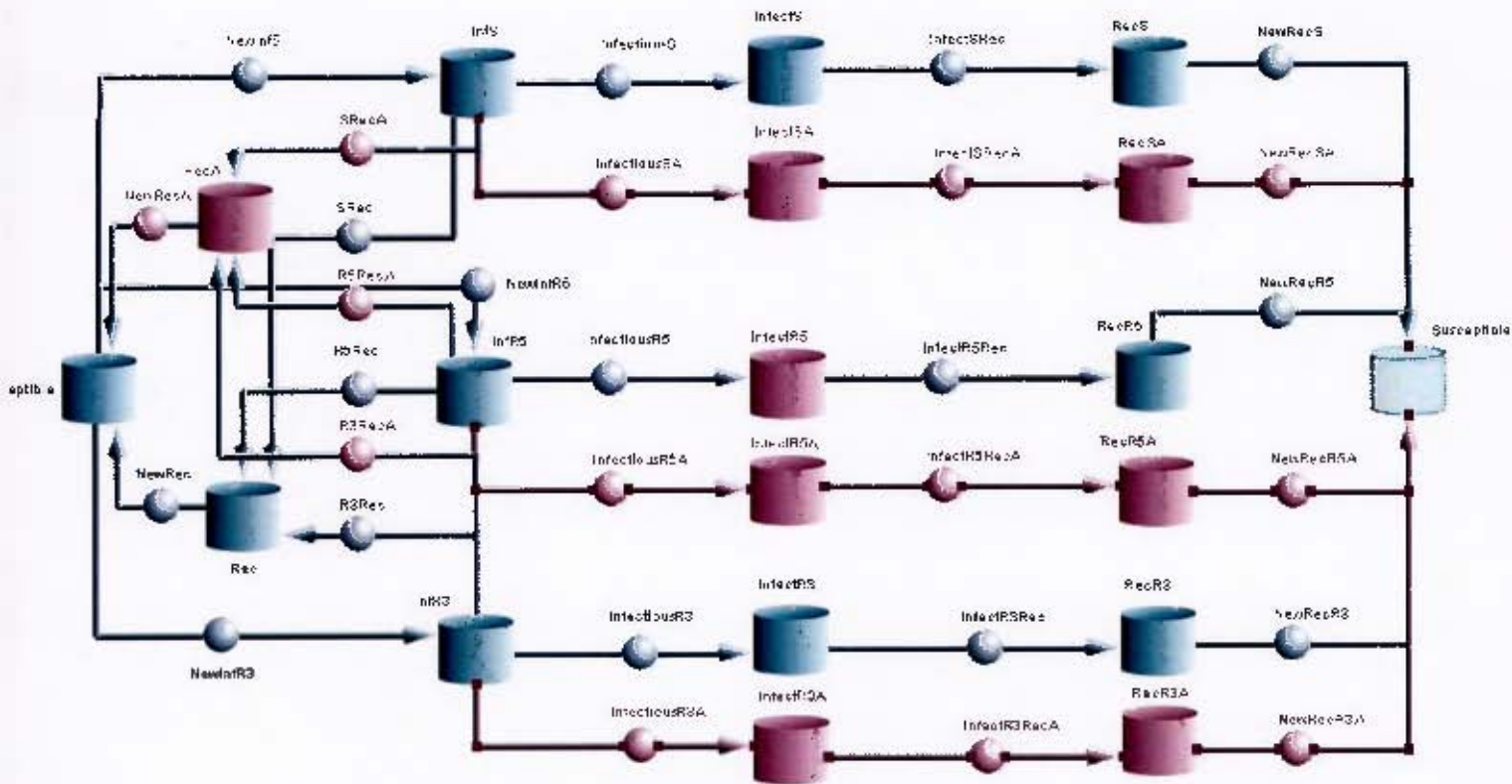


Figure 4.6: A model of resistance incorporating infectiousness, recovery and treatment

Here upon being infected with a Res0, Res3 or Res5 infection, a proportion of the infected population is treated with SP and the residual with ACT. There are now two sets of flows out of the InfS, InfR5 and InfR3 stocks as those treated with ACT will become infectious and recover at rates different to those treated with SP. You will notice that there are two stocks labelled Susceptible in the model. These are in fact just the same stock that has been shown in two places to facilitate easier reading of the model. The equations underlying Figure 4.6 follow.

$$\begin{aligned}
 \frac{dSus}{dt} = & \text{NewRecS} + \text{NewRecR5} + \text{NewRecR3} + \text{NewRecSA} \\
 & + \text{NewRecR5A} + \text{NewRecR3A} + \text{NewRec} + \text{NewRecA} - \text{NewInfS} \\
 & - \text{NewInfR3} - \text{NewInfR5}
 \end{aligned} \tag{4.18}$$

$$\frac{dInfS}{dt} = NewInfS - InfectiousS - InfectiousSA - SRec - SRecA \quad (4.19)$$

$$\frac{dInfR5}{dt} = NewInfR5 - InfectiousR5 - InfectiousR5A - R5Rec - R5RecA \quad (4.20)$$

$$\frac{dInfR3}{dt} = NewInfR3 - InfectiousR3 - InfectiousR3A - R3Rec - R3RecA \quad (4.21)$$

$$\frac{dInfectS}{dt} = InfectiousS - InfectSRec \quad (4.22)$$

$$\frac{dInfectSA}{dt} = InfectiousSA - InfectSRecA \quad (4.23)$$

$$\frac{dInfectR5}{dt} = InfectiousR5 - InfectR5Rec \quad (4.24)$$

$$\frac{dInfectR5A}{dt} = InfectiousR5A - InfectR5RecA \quad (4.25)$$

$$\frac{dInfectR3}{dt} = InfectiousR3 - InfectR3Rec \quad (4.26)$$

$$\frac{dInfectR3A}{dt} = InfectiousR3A - InfectR3RecA \quad (4.27)$$

$$\frac{dRecS}{dt} = InfectSRec - NewRecS \quad (4.28)$$

$$\frac{dRecSA}{dt} = InfectSRecA - NewRecSA \quad (4.29)$$

$$\frac{dRecR5}{dt} = InfectR5Rec - NewRecR5 \quad (4.30)$$

$$\frac{dRecR5A}{dt} = InfectR5RecA - NewRecR5A \quad (4.31)$$

$$\frac{dRecR3}{dt} = InfectR3Rec - NewRecR3 \quad (4.32)$$

$$\frac{dRecR3A}{dt} = InfectR3RecA - NewRecR3A \quad (4.33)$$

$$\frac{dRec}{dt} = SRec + R5Rec + R3Rec - NewRec \quad (4.34)$$

$$\frac{dRecA}{dt} = SRecA + R5RecA + R3RecA - NewRecA \quad (4.35)$$

In Figure 4.4 it was shown that not all infections are sensitive to treatment and hence treatment fails when parasites are resistant to the drug. The aspect of treatment outcome is included in Figure 4.7.

Here early and late treatment failures result from Res0, Res3 and Res5 infections and are sent to their own Failure stock owing to differential failure rates. From the Early and Late Treatment Failure stocks, the failures are rescued with quinine before they are moved back to the Susceptible stock. There are also two sets of treatment failure flows for SP and ACT because the treatment regimes are assumed to exhibit different levels of resistance and hence different failure rates. Hence the key development from Figure 4.6 to Figure 4.7 is that Res0, Res3 and Res5 infections do not have 100% cure rates. There is now an allowance for treatment failures which is the proxy that is used for resistance to SP. It must also be noted that because there is no evidence of resistance artemisinin, one should technically have zero early treatment failures for those on ACT. However, a small percentage of failures do result due to incorrect dosage, poor adherence etc. Hence the model allows for a small percentage of failures from all infection strains under both treatments to account for issues such as incorrect dosage and poor adherence.

It is also possible to include the birth and death rates into the model through δ as seen in the following equations. The assumption used is that births will balance deaths. These forces though not visible in the flowchart, will be included in the equations underlying Figure 4.7. Note that the terms in the equations will be expanded once the flows have been discussed in more detail. The equations underlying Figure 4.7 follow.

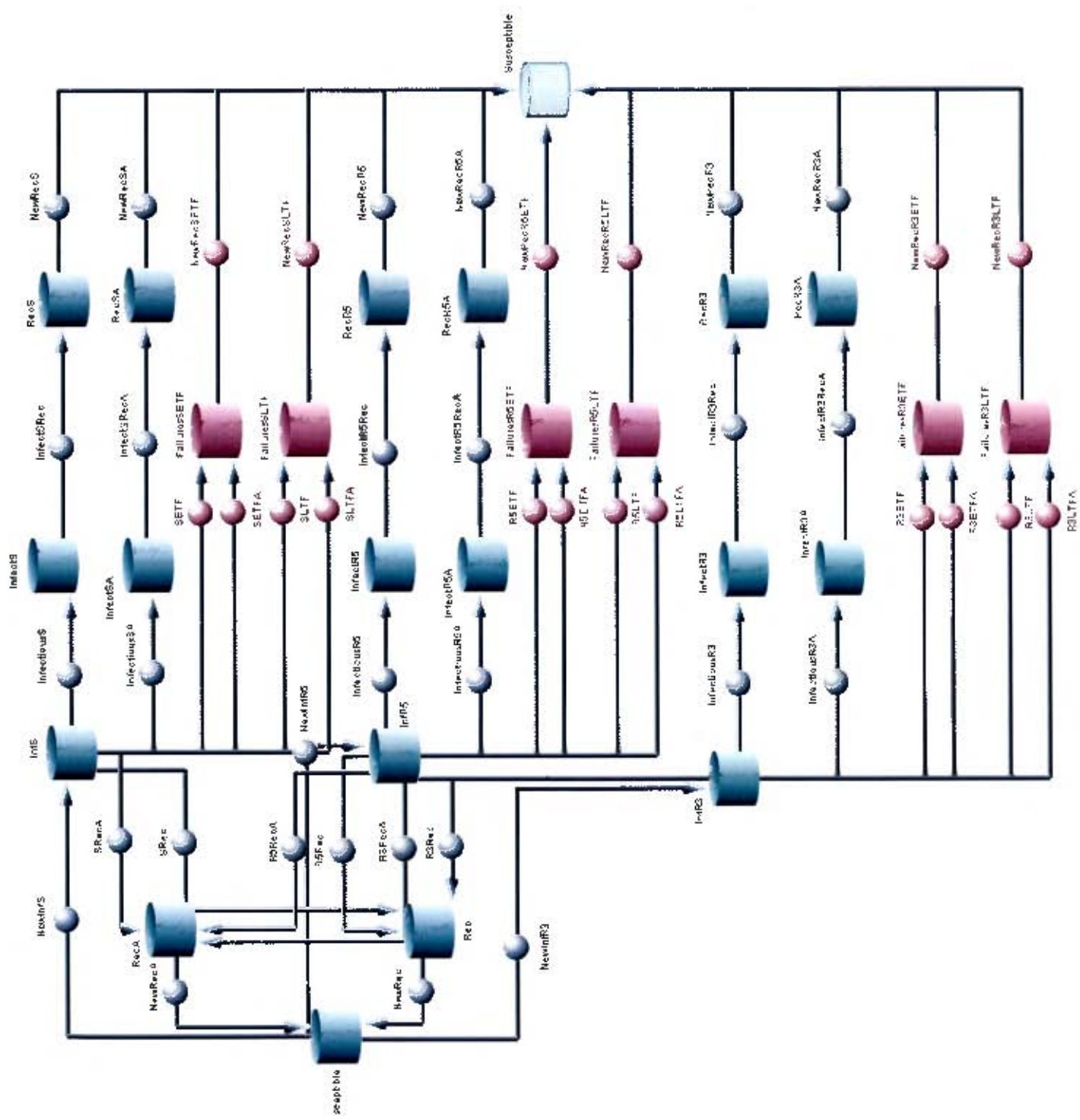


Figure 4.7: A model of resistance incorporating infectiousness, recovery, treatment and treatment outcome 49

$$\begin{aligned}
\frac{dSus}{dt} = & \delta + NewRecS + NewRecR5 + NewRecR3 + NewRecSA \\
& + NewRecR5A + NewRecR3A + NewRec + NewRecA \\
& + NewRecR5ETF + NewRecR5LTF + NewRecR3ETF \\
& + NewRecR3LTF + NewRecSETF + NewRecSLTF \\
& - NewInfS - NewInfR3 - NewInfR5 - \delta Sus \quad (4.36)
\end{aligned}$$

$$\begin{aligned}
\frac{dInfS}{dt} = & NewInfS - InfectiousS - InfectiousSA - SRec - SRecA \\
& - SETF - SETFA - SLTF - SLTFA - \delta InfS \quad (4.37)
\end{aligned}$$

$$\begin{aligned}
\frac{dInfR5}{dt} = & NewInfR5 - InfectiousR5 - InfectiousR5A - R5Rec - R5RecA \\
& - R5ETF - R5ETFA - R5LTF - R5LTFA - \delta InfR5 \quad (4.38)
\end{aligned}$$

$$\begin{aligned}
\frac{dInfR3}{dt} = & NewInfR3 - InfectiousR3 - InfectiousR3A - R3Rec - R3RecA \\
& - R3ETF - R3ETFA - R3LTF - R3LTFA - \delta InfR3 \quad (4.39)
\end{aligned}$$

$$\frac{dInfectS}{dt} = InfectiousS - InfectSRec - \delta InfectS \quad (4.40)$$

$$\frac{dInfectSA}{dt} = InfectiousSA - InfectSRecA - \delta InfectSA \quad (4.41)$$

$$\frac{dInfectR5}{dt} = InfectiousR5 - InfectR5Rec - \delta InfectR5 \quad (4.42)$$

$$\frac{dInfectR5A}{dt} = InfectiousR5A - InfectR5RecA - \delta InfectR5A \quad (4.43)$$

$$\frac{dInfectR3}{dt} = InfectiousR3 - InfectR3Rec - \delta InfectR3 \quad (4.44)$$

$$\frac{dInfectR3A}{dt} = InfectiousR3A - InfectR3RecA - \delta InfectR3A \quad (4.45)$$

$$\frac{dRecS}{dt} = InfectSRec - NewRecS - \delta RecS \quad (4.46)$$

$$\frac{dRecSA}{dt} = InfectSRecA - NewRecSA - \delta RecSA \quad (4.47)$$

$$\frac{dRecR5}{dt} = InfectR5Rec - NewRecR5 - \delta RecR5 \quad (4.48)$$

$$\frac{dRecR5A}{dt} = InfectR5RecA - NewRecR5A - \delta RecR5A \quad (4.49)$$

$$\frac{dRecR3}{dt} = InfectR3Rec - NewRecR3 - \delta RecR3 \quad (4.50)$$

$$\frac{dRecR3A}{dt} = InfectR3RecA - NewRecR3A - \delta RecR3A \quad (4.51)$$

$$\frac{dRec}{dt} = SRec + R5Rec + R3Rec - NewRec - \delta Rec \quad (4.52)$$

$$\frac{dRecA}{dt} = SRecA + R5RecA + R3RecA - NewRecA - \delta RecA \quad (4.53)$$

$$\frac{dFailuresSETF}{dt} = SETF + SETFA - NewRecSETF - \delta FailuresSETF \quad (4.54)$$

$$\frac{dFailuresSLTF}{dt} = SLTF + SLTFA - NewRecSLTF - \delta FailuresSLTF \quad (4.55)$$

$$\frac{dFailuresR5ETF}{dt} = R5ETF + R5ETF A - NewRecR5ETF - \delta FailuresR5ETF \quad (4.56)$$

$$\frac{dFailuresR5LTF}{dt} = R5LTF + R5LTF A - NewRecR5LTF - \delta FailuresR5LTF \quad (4.57)$$

$$\frac{dFailuresR3ETF}{dt} = R3ETF + R3ETF A - NewRecR3ETF - \delta FailuresR3ETF \quad (4.58)$$

$$\frac{dFailuresR3LTF}{dt} = R3LTF + R3LTF A - NewRecR3LTF - \delta FailuresR3LTF \quad (4.59)$$

where δ is the birth/death rate and those stocks and flows ending in 'A' refer to the ACT treatment arm.

The model thus presented in Figure 4.7 is thus the full and basic model of resistance to be used in this thesis. From here on it will be referred to as the Base model. Thus far the model has stratified infection according to mutation category (adapted from Watkins et al. [2005] rather than the sensitive/resistant classification used in Koella and Antia [2003]. It also incorporated the direct modeling of infectiousness which allows one to make use of available gametocytemia data as an improvement to the gametocyte switch rate parameter used in Pongtavornpinyo [2006]. But the model has not yet incorporated the pharmacokinetic properties as was done in Prudhomme-O'Meara et al. [2006]. This aspect, for reasons discussed later is incorporated in an extension of the base model presented in Chapter 5.

4.1.2 Expanding the final model

In this section, the stocks and flows in the final model will be described in more detail. Though this final model is more complicated than the initial SIRS (Sus \rightarrow Inf \rightarrow Rec \rightarrow Sus) model, its essence is still the same: Susceptible individuals become infected through the transmission rates and recover to become susceptible again through the recovery rates.

Stocks

Table 4.1 provides a description of all the stocks used in this model.

Table 4.1: Description of Stocks used in the base model

Stock	Description: Proportion of the population who are
Sus	Susceptible individuals
InfS	Infected with drug-sensitive Res0 strain (0 mutations)
InfR5	Infected with drug-resistant Res5 strain(5 mutations)
InfR3	Infected with drug-resistant Res3 strain(3 mutations)
InfectS	Infectious with Res0 parasites and treated with SP
InfectR5	Infectious with Res5 parasites and treated with SP
InfectR3	Infectious with Res3 parasites and treated with SP
InfectSA	Infectious with Res0 parasites and treated with ACT
InfectR5A	Infectious with Res5 parasites and treated with ACT
InfectR3A	Infectious with Res3 parasites and treated with ACT
Rec	Recovered without becoming infectious and treated with SP
RecS	Recovered after being infectious with Res0 parasites and treated with SP
RecR5	Recovered after being infectious with Res5 parasites and treated with SP
RecR3	Recovered after being infectious with Res3 parasites and treated with SP
RecA	Recovered without becoming infectious and treated with ACT
RecSA	Recovered after being infectious with Res0 parasites and treated with ACT
RecR5A	Recovered after being infectious with Res5 parasites and treated with ACT
RecR3A	Recovered after being infectious with Res3 parasites and treated with ACT
FailuresSETF	Early treatment failures after being infected with a Res0 infection
FailuresSLTF	Late treatment failures/recrudescences after being infected with a Res0 infection
FailuresR5ETF	Early treatment failures after being infected with a Res5 infection
FailuresR5LTF	Late treatment failures/recrudescences after being infected with a Res5 infection
FailuresR3ETF	Early treatment failures after being infected with a Res3 infection
FailuresR3LTF	Late treatment failures/recrudescences after being infected with a Res3 infection

Rates of Flow

There are four categories of rates in this final model; each of which will be described separately. These categories are the rates of infection transmission, rates determining infectiousness and the rates determining treatment and treatment outcome.

The transmission rate

Though the rate of transmission (commonly denoted as h) takes on many forms, at its core it may be described as

$$h = \text{EIR} \times b_2 \quad (4.60)$$

$$= mawb_2 \quad (4.61)$$

where m is the number of mosquitoes per human, a is the number of bites per mosquito, b_2 is the probability that a bite from a mosquito will lead to infection in the human (human susceptibility) and w is the proportion of mosquitoes with sporozoites in their blood (probability of infectious mosquitoes). [Macdonald, 1957] As mentioned in Section 2.4.1 the form of the h used in this model is the same as that of Koella and Antia [2003].

The entomological inoculation rate which is the number of infectious bites per human per day may then be described as the product of the human-biting rate, the proportion of infected mosquitoes and the probability of the mosquitoes surviving to become infectious. These entities will be dealt with individually. The human biting rate is simply equivalent to $m \times a$ i.e. the product of the number of mosquitoes per human (m) and the number of bites per mosquito (a). The probability of an infected mosquito becoming infectious is a function of the force of mosquito mortality (μ) and the parasite incubation period in the mosquito. (τ) If one assumes that survival is constant over a vector's lifetime, then one implies an exponential distribution of survival times. [Smith and McKenzie, 2004] As result the probability of a mosquito or cohort of mosquitoes surviving the parasite incubation time (τ) is

$$Pr[\text{survival to time } \tau] = e^{-\mu\tau} \quad (4.62)$$

The proportion of infected mosquitoes has been described as the ratio of two waiting times, viz. the time to either death or infection and the time to infection presented as

$$\text{Proportion of infected mosquitoes} = \frac{1}{\mu + ab_1X} \div \frac{1}{ab_1X} \quad (4.63)$$

$$= \frac{ab_1X}{\mu + ab_1X} \quad (4.64)$$

where a is the number of bites per mosquito, b_1 is the probability that a susceptible mosquito will become infected after biting an infectious human and X is the proportion of infectious people in the population. Thus the form of the transmission rate h may be written as

$$h = \text{EIR} \times b_2 \quad (4.65)$$

$$= (ma) \times \left(\frac{ab_1X}{\mu + ab_1X} \right) \times (e^{-\mu\tau}) \times b_2 \quad (4.66)$$

$$= \frac{ma^2b_1b_2e^{-\mu\tau}X}{\mu + ab_1X} \quad (4.67)$$

Koella and Antia [2003] used separate transmission rates for sensitive and resistant infections. The same will be done in this model. Different rates of transmission will be used for the three infection strains under investigation in this model viz Res0 infections (S), Res3 infections (R3) and Res5 infections (R5). Differences in the rates of transmission are captured through two parameters viz. the human infectivity parameter b_1 and the proportion of infectious population parameter X . The human infectivity parameter values are different for each infection type of infection owing to the transmission cost of resistance. [Koella and Antia, 2003] The proportion of infectious population for each strain is depended on those stocks that measure the infectious population as well as the failure stocks given the assumption that all failures become infectious. Thus the inoculation rates for each of the infection strains are

$$h_S = \frac{ma^2b_2e^{-\mu\tau}b_{1S}(\text{Tot Infectious } S)}{\mu + a(b_{1S}(\text{Tot Infectious } S) + b_{1R5}(\text{Tot Infectious } R5) + b_{1R3}(\text{Tot Infectious } R3))} \quad (4.68)$$

$$h_{R5} = \frac{ma^2b_2e^{-\mu\tau}b_{1R5}(\text{Tot Infectious } R5)}{\mu + a(b_{1S}(\text{Tot Infectious } S) + b_{1R5}(\text{Tot Infectious } R5) + b_{1R3}(\text{Tot Infectious } R3))} \quad (4.69)$$

$$h_{R3} = \frac{ma^2b_2e^{-\mu\tau}b_{1R3}(\text{Tot Infectious } R3)}{\mu + a(b_{1S}(\text{Tot Infectious } S) + b_{1R5}(\text{Tot Infectious } R5) + b_{1R3}(\text{Tot Infectious } R3))} \quad (4.70)$$

where

$$\text{Tot Infectious } S = \text{Infect}S + \text{Infect}SA + \text{Failures}SETF + \text{Failures}SLTF \quad (4.71)$$

$$Tot\ Infectious\ R5 = InfectR5 + InfectR5A + FailuresR5ETF + FailuresR5LTF \quad (4.72)$$

$$Tot\ Infectious\ R3 = InfectR3 + InfectR3A + FailuresR3ETF + FailuresR3LTF \quad (4.73)$$

The last parameter to be discussed now is b_2 ; the probability that a bite from an infectious mosquito will lead to human infection. Thus it is an estimate of human susceptibility and is related to immunity and drug level in the bloodstream. Long term immunity is not included in this model and since the model only allows those who have no drug in their bloodstream to become infected, a uniform value of b_2 is assumed for all infection strains.

The treatment outcome rates

Treatment outcome may be categorized into Cured (sensitive to treatment) and Failed, where treatment failure may be early treatment failure or late treatment failure. In Koella and Antia [2003] the rate of recovery is the inverse of the duration of infection. Hence at equilibrium if infections that are cured last for τ days on average, then individuals recover once every τ days or at a rate of $\frac{1}{\tau}$. As not all infections are sensitive to treatment, the rate of flow needs to factor in the probability of treatment cure denoted as ACPR (adequate clinical and parasitological response). At the start of treatment, the time taken for SP to clear parasites for those who are sensitive to treatment and do not become infectious is denoted as τ_0 and hence from InfS, InfR3 and InfR5, the populations move at a rate of $f \times p_{ACPR} \times (1 - p_{Inf_}) \times \frac{1}{\tau_0}$ to the Recovered stock where f is the proportion of individuals treated with SP, p_{ACPR} is the probability of treatment cure, $(1 - p_{Inf_})$ is the probability of not becoming infectious and $_$ represents the infection strain suffix S, R3 or R5.

The treatment failure rates depend on whether an early or late treatment failure has occurred. The rates are generally a function of the probability of treatment failure, the drug type (SP or ACT) and the time to treatment failure. Thus the rate of flow from InfS, InfR3 and InfR5 to an Early Treatment Failure stock for an individual treated with SP is given by $p_{ETF} \times f \times \frac{1}{ETFday}$ where p_{ETF} is the probability of early treatment failure, $ETFday$ is the time to early treatment failure and f is the proportion of individuals treated with SP. The probabilities of treatment failure and

the time to treatment failure are stratified according to infection strain and whether the failure was early or late. Once treatment failure has occurred, individuals leave the failure stocks and move into a recovery stocks at a rate of $\frac{1}{q}$ where q is the duration of quinine treatment.

The rates of infectiousness

The rates determining the proportion of the population that becomes infectious are dependent on the probability of becoming infectious as well as the time to developing gametocytemia. If it takes the population on average x days to develop gametocytemia, then the equilibrium rate of gametocytemia development is $\frac{1}{x}$ or 1 person every x days. Since not all infected individuals will become infectious, the probability of becoming infectious or the probability of gametocyte development $p_{Inf_}$ will need to be included in these rates. This probability is stratified by infection type where $_$ can take on categories S, R3 and R5. Further since those who are treated with SP will have different rates of gametocytemia than ACT (ACT's short half life inhibits the development of gametocytemia), a drug treatment factor f must also be included in the rates of infectiousness calculations where f is the proportion of the infected population that is treated with SP and $(1 - f)$ is the proportion of the population that is treated with ACT. Thus if the time to gametocytemia is denoted as $gamestart_$ and the probability of gametocytemia is denoted as $p_{Inf_}$, the rate of infectiousness for those treated with SP is $f \times p_{Inf_} \times \frac{1}{gamestart_}$ where $_$ represents the strain of infection S, R3 or R5. However since all treatment failures are assumed to be infectious, these rates are relevant to only infections that are sensitive to treatment. The probability of being sensitive to infection also needs to be factored into these equations. Early and late treatment failures are denoted as ETF and LTF respectively while sensitive infections are denoted as ACPR (adequate clinical and parasitological response). The rate of infectiousness for those treated with SP who are sensitive to treatment (movement from InfS to InfectS) is $f \times p_{SACPR} \times p_{InfS} \times \frac{1}{gamestartS}$.

Individuals who become infectious cease to be so after the gametocytes have been cleared. They are moved into recovery stocks when this occurs. These gametocyte clearance rates are dependent on the treatment type (SP or ACT) as well as the strain of infection (S, R3 or R5). As such they are denoted as $gamedur_A$ where rates ending in 'A' represent the ACT treatment regime. Thus the rate of gametocyte clearance for those treated with ACT is $(1 - f) \times \frac{1}{gamedur_A}$ where $_$ represents the strain of infection.

Rates of Transmission and Recovery

Given that the final model equations used descriptions such as NewInfS and SRecA to describe movements between stocks, Table 4.2 provides the mathematical description of these terms. Descriptions of the parameters used are provided in Table 4.9.

Table 4.2: Description of Flows in the model

	Flow	Value
Sus → InfS	Susb (Births)	$\delta \times 1000$
Sus → InfR5	NewInfS	$hInfS \times Sus$
Sus → InfR3	NewInfR5	$hInfR5 \times Sus$
	NewInfR3	$hInfR3 \times Sus$
InfS → Rec	SRec	$f \times PSACPR \times (1 - p_{InfS}) \times \frac{1}{r_0} \times InfS$
InfS → RecA	SRecA	$(1 - f) \times PSACPRA \times (1 - p_{InfSA}) \times \frac{1}{r_{0A}} \times InfS$
InfR3 → RecR3	R3Rec	$f \times PR3ACPR \times (1 - p_{InfR3}) \times \frac{1}{r_0} \times InfR3$
InfR3 → RecR3A	R3RecA	$(1 - f) \times PR3ACPRA \times (1 - p_{InfR3A}) \times \frac{1}{r_{0A}} \times InfR3$
InfR5 → RecR5	R5Rec	$f \times PR5ACPR \times (1 - p_{InfR5}) \times \frac{1}{r_0} \times InfR5$
InfR5 → RecR5A	R5RecA	$(1 - f) \times PR5ACPRA \times (1 - p_{InfR5A}) \times \frac{1}{r_{0A}} \times InfR5$
Rec → Sus	NewRec	$\frac{1}{r_1} \times Rec$
RecA → Sus	NewRecA	$\frac{1}{r_{1A}} \times RecA$
RecS → Sus	NewRecS	$\frac{1}{r_{1S}} \times RecS$
RecSA → Sus	NewRecSA	$\frac{1}{r_{1SA}} \times RecSA$
RecR5 → Sus	NewRecR5	$\frac{1}{r_{1R5}} \times RecR5$
RecR5A → Sus	NewRecR5A	$\frac{1}{r_{1R5A}} \times RecR5A$
RecR3 → Sus	NewRecR3	$\frac{1}{r_{1R3}} \times RecR3$
RecR3A → Sus	NewRecR3A	$\frac{1}{r_{1R3A}} \times RecR3A$
FailuresSETF → Sus	NewSusSETF	$\frac{1}{q_{SETF}} \times FailuresSETF$
FailuresSLTF → Sus	NewSusSLTF	$\frac{1}{q_{SLTF}} \times FailuresSLTF$
FailuresR5ETF → Sus	NewSusR5ETF	$\frac{1}{q_{R5ETF}} \times FailuresR5ETF$
FailuresR5LTF → Sus	NewSusR5LTF	$\frac{1}{q_{R5LTF}} \times FailuresR5LTF$
FailuresR3ETF → Sus	NewSusR3ETF	$\frac{1}{q_{R3ETF}} \times FailuresR3ETF$
FailuresR3LTF → Sus	NewSusR3LTF	$\frac{1}{q_{R3LTF}} \times FailuresR3LTF$

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Table 4.2 - Continued

	Flow	Value
InfS → InfectS	InfectiousS	$f \times p_{SACPR} \times p_{InfS} \times \frac{1}{gamestartS} \times InfS$
InfS → InfectSA	InfectiousSA	$(1 - f) \times p_{SACPRA} \times p_{InfSA} \times \frac{1}{gamestartSA} \times InfS$
InfR5 → InfectR5	InfectiousR5	$f \times p_{R2ACPR} \times p_{InfR5} \times \frac{1}{gamestartR5} \times InfR5$
InfR5 → InfectR5A	InfectiousR5A	$(1 - f) \times p_{R2ACPRA} \times p_{InfR5A} \times \frac{1}{gamestartR5A} \times InfR5$
InfR3 → InfectR3	InfectiousR3	$f \times p_{R1ACPR} \times p_{InfR3} \times \frac{1}{gamestartR3} \times InfR3$
InfR3 → InfectR3A	InfectiousR3A	$(1 - f) \times p_{R1ACPRA} \times p_{InfR3A} \times \frac{1}{gamestartR3A} \times InfR3$
InfectR5 → RecR5	InfectR5Rec	$f \times \frac{1}{gamedurR5} \times InfectR5$
InfectR5A → RecR5A	InfectR5RecA	$(1 - f) \times \frac{1}{gamedurR5A} \times InfectR5A$
InfectS → RecS	InfectSRec	$f \times \frac{1}{gamedurS} \times InfectS$
InfectSA → RecSA	InfectSRecA	$(1 - f) \times \frac{1}{gamedurSA} \times InfectSA$
InfectR3 → RecR3	InfectR3Rec	$f \times \frac{1}{gamedurR3} \times InfectR3$
InfectR3A → RecR3A	InfectR3RecA	$(1 - f) \times \frac{1}{gamedurR3A} \times InfectR3A$
InfS → Failures-SETF	SETF	$f \times p_{SETF} \times \frac{1}{SETFday} \times InfS$
InfS → FailuresSLTF	SLTF	$f \times p_{SLTF} \times \frac{1}{SLTFday} \times InfS$
InfR5 → FailuresR5ETF	R5ETF	$f \times p_{R5ETF} \times \frac{1}{R5ETFday} \times InfR5$
InfR5 → FailuresR5LTF	R5LTF	$f \times p_{R5LTF} \times \frac{1}{R5LTFday} \times InfR5$
InfR3 → FailuresR3ETF	R3ETF	$f \times p_{R3ETF} \times \frac{1}{R3ETFday} \times InfR3$
InfR3 → FailuresR3LTF	R3LTF	$f \times p_{R3LTF} \times \frac{1}{R3LTFday} \times InfR3$
InfS → Failures-SETFA	SETFA	$(1 - f)p_{SETFA} \times \frac{1}{SETFAday} \times InfSA$
InfS → FailuresSLTFA	LTFA	$(1 - f)p_{SLTFA} \times \frac{1}{SLTFAday} \times InfSA$
InfR5 → FailuresR5ETFFA	R5ETFFA	$(1 - f)p_{R5ETFFA} \times \frac{1}{R5ETFFAday} \times InfR5A$
InfR5 → FailuresR5LTFFA	R5LTFFA	$(1 - f)p_{R5LTFFA} \times \frac{1}{R5LTFFAday} \times InfR5A$
InfR3 → FailuresR3ETFFA	R3ETFFA	$(1 - f)p_{R3ETFFA} \times \frac{1}{R3ETFFAday} \times InfR3A$
InfR3 → FailuresR3LTFFA	R3LTFFA	$(1 - f)p_{R3LTFFA} \times \frac{1}{R3LTFFAday} \times InfR3A$

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morbidity and mortality and results in approximately 4400 – 67000 malaria-related deaths each year for all age groups. It has been estimated that malaria constitutes 15% of the disease burden in the population with higher estimates for children under the age of two. [Bradbury and Edward, 2001]

The Lubombo Spatial Development Initiative (LSDI) is a cross-border collaboration between the governments of South Africa, Mozambique and Swaziland aimed at economic development of the Lubombo region. The geographic area targeted by this initiative is southern Mozambique. [LSDI, 2005] The LSDI has an extensive and successful malaria control programme. Though indoor residual spraying had been in use since 1943, the LSDI began its comprehensive spraying programme in 2000. This programme reported dramatic reductions mosquito prevalence and malaria transmission. [Mabaso et al., 2004] In Mozambique the study aimed to provide surveillance of parasite prevalence and DHFR and DHPS mutations over a 5 year period prior to and following the introduction of ACT. With regards to drug treatment strategy, SP was the first line treatment in southern Mozambique at the start of the study until it was replaced by ACT(artesunate and SP) in 2004. [Enosse et al., 2008] The data that is used to inform the parameters and starting conditions of the model simulation comes from the LSDI and South East African Combination Antimalarial Therapy Evaluation (SEACAT) project for the period 1999 to 2007. The SEACAT study is a joint collaboration between Mozambique, Swaziland and South Africa to assess the effectiveness of artemisinin based combination therapy in curbing the development and spread of resistance. [SEACAT, 2001] The SEACAT study was a randomised control trial where patients infected with malaria parasites in Mozambique were followed for a period of 42 days between 2003 and 2004.

4.2.2 Parameters and their sources

Given that the model is run in a setting suitable to Mozambique, parameters as displayed in Table 4.9, have been derived from data where data has been available. All data analysis was performed in STATA Ver8.2.[STATA, 2008] Otherwise referenced values were used or assumptions made. Where data analysis has driven the choice of parameters, the full output is available in the Appendices.

Resistance categories

Resistance to SP has already been classified according to Res0, Res3 and Res5 infections. As mentioned in the discussion of Wirichada Pongtivorin-pinyo's PhD thesis, resistance will be assessed using mutation counts directly rather than through clinical outcomes. Thus DHFR and DHPS markers are used to create the Res0, Res3 and Res5 categories. The resistance categories will be classified according to Table 4.3. The Res3 infection category consists of infections that have the DHFR triple (108+51+59) as well as two DHFR markers and 1 DHPS marker. However because of the sequential accumulation of mutations, humans generally acquire the three DHFR markers before the DHPS markers and hence Res3 infections will pre-dominantly reflect the DHFR triple mutation.

Table 4.3: Resistance Classification by Mutation

Resistance Class	DHFR Mutations	DHPS Mutations
Res0	0	0
Res3	108 + 51, 108 +59,108 + 51 + 59	437, 540
Res5	108 + 51 + 59	437 + 540

Vector parameters

Mosquito density (number of mosquitoes per human) has decreased over the years through the use of extensive vector control in Mozambique from 2000.[Casimiro et al., 2007] The starting value for mosquito density was assumed to be 1.5 per human, with a sensitivity range of 1 to 2. This starting value is further decreased in time due to the introduction of vector control. Sharp et al. [2007] provides parasite prevalence rates between 1999 and 2005 and personal communication with the Medical Research Council provided prevalence rates for 2006 and 2007. Raman [2008] A linear regression was performed between the parasite prevalence and time (years) and the relationship was applied to the starting value of mosquito density. Output of this regression is presented below. The slope coefficient was -0.07725 (annually) with a 95% confidence interval of (-0.0622; -0.0923) and an R² of 95.5% and hence mosquito density will be decreased annually using this slope coefficient.

Regression between parasite prevalence and time

regress prevalence time

Source	SS	df	MS	Number of obs = 9		
Model	.358053762	1	.358053762	F(1, 7)	=	147.52
Residual	.016990253	7	.002427179	Prob > F	=	0.0000
				R-squared	=	0.9547
				Adj R-squared	=	0.9482
Total	.375044015	8	.046880502	Root MSE	=	.04927

prevalence	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
time	-.07725	.0063603	-12.15	0.000	-.0922896	-.0622104
_cons	.7539167	.0357912	21.06	0.000	.6692839	.8385495

The value for the human biting rate is 0.3 with a sensitivity range of 0.27 to 0.33. The human biting rate differs between low and high transmission settings. Given that Mozambique is a low transmission area, a value for the human biting rate was selected according to referenced values. The mosquito mortality rate value is 0.1 with a sensitivity range of 0.08 to 0.12 and the parasite incubation period is 11 days. These values have been referenced widely (see Table 4.9) and used extensively.

Host parameters

In this model, the human birth rate and death rate are assumed to be balanced. The estimated birth rate for Mozambique is 38 births per 1000 people per year. [CIA, 2008, Encarta, 2008] The probability of human susceptibility b_2 captures the infectiousness of mosquitoes to humans and has been assigned a value of 0.8 as was used in Laxminarayan [2004]. The probability of human infectiousness parameters (b_1) have been derived from the data. The carriage of gametocytes in the sexual stage of the parasite's development in the human is responsible for infection of mosquitoes. There is a log-sigmoid relationship between gametocyte density and infectivity to a mosquito. [Barnes and White, 2005] This infectivity is thus the value of the human infectiousness parameter b_1 . Human infectivity was calculated by taking the gametocyte density in patients on day 7 and applying the log-sigmoid equation of Jeffery and Eyles [1955] adapted in Barnes and White

[2005]. Day 7 was chosen as this day represented the highest average gametocyte density in patients. The Barnes and White [2005] log-sigmoid relationship is

$$Infectivity = \frac{13.07848 + 68.50295}{1 + e^{-2.501418(\log_{10}(gamedens) - 2.508097)}} \quad (4.74)$$

The Jeffery and Eyles [1955] estimates for infectivity based on gametocyte density data are presented in Table 4.4. These figures reflect how artemisinin acts upon gametocytes in addition to parasites.

Table 4.4: Infectivity

Infection	Treatment	
	SP	ACT
Res0	0.20	0.2
Res3	0.24	0.2
Res5	0.30	0.2

Because not all infected humans develop gametocytes as parasites are often cleared through drug treatment during the asexual stages, the probability of developing gametocytes is used to determine those who become infectious. The probability of developing gametocytes is presented in Table 4.5. Full details of the calculations are available in the Appendices.

Table 4.5: Gametocyte Prevalence

Infection	Treatment	
	SP	ACT
Res0	0.20	0.001
Res3	0.53	0.2
Res5	0.60	0.28

As mentioned in earlier, the time to gametocytemia as well as the duration of gametocytemia are used to determine the rate of inflow to and outflow from the Infectious stocks. The time to and duration of gametocytemia were calculated for those individuals who are sensitive to treatment and excludes those who had gametocytes at the start of treatment (day 0). This

is necessary as it assumed that if gametocytes are present on day 0, they are from a previous infection rather than the current one. In order to exclude these individuals as well as those who failed treatment, a survival analysis was performed using informative censoring. The results of this analysis are available in the appendices. Thus the time to gametocytemia was calculated as the median of the number of days before the start of gametocytemia and the duration is the median difference between the start and stop times of gametocytemia. The estimates along with their inter-quartile ranges are presented in Table 4.6. These estimates and their inter-quartile ranges show that under ACT, gametocytemia started later and had a shorter duration. Of interest in Table 4.6 is the relationship between gametocyte duration and start time for Res3 and Res5 infections. It is generally expected that Res5 infections having a selective advantage over Res3 infections would have a longer gametocyte duration. This does not appear to be the case under ACT. This anomaly may be due to the censoring process and will be discussed in detail in Chapter 7.

Table 4.6: Gametocyte start time and duration

	Treatment	
Gametocyte Start time		
Infection	SP	ACT
Res0	7 (7, 14)	14 (7, 21)
Res3	14 (7, 21)	17 (7, 21)
Res5	7 (7, 14)	10 (7, 14)
Gametocyte Duration		
Infection	SP	ACT
Res0	21 (7, 14)	14 (7, 21)
Res3	21 (7, 21)	14 (7, 21)
Res5	21 (7, 14)	11 (7, 14)

The treatment outcome probabilities were classified by both mutation category and drug. Individuals could either be cured or have an early or late treatment failure. These probabilities were estimated from the SEACAT study data and are presented in Table 4.7. As these are sample estimates it is important to assess their variability. As result these estimates will later be subjected to a sensitivity analysis.

Table 4.7: Treatment Outcome:SP and ACT

Infection	Treatment Outcome		
	SP		
	Cure	ETF	LTF
Res0	0.97	0.02	0.01
Res3	0.69	0.06	0.25
Res5	0.59	0.06	0.35
ACT			
Res0	0.97	0.02	0.01
Res3	0.94	0.04	0.02
Res5	0.94	0.04	0.02

Drug Parameters

The period of chemoprophylaxis values for SP from Watkins and Mosobo [1993] have been referenced widely and used extensively. They represent the time periods at which one may be susceptible to certain reinfections and the time in which SP is totally eliminated from the bloodstream. Watkins and Mosobo [1993] have found that the period of chemoprophylaxis for SP is 52 days i.e. it takes an average of 52 days for SP to be fully eliminated from an individual's bloodstream. This period of 52 days characterises the entire recovery process, where individuals may only move back to the susceptibles stock if 52 days has passed, or the individual is susceptible to all strains of infection.

The parameters on the time to treatment failure have been estimated from the data. Early treatment failures are all those whose time to treatment failure was less than or equal to 3 days and late treatment failures included those whose time to failure was greater than 3 days. These treatment failures exclude those whose treatment failed due to reinfection. The probabilities of treatment failure were also estimated from the data; the full output of which is presented in the appendices.

The proportion of treatment with SP f is a time-dependent function owing to ACT being introduced only in 2004. The treatment proportions are presented in Table 4.8. Year on year changes in f are decreased in a linear fashion.

Table 4.8: Proportion of treatment with SP and ACT

Year	Treatment	
	SP (f)	ACT (1-f)
1999	100%	0
2000	100%	0
2001	100%	0
2002	100%	0
2003	100%	0
2004	99%	1%
2005	69%	31%
2006	0	100%
2007	0	100%

Table 4.9 summarises all the parameters used in the model. The column headed 'Type' classifies parameter values as sourced from References (R), Data (D) or Assumptions (A).

Table 4.9: Summary of Model Parameters

Name	Description	Value	Unit	Range	Type	Source
Vector Parameters						
m	Mosquito density – No. of mos per human	$1.5(1 - 0.00021 \times \text{time}(\text{days}))$	$\frac{\text{Mosquitoes}}{\text{Human}}$	(1,2)	A&D	
a	Human biting rate	0.3	bites p/day	(0.27,0.33)	R	Koella and Antia [2003], Laxminarayan [2004], Klein et al. [2008], Dietz et al. [1974]
μ	Mosquito mortality rate	0.1	mos/day	(0.08, 0.12)	R	Koella and Antia [2003], Laxminarayan [2004], Klein et al. [2008], Gu et al. [2003]
τ	Parasite incubation time in vector	11	day	(10, 12)	R	Koella and Antia [2003], Laxminarayan [2004], Klein et al. [2008], Davidson and Draper [1953], Dietz et al. [1974]

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Table 4.9 – Continued

Name	Description	Value	Unit	Range	Type	Source
Host Parameters						
δ	Daily birth/death rate	$\frac{38}{1000} \times \frac{1}{365}$	deaths/day	1.041×10^{-4}	R	CIA [2008], Encarta [2008]
b_2	Infectiousness of mosquitoes to humans (Human Susceptibility)	0.8	prob	(0.65,0.95)	R	Laxminarayan [2004], Gu et al. [2003]
b_{1S}	Infectiousness of humans to mosquitoes (R0)	SP=0.2; ACT=0.2	prob	(0.1,0.3) (0.1,0.3)	D	
b_{1R5}	Infectiousness of humans to mosquitoes (R5)	SP=0.3; ACT=0.2	prob	(0.2, 0.4) (0.1,0.3)	D	
b_{1R3}	Infectiousness of humans to mosquitoes (R3)	SP=0.24; ACT=0.2	prob	(0.14, 0.34) (0.1, 0.3)	D	
Gstart.	Time to gametocytemia (SP)	R0=7 R3=14 R5=7	prob	(5,9) (12,16) (5,9)	D	
Gstart.	Time to gametocytemia (ACT)	R0=14 R3=17 R5=10	prob	(12,16) (15,19) (10,12)	D	
Gdur.	Duration of gametocytemia (SP)	R0=21 R3=21 R5=21	prob	(19,23)	D	

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Table 4.9 – Continued

Name	Description	Value	Unit	Range	Type	Source
Gdur-	Duration of gametocytemia (ACT)	R0=14 R3=14 R5=11	prob	(12,16) (12,16) (10,12)	D	
<i>p</i> _{Inf-}	Probability of gametocytemia (SP)	R0=0.2; R3=R0*2.5 R5=R0*2.6	prob	(0.15, 0.25) (2.3, 2.7) (2.4, 2.8)	D	
<i>p</i> _{Inf-A}	Probability of gametocytemia (ACT)	R0=0.1; R3=R0*2 R5=R0*2.2	prob	(0.05, 0.15) (1.8, 2.2) (2, 2.4)	D	

Drug Parameters

<i>r</i> (SP)	Parasite clearance time	<i>r</i> 0 = 7	day	(5, 9)	R/D	Watkins and Mosobo [1993], Prudhomme-O'Meara et al. [2006]
	Recovery rate (Rec);	<i>r</i> 1 = 45		(43, 47)		
	Recovery rate (RecS)	<i>r</i> 1 <i>S</i> = 24		(22, 26)		
	Recovery rate (RecR5)	<i>r</i> 1 <i>R</i> 5 = 24		(22, 26)		
	Recovery rate (RecR3)	<i>r</i> 1 <i>R</i> 3 = 17		(15, 19)		
<i>r</i> (ACT)	Parasite clearance time;	<i>r</i> 0 <i>A</i> = 4	day	(3, 5)	D	
	Recovery rate (RecA);	<i>r</i> 1 <i>A</i> = 48		(46, 50)		
	Recovery rate (RecSA)	<i>r</i> 1 <i>S</i> <i>A</i> = 24		(22, 26)		
	Recovery rate (RecR5A);	<i>r</i> 1 <i>R</i> 5 <i>A</i> = 28		(26, 30)		
	Recovery rate (RecR3A)	<i>r</i> 1 <i>R</i> 3 <i>A</i> = 24		(22, 26)		

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Table 4.9 – Continued

Name	Description	Value	Unit	Range	Type	Source
<i>q</i>	Period of Chemoprophylaxis for Quinine	$q = 7$ $qSETF = q + 43$ $qSLTF = q + 24$ $qR5ETF = q + 43$ $qR5LTF = q + 24$ $qR3ETF = q + 43$ $qR3LTF = q + 35$	day	(5, 9)	R/D	Barnes [2008]
<i>R</i>	Days to treatment failure (SP)	$SETF_{day} = 2$ $SLTF_{day} = 21$ $R5ETF_{day} = 3$ $R5LTF_{day} = 21$ $R3ETF_{day} = 2$ $R3LTF_{day} = 10$	day	(1.5, 2.5) (19, 23) (2.5, 3.5) (19, 23) (1.5, 2.5) (8, 12)	D	
<i>R</i>	Days to treatment failure (ACT)	$SETF_{Aday} = 3$ $SLTF_{Aday} = 21$ $R5ETF_{Aday} = 3$ $R5LTF_{Aday} = 21$ $R3ETF_{Aday} = 3$ $R3LTF_{Aday} = 21$	day	(2.5, 3.5) (19, 23)	D	

Continued on Next Page...

Table 4.9 – Continued

Name	Description	Value	Unit	Range	Type	Source
p	Probability of Treatment Failure (SP)	$p_{SETF} = 0.02$ $p_{SLTF} = 0.01$ $PR_{5ETF} = 3p_{SETF}$ $PR_{5LTF} = 35p_{SLTF}$ $PR_{3ETF} = 3p_{SETF}$ $PR_{3LTF} = 25p_{SETF}$	prob	(0.015,0.025) (0.005,0.015) (2.5,3.5) (32,38) (2.5,3.5) (22,28)	D	
p	Probability of Treatment Failure (ACT)	$p_{SETFA} = 0.02$ $p_{SLTFA} = 0.01$ $PR_{5ETFA} =$ $2p_{SETFA}$ $PR_{5LTFA} =$ $2p_{SLTFA}$ $PR_{3ETFA} =$ $2p_{SETFA}$ $PR_{3LTFA} =$ $2p_{SLTFA}$	prob	(0.015,0.025) (0.005,0.015) (1.5,2.5)	D	
f	Proportion of SP treatment	Varies between 1 and 0	prob		D	

4.2.3 Start-up conditions for the simulation and Model Assumptions

The model is run for a period of 4000 days; approximately 11 years. The simulation is started at the conditions present in 1999 before the onset of extensive vector control. The proportions of the population present in each of stocks at the start of the simulation are presented in Table 4.10. These figures have been obtained from the LSDI study in Mozambique. The LSDI study provided data on parasite prevalence by mutation as at 1999. This data was then used to apportion individuals between stocks of the same mutation to get the model started. Because ACT was only introduced at a later stage, all stocks relating to ACT remain at zero until its time of introduction. While the values of the stocks are proportions of a population, the model is run on a hypothetical population of 1000 people to facilitate easier reading. This population has not been stratified according to gender, age or location.

The following assumptions have been made for the base model.

1. The human population is homogenous in that people are equally at risk of malaria infection given that they are equally likely to be bitten by the anopheles mosquito.
2. Given that Mozambique is a low transmission area, there is no developed or potential for developing long-term immunity to malaria. Temporary immunity only is included in the model.
3. All infected proportions of the population received treatment.
4. All treatment failures are assumed to be infectious.
5. There is no resistance to artemisinin or its derivatives and thus all resistance that develops is for SP only.
6. While treatment failure is a proxy for resistance, sensitive infections may result in treatment failure due to inter alia incorrect dosage, poor adherence and vomiting.
7. There is no superinfection (multiple infections before parasites of the first infection have been cleared) in the model.
8. There are no reinfections (infections that occur once parasites have been cleared but drug has not been totally eliminated from the bloodstream) in the model.

Table 4.10: Start-up conditions of the Simulation

Stock	Proportion of the population in 1999
Sus	0.25
InfS	0.328
InfR5	0.004
InfR3	0.053
InfectS	0.2
InfectR5	0.004
InfectR3	0.05
InfectSA	0
InfectR5A	0
InfectR3A	0
Rec	0.02
RecS	0.01
RecR5	0.004
RecR3	0.023
RecA	0
RecSA	0
RecR5A	0
RecR3A	0
FailuresSETF	0.001
FailuresSLTF	0.001
FailuresR5ETF	0.002
FailuresR5LTF	0.016
FailuresR3ETF	0.013
FailuresR3LTF	0.021

Chapter 5

Results

This chapter presents the results of the base model as well as test of sensitivity for the parameters used as inputs in the model. Extensions of the base model will also be presented in this chapter.

5.1 Base model Results

Interventions against malaria come in two main forms viz. antimalarial drug treatment and vector control. Depending on the intervention being implemented, different parameters will be affected. Since the parameters chosen in this model are suitable to a Mozambiquan setting, the model will need to reflect the corresponding antimalarial interventions.

Two interventions that were implemented in Mozambique were chosen to be modeled viz. vector control through indoor residual spraying from 2000 and a change of antimalarial drug treatment through the introduction of Artemisinin-based Combination Therapy in 2004. Given that indoor residual spraying affects number of mosquitoes available to transmit malaria, its effect is captured through the mosquito density parameter m . The introduction of ACT is captured through the treatment parameter f where f is the proportion of SP treatment and $(1 - f)$ is the proportion of ACT treatment.

The software used is Berkeley MadonnaTMX 8.3.22 for Macintosh; software aimed at the modeling and analysis of dynamic systems. [Berkeley-Madonna, 2008] The base model is run for a period of 4000 days (approximately 11 years) with time steps of 0.5 resulting in a total of 8000 iterations. The Runge-Kutta 4 integration method, part of the Runge-Kutta family of implicit and explicit iterative methods for the approximation of solutions to

ordinary differential equations, is used with starting conditions as malaria prevalence in Mozambique in 1999. The model code is provided in Appendix D. The layout of the code is such that the details of the model run are presented first: iteration technique, length of the run and time step size. This is followed by the differential equations with their starting values, equations of the flows and finally parameter values.

The graphs presented throughout the rest of this and the two following chapters are direct outputs from the modeling software. As result they are limited by the capabilities of the software. The software does not allow one to display units of the axes of graphs or change the axes titles to enable easier reading. In order to mitigate this problem Table 5.1 provides a list of stocks and flows that have been graphed with their units and explanations. It must be noted that many of the stocks with their explanations have already been presented in earlier tables. Further where the units are people, it is the number of people out of a total of 1000 which is the size of the simulated population. A feature of Berkeley Madonna is that all graphed items are suffixed by a number to indicate the number of the run. Hence where an item like Prevalence has been graphed once, it will be presented in the legend as Prevalence:1.

The impact of the interventions can only be investigated once the model has reached a steady state. Thus the model is first simulated without any interventions i.e. as if 100% SP treatment continued unabated and there was no vector control. At the steady state, transmission of malaria is balanced by the recovery process and prevalence of total malaria and the number of treatment failures has stabilised. Given these conditions, model outcomes on prevalence and resistance over time, will be due to the treatment interventions tested on the model. Figures 5.1 and 5.2 shows the steady state conditions of the model without any treatment interventions.

The total infection rate and recovery rate balance each other out very quickly meeting the conditions of a steady state. Prevalence also reaches a stable point in the first 500 days of simulation. The EIR of all infections is stable almost immediately and the number of treatment failures (the proxy for resistance) also reaches stability fairly quickly. The steady state appears to be reached in the first 500 days of simulation. Thus testing of scenarios occurs after this steady state has been reached.

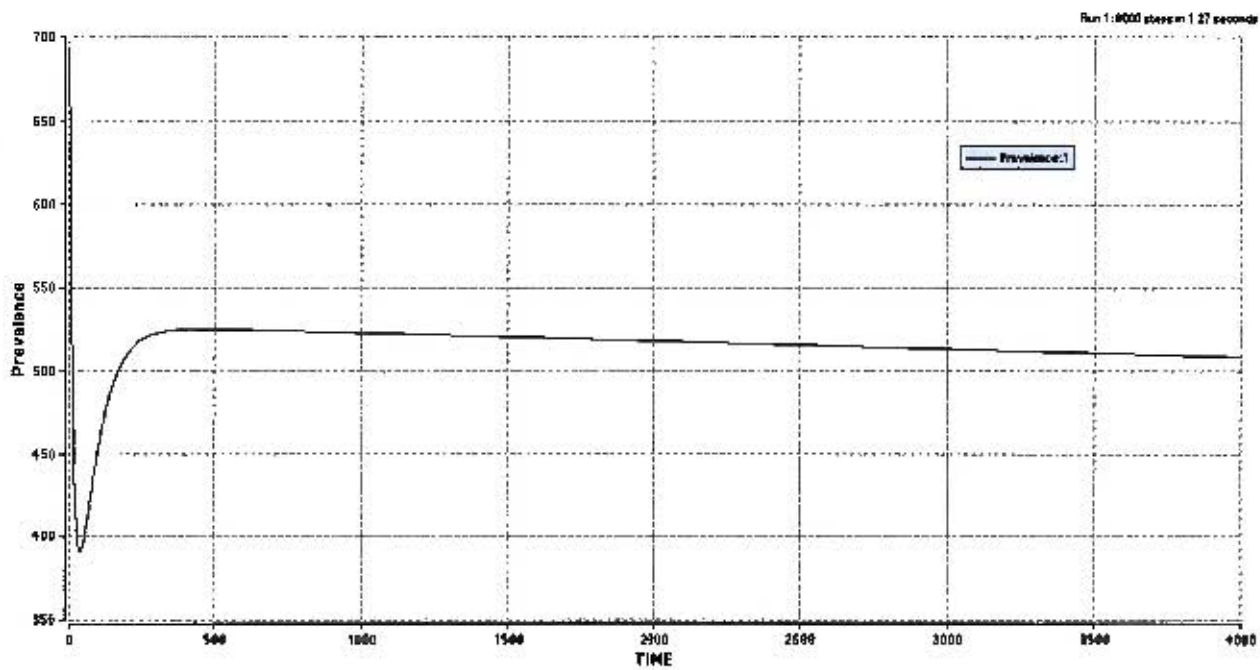
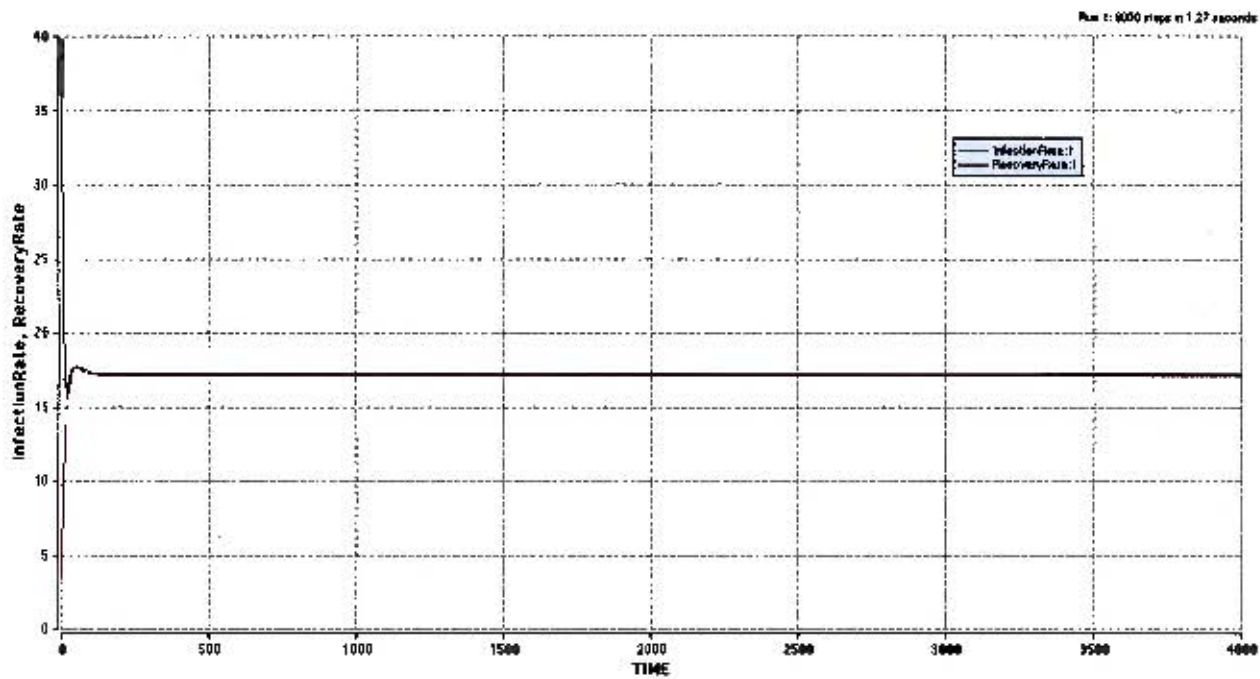


Figure 5.1: Steady state conditions: 1 (Basic model)

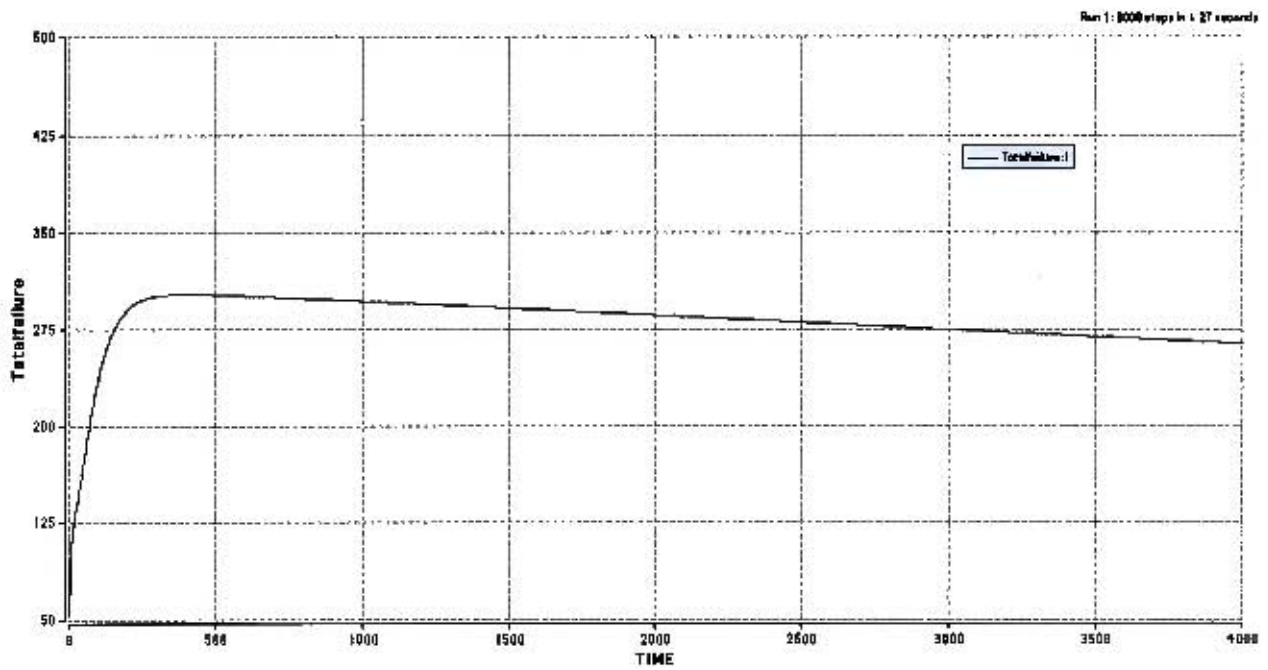
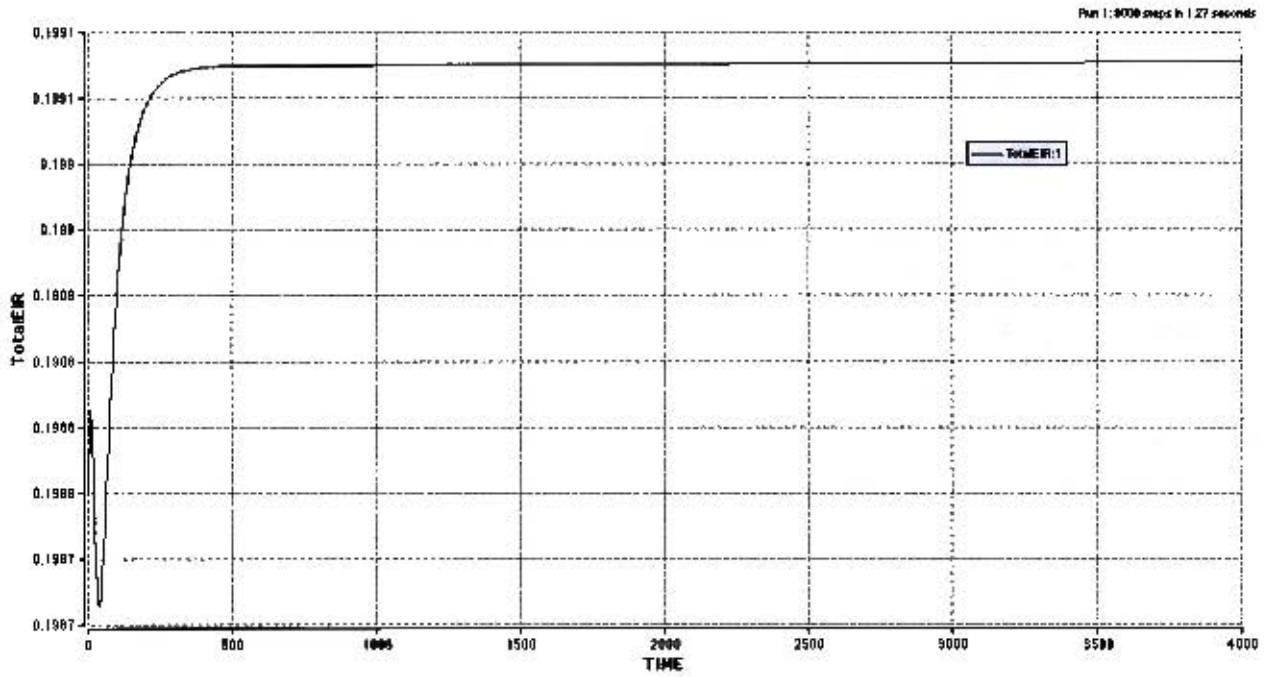


Figure 5.2: Steady state conditions: 2 (Basic model)

Table 5.1: Description of Graphical Outputs

Output	Description	Unit
Infection Rate	Total Number of new infections	people
Recovery Rate	Total Number of new recoveries	people
Prevalence	Total Infected population	people
TotalFailure	Total number of Treatment Failures	people
TotR5Failure	Total number of Res5 Treatment Failures	people
TotR3Failure	Total number of Res3 Treatment Failures	people
Sus	Number of Susceptible people	people
TotInfS	Total number of Res0 Infections	people
TotInfR5	Total number of Res5 Infections	people
TotInfR3	Total number of Res3 Infections	people
TotalEIR	Total number of Infectious bites	bites/human/day
EIRS	Total number of Infectious Res0 bites	bites/human/day
EIRR5	Total number of Infectious Res5 bites	bites/human/day
EIRR3	Total number of Infectious ResR3 bites	bites/human/day
R5toR3	Ratio of Res5 to Res3 Infections	Ratio
m	Mosquito Density	mosquitoes per human
f	SP Treatment proportion	Percentage

The model is now ready for investigating the effects of Mozambique's antimalarial interventions. Figure 5.3 depicts the trends in the hypothetical susceptible and infected population. This graph is shown in conjunction with graphs of mosquito density and treatment proportion to assess the impact of the policy interventions. Indoor residual spraying is initiated at time 500 once the steady state has been reached. This is seen through the decrease in m from this time point. The period of change-over from SP to ACT corresponds to time 1825 to time 2555. Details of this change-over strategy are provided in Section 4.2.2.

As can be seen, after an initial adjustment at the model start-up, the susceptible population increases considerably showing a decrease in overall malaria prevalence across the three infection strains. Sensitive infections while high initially decrease quickly to zero in the first 500 days. Res3 infections (infections with the DHFR triple mutation) increase dramatically in the first 500 days, decrease slightly in the next 1000 days and thereafter

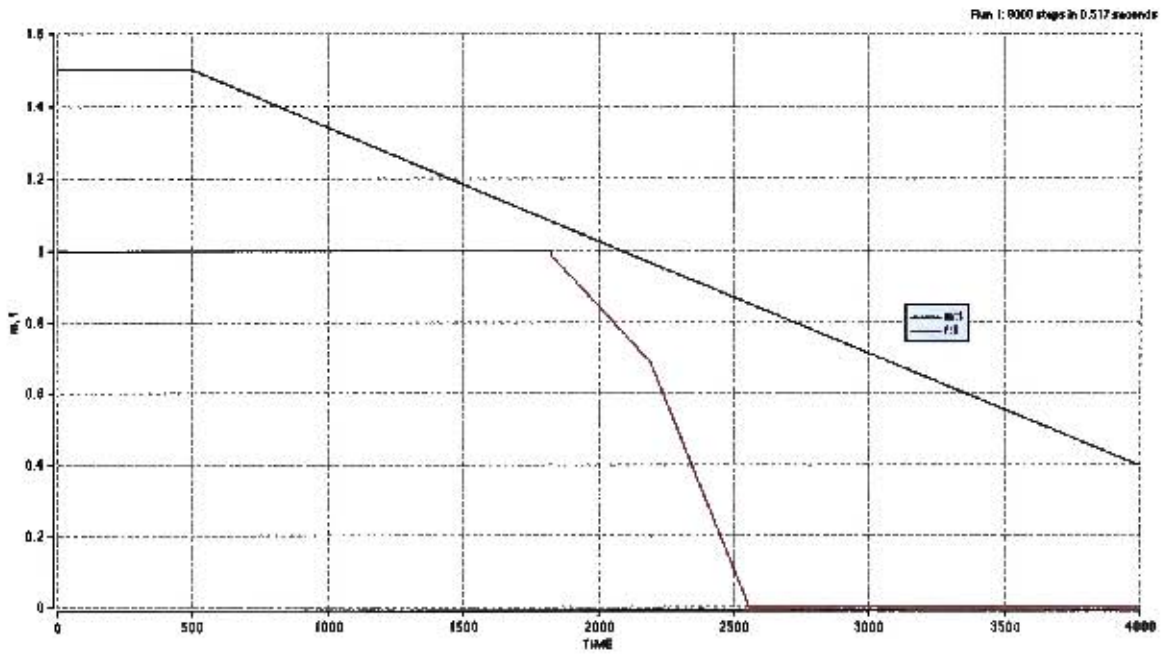
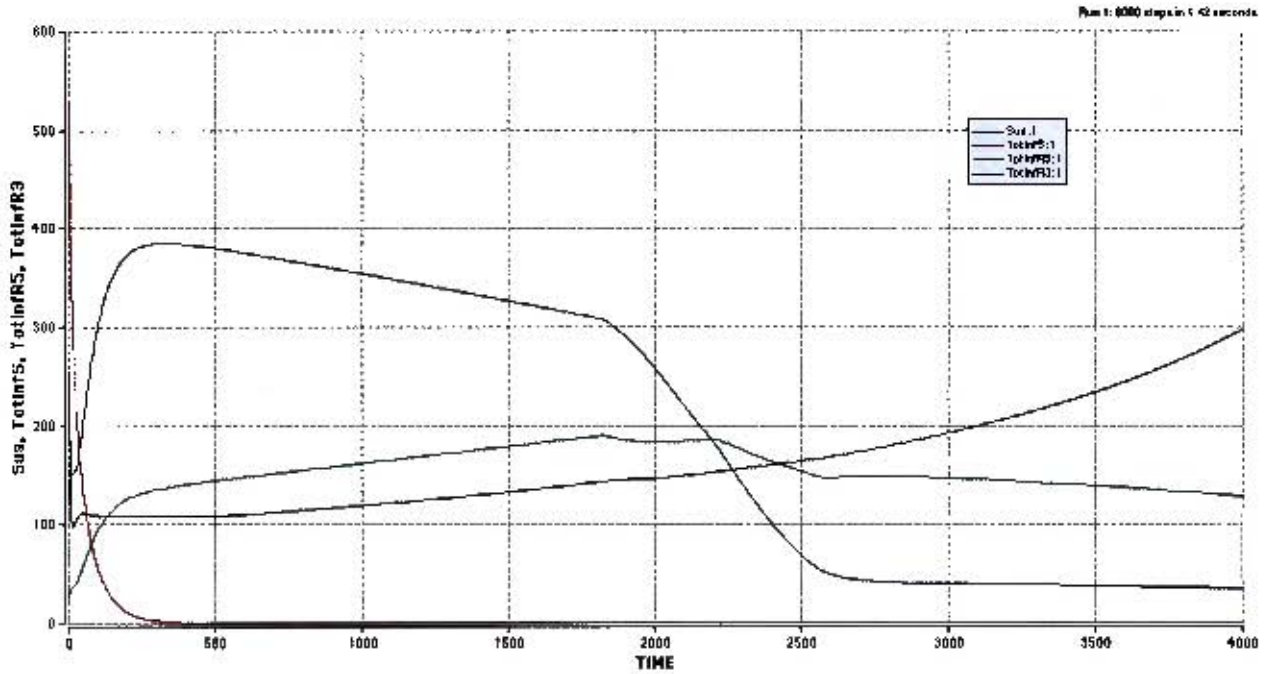


Figure 5.3: Trends in the Susceptible and Infected Population (Base model)

decrease to zero till the end of the simulation period. Res3 infections decrease rather fast during the period of change-over from SP to ACT and the steady decrease that occurs at other times corresponds with the vector control that decreases mosquito density continuously. While sensitive and Res3 infections were high at the start of the simulation, Res5 infections (infections with the DHFR triple and the DHPS double) start off quite low and increase steadily till day 2000, where they decrease slightly but remain at that level till the end of the simulation. It also appears that were it not for the change-over in policy to ACT Res5 infections would have eventually overtaken Res3 infections anyway but does so faster because of the introduction of ACT.

When viewed in conjunction with the mosquito density parameter m , the most that can be said is that the steady decrease in m may have lead to an overall decrease in infection which may be viewed through a steady increase in the susceptible population. This is because both the introduction of ACT and vector control may have contributed to this decrease. The direct ramifications of the IRS policy intervention will be discussed in Chapter 6 entitled Scenario Testing where it will be tested alone. Though the ramifications of the ACT policy will also be explored fully in the afore-mentioned chapter, its associations with the infection strains are quite noticeable. Sensitive infections are reduced to zero during the period at which $f = 1$. During this period, Res5 infections remain low while Res3 infections reach a high stable point. The decrease in f from 0.68 to 0 is accompanied by a decrease to almost zero in Res3 infections and a slight decrease in Res5 infections. The susceptible population while increasing steadily when $f = 1$ increases even faster as ACT coverage approaches 100%.

Figure 5.4 shows overall prevalence and infection composition of malaria in a Mozambiquan setting.

Prevalence of malaria, that is total infection (Res0, Res3 and Res5 infections) decreases by approximately 70% during the 11 year period of simulation. While total infection decreases, the composition of infection changes considerably. The ratio depicted is the ratio of Res5 infections to Res3 infections. This ratio remains below unity or 1 while $f = 0$. Thereafter it escalates quickly past 1 to more than 3.5 as ACT gains 100% coverage.

In Figure 5.5 the EIR's represent the number of infectious bites per human per day. As vector control comes into play from time 500, the EIR's for Res0 and Res3 strains decrease until the ACT coverage reach 100% while the EIR for Res5 infections remains relatively constant. Thereafter, the EIR for Res5 infections increases as is to be expected given that total Res5 infections increased and the EIR for Res3 infections decreases until the end of the simulation period. TotR3Failures and TotR5Failures represent those individuals infected with a Res3 or Res5 infection respectively who having developed resistance to the SP either through an early or late treatment failure. One of the model assumptions is that Treatment failure, while it is being used as a proxy for resistance, may also be caused by other factors such as incorrect dosage and vomiting. Thus while there are still some early treatment failures when ACT coverage is 100%, these treatment failures are not indicative of resistance as to date there is no resistance to artemisinin in artemisinin-based combination therapy in Mozambique. One can see that Res3 treatment failures while high initially decrease very gradually due to vector control but experience a substantial decrease when ACT coverage reaches 100%. Res5 infections on the other hand increase steadily even when vector control is in effect and then decreases once ACT comes into effect but still remains higher than Res3 infections. Thus it appears that while ACT decreases total resistance, it results in more Res5 resistant infections than Res3 resistant infections. These results will be further explored in Chapter 6.

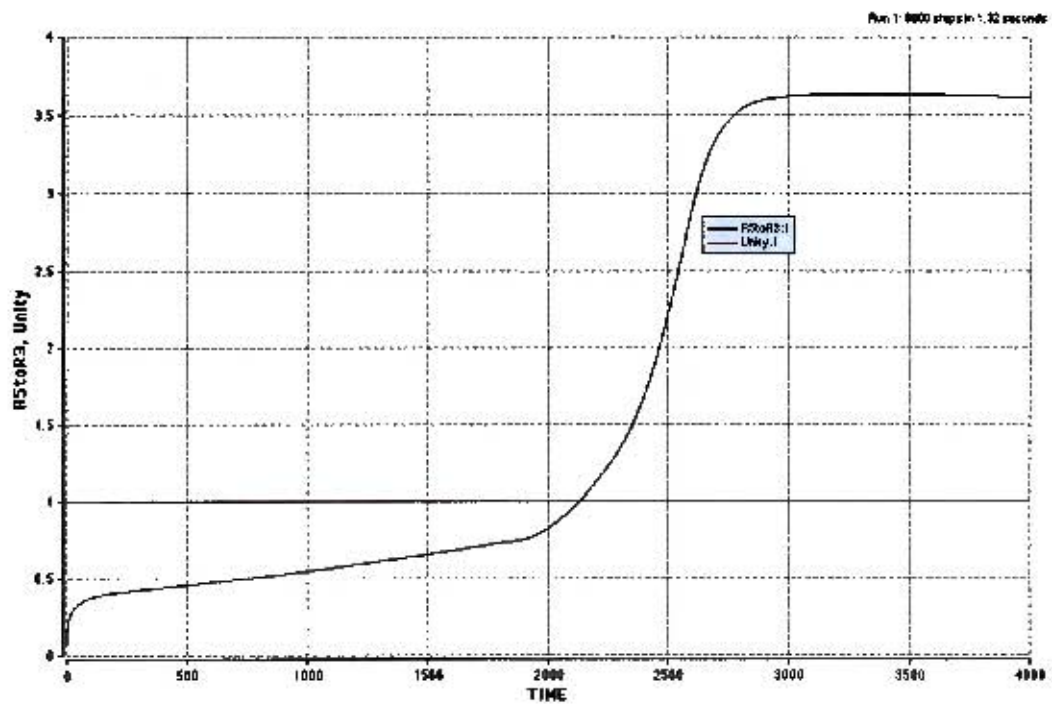
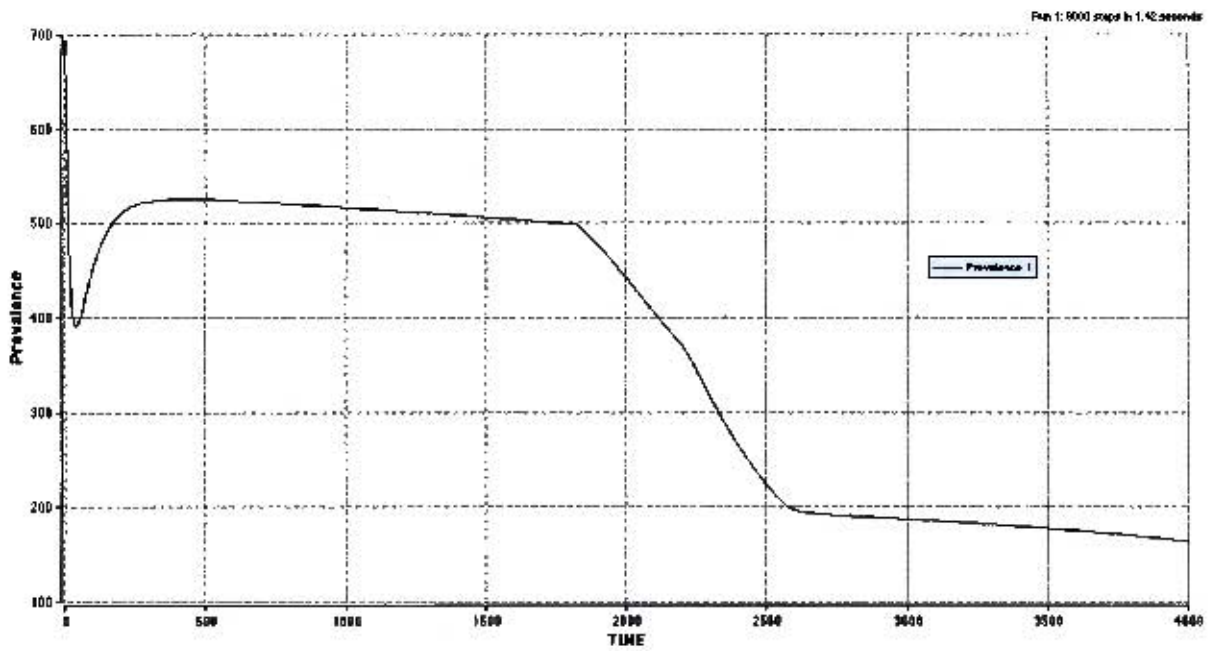


Figure 5.4: Prevalence and Infection composition (Base model)

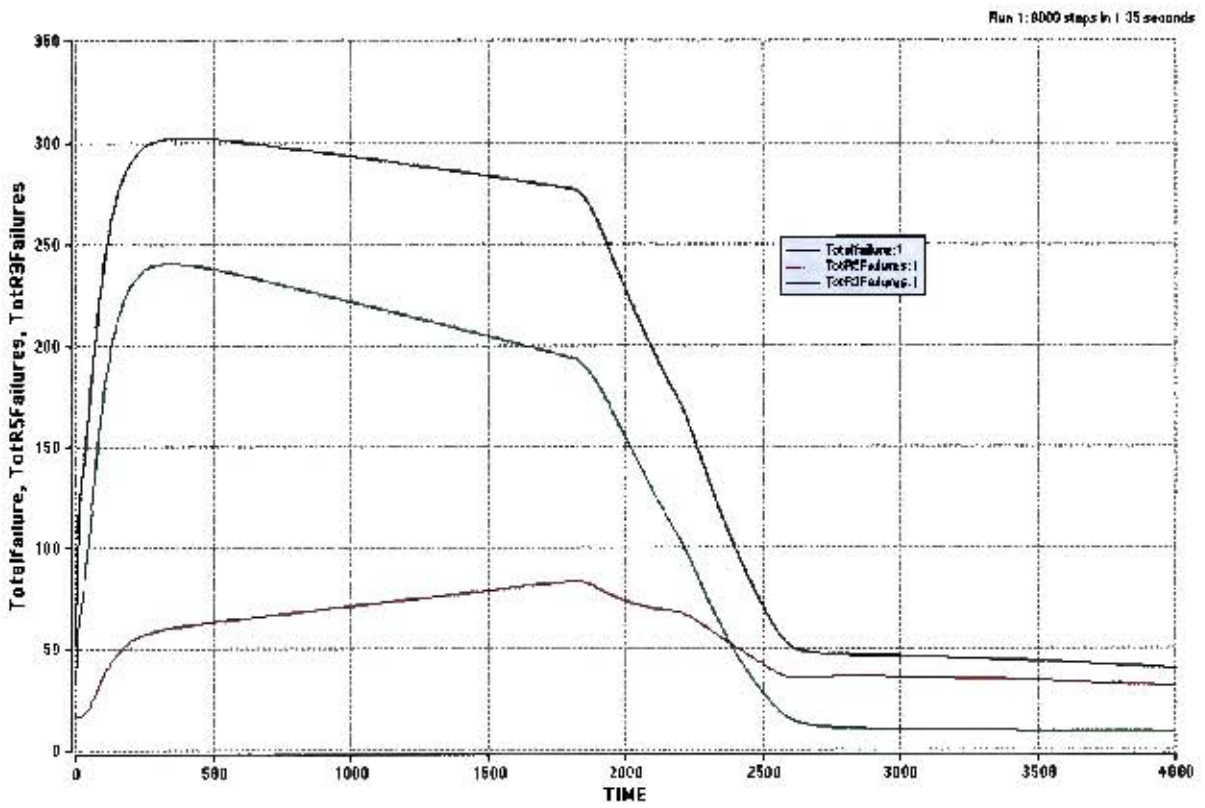
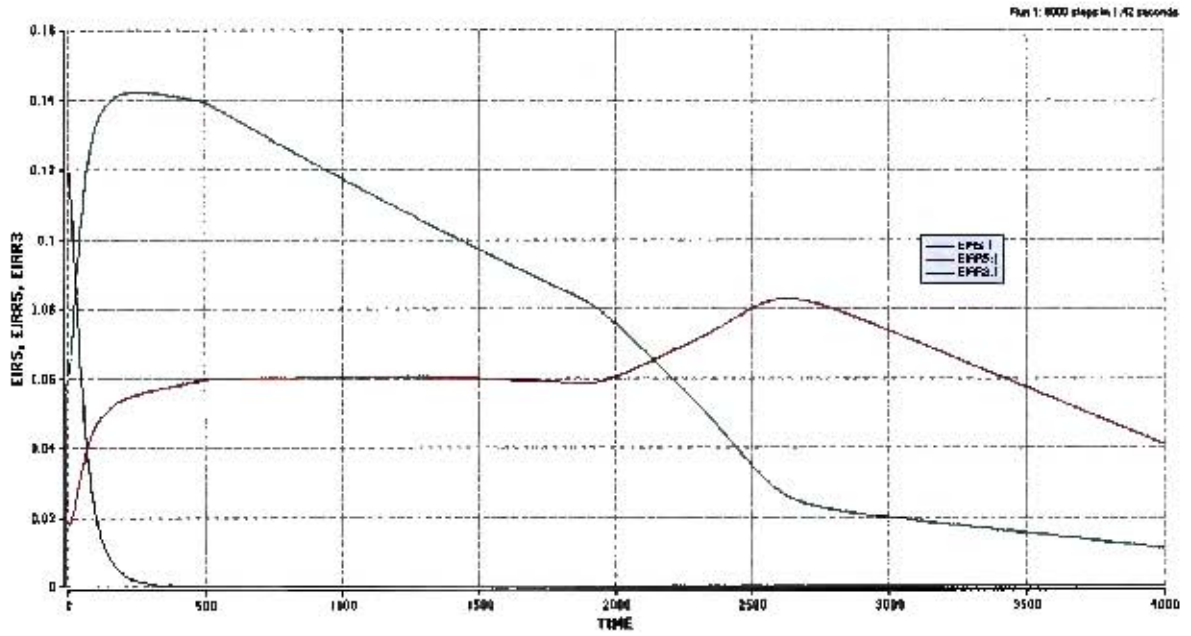


Figure 5.5: Entomological Inoculation Rates and Failure Rates (Base model)

It is of interest to compare the results of the base model to actual data recovered from the SEACAT and LSDI studies conducted in Mozambique. Figures 5.6 and 5.7 show observed data for the prevalence and individual mutation prevalence of malaria in Mozambique. The prevalence and infection rates here have been expressed in percentages rather than people (out of 1000) as was the case in earlier graphs.

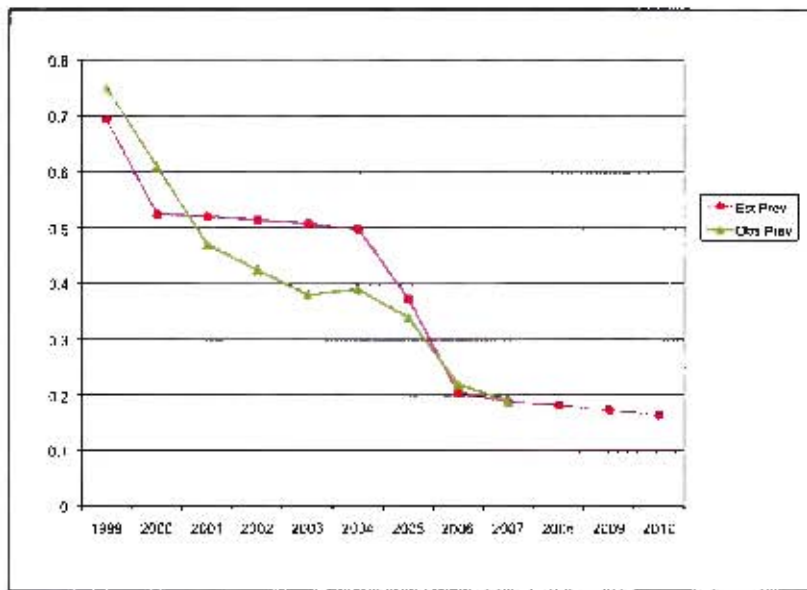


Figure 5.6: Comparison of model prevalence to observed prevalence from Mozambique

Figure 5.6 shows that prevalence drops quite dramatically in the eight years for which data is available. Prevalence decreases from 75% to just below 20% which is in line with the model results that show a reduction of prevalence from 75% to approximately 16%. Thus the model appears to estimate correctly the overall effectiveness of the antimalarial interventions. But the model appears to underestimate the effect of vector control as shown by the sharp decrease in the observed prevalence and gradual decrease in the estimated prevalence. This is particularly evident between 2000 and 2004 when vector control was the only antimalarial intervention (apart from the use of SP). However, once ACT coverage is 100%, the model correctly estimates the decrease in prevalence through a combination of both treatment

strategies.

Figure 5.7 plots observed rates of infection in Mozambique for the period 1999 to 2007 and shows that while prevalence has decreased dramatically, the composition of infection strains has also changed from the conditions prevalent in 1999. In the case of infections sensitive to SP treatment, the number of infections decreases quickly in the first four years to just above zero and then decreases slowly to zero over a period of approximately 3 years. The model also shows this decrease in Sensitive infections as illustrated in Figure 5.3; albeit at a much faster pace. This decrease is alongside marked increases in Res3 infections as also captured in the simulated model. These infections decrease rapidly as ACT coverage reaches 100%. Observed Res5 infections remain low until ACT coverage reaches 100% and then increase to overtake Res3 infections. The simulated model shows that Res5 infections remain low but increase steadily. When ACT coverage reaches 100%, Res5 infections overtake Res3 infections and remain high for the duration of the simulation. It must be noted here that the model overestimates the increases in both Res3 and Res5 infections.

Hence the magnitude of the impact of the antimalarial interventions of artemisinin-based combination therapy have been correctly captured by the model while the model underestimates the magnitude of the impact of vector control. However, the trends and effects of these interventions are certainly depicted in the model results though changes seem to occur too fast in the model.

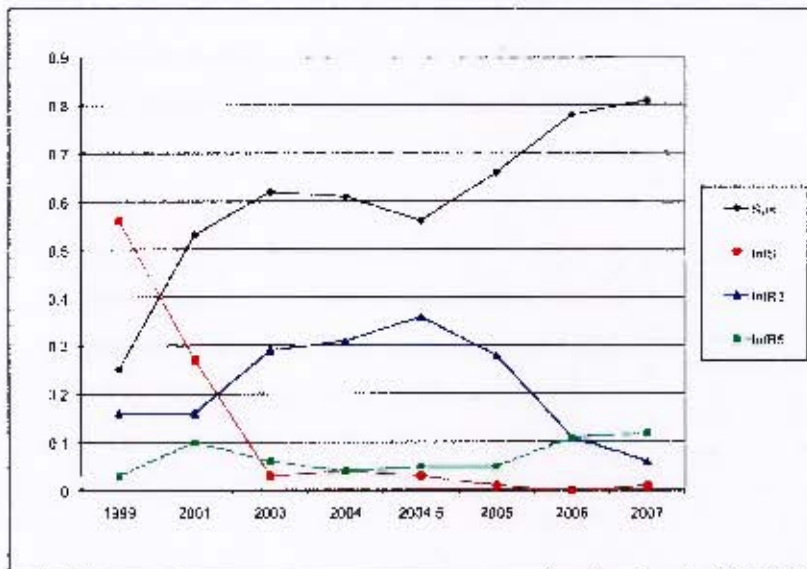


Figure 5.7: Prevalence and Infection composition: Observed Data from Mozambique

5.2 Sensitivity Testing

Table 4.9 provides the ranges for each parameter that will be tested in the sensitivity analysis. Sensitivity testing of the parameter values is conducted in this section whereas scenario testing is performed in Chapter 6. The sensitivity of individual parameters is tested by running the model with varied values of each parameter and assessing the effect of its change graphically.

The first group of parameters to be tested were the vector parameters as labelled in Table 4.9. When the parameters were tested individually, the model exhibited sensitivity to the mosquito density parameter m . Figure 5.8 shows Sus, Prev and TotRec to be somewhat more sensitive to changes in m than the distribution between the infection strains.

The next group of parameters to be tested were the host parameters. Graphs of these and other sensitivity tests are presented in Appendix B. Changes in the drug elimination parameter r_0 impacted both the magnitude and timing of movements in Res0, Res3 and Res5 infections as seen in

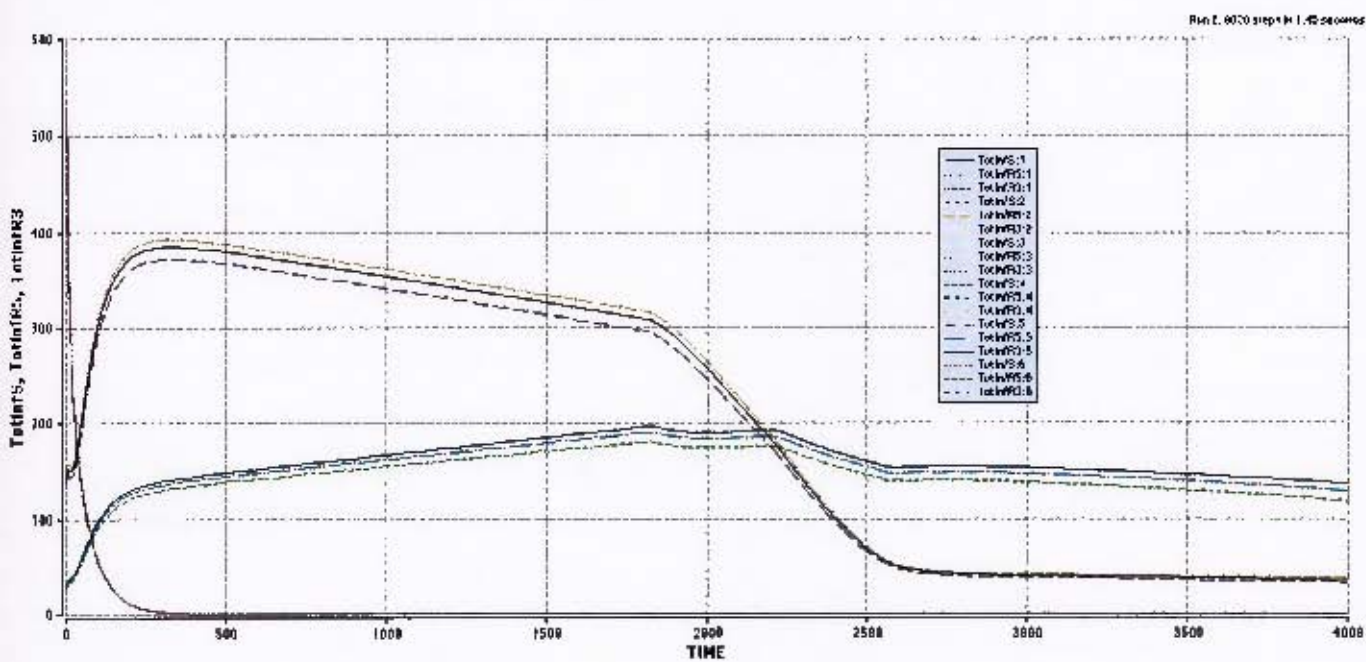
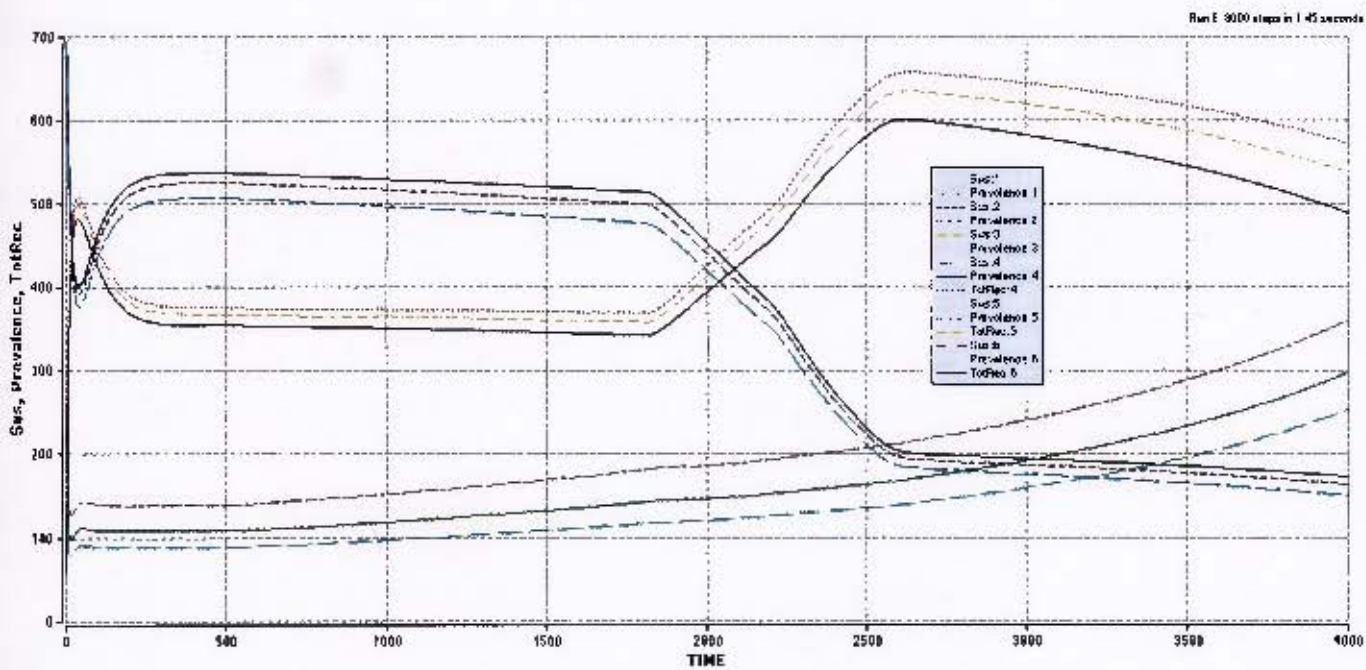


Figure 5.8: Sensitivity Testing: Mosquito Density m

Figure B.1 while affecting prevalence, total failures and susceptibility to a lesser extent.

The human infectiousness parameters b_1 and the time to and duration of gametocytemia were tested for sensitivity against prevalence and EIR's. Changes in the human infectiousness parameters did not impact total prevalence greatly, but the following parameters influenced the composition of infection strains and the EIR's for Res3 and Res5 infections greatly viz. the time to and duration of gametocytemia for Res3 and Res5 infections that were treated with SP. This is presented in Figure B.2. Treatment outcome parameters were also tested for sensitivity to the model. While changes in the treatment outcome probabilities did not impact overall prevalence, the EIR's for Res3 and Res5 infections were sensitive to changes in the probabilities of early treatment failure as depicted in Figure B.3. The sensitivity test results for time to failure were very similar to that of the treatment outcome probabilities and are depicted in Figure B.4.

5.3 Extension of Base Model: Pharmacokinetic properties of SP

The models in this thesis aim to make three adaptations to previous models viz. model infections stratified by mutations rather than sensitive/resistant, use gametocyte data to inform human infectiousness and model infectiousness directly, and model the pharmacokinetic properties of SP. The base model incorporates the the first two components and this extension of the model incorporates the infection stratification and pharmacokinetic properties of SP. The joint modeling of these three aspects is discussed further in Chapter 7.

In the base model, infected individuals who are sensitive to treatment take 52 days to recover to a state where they may be infected again with a Res0, Res3 or Res5 infection. Usually models use the parasite clearance time as the recovery time in a model in order to reach the susceptible state. This is not strictly true because even though one's parasites have cleared, there is still enough residual SP in the bloodstream to counter infection with Res3 or Res0 infections. The assumption in the base model is that individuals may not be reinfected with malaria until SP has been totally eliminated from the bloodstream i.e.until individuals have passed through the recovered state. However, it is true that during the SP elimination phase, a stage is reached

where SP drug levels are low enough to allow some Res5 and even Res3 infections. Thus the pharmacokinetic properties of SP will be included in the base model in order to relax this assumption.

5.3.1 Model Building

Throughout this model building procedure, a number of stocks and flows are referred to by name. A description of these stocks and flows are provided in Tables 5.2 and C.2 respectively. A description of the parameters used to inform the flows is provided in Table C.1. In order to incorporate the pharmacokinetic properties of SP, one may add five more stocks to the model as has been done in Figure 5.9. This incorporation has been done in accordance with Prudhomme-O'Meara et al. [2006] as discussed in the Literature Review. Additions to the previous model are depicted in red. Note once again that aliases of a few stocks have been used to enable easier illustration.

The focus in this extension of the model is on the pharmacokinetic properties of SP. Because of this, becoming infectious is not included in this model owing to an overlap in the timing of the two processes. For example, an individual's development of gametocytemia occurs at the same time as SP is being gradually eliminated from the bloodstream. Hence the modeling of the pharmacokinetic properties of SP takes precedence because it was not modeled in the base model. Further there is insufficient gametocyte data to model both aspects simultaneously and in the absence of data, we can model only the PK component. As will be presented later, the gametocyte data is still used to limited effect in this model extension. In the base model, once an individual recovered from an infection, they were moved to a recovery stock where they experienced temporary immunity to infection until SP was fully eliminated from their bloodstream. This assumption is not true because though one experiences temporary immunity from sensitive infections, one is still susceptible to certain resistant strains of infection. Thus the recovery process in the base model is broken down to reflect the drug elimination process more clearly.

In this model, after being infected with a Res0 infection, a person is treated with a therapeutic dose of SP. A patient is theoretically always susceptible to a fully resistant reinfection.[Hastings et al., 2002] This model does not allow for superinfection and hence the time between the onset of infection and susceptibility to a Res5 infection is the parasite clearance time.

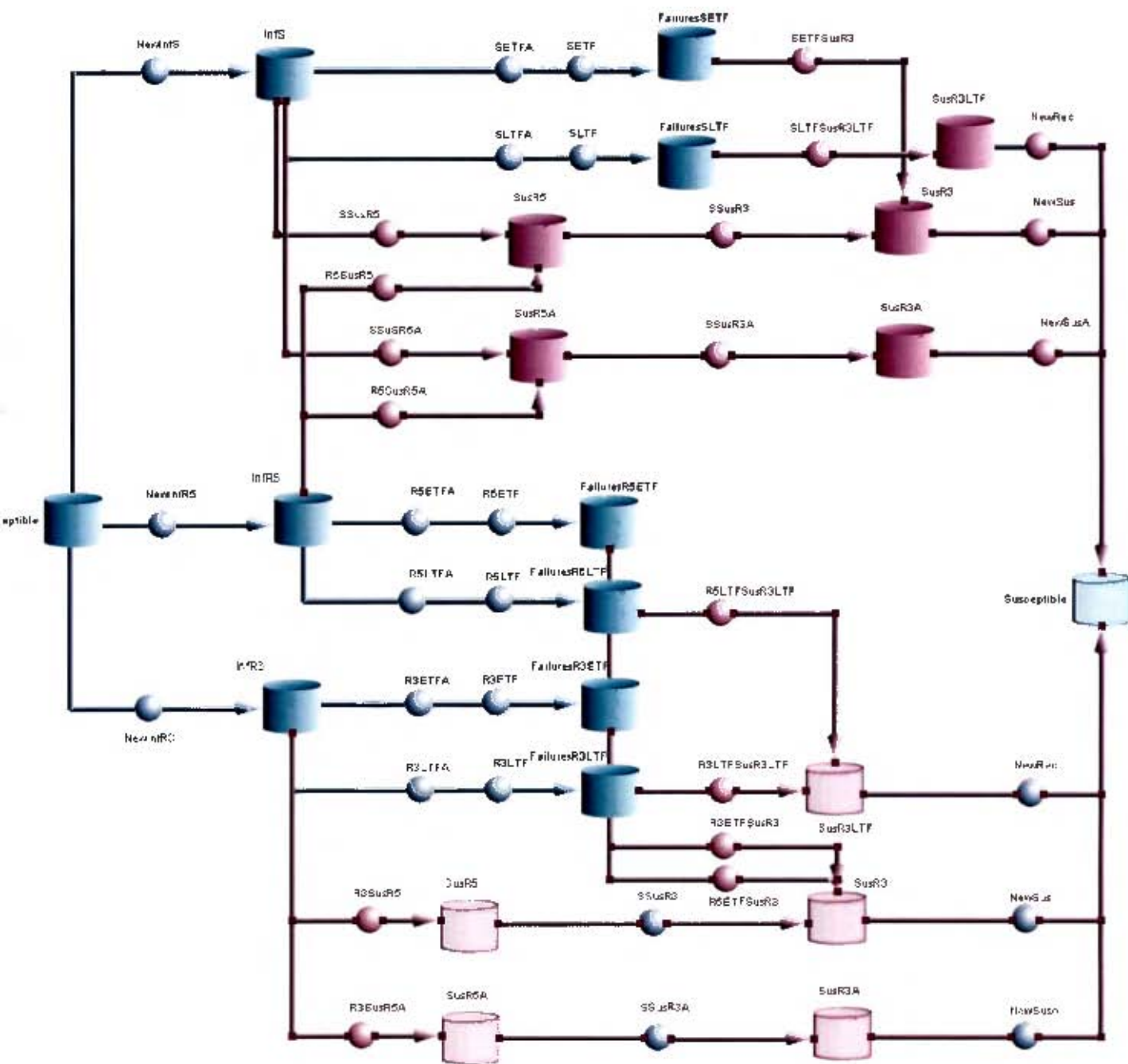


Figure 5.9: A model of resistance with the pharmacokinetic properties of SP

Thus after having being infected with a Res0 infection and treated with SP, the population moves to the SusR5 stock where they are susceptible to Res5 infections only but there is still sufficient drug in the bloodstream to counter Res0 and Res3 infections. As the drug concentration reduces further in the bloodstream, the population in the SusR5 stock becomes susceptible to Res5 and Res3 infections. They are then moved to SusR3 where there is sufficient drug to counter a Res0 infection but not Res3 and Res5 infections. As the drug is totally eliminated from the bloodstream, populations are once again susceptible to all strains of infection. This is the infection path for populations infected with sensitive Res0, Res3 and Res5 infections. This can be seen in Figure 5.9. Upon being infected with a Res0, Res3 or Res5 infection, a proportion of the infected population is treated with SP and the residual with ACT. Individuals will have residual SP in their blood after the elimination of artemisinin at levels that allow reinfections of R3 and R5 type. [Hastings et al., 2002] Thus the pharmacokinetic properties of SP are also included in the model for both treatment arms. Stocks that are suffixed with 'A' are for infections treated with ACT.

As was the case previously, early and late treatment failures result from Res0, Res3 and Res5 infections and are sent to their own Failure stock. Thereafter they are hospitalised and rescued with quinine. There is no drug interaction between quinine and SP and once the quinine has been eliminated from the bloodstream, a level of SP remains providing some protection against Res0 or sensitive infections. Hence both early and late treatment failures become susceptible to both Res3 and Res5 reinfections after they have been rescued. Early treatment failures move into the SusR3 stock and Late treatment failures move into their own SusR3LTF stock from where they become susceptible again once SP has been fully eliminated from their bloodstream. The reason for separate stocks stems from the different drug elimination rates for those rescued from early and late treatment failures because LTF's occur later than early treatment failures. It must be noted here that early treatment failures move to the SusR3 stock only because they reach complete susceptibility at the same rate as those individuals in the SusR3 stock. Thus it is a matter of modeling convenience. The equations underlying Figure 5.9 are available in Appendix C.

Given that susceptibility to Res3 and Res5 infections in the recovery process has been included in Figure 5.9, it is logical to allow for the reinfections to take place. The model has been adjusted in Figure 5.10. Additions to

the previous model are depicted in red.

At the SusR5 stage (for both SP and ACT), reinfections of the Res5 type are possible and hence there are flows from SusR5 and SusR5A to the Res5 stock. At the SusR3 stage, reinfections of both Res3 and Res5 types are possible and hence there are flows from SusR3, SusR3A and SusR3LTF to both the Res5 and Res3 stocks. The equations underlying Figure 5.10 are available in Appendix C. This model will be referred to as the Pharmacokinetic (PK) model.

Before the stocks and flows of the PK model are discussed in more detail, a summary of the population flow in the model is presented in Figure 5.11.

In one cycle of the model, the susceptible population may either be infected with or remain susceptible to a malaria infection. If they are infected, they may be infected with parasites of varying degrees of resistance to SP. Depending on their infection and the current national drug policy, they will be treated with either SP or ACT. At this point the treatment is either successful or it fails. If treatment is successful then individuals proceed through the SP elimination stages subject to the possibility of reinfections until they are susceptible to all strains of infection once again. If treatment fails, individuals are sent to hospital to be rescued with quinine. Upon treatment with SP or ACT or re-treatment with quinine, individuals may recover and become susceptible to all three types of infection again or they may have reinfections. These reinfections may be resistant to SP and this portion of the population is subjected to the treatment process once again.

The additional stocks to be used in the model are presented in Table 5.2

Table 5.2: Description of Additional Stocks used in the final model

Stock	Description: Proportion of the population who are
SusR5	Treated with SP and Susceptible to Res5 reinfections only
SusR3	Treated with SP and Susceptible to Res3 and Res5 reinfections only
SusR5A	Treated with ACT and Susceptible to Res5 reinfections only
SusR3A	Treated with ACT and Susceptible to Res3 and Res5 reinfections only
SusR3LTF	Late Treatment failures and susceptible to Res3 and Res5 reinfections only

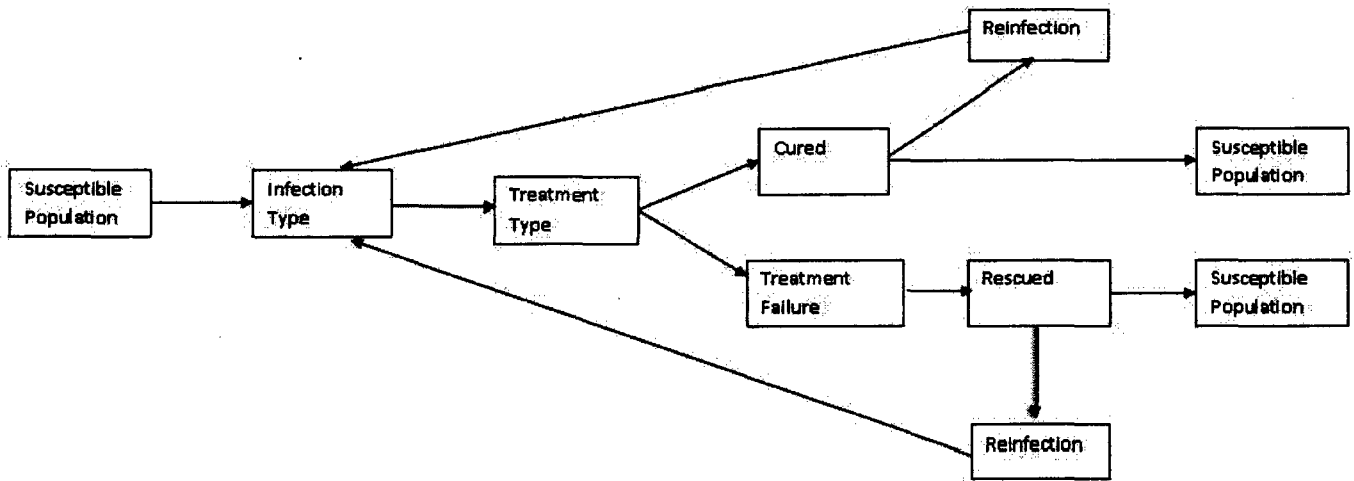


Figure 5.11: A summary of population flow

Additional Rates to be included: Reinfections

Reinfections occur from the SusRes5, SusRes3 and SusRes3LTF boxes for those treated with SP and ACT. The rate of reinfection is denoted as $\pi \times h$, where π is the probability of reinfection and h is the transmission rate. The rates of reinfection depend on the strain of reinfection i.e. Res3 or Res5 infection as well as the treatment regime. Hence if reinfection of Res5 infections is permissible for those on ACT, the rate of reinfection is $\pi_A \times h_{In}fR5$ and likewise for Res3 infections.

Additional Rates to be included: SP Elimination Rates

The SP elimination rates that correspond to levels of SP that are protective against reinfections of decreasing resistance type are broken down into stages as depicted in Figure 5.12. By disallowing superinfection the waiting time between the onset of infection and the time when the individual is susceptible to Res5 infections is given by the parasite clearance time. The path is only for those individuals who are cured by SP. For example for individuals with Res3 infections who are treated with and sensitive to SP, their parasite clearance time is denoted as τ_0 days and hence move from InfR3 to SusR5 at a rate of $f \times p_{R3ACPR} \times \frac{1}{\tau_0}$ where f is the proportion of SP treatment and

pr_{3ACPR} is the probability of treatment cure for Res3 infections. Figure 5.12 depicts these SP elimination rates. Likewise the rate of flow from InfR3 to SusR5A is $(1 - f) \times pr_{5ACPR} \times \frac{1}{r_0}$. Thereafter the waiting time till SP has been eliminated to the level that individuals are susceptible to Res3 and Res5 reinfections is denoted as r_1 . Thus from SusR5 and SusR5A the population moves at a rate of $\frac{1}{r_1}$ to SusR3 and SusR3A respectively. The residual time taken for SP to be fully eliminated from the bloodstream is denoted as r_2 and hence from SusR3 and SusR3A the populations move at a rate of $\frac{1}{r_2}$ back to the Susceptible stock.

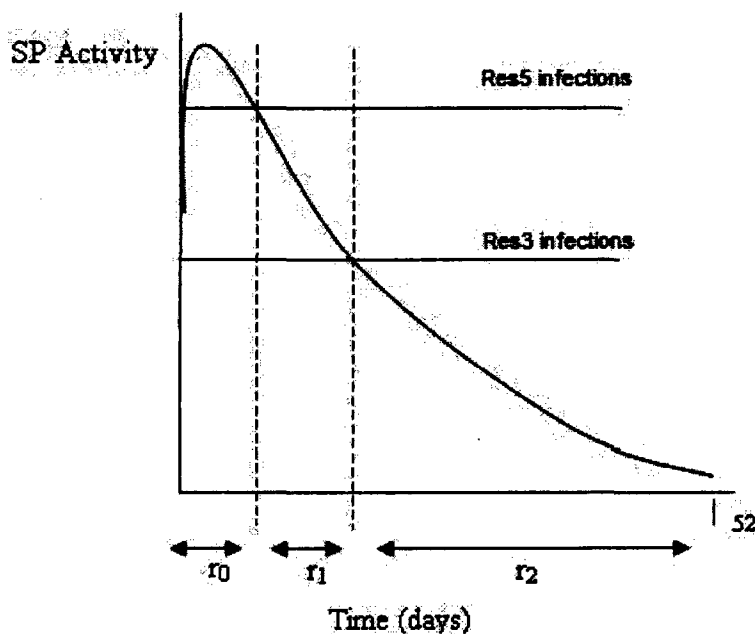


Figure 5.12: SP Elimination Rates

Alternative description of Human infectiousness parameter b_1

In the base model, because infectiousness was modeled directly, b_1 represented the infectivity of each infection strain and the infectious population were used in the inoculation rate calculation. In the PK model, because there is no distinction between infected and infectious individuals, the InfS, InfR3 and InfR5 stocks are used in the inoculation calculation. In order to allow for the use of infectious populations only, these stocks were multiplied

by the probability of becoming infectious. This was achieved by allowing b_1 to be the product of the probability of developing gametocytes and the infectivity of each infection strain. Thus $b_1 \times Inf_.$ in the PK model was equal to $b_1 \times Infect_.$ in the base model.

Rates of Transmission and Recovery

Table C.1 in Appendix C provides descriptions of the additional parameters used in the PK model and Table C.2 provides the mathematical description of the additional rates.

With regards to the drug parameters, the period of chemoprophylaxis values for SP from Watkins and Mosobo [1993] have been referenced and used extensively. They represent the time periods at which one may be susceptible to certain reinfections and the time in which SP is totally eliminated from the bloodstream. Though one is theoretically always susceptible to Res5 reinfections, Watkins and Mosobo [1993] show that Res5 reinfections tend to occur after the first 7 days. Thereafter, a further 8 days pass on average before individuals are susceptible to both Res3 and Res5 reinfections. Thereafter it takes a further 37 days on average before SP has been fully eliminated and individuals are susceptible to all strains of infection. The r_{2LTF} parameter is specific to those individuals who have experienced late treatment failure and have been rescued with quinine. Once the quinine has been eliminated from their bloodstream, SP is still present from their initial treatment. Given that the full period of chemoprophylaxis for SP is 52 days and the time to late treatment failure is on average 21 days with a 7 day treatment and PoC of quinine, the average time remaining in which individuals are susceptible to both Res3 and Res5 reinfections is $52 - 21 - 7 = 24$ days.

Start-up conditions for the simulation and Model Assumptions

The model is run for a period of 4000 days. The simulation is started at the conditions present in 1999 before the onset of extensive vector control. The proportions of the population present in each of stocks at the start of the simulation are data driven and presented in Table 5.3. These figures have been obtained from the LSDI study in Mozambique. The LSDI study provided data on parasite prevalence by mutation as at 1999. This data was then used to apportion individuals between stocks of the same mutation to get the model started. Because ACT was only introduced at a later stage,

all stocks relating to ACT remain at zero until its time of introduction. The initial distribution of Infections has changed as the drug elimination process occurs simultaneously with the development of gametocytemia which means that numbers previously distributed between infected and infectious stocks are now distributed between the infected and SP elimination stocks. The assumptions presented in Section 4.2.3 still apply with the exception of Assumption 8 (no reinfections) which has now been relaxed.

Table 5.3: Start-up conditions of the Simulation (PK model)

Stock	Proportion of the population in 1999
Sus	0.25
InfS	0.38
InfR5	0.011
InfR3	0.097
SusRes5	0.095
SusRes3	0.111
SusRes5A	0
SusRes3A	0
SusRes3LTF	0.002
FailuresSETF	0.001
FailuresSLTF	0.001
FailuresR5ETF	0.002
FailuresR5LTF	0.016
FailuresR3ETF	0.013
FailuresR3LTF	0.021

5.3.2 Results

As was the case with the base model, issues relating to the graphical output apply to the PK model results. Table 5.4 provides details on the graph outputs and their units that have not already been defined.

Table 5.4: Description of Graphical Outputs

Output	Description	Unit
TotETFFailure	Total number of Early Treatment Failures	people
TotLTFFailure	Total number of Late Treatment Failures	people
TotalSus	Total number of Susceptible people	people
Res3Reinfections	Total number of Res3 Reinfections	people
Res5Reinfections	Total number of Res5 Reinfections	people
SusR5	Susceptible to Res5 reinfections only (SP)	people
SusR3	Susceptible to Res3 and Res5 reinfections only (SP)	people
SusR5A	Susceptible to Res5 reinfections only (ACT)	people
SusR3A	Susceptible to Res3 and Res5 reinfections only (ACT)	people
SusR3LTF	LTF and susceptible to Res3 and Res5 reinfections only	people

As with the base model, the PK model needs to be run without the influence of the vector control and the ACT policy in order to assess if the malaria system is stable i.e. a steady state is reached. As seen in Figures C.1 and C.2 the model reaches a steady state within the first 150 days of simulation. Thus the introduction of policy interventions needs to occur once this steady state has been reached. The model has been tested for sensitivity to the start-up conditions and has been found to be robust to these assumptions.

Figure 5.13 shows the infection patterns resulting from the PK model. The model looks very different from the base model. Here the Res0 and Res3 infections are driven to zero within the first 250 days of the simulation while Res5 infections increase dramatically from its initial value and remain stable until the introduction of ACT where they decrease slowly. It appears that the Res0 infections again have been driven to zero before the model reaches a steady state whereas Res3 infections decreased to zero approximately 100 days after the model reached a steady state. As can be seen in Figures 5.6 and 5.7, the observed data from Mozambique showed quite the opposite effect where Res3 infections dominated and Res5 infections remained low

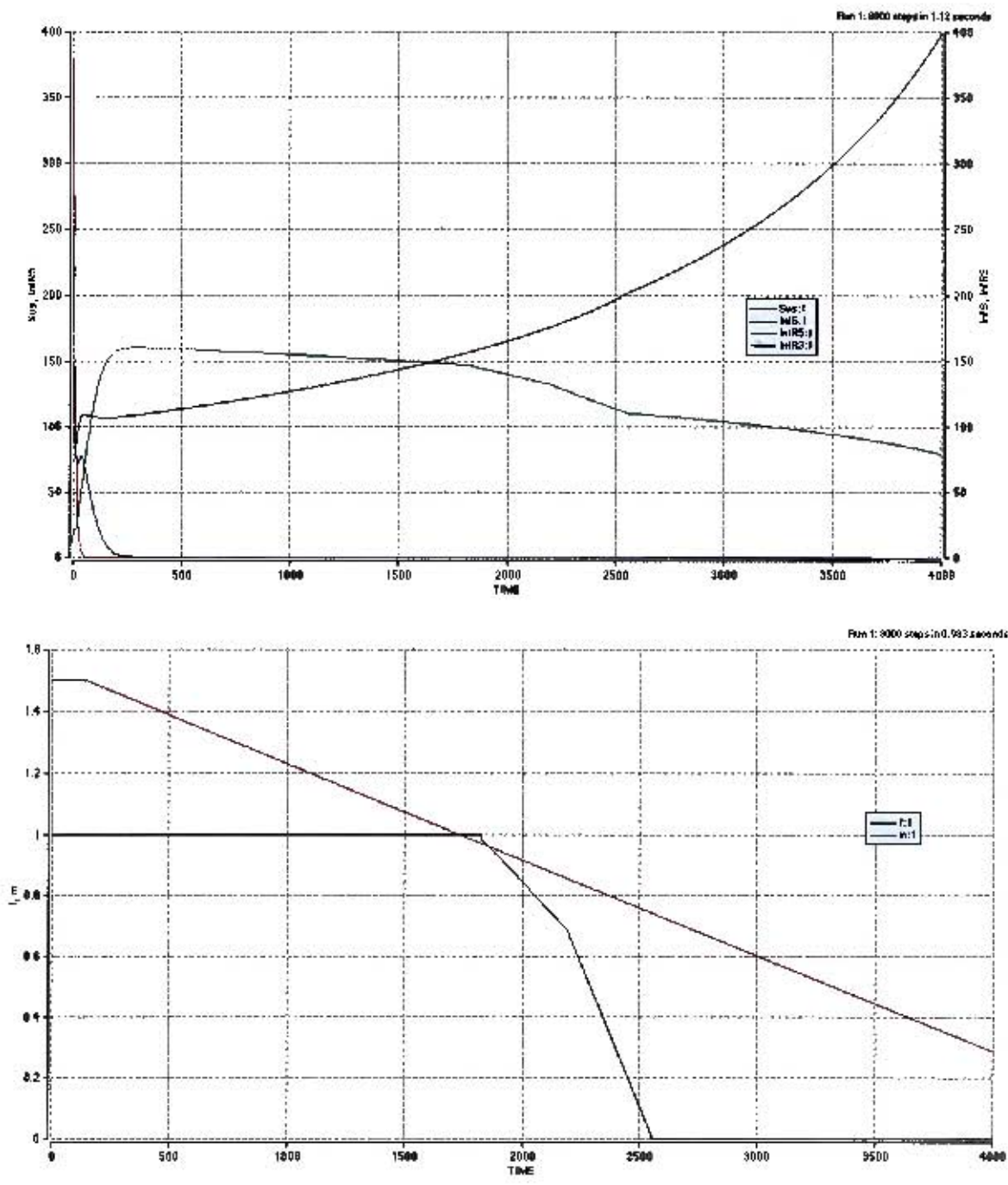


Figure 5.13: Trends in Susceptible and Infected Populations (PK model)

until the introduction of ACT.

Figure 5.14 depicts the prevalence and entomological inoculation rates for the PK model. Since the PK model breaks the recovery process down into stages where individuals have cleared the current infection but do not have enough drug in their bloodstream to counter all reinfections, total susceptibility has been defined $TotalSus = Sus + SusR5 + SusR3 + SusR5A + SusR3A + SusR3LTF$ to incorporate all levels of susceptibility. However, all new infections occur from the *Sus* pool of individuals and all reinfections occur from the remaining stocks in the *TotalSus* definition. Prevalence is still defined as the sum of all infection strains and failures. Given the sharp decline in Res0 and Res3 infections, prevalence starts low at approximately 20% and decreases further over the period of the simulation to approximately 9%. Total susceptibility increases dramatically in first 100 days of the simulation to levels of approximately 80% and increases further as prevalence decreases. Predictably, the EIR for Res0 and Res3 infections decrease quickly to zero while the EIR for Res5 infections rises initially but decreases steadily as the effects of vector control and ACT are felt in the model.

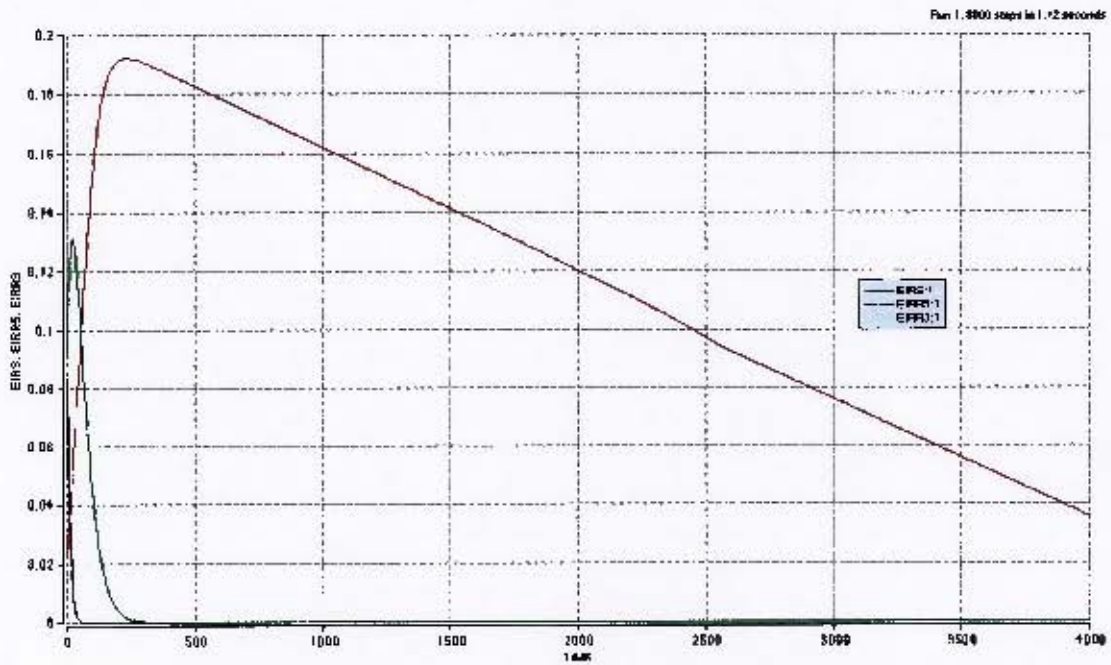
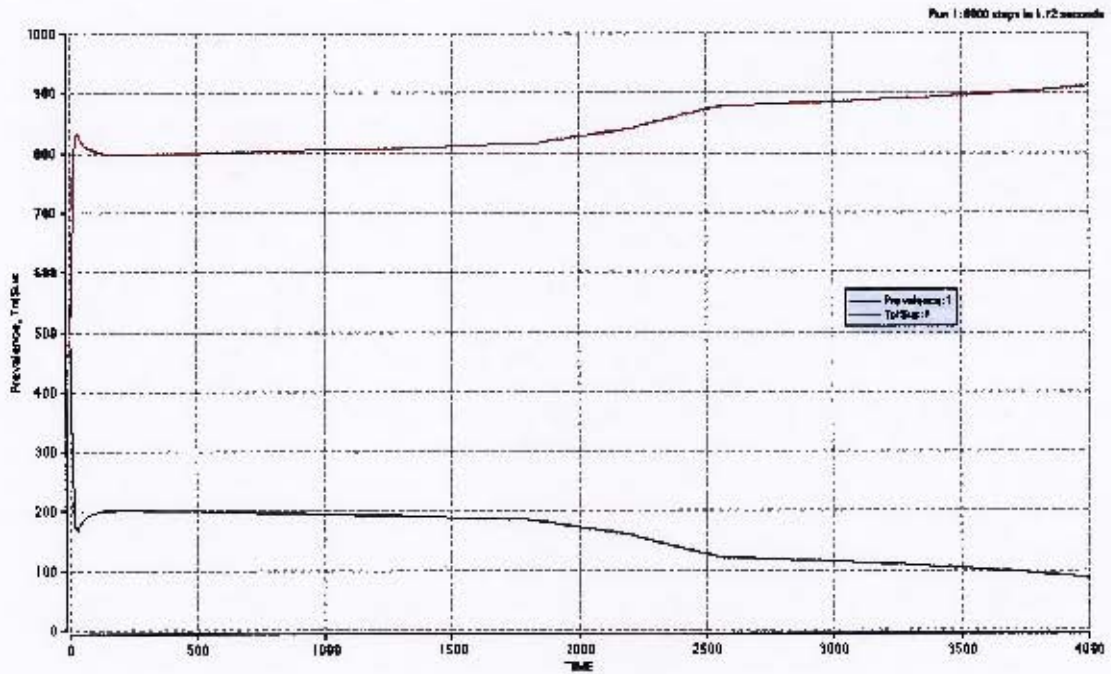


Figure 5.14: Total Susceptibility, Prevalence and EIR (PK model)

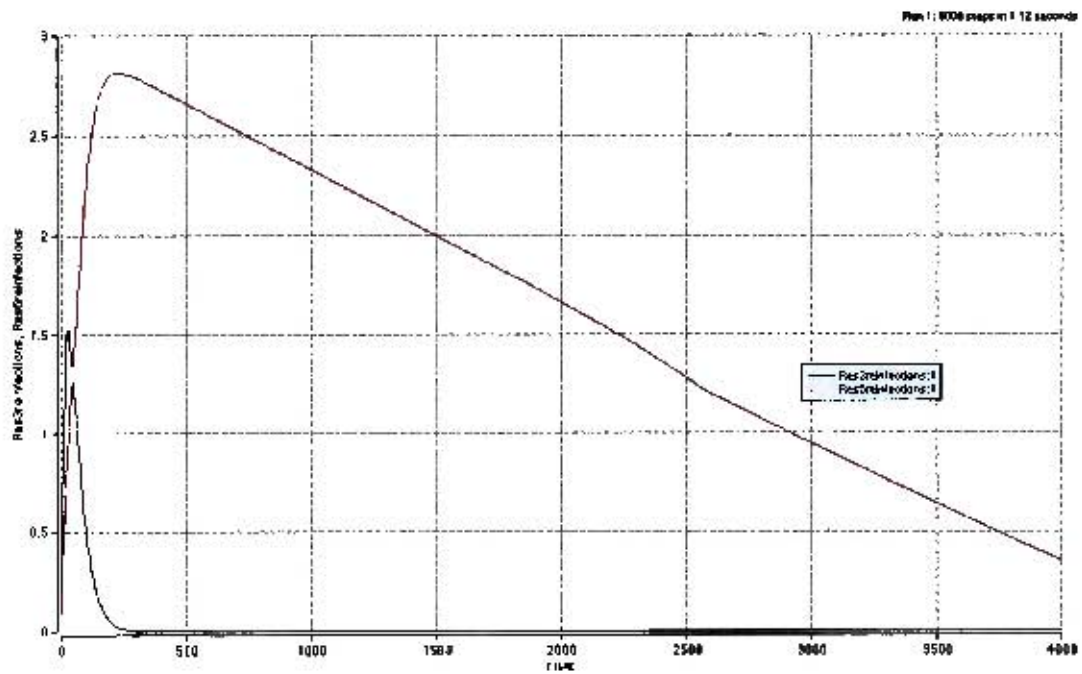
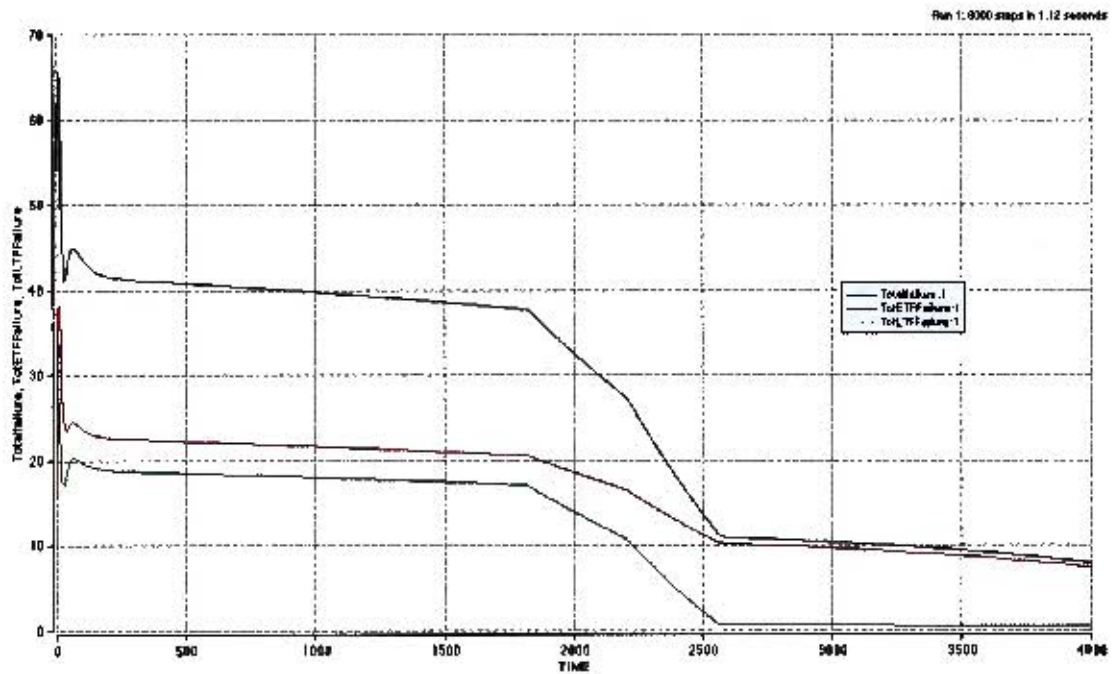


Figure 5.15: Failure and Reinfec Rates

Figure 5.15 shows that while there were more early treatment failures than late treatment failures, both rates decreased steadily as mosquito density decreased through vector control, and fell sharply at the introduction of ACT and late treatment failures declined almost to zero as 100% ACT coverage was achieved. Reinfection rates for Res1 infections decreased to zero quickly as Res1 infections were forced to zero. Reinfection rates for Res5 infections however started off low and decreased further as the effects of vector control and ACT were felt in the model.

Figure 5.16 shows changes in the levels of susceptibility to Res0, Res3 and Res5 infections. When SP coverage was 100% the susceptibility stocks (SusR5, SusR3 and SusR3LTF) reached a stable value quickly. Once ACT was introduced, the corresponding susceptibility stocks (SusR5A, SusR3A) increase and then decrease gradually as ACT reduces prevalence.

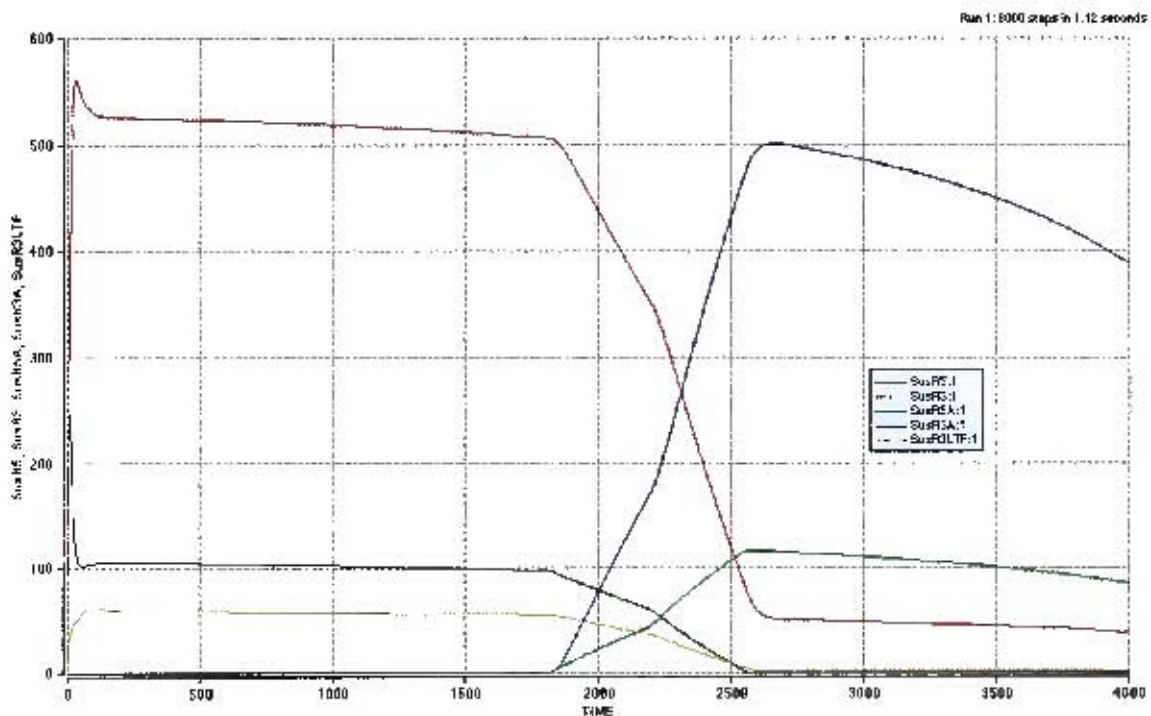


Figure 5.16: Levels of Susceptibility

5.3.3 Sensitivity Testing of PK model

As was the case with the base model, the PK model was also tested for sensitivity to parameter values by changing the sets of values individually. The graphs of the sensitivity analysis are available in Appendix C. The model proved to be robust to changes in parameter values. While the base model showed sensitivity to the gametocytemia-related parameters and treatment outcome probabilities, the PK model exhibited mild sensitivity only to the period of chemoprophylaxis parameters r_0 and r_2 and the human infectiousness parameter b_1 . The model was not sensitive to the other period of chemoprophylaxis parameter r_1 . Figure C.3 shows the PK model's insensitivity to changes in the mosquito density parameter while Figure C.4 shows the mild sensitivity that the PK model showed to changes in r_0 , the parasite clearance time. Figure C.5 shows the great sensitivity that Res3 and Res5 infections show to changes in the human infectiousness parameter (b_{1R5SP}) i.e. the probability of an infectious bite leading to a Res5 infection in a susceptible mosquito for those treated with SP. It must be noted that sometimes the effects are so great that the Res3 infections increase to levels greater than Res5 infections until such time as ACT coverage reaches 100% i.e. the same disease composition displayed in the base model results and the observed data illustrated in Figure 5.7. This sensitivity will be elaborated on in Chapter 7.

The PK model has underestimated prevalence greatly and has not estimated correctly the changing composition of infection strains. Its results are in direct contrast to observed data as well as the base model results. The success or lack thereof of this attempt to include the pharmacokinetic properties of SP into the model will be discussed in Chapter 7.

Chapter 6

Scenario Testing

This chapter will explore the impact of policy changes on the base model and the related impact on the system of malaria presented in Chapter 3. Two of main areas of antimalarial interventions are vector control and drug treatment. Policy changes in both these areas will be tested on the base model.

6.1 Scenario Testing of Vector control

The scenario testing will be performed on the base model before any interventions are applied i.e. without the effect of vector control and the change to ACT strategies. With vector control strategies, one may consider implementing indoor residual spraying, the effect of which is chosen to impact the mosquito density parameter or one may implement the use of insecticide treated bed-nets which reduces the human biting rate a . These strategies may also be investigated with regards to the pressure and timing of the interventions. The impact of both these strategies will be investigated. Vector control strategies play an important role in achieving the objective of eradicating malaria as it focuses on prevention of mosquito bites as opposed to reactive drug treatment.

6.1.1 Indoor Residual Spraying

The impact of the pressure of Indoor residual spraying is examined in Figure 6.1 where prevalence is once again measured in number of people out of 1000. The values for spraying pressure have been derived from the year on year decrease in mosquito prevalence as result of IRS, used in the base

model to decrease the mosquito density parameter m . The existing strategy in Mozambique resulted in a year on year decrease in mosquito prevalence of 8%. The strategies tested range from a spraying pressure value of 0 (no IRS intervention) to a year on year decrease of 11% (zero mosquito density).

The first graph in Figure 6.1 shows the decrease in prevalence that could occur for a particular spraying pressure. If no intervention occurred prevalence would remain as high as 50% of the population (500/1000 people) where as the current treatment strategy of 8% pressure reduces prevalence to approximately 38% of the population. While the figure shows that increasing spraying pressure may lead to zero prevalence or the eradication of malaria it must be noted that the scenario test does not model certain issues. For example, the test ignores the development of resistance by the *Anopheles* mosquito to the spray used. It also ignores the costs involved in increasing spraying pressure; an important factor for struggling developing country health budgets. The second graph in Figure 6.1 shows the decrease in prevalence through time for each of the spraying pressures and shows that in most cases, the primary decline in prevalence occurs some 2500 days (\approx 6.5 years) after initiation. It must be noted that these graphs show the effect of IRS only alongside the 1999 drug treatment policy of 100% SP coverage.

Figure 6.2 shows the effect on prevalence if one delays the initiation of the IRS strategy. As can be seen from both graphs, a delay in the initiation of IRS leads to an increase in final prevalence over the 11 year period. It can also be seen from the second graph that while the current strategy that started at time 500 lead to a decrease in prevalence of approximately 30%, strategies initiated as late as time 2000 also lead to a substantial decrease in prevalence of approximately 15% or more. Thereafter, decreases in prevalence differ little from what would have been the case if the IRS was never initiated i.e. initiated at time 4000. A longer time period is necessary in order to see the full effect of the strategies initiated late in the scenario test.

6.1.2 Insecticide Treated Nets

The rollout of insecticide treated nets would lead to a decrease in the human biting rate. The impact of this rollout is tested via a percentage annual decrease in the biting rate. Thus pressure on the ITN strategy refers to the percentage decrease of prevalence achieved through the roll out of ITN's. A higher rollout leads to a greater proportion of the population having access

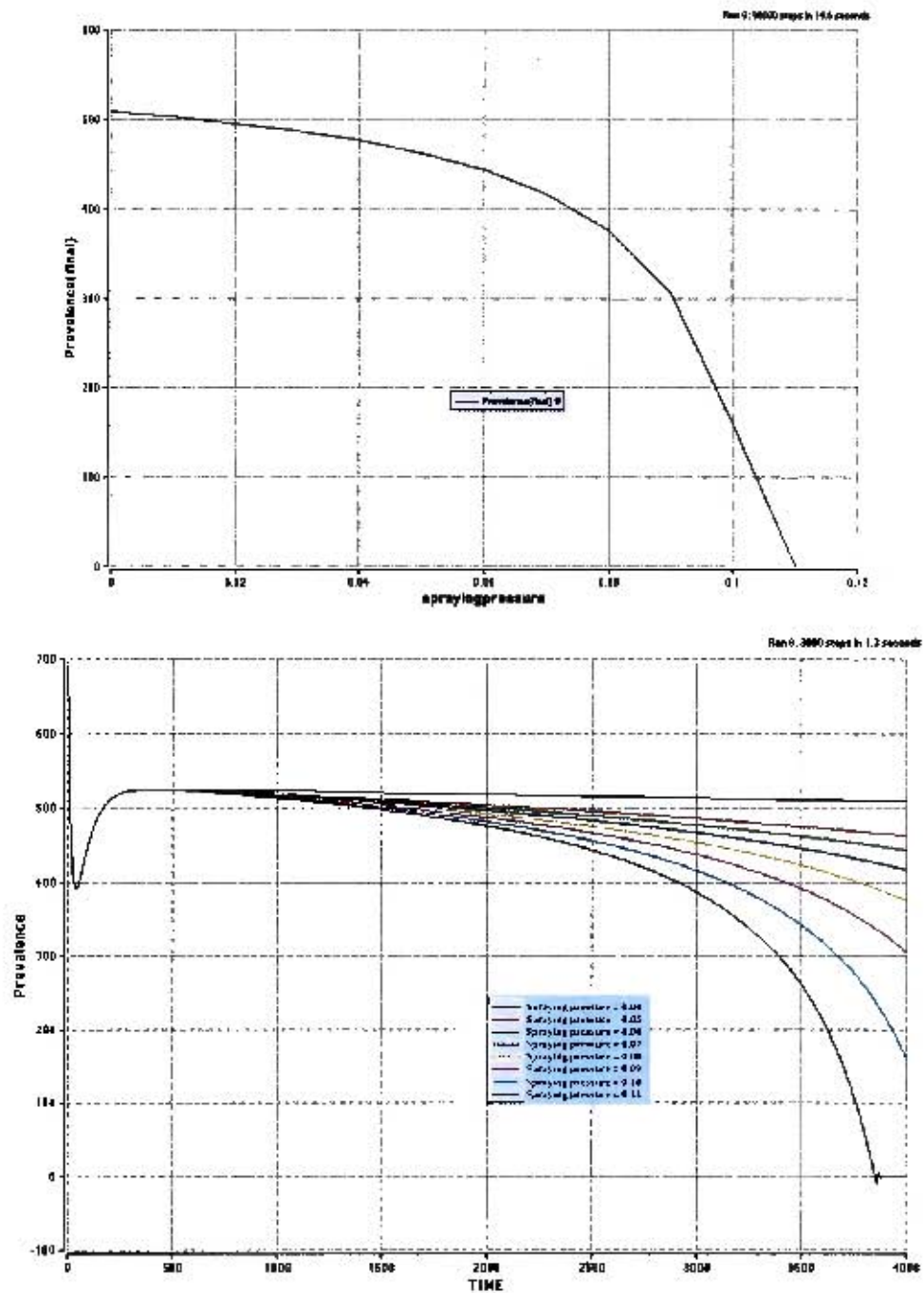


Figure 6.1: Effect of Different IRS pressures on Prevalence

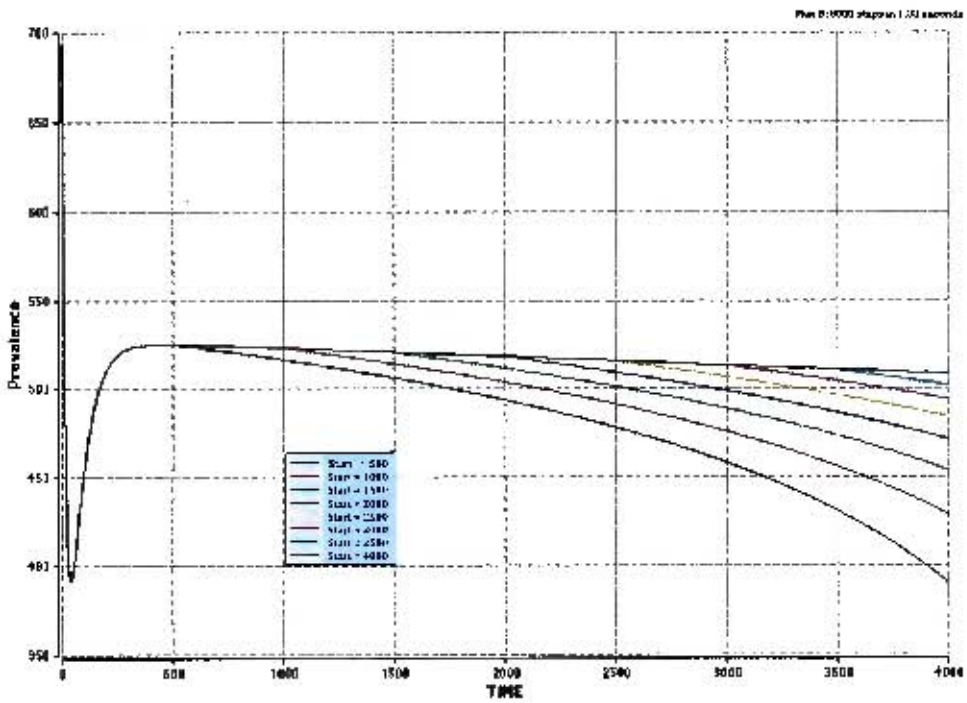
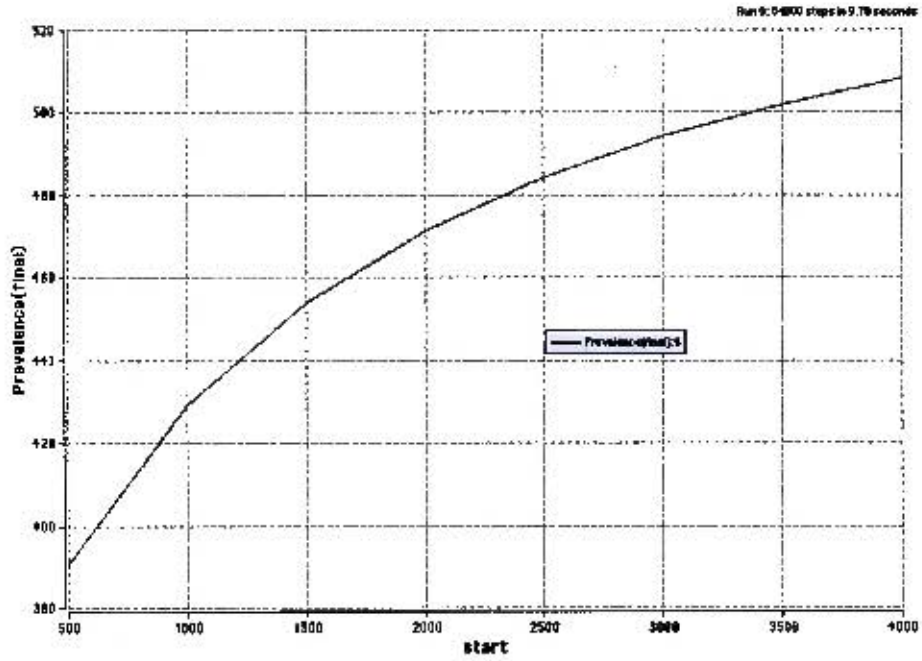


Figure 6.2: Effect of Different start times for the IRS strategy on Prevalence

to ITN's which leads to a decrease in the overall human biting rate. The first graph in Figure 6.3 shows the effect of changes in the pressure of the roll out of ITN's on prevalence. Pressure was varied between 0% (no rollout) and 10% which decreases the biting rate to just above zero in the eleven year period.

Figure 6.3 shows that ITN pressure would need to be at least 8% in order for prevalence to drop by $\frac{1}{3}$ after which the decrease in prevalence gains momentum. While prevalence appears to be decreasing as ITN pressure increases, it must be noted that resistance of vectors to insecticide in the nets has not been accounted for and may well lead to an increase in prevalence. At face value it appears as if indoor residual spraying has a more marked effect on prevalence and that it should be chosen over ITN's but judgement would need to be made after a thorough cost analysis with regards to the cost of the nets and spray as well as the costs associated with implementation. A country's infrastructure and health infrastructure would greatly affect a decision such as this. The second graph shows the effect on prevalence if IRS and ITN's are applied simultaneously with equal pressures. Here the application of these interventions at pressures greater than 8% more than halves prevalence and pressures of 10% or higher reduce prevalence to zero. While the results show that vector control can result in the eradication of malaria, the model excludes key issues like the emergence of resistance to the insecticide used in IRS or ITNs and the infrastructure to allow the implementation of these interventions.

6.1.3 Application of Findings to System Dynamics Diagram

The System Dynamics diagram presented in Section 3.2 provides an overview of many of the forces that impact on malaria transmission and antimalarial interventions. This diagram is intended as a decision support tool to allow one to assess the interdependencies of factors affecting the malaria system.

As seen in Figure 3.2 vector control measures have a direct impact on transmission; reducing transmission which decreases malaria prevalence. The diagram also provides insight into other factors concerning vector control. Firstly unlike Mozambique, areas of high transmission result in the development of immunity to malaria. A decrease in transmission through vector control through time hampers the development of immunity. This is especially true in the case of children where children are protected from

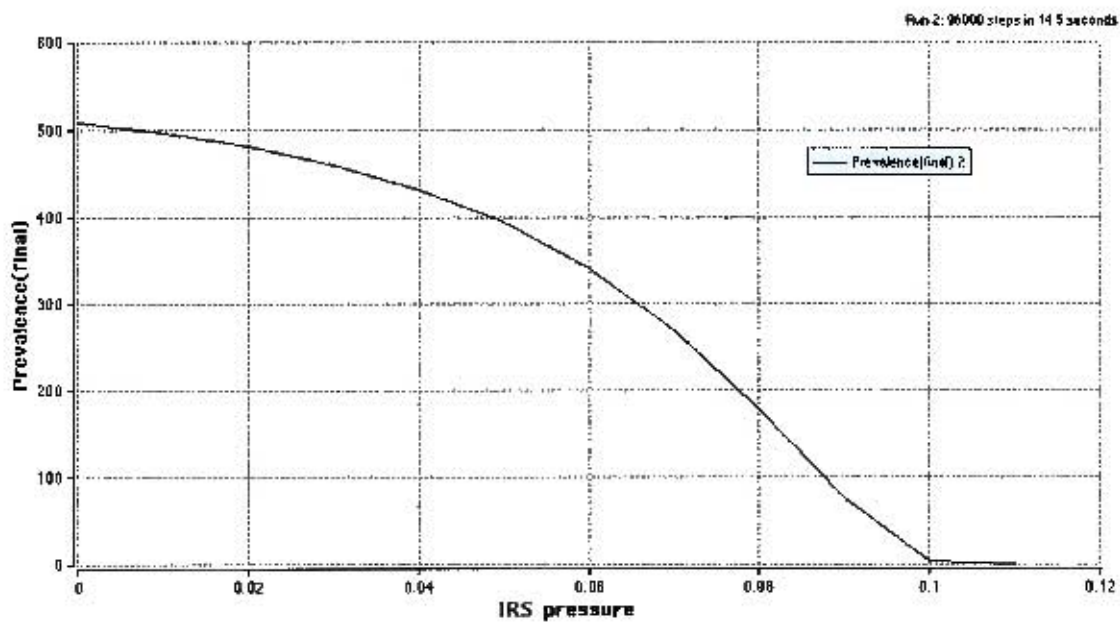
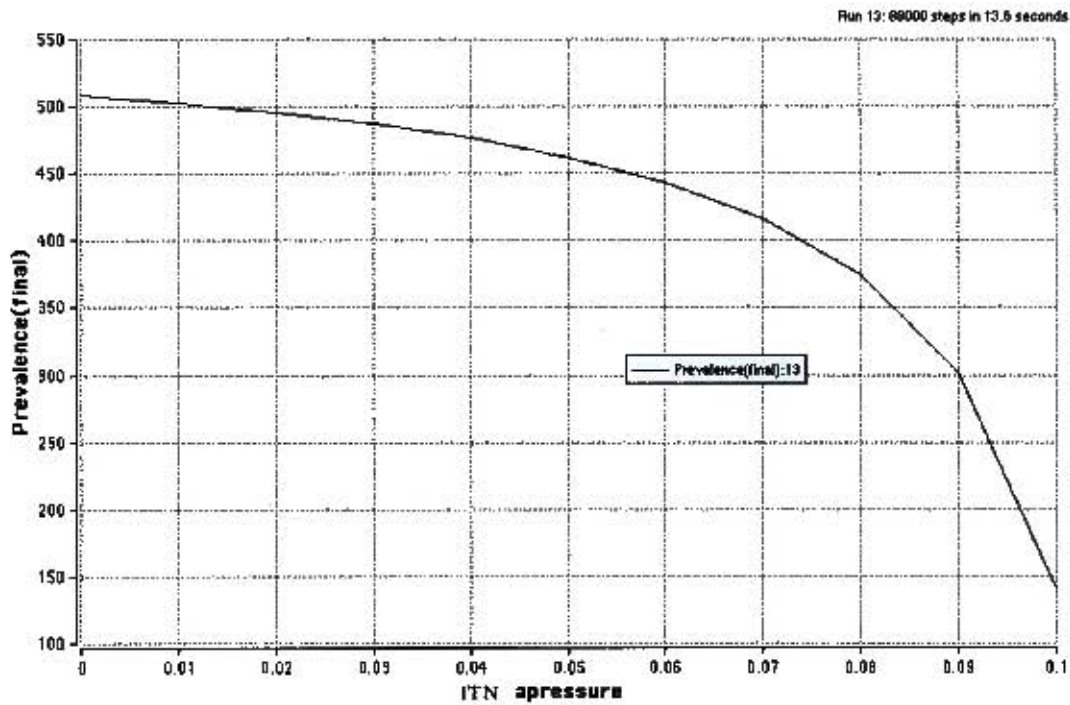


Figure 6.3: Effect of Different values for Pressure for the ITN strategy and the joint effect of ITN and IRS on Prevalence

malaria through the use of bednets and are not given the opportunity to develop immunity. Upon reaching adulthood, this lack of immunity may result in more severe malaria. Hence the use of vector control and the pressure in its implementation will need to be weighed up against the effects of not developing immunity.

Other insights provided by the System Dynamics diagram include the development of resistance by mosquitoes to the insecticide used in spraying and bednets. Increased pressure in the use of IRS and ITN's can lead to the development of resistance by mosquitoes to the pesticide which would ultimately lead to an increase in malaria transmission and waste of valuable resources. Thus the impact of resistance and counter-measures such as using combinations of sprays etc will also need to be assessed before the roll-out of vector control. Another issue that will need to be considered is the impact of the implementation of the vector control. If the implementation of the IRS or rollout of ITN's is sub-standard, it may impact negatively on reducing transmission. For example, if sub-therapeutic doses of insecticide are used in the IRS or ITN's (at the manufacturer), this may lead to an increase in the development of resistance to the insecticide. Further if the IRS is incorrectly performed, this may reduce the impact of IRS on transmission. Hence adequate training of workers is also imperative in this regard. The existing infrastructure in a country may also impact the implementation of vector control policies and is a point of consideration when deciding to implement these policies.

6.2 Scenario Testing of Antimalarial Drug Treatment

Once again the scenario testing will be performed on the base model without the effect of existing vector control and the change in drug treatment strategies. With drug therapy, governments may choose to roll-out different combinations of drugs, at different drug pressures as well as introduce the drug strategies at different stages of drug resistance. The impact of using ACT at different pressures as well as the time of introduction will be tested in the following sections.

6.2.1 Artemisinin-based Combination Therapy: The impact of drug pressure

The treatment coverage of SP and ACT is captured in the treatment parameter f where f represents the proportion of SP treatment and $(1 - f)$ represents the proportion of ACT treatment of infection. The parameter $f_{pressure}$ is equal to 1 when SP coverage is 100% and 0 when ACT coverage is 100%.

The first graph in Figure 6.4 shows the decrease in prevalence that could occur for a particular treatment pressure. The time of introduction of ACT is held fixed at the value used in the base model. If ACT was never introduced in Mozambique, prevalence would remain as high as 52% of the population where as the current treatment strategy of 0% pressure reduces prevalence to approximately 20% of the population; a decrease of 62%. The second graph in Figure 6.4 shows the decrease in prevalence through time for each of the ACT treatment pressures and shows that in most cases, the primary decline in prevalence occurs over the first 500 days after initiation. It must be noted that these graphs show the effect of drug treatment with ACT only and ignores vector control.

Figure 6.5 shows the effect on prevalence if one delays the introduction of the ACT treatment strategy. The treatment pressure is held fixed at 100% ACT; the current ACT strategy in Mozambique. As can be seen from both graphs, a delay in the introduction of ACT leads to an increase in final prevalence over the 11 year period. It can also be seen that from the first graph that the marginal decrease in prevalence from starting ACT treatment earlier than time 3000 is very low. The second graph shows that starting ACT treatment as late as time 3500 would still achieve a substantial decrease in prevalence. This shows that ACT is a fast acting agent in the decrease of prevalence. It must be noted that while these graphs show very positive results, 100% ACT coverage assumes that all infected individuals receive treatment promptly and correctly and that the existing infrastructure is available in the country to implement this.

The first graph in Figure 6.6 shows the impact a delayed introduction of ACT has on total resistance. Total number of failures is the proxy used for resistance. Thus delaying the introduction of ACT delays the decrease in resistance that occurs approximately 500 days after ACT comes into use. The time of introduction of ACT is then key to reducing resistance to SP

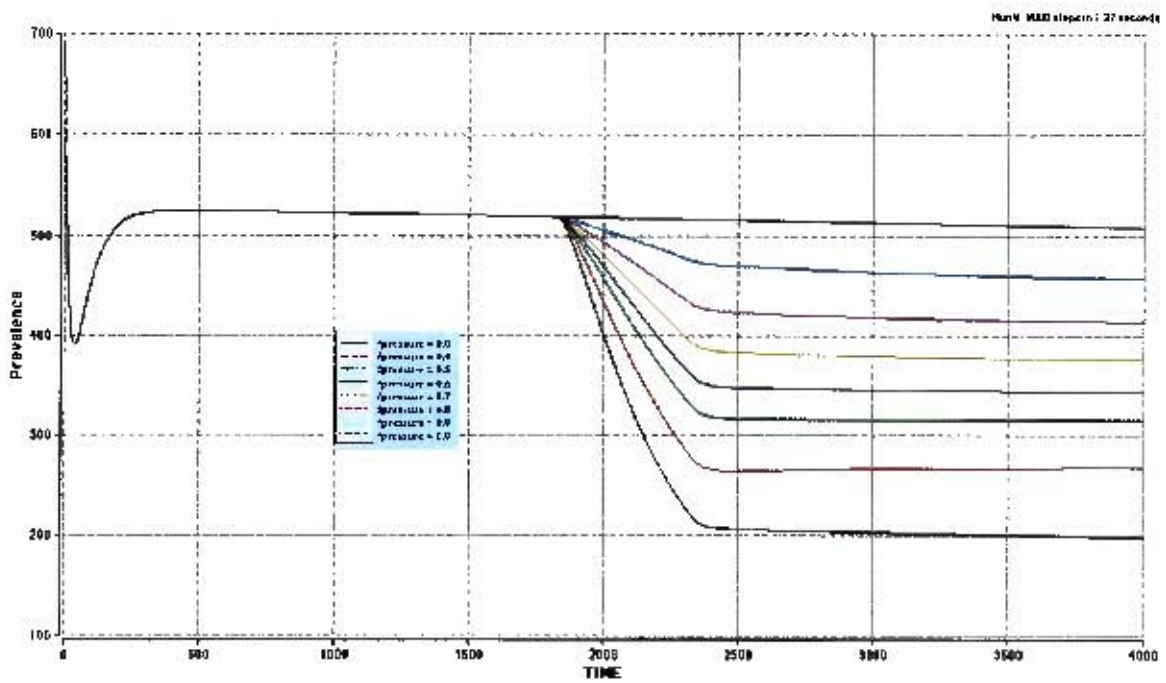
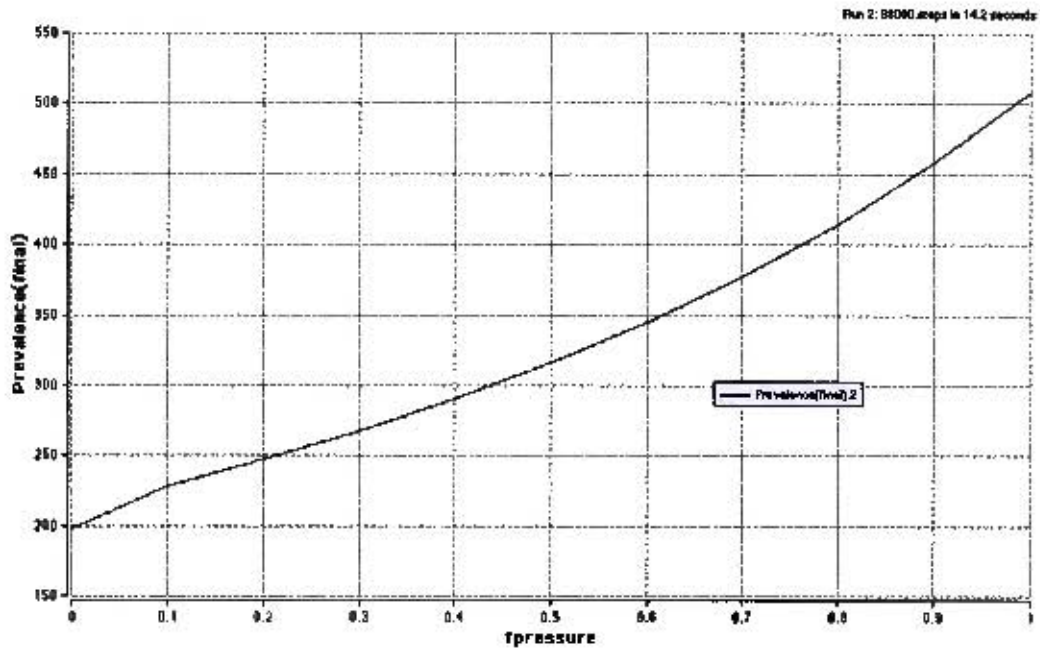


Figure 6.4: Effect of Different ACT pressures on Prevalence

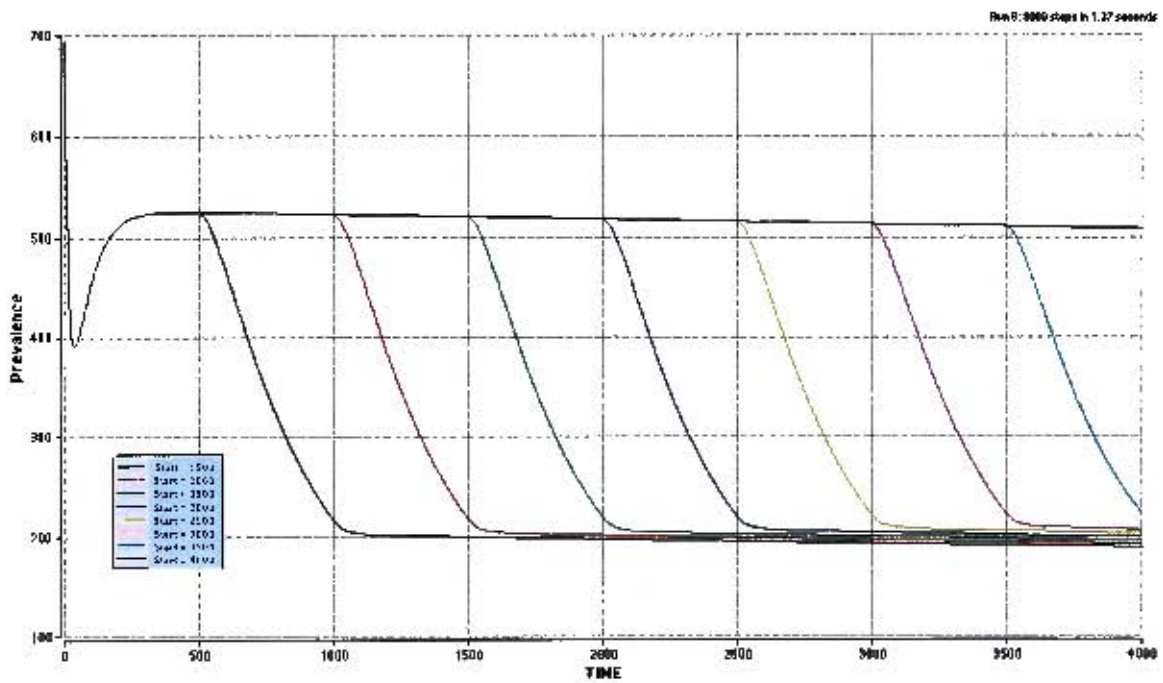
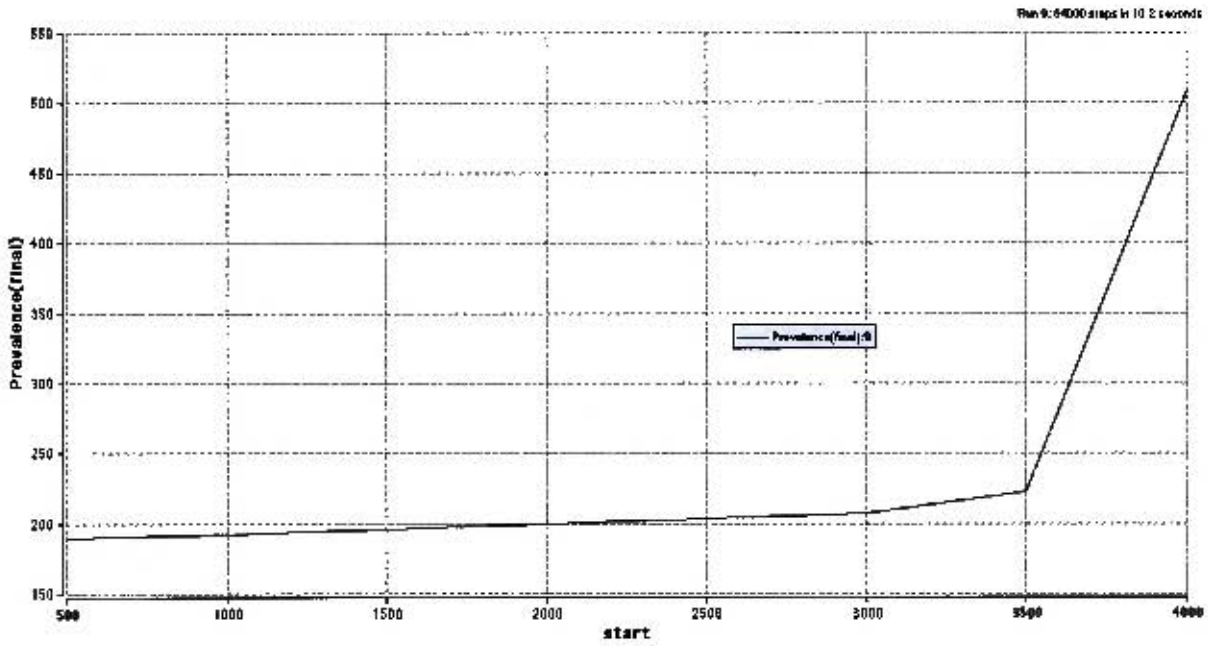


Figure 6.5: Effect of Different start times for ACT treatment on Prevalence

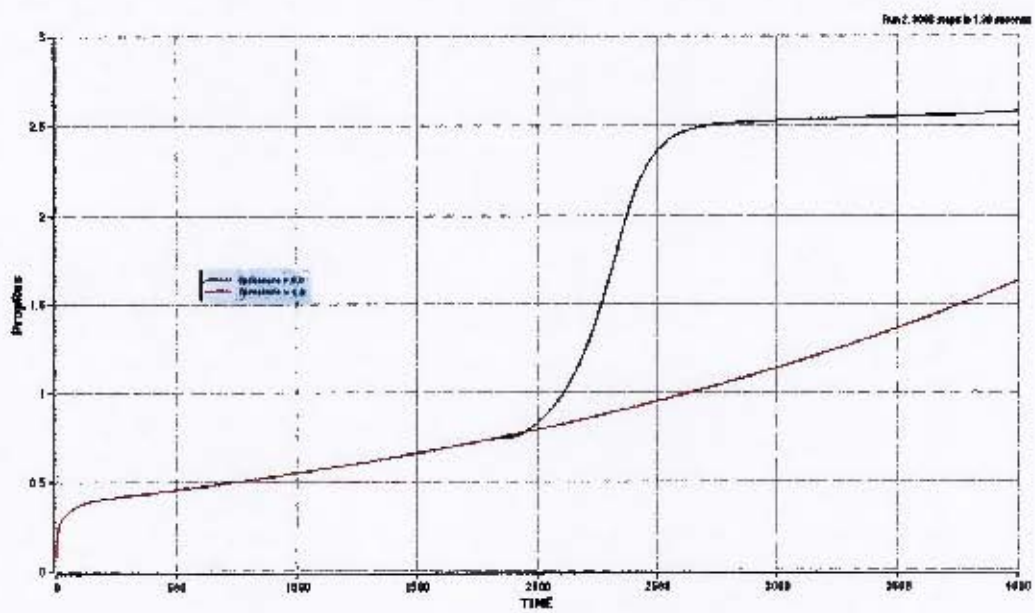
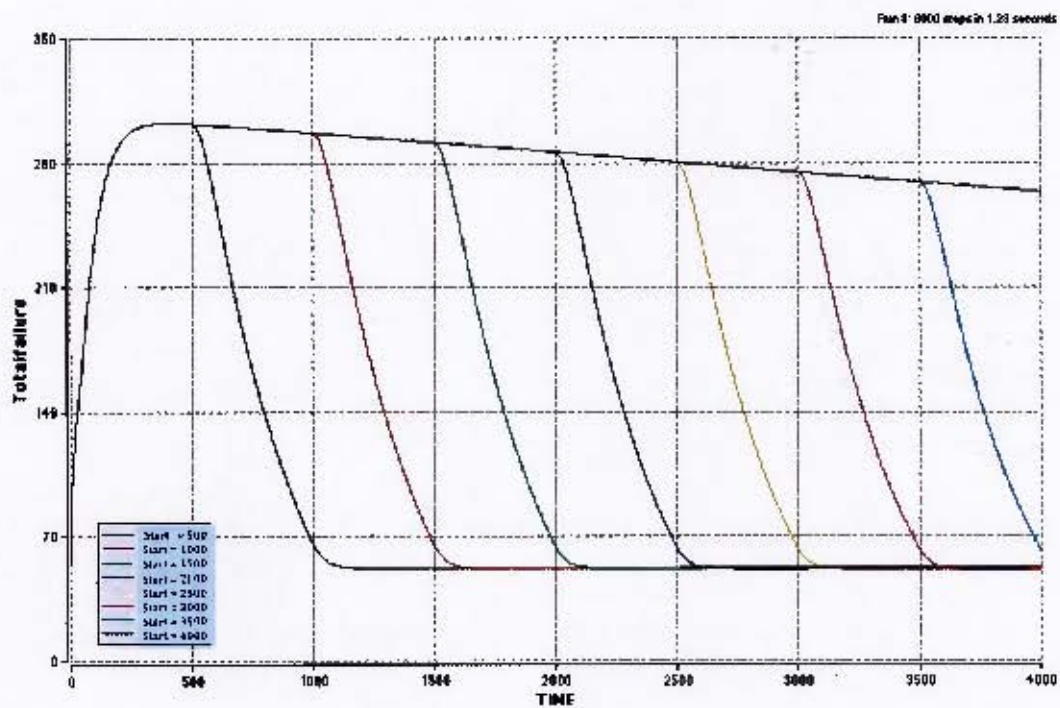


Figure 6.6: Effect of ACT on Total Failures and the ratio of Res5 and Res3 infections

higher drug price will increase the proportion of the health budget occupied by drug costs and this will take funding away from other health concerns. Thus the opportunity cost of deploying ACT needs to be taken into consideration. Governments in developing countries could seek to obtain subsidies to partially or fully relieve this burden to their health budget. Further, adequate coverage of ACT requires proper infrastructure (transport networks, health facilities) and training of health workers.

Implementation of and government policy with regards to ACT deployment is key to preserving the efficacy of artemisinin. Because of its high price and known efficacy, counterfeit artemisinin-based drugs may be available on the market and these may result in the development of resistance to artemisinin. This could be case where counterfeit drugs with sub-therapeutic levels of artemisinin are sold to the poor or artemisinin is available in the private market as a monotherapy.

Chapter 7

General Discussion

This chapter presents the general discussion surrounding the model development and model results. There will first be a general discussion surrounding the model findings which will be followed by a discussion on limitations of the model and modeling methodology.

7.1 Model Results

The base model results show that Vector Control and Artemisinin-based Combination therapy could be employed successfully to reduce prevalence substantially. While prevalence decreased, the composition of infection strains changed such that Res3 infections decreased to very low levels and Res5 infections increased to levels higher than the Res3 infections. This change happened fast and occurred during the change-over of drug policy from SP to ACT. This represents an increase in the prevalence of the DHFR triple and DHPS double mutations, and these mutations have a higher treatment failure rate than the DHFR triple mutation. The model also shows a similar change in composition between Res3 and Res5 failures where Res3 failures decrease to zero and Res5 failures remain at a higher level. This change in composition also occurred during the ACT change-over period. Given that treatment failure is the proxy used for resistance in this model, the model shows that the use of ACT has decreased total prevalence and total resistance but has resulted in a higher prevalence of Res5 mutations and Res5 failures over Res3 mutations and failures respectively.

When comparing the PK model with the base model, one can see that the PK model, underestimated prevalence substantially. Further, Res3 in-

fections were decreased to zero quickly; a finding very much at odds with observed data which showed that Res3 infections increase to high levels and then decrease once ACT becomes the drug in use. The modeling reason behind the decrease of Res0 and Res3 infections is that the number of new infections could not keep up with the number of treatment failures and treatment cures i.e. the individuals were leaving the InfS and InFR3 stocks faster than they were entering them and thus the stocks decreased eventually to zero. The Res3 infection rate is dependent on inter alia the number of susceptible individuals available to be infected as well as the proportion of Res3 infected mosquitoes. As InFR3 decreases, the proportion of Res3 infected mosquitoes decreases and this would decrease the h_{InfR3} which would decrease the number of new Res3 infections. Thus this is a positive feedback process. Further the Susceptible stock takes on values greater than or equal to that of the base model for the entire simulation period and hence this does not contribute to the low number of new Res3 infections.

In the base model those sensitive to treatment were moved to a recovery stock regardless of whether they became infectious or not. By decomposing the recovery process into several stocks in the PK model, one is effectively elongating the recovery process. This is because if it takes one r days to move from stock A to stock C where $r = s + t$ and it takes s days to move from stock A to stock B and t days to move from stock B to stock C, it takes longer to move from A to C via B than from A to C directly. This is because $\frac{1}{r} \leq \frac{1}{s} \times \frac{1}{t}$ if r, s and $t \geq 1$. These rates of flow only apply once a model has reached a steady state. Individuals also leave the infected stocks at rates faster than in the base model and this has a major impact on the proportion of infected individuals. This is also seen in the sensitivity of the PK model to r_0 ; the rate at which those who are cured leave the infected stocks.

The composition of Res3 and Res5 infections was also very sensitive to the human infectiousness parameter b_1 . This parameter was defined differently in the base model and the PK model. In the base model, because infectiousness was modeled directly, b_1 represented the infectivity of each infection strain and the infectious population were used in the inoculation rate calculation. In the PK model, because there is no distinction between infected and infectious individuals, the InfS, InFR3 and InFR5 stocks are used in the inoculation calculation. In order to allow for infectious populations only, these stocks were multiplied by the probability of becoming infectious. This

was achieved by allowing b_1 to be the product of the probability of developing gametocytes and the infectivity of each infection strain. Thus $b_1 \times Infect_$ in the PK model was equal to $b_1 \times Infect_$ in the base model. The PK model was very sensitive to changes in b_1 ; so much so that decreasing the value of b_{1R5SP} to levels just below b_{1R3SP} would suddenly increase the number of Res3 infections to levels higher than Res5 infections which increase only after ACT is in use. Perhaps explicit modeling of the infectiousness process could serve to improve the PK model, or perhaps, infectiousness plays a greater role in the model dynamics than the SP elimination process.

7.2 Model Parameters

This section discusses some of the parameters used in model and difficulties and strengths associated with the use of these parameters.

The human infectiousness parameter b_1 was derived from gametocyte data recorded in the SEACAT study. The base model allowed the direct use of gametocyte data where as models such as Pongtavornpinyo [2006] use parasite density information and a gametocyte switching rate to obtain gametocyte densities. There are problems with getting good estimates of characteristics of gametocytemia using data from the SEACAT clinical trials. The design of these trials are aimed at measuring asexual parasite distributions and hence both the length of observation and the intervals at which measurements are taken, are not optimal for observing gametocytes. In addition, patients get withdrawn if they prove to be resistant to treatment and don't clear their asexual parasites. Since gametocytes lag asexual parasites, this means that gametocyte distributions for failures are often truncated or censored leading to difficulties in getting unbiased estimates of gametocyte distribution characteristics. Thus gametocyte density was calculated using informative censoring where all those who failed treatment were censored out of the calculations. Hence infectiousness data was only used for those who were sensitive to treatment in the base model. If full gametocytemia distributions were available for all patients, then infectiousness could be modeled to better effect.

The human susceptibility parameter was assumed to be a referenced constant value in both the PK and base model. Because long-term immunity and drug level were not included in the base model, b_2 was constant for all inoculation rates. However, in the PK model, once drug level became

a factor in the model, the b_2 values should change for the reinfection rates i.e. reinfection inoculation rates where the individual already has residual drug present in their bloodstream. In the PK model, the drug level factor was modeled implicitly through the multiplication of the inoculation rate by the probability of becoming reinfected and b_2 was kept constant as result. However b_2 could be modeled directly to greater effect.

The inoculation rate was developed in detail and includes vector parameters and human parameters. It is updated in each iteration of the model based on the changing composition of infection strains. In this manner, the inoculation rate allows one to model the spread of resistance and the DHFR triple and the quintuple mutations. As such this dynamic inoculation rate is more useful than using a constant EIR value as was done in Prudhomme-O'Meara et al. [2006]. However there are other improvements that can be made that would enhance the value of this inoculation rate. For example, explicit modeling of the vector population would better inform the parameters used in the inoculation rate. This additional modeling could have many benefits. Firstly and perhaps most importantly, the effects of vector control through indoor residual spraying and insecticide-treated bed-nets could be modeled directly on the mosquito population rather than on individual parameters. This direct modeling would enable mosquito parameters to be updated with each iteration. Further the process of mosquitoes infecting humans could be modeled explicitly through the interaction of the two populations. This technique would be very beneficial to the Mozambiquan situation as vector control was an important aspect of the Lubombo Spatial Development Initiative and its effectiveness appears to have been underestimated in the base model when compared to the rapid decrease in parasite prevalence shown in Appendix A.

7.3 Model Limitations

The base and PK model have several limitations. These limitations impact on the model results. Their inclusion in the modeling process could make results more realistic. These are areas for further research.

7.3.1 Genetic modeling of resistance

Past epidemiological models like Koella and Antia [2003] have modeled resistance through treatment outcome i.e. treatment failures were used as the

proxy for resistance. The models presented in this thesis chose to stratify infections according to mutation category rather than sensitive/resistant, where some mutations categories though more prone to resistance than others are still sensitive to treatment. Treatment failure was still used as the proxy for resistance but aspects like the selective transmission advantage of parasites with the quintuple mutation were applied to all such parasites rather than just the resistant ones. However, using treatment failure as a proxy for resistance may be problematic as treatment may fail for a number of reasons including vomiting and incorrect dosage. Hence modeling of resistance directly i.e. genetically as was done in Watkins et al. [2005] could provide a better estimate of the dynamics of resistance and these results could then be used to inform parameters in an epidemiological model like the base model.

7.3.2 Patient specific parameters

The base and PK model exclude important patient-specific parameters that can have a great impact on treatment outcome of malaria. Issues such as patient adherence, adequately trained health professionals, access to healthcare facilities and transport costs have not been included in the model. These issues are very relevant to developing countries where lack of education and cultural stigmas may affect patient adherence. These countries may lack the infrastructure to enable access for all to primary healthcare facilities and poverty-stricken communities may lack the funds to pay transport costs to use these facilities. Inclusion of factors like patient compliance in a malaria model could help provide an indication of the impact poor adherence has on the development of resistance where sub-therapeutic levels of the drug remain in the patient's bloodstream. While the base model assumed that all infected individuals are treated in Mozambique, this may not be the case in other parts of Mozambique or other countries altogether. In order for this model to be a tool applicable to any malaria setting, inclusion of factors like access to healthcare would make the model more realistic and a better decision-making tool.

7.3.3 Other limitations

One factor that may have a great impact on resistance in African countries that has been ignored in the base and PK model is that of migration. Imported malaria cases from other countries or geographical regions where different treatment strategies are in place could be disastrous for the effec-

tiveness of the treatment strategy in the host country. This is because an individual from a region carrying parasites that are resistant to drug A could migrate to another country where drug A is the treatment strategy and resistance has not yet developed. Mosquitoes would then bite that migrant and may then pass on this resistant strain to others and thus resistance is born prematurely. Allowances for migration could also result in the relaxation of the balanced birth and death rate assumption by allowing the population level to fluctuate as result of migration to and from the host country.

Other factors not included in the model include age and ethnicity. Stratifying models for different age groups could provide better insight into dynamics of children as opposed to adults especially with regards to the development and benefit of immunity. For example, adults and children would be exposed to mosquitoes at different times of the day and at different levels especially since children are generally protected under bednets while sleeping. This could impact on the development of immunity in children which may lead to increased severity of malaria later on.

Another important factor that could be included in the model is that of the HIV/Aids epidemic. This is particularly relevant to the African case which carries a substantial portion of the HIV/Aids burden. The impact of HIV/Aids could be incorporated into the model through differential birth and death rates, and the human susceptibility parameter b_2 . By allowing for differential birth and death rates, one is relaxing the assumption of balanced birth and death rates. Incorporating HIV into the model may result in a higher death rate than birth rate. There has been evidence in favour of and against the relationship between HIV/Aids and malaria, but its inclusion in the model could help add to the body of evidence. [Colebunders et al., 1990, Atzori et al., 1993]

7.4 Model methodology

Differential equation modeling was the technique of choice in this thesis. The model was performed on a population basis rather than on an individual level. The benefit of a population-based model is that individual variations are averaged out to obtain general outcomes of the malaria process and these could be used to inform policy. Thus outcomes such as the number of new infections, percentage of resistance, spread of resistance and recovery rates could be used to perform economic costings and feasibility

studies of antimalarial drug strategies. On the other hand individual based models may provide one with better insight into the epidemiology of malaria infections. Further, stochastic parameters could be used to good effect in individual based models where these parameters are time dependent and each iteration of model informs and updates parameter values. This may help to better inform the modeling of the spread of resistance.

The danger with using population based models is that they are models of averages where the rates between stocks are rates that exist at equilibrium only. Thus the model needs a warm up period to reach a steady state. This is not always a desirable feature of modeling process because sometimes certain stocks are driven down to zero in order to reach that steady state. For example, in the case of the base model where Res0, Res3 and Res5 stocks exist in a competitive environment with Res3 and Res5 stocks having an advantage over Res0 infections in terms of infectiousness and treatment failure, Res0 infections were decreased to zero before a steady state was even reached. Thus the effect of antimalarial interventions was tested on the remaining infection strains only.

Other modeling techniques exist in the Operations Research toolkit than can be used to model the malaria disease. For example an individual-based model could be constructed using a program called Simul8 where individuals are monitored as they move through different stages in the disease process.[Simul8-Corporation, 2008] One of the benefits of using Simul8 is that it is a visually based simulation which may be easily used by and explained to non-mathematical audiences. Other issues that may also be included in this simulation include patient characteristics such as age and ethnicity, compliance and costs associated with attending health care facilities. Using a model like this would also enable one to allow for a stream of imported malaria cases to enter the model and watch their progress and effect on resistance through time. This simulation program would not be useful to malaria alone but to other diseases as well.

7.5 The Causal Map of Malaria Dynamics and Control

The Causal map of malaria dynamics and control presented in Chapter 3 was created to serve as an aid to decision-making. In this thesis this map was not simulated but used rather to inform the discussion based on the base

model results. This map may however be simulated using programs such as Vensim [www.vensim.com]; an open-source software. The major reason for not simulating the map in this thesis was that information on the parameter values could not always be obtained. For example information would be required on training of health workers, patient adherence, the numbers of counterfeit drugs on the market and so on. Hence simulating this model would require a very large databank or at least a large number of assumptions. It is with this in mind that it was decided that this map would serve as a better tool if it was used to inform discussion as the interdependencies and relationships between variables need to be properly understood in order to make effective policy decisions. This map is also very useful in exploring the far-reaching ramifications of changes in antimalarial policy.

7.6 The Operations Research Toolkit

The differential equation modeling of malaria has provided much insight into spread of resistance and the effect of antimalarial interventions in Mozambique. The conclusions and achievements of this modeling approach are discussed in Chapter 8. Other techniques exist in the OR toolkit to complement and substitute this model. Perhaps a multi-disciplinary approach to disease modeling could overcome the flaws associated with each individual technique.

Chapter 8

Conclusion

This chapter presents a final summary of the models used in this thesis and key findings and conclusions. It also highlights areas for further research.

8.1 Model Summary

This thesis focused on building a model of the spread of resistance to Sulfadoxine/Pyrimethamine (SP) in a setting where both SP and artemisinin-based combination therapy (ACT) with SP as the partner drug are the first line therapies for malaria. The model aimed to assess the spread (and not the emergence) of resistance taking into account the pharmacokinetic properties of the drugs in question as well as selection properties of the SP-resistant strain of infection. The model itself is suitable to any low transmission setting where antimalarial drug resistance exists but the country of choice in this modeling exercise was Mozambique. The model was calibrated using parameters specific to the malaria situation in Mozambique. This model was intended to be used to aid decision making in countries where antimalarial drug resistance exists to help prevent resistance spreading to such an extent that drugs lose their usefulness in curing malaria.

The modeling technique of choice was differential equation modeling; a simulation technique that falls under the System Dynamics banner in the Operations Research armamentarium. It is a technique that allowed the modeling of stocks and flows that represent different stages or groupings in the disease process and the rate of movement between these stages respectively. The base model that was built allowed infected individuals to become infectious, to be treated with SP or ACT and to be sensitive to or fail

treatment. Individuals were allowed a period of temporary immunity where they would not be reinfected until the residual SP had been eliminated from their bloodstream. The base model was then further developed to include the pharmacokinetic properties of SP where individuals were allowed to be reinfected with certain strains of infection given the level of residual drug in their bloodstream after their current infection had been cleared.

Parameters for both these models were either referenced values, assumptions or derived from data. The data used to inform these parameter values came from SEACAT study and the Lubombo Spatial Development Initiative. Some parameters were deterministic where as others like the mosquito density were stochastic i.e. they were allowed to vary with time and be updated with each iteration of the model. Some parameters were also treatment specific or mutation specific.

The models used in this thesis were built with idea of expanding on previous models and using available data to improve parameter estimates. The model at its core is similar to the resistance model used in Koella and Antia [2003] where differential equation modeling is used to monitor a population as it becomes infected with a sensitive or resistant infection and then recovers. The inoculation rate is a dynamic function of host and vector parameters. The inclusion in the model of the PK component was derived from Prudhomme-O'Meara et al. [2006] where individuals could be reinfected depending on the residual drug in their bloodstream. Rather than modeling simply sensitive and resistant infections, mutations categories were used as was the case in Watkins et al. [2005] population genetics model. The use of mutation categories allowed one to use parameters specific to these categories rather than the sensitive/resistant stratification and this is particularly relevant in Mozambique where all mutation categories still exhibit some degree of sensitivity to treatment i.e. total resistance has not yet developed for any particular mutation category. The last adaptation of the model was to use gametocyte information directly to determine human infectiousness rather than through using a gametocyte switching rate (constant multiplier used to convert parasite density to gametocyte density) as was done in Pongtavornpinyo [2006]. Hence the models thus created in this thesis seek to adapt previous models to improve the parameter estimation and examination of the impact that antimalarial interventions have on the malaria system.

8.2 Key findings and conclusions

The following are key findings from the modeling procedure used in this thesis.

1. The model simulated that the existing vector control and drug policy in Mozambique (Vector control from time 500 and the introduction of ACT at time 1825) had the major effect of decreasing total prevalence of malaria by approximately 70% in the 11 year modeling period.
2. The distribution of Res3 and Res5 infections is predicted to change over the modeling period with Res3 infections initially increasing and then decreasing while Res5 infections started low and increased to overtake Res3 infections around time 2200. The ratio of Res5 to Res3 infections increases gradually to 1 and then increases rapidly to 3.5 where it stays at that level thereafter. The timing of the change in this composition of infection corresponds with the introduction of ACT and thus the model postulates that the use of ACT prompted the increased prevalence of quintuple parasites over DHFR triple and sensitive parasites.
3. The total number of failures decreased substantially after the introduction of ACT. The model simulates that the total failures decreased to 17% of its previous level. The model allows for treatment failures to occur with all infection strains under all treatments to incorporate the probability of treatment failure for reasons other than resistance such as vomiting and incorrect dosage. It is important to note this as resistance to artemisinin has not yet developed and hence those treated with ACT should technically not have any early treatment failures. This is one of issues associated with using a proxy of resistance instead of modeling resistance directly. Even with these limitations, the model still shows that ACT decreased the spread of resistance substantially. The model also showed in the scenario testing that a delayed introduction of ACT would increase the total number of resistant cases in the 11 year simulation period. The composition of failures also changed in line with infection as Res3 failures decreased to near zero while Res5 infections remained at a higher level. This change in composition also occurred during the change over period to ACT.
4. The results of the base model corresponded with the observed data from the SEACAT study in terms of the magnitude and the trends

of the impact of the change to ACT policy, but underestimated the impact of the vector control strategies.

5. The model exhibited sensitivity to mosquito density parameter as well as the parameters associated with gametocytemia i.e. time to and duration of gametocytemia. Given the limitations in the estimation of these parameters discussed in the previous chapter, further modeling could provide more insight into the effects of these parameters on the model.
6. The PK model underestimated prevalence greatly and drove Res0 and Res3 infections to zero. The discussion chapter highlighted problems associated with the PK model and further modeling and particularly the inclusion the infectiousness component could improve this model's results and render them more realistic.
7. The Scenario testing of the base model predicted that vector control is an effective strategy to reduce prevalence and that it is sensitive to the time at which the control is started as it decreased prevalence very gradually. The model however did underestimate the decrease in prevalence compared to rapid effect of vector control noted in Sharp et al. [2007].
8. The Scenario testing of the base model predicted that the introduction of ACT in Mozambique had a greater impact on reducing prevalence than vector control (through both insecticide treated bednets and indoor residual spraying). It was also found that the start time of the ACT strategy did not decrease the effect on prevalence as ACT was a fast acting strategy.
9. The Scenario testing also showed that the ratio of Res5 to Res3 infections increased faster when ACT was the treatment policy than when SP was the policy. Thus higher values of this ratio appear to be associated with ACT being the treatment strategy in place.
10. Differential equation modeling is an effective modeling tool to capture the spread of disease and to test the effects of policy interventions as it allows one to assess these effects on populations and averages out individual-level intricacies to better inform policy decisions.

8.3 Conclusions

The models presented in this thesis have suggested that while vector control and artemisinin-based combination therapy are effective interventions to decrease malaria prevalence, the use of artemisinin-based combination therapy appears to be associated with an increase in the prevalence of Res5 infections over Res3 infections and this could lead to increased resistance to SP in due course.

The discussion chapter has already highlighted areas of further research for the disease-specific parts of the model i.e. aspects to include and parameter estimation. Methodologically, the disease could be modeled on an individual basis (as opposed to a population basis) using a program like Simul8 and this would allow the modeling of patient-specific parameters such as compliance and economic status. Stochastic parameters could be used to greater effect in the model where parameters are updated with each iteration that the model is run. System delays could also be incorporated into models rather than moving populations at average equilibrium rates. Greater collaboration with modelers from other disciplines could add to the body of disease modeling methodologies to improve the understanding of disease dynamics to enable better-policy making.

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Appendix A

Data Analysis output

A.1 Gametocyte Infectivity

```
. gen infectday7=13.07848+68.50295/(1+exp(-2.501418*(log10(gamedens7)-2.508097)))  
(336 missing values generated)
```

```
. replace infectday7=. if gamedens7==.  
(0 real changes made)
```

```
. sort mutcat trt
```

```
. by mutcat trt:means gamedens7 infectday7
```

```
-----  
-> mutcat = 0, trt = SP
```

Variable	Type	Obs	Mean	[95% Conf. Interval]	
gamedens7	Arithmetic	19	7.368421	-2.140801	16.87764
	Geometric	3	38.83958	5.015804	300.7519
	Harmonic	3	30.40477	.	.
infectday7	Arithmetic	3	20.44743	9.676145	31.21872
	Geometric	3	20.11043	11.391	35.5043
	Harmonic	3	19.74902	12.34162	49.39679

Missing values in confidence interval(s) for harmonic mean indicate that confidence interval is undefined for corresponding variable(s). Consult Reference Manual for details.

-> mutcat = 0, trt = SP/ART

Variable	Type	Obs	Mean	[95% Conf. Interval]	
gamedens7	Arithmetic	16	10.75	-6.219806	27.71981
	Geometric	3	38.83958	2.642964	570.7655
	Harmonic	3	28.07379	.	.
infectday7	Arithmetic	3	21.58244	.5612327	42.60364
	Geometric	3	20.57955	8.212574	51.56943
	Harmonic	3	19.72204	10.80139	113.2676

Missing values in confidence interval(s) for harmonic mean indicate that confidence interval is undefined for corresponding variable(s). Consult Reference Manual for details.

-> mutcat = 1, trt = SP

Variable	Type	Obs	Mean	[95% Conf. Interval]	
gamedens7	Arithmetic	119	111.3613	-12.71122	235.4339
	Geometric	36	70.16506	44.11494	111.5979
	Harmonic	36	40.4936	31.24822	57.50863
infectday7	Arithmetic	36	27.22911	22.13105	32.32717
	Geometric	36	24.54937	21.2387	28.37609
	Harmonic	36	22.74291	20.33858	25.7919

-> mutcat = 1, trt = SP/ART

Variable	Type	Obs	Mean	[95% Conf. Interval]	
----------	------	-----	------	----------------------	--

gamedens7	Arithmetic	137	3.525547	.2301031	6.820992
	Geometric	9	34.6941	16.7393	71.90744
	Harmonic	9	25.31837	16.62468	53.07146
infectday7	Arithmetic	9	20.89356	14.97803	26.80909
	Geometric	9	19.87373	15.53453	25.42497
	Harmonic	9	19.07521	15.757	24.16378

-> mutcat = 2, trt = SP

Variable	Type	Obs	Mean	[95% Conf. Interval]	
gamedens7	Arithmetic	41	186.439	46.90248	325.9756
	Geometric	18	113.7136	45.98377	281.2032
	Harmonic	18	39.2478	25.49868	85.17483
infectday7	Arithmetic	18	36.38591	24.95211	47.81971
	Geometric	18	30.09216	21.98506	41.1888
	Harmonic	18	25.40905	20.06304	34.63895

-> mutcat = 2, trt = SP/ART

Variable	Type	Obs	Mean	[95% Conf. Interval]	
gamedens7	Arithmetic	37	10.62162	-1.479597	22.72284
	Geometric	6	37.51113	11.25642	125.0029
	Harmonic	6	24.9221	14.13593	105.1711
infectday7	Arithmetic	6	22.32611	12.21424	32.43799
	Geometric	6	20.79912	13.65637	31.67777
	Harmonic	6	19.57102	14.37044	30.67053

A.2 Gametocyte Prevalence

. tabulate mutate gprevfinal if trt==0&day==42,row

```

+-----+
| Key    |
+-----+
|  frequency  |
| row percentage |
+-----+

```

mutate	gprevfinal		Total
	0	1	
0	4	1	5
	80.00	20.00	100.00
1	7	3	10
	70.00	30.00	100.00
2	9	10	19
	47.37	52.63	100.00
3	99	111	210
	47.14	52.86	100.00
4	17	19	36
	47.22	52.78	100.00
5	32	49	81
	39.51	60.49	100.00
Total	168	193	361
	46.54	53.46	100.00

. tabulate mutate gprevfinal if trt==1&day==42,row

```

+-----+
| Key    |
+-----+

```

```

|-----|
|  frequency  |
| row percentage |
|-----|

```

mutate	gprevfinal		Total
	0	1	
0	2	0	2
	100.00	0.00	100.00
1	3	0	3
	100.00	0.00	100.00
2	6	5	11
	54.55	45.45	100.00
3	106	26	132
	80.30	19.70	100.00
4	18	6	24
	75.00	25.00	100.00
5	28	11	39
	71.79	28.21	100.00
Total	163	48	211
	77.25	22.75	100.00

A.3 Gametocyte Survival Analysis

```
. stset gamestart, failure(gamecens)
```

```

failure event:  gamecens != 0 & gamecens < .
obs. time interval:  (0, gamestart]
exit on or before:  failure

```

```

-----
6675 total obs.
  27 event time missing (gamestart>=.)          PROBABLE ERROR
615 obs. end on or before enter()
-----

```

```

6033 obs. remaining, representing
1854 failures in single record/single failure data
172602 total analysis time at risk, at risk from t =      0
        earliest observed entry t =                      0
        last observed exit t =                          42

```

```
. stsum,by(mutate)
```

```

      failure _d: gamecens
analysis time _t: gamestart

```

mutate		time at risk	incidence rate	no. of subjects	----- Survival time -----		
					25%	50%	75%
0		18333	.0157094	648	7	.	.
1		7002	.0128535	252	7	.	.
2		10341	.0139252	360	14	.	.
3		86844	.008498	2900	28	.	.
4		14946	.007226	478	.	.	.
5		27720	.0133117	1080	14	.	.
total		165186	.0105154	5718	14	.	.

```
. sts list,by(mutate) compare
```

```

      failure _d: gamecens
analysis time _t: gamestart

```

mutate	time	-----Survivor Function-----					
		0	1	2	3	4	5
1	1	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
6	6	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
11	11	0.7222	0.7407	0.8205	0.8674	0.8630	0.7632
16	16	0.6250	0.7018	0.6410	0.7955	0.8016	0.6905

21	0.5833	0.7018	0.6154	0.7535	0.8016	0.6532
26	0.5833	0.7018	0.6154	0.7535	0.8016	0.6532
31	0.5556	0.6192	0.5897	0.7245	0.7584	0.6321
36	0.5556	0.6192	0.5897	0.7245	0.7584	0.6321
41	0.5556	0.6192	0.5897	0.7245	0.7584	0.6321
46

```
. sts graph,by(mutate)
```

```
      failure _d: gamecens
      analysis time _t: gamestart
```

```
. sts test mutate
```

```
      failure _d: gamecens
      analysis time _t: gamestart
```

Log-rank test for equality of survivor functions

mutate	Events observed	Events expected
0	288	196.37
1	90	74.16
2	144	110.48
3	738	894.80
4	108	149.41
5	369	311.78
Total	1737	1737.00

```
      chi2(5) = 122.18
      Pr>chi2 = 0.0000
```

```
. stcox mutate
```

```
      failure _d: gamecens
      analysis time _t: gamestart
```

```

Iteration 0: log likelihood = -14728.803
Iteration 1: log likelihood = -14719.01
Iteration 2: log likelihood = -14719.002
Refining estimates:
Iteration 0: log likelihood = -14719.002

```

Cox regression -- Breslow method for ties

```

No. of subjects =          5718                Number of obs =          5718
No. of failures =          1737
Time at risk    =          165186
Log likelihood  = -14719.002
LR chi2(1)      =          19.60
Prob > chi2    =          0.0000

```

_t	Haz. Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
mutate	.9298628	.0151322	-4.47	0.000	.9006723 .9599994

A.4 Time to Gametocytemia

```

. tabstat gamestart if trt==0&gamecens==1&trtoutcome==1&gamestart!=0& day==42,
> stats(n mean p50 p25 p75) by(mutate)

```

Summary for variables: gamestart
by categories of: mutate

mutate	N	mean	p50	p25	p75
0	32	11.15625	7	7	14
1	10	11.9	7	7	14
2	12	11.08333	10.5	7	14
3	61	13.08197	14	7	21
4	8	14	10.5	7	21
5	16	11.375	7	7	14

```

Total |          139  12.23741          7          7          14
-----

```

```

. tabstat gamestart if trt==1&gamecens==1&trtoutcome==1&gamestart!=0& day==42,
> stats(n mean p50 p25 p75) by(mutate)

```

Summary for variables: gamestart
by categories of: mutate

```

mutate |          N          mean          p50          p25          p75
-----+-----
      2 |          3  16.33333          14           7          28
      3 |          6  16.33333         17.5           7          21
      4 |          1           7           7           7           7
      5 |          6  11.66667         10.5           7          14
-----+-----
Total |         16           14           14           7          21
-----

```

A.5 Duration of Gametocytemia

```

. tabstat gamedur if trt==0&gamecens==1&trtoutcome==1&gamestart!=0& day==42, st
> ats(n mean p50 p25 p75)

```

Summary for variables: gamedur
by categories of: mutate

```

mutate |          N          mean          p50          p25          p75
-----+-----
-----+-----
Total |         139  20.64748           21           14          35
-----

```

```

. tabstat gamedur if trt==1&gamecens==1&trtoutcome==1&gamestart!=0& day==42, st
> ats(n mean p50 p25 p75)

```

Summary for variables: gamedur

by categories of: mutate

mutate	N	mean	p50	p25	p75
Total	16	9.625	7	7	14

A.6 Treatment Outcome Analysis

Treatment outcome 1 - Adequate Clinical and Parasitological Response (ACPR)

Treatment outcome 2 - Early Treatment Failure

Treatment outcome 3 - Late Treatment Failure

. by trt: tabulate mutate trtoutcome if day==0, row

-> trt = 0

Key
frequency
row percentage

mutate	trtoutcome			Total
	1	2	3	
0	75	0	0	75
	100.00	0.00	0.00	100.00
1	26	0	0	26
	100.00	0.00	0.00	100.00
2	30	2	0	32

	93.75	6.25	0.00	100.00
3	170	11	17	198
	85.86	5.56	8.59	100.00
4	25	3	3	31
	80.65	9.68	9.68	100.00
5	45	5	32	82
	54.88	6.10	39.02	100.00
Total	371	21	52	444
	83.56	4.73	11.71	100.00

-> trt = 1

trtoutcome	Freq.	Percent	Cum.
1	190	94.06	94.06
2	10	4.95	99.01
3	2	0.99	100.00
Total	202	100.00	

A.7 Treatment Failure Analysis

-> trt = SP, trtoutcome = 2

Summary for variables: timetofailure2
by categories of: mutate

mutate	N	mean	p50	p25	p75
--------	---	------	-----	-----	-----

that would have decreased only slightly if ACT was never rolled out. The second figure in Figure 6.6 depicts the effect of different treatment pressures on the distribution of Res5 and Res3 infections. PropRes is the ratio of Res5 infections to Res3 infections. It appears that when ACT coverage is 100% ($f_{\text{pressure}}=0\%$), the ratio of Res5 infections to Res3 infections is greater than when SP coverage is 100%. This finding is also supported by the observed data in Mozambique that while ACT has decreases prevalence greatly, it has increased the distribution of Res5 infections over Res3 infections. Given that the presence of the mutations provides a basis for the development of resistance, these findings show the potential for an increase of resistance to SP.

6.2.2 Application of Findings to System Dynamics Diagram

In Figure 3.5, one sees that an increase in the proportion of ACT leads to an increase in the number of recoveries and hence a decrease in prevalence as well as an increase of resistance to the partner drug SP. In the case of artemisinin-based combination therapy, the artemisinin acts on gametocyte development and serves to decrease human infectiousness owing to a much faster parasite clearance rate than SP. This decrease in human infectiousness to mosquitoes will also further decrease the number of infected mosquitoes which helps to decrease prevalence. However, if ACT does increase the resistance to the partner drug SP in this case, this would shorten the useful therapeutic life of SP and the need for a change in partner drug would occur sooner than would otherwise have been the case. The change of drug would also be an added cost to government. Thus the pressure of ACT implementation will need to be weighed against the existing level of resistance to the partner drug in order to maximise the useful therapeutic life of the drug. This issue could be made irrelevant by choosing a new partner drug to artemisinin. However, this new drug may add to the cost of an already expensive drug strategy.

The successful use of ACT, besides having positive implications for prevalence is also largely dependent on successful implementation i.e. even though government may plan for a certain level of pressure, obstacles to implementation may result in a lower realised level of pressure. As result, governments will need to take heed of the following issues to aid the successful implementation of ACT. Artemisinin-based drugs are costly to obtain and are more expensive than drugs like chloroquine and SP. As such, in order to justify this cost its implementation needs to be thorough. Further, this

2	1	1	1	1	1
3	9	.8888889	1	0	2
4	3	.6666667	0	0	2
5	4	1.25	1.5	.5	2

Total	17	.9411765	1	0	2

-> trt = SP, trtoutcome = 3

Summary for variables: timetofailure2
by categories of: mutate

mutate	N	mean	p50	p25	p75
3	17	14.76471	7	7	21
4	3	25.66667	28	7	42
5	32	24.34375	21	17.5	28

Total	52	21.28846	21	7	28

-> trt = SP/ACT, trtoutcome = 2

Summary for variables: timetofailure2
by categories of: mutate

mutate	N	mean	p50	p25	p75
3	2	1	1	0	2

Total	2	1	1	0	2

-> trt = SP/ACT, trtoutcome = 3
no observations

Appendix B

Sensitivity Testing Outputs

The following graphs are outputs of the sensitivity testing on the Base model.

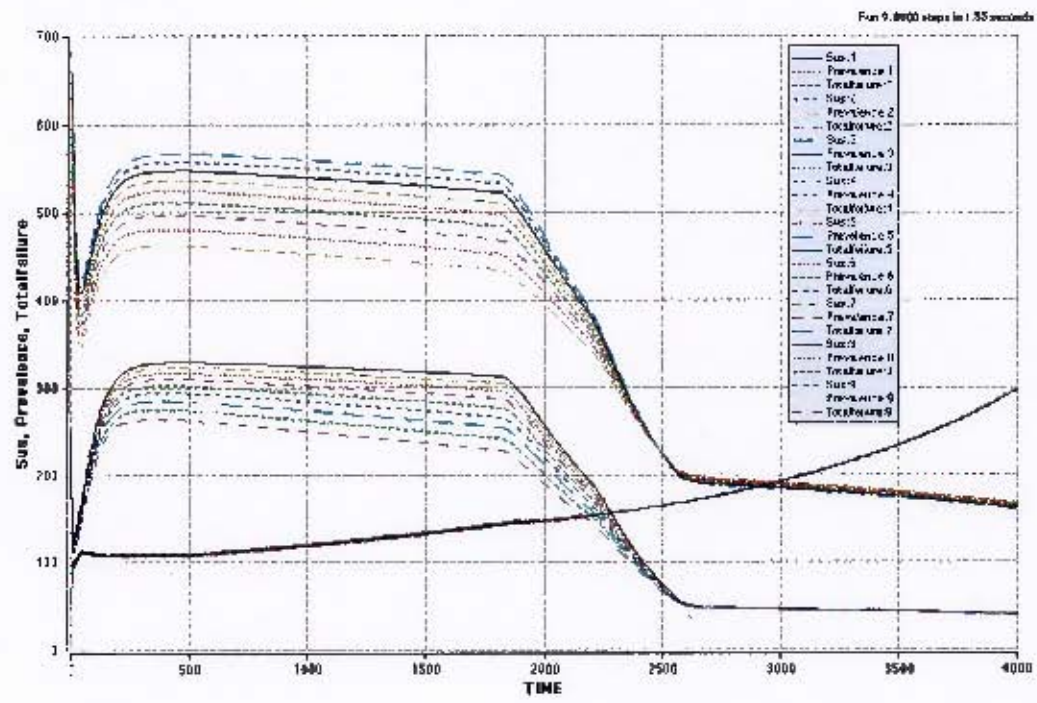
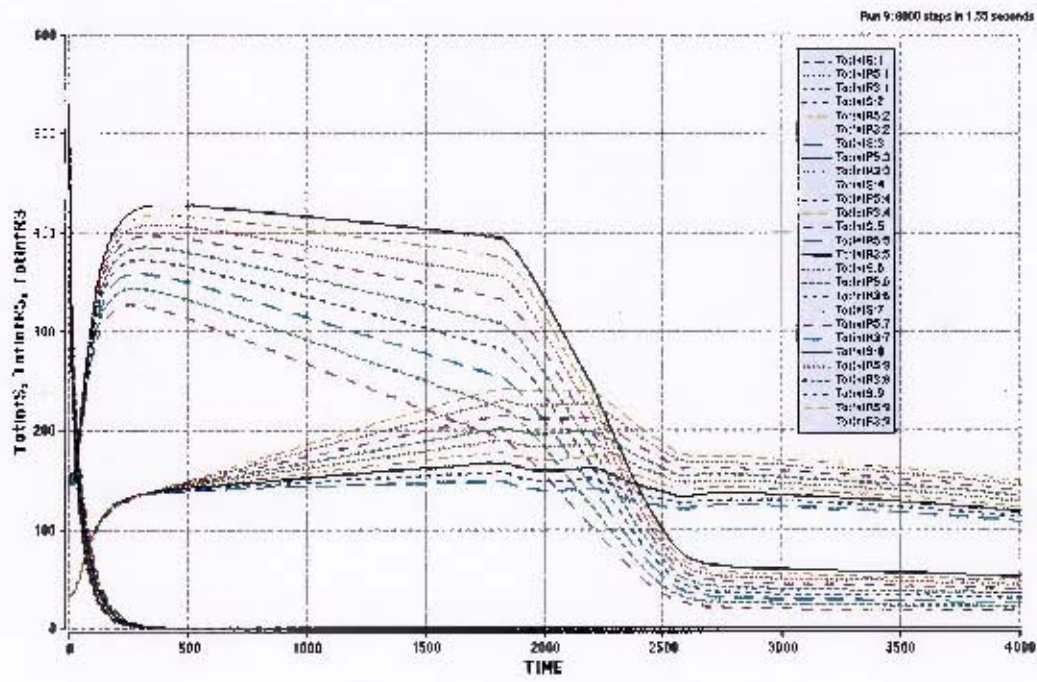


Figure B.1: Sensitivity Testing: Recovery Time (τ_0)
152

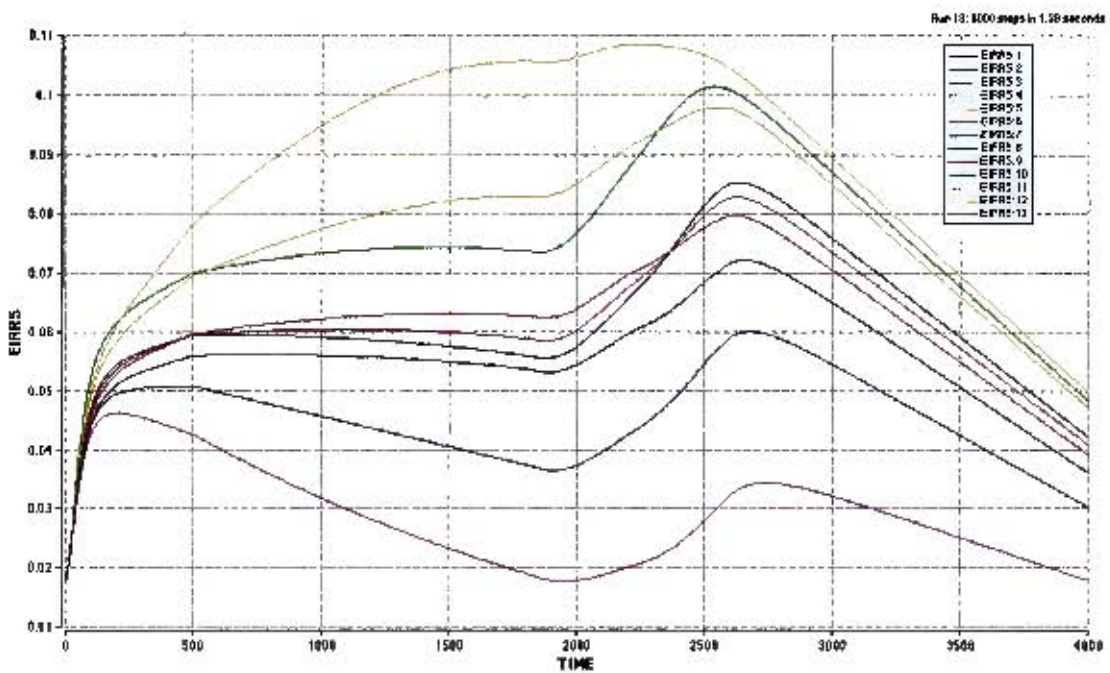
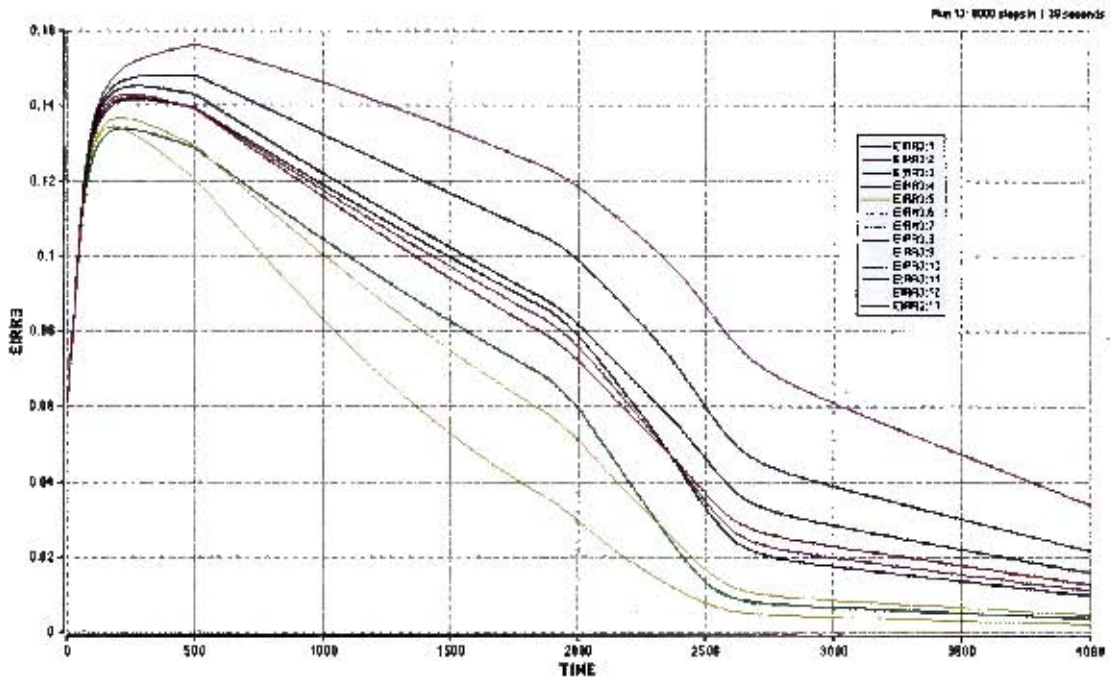


Figure B.2: Sensitivity Testing: Human Infectiousness

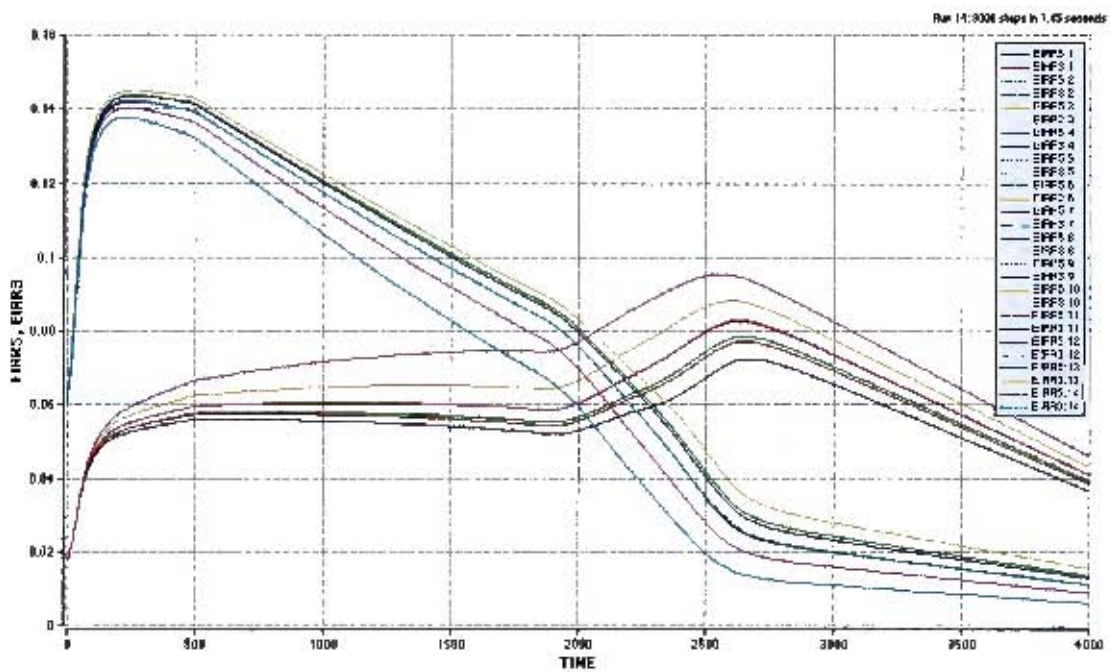
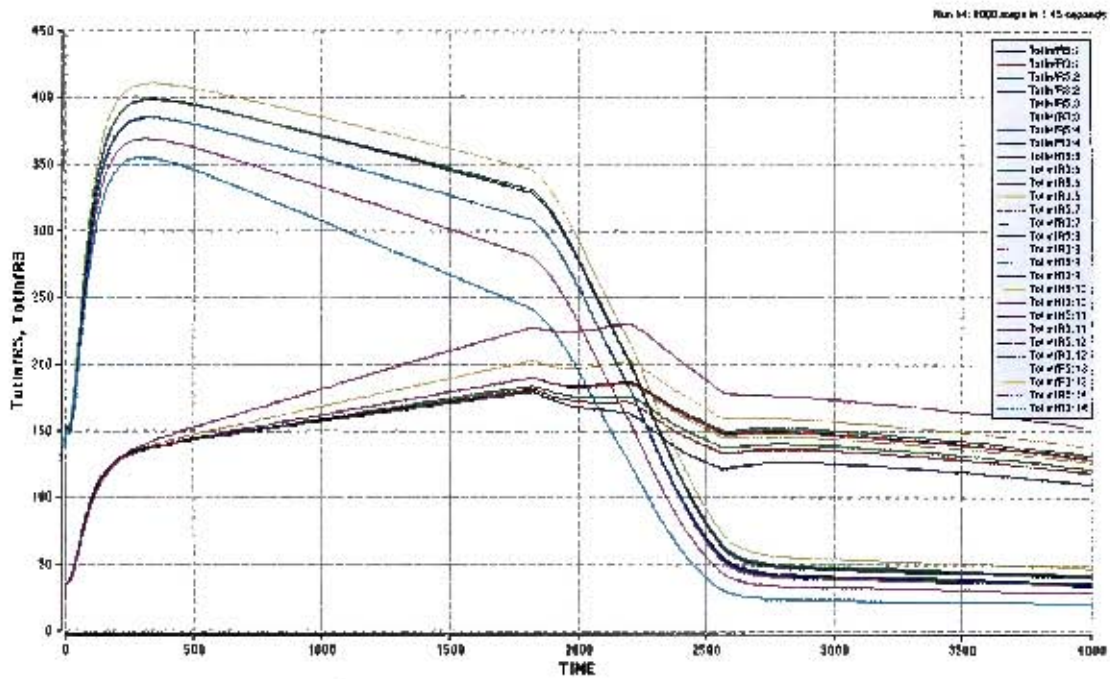


Figure B.3: Sensitivity Testing on EIR's: Treatment outcome

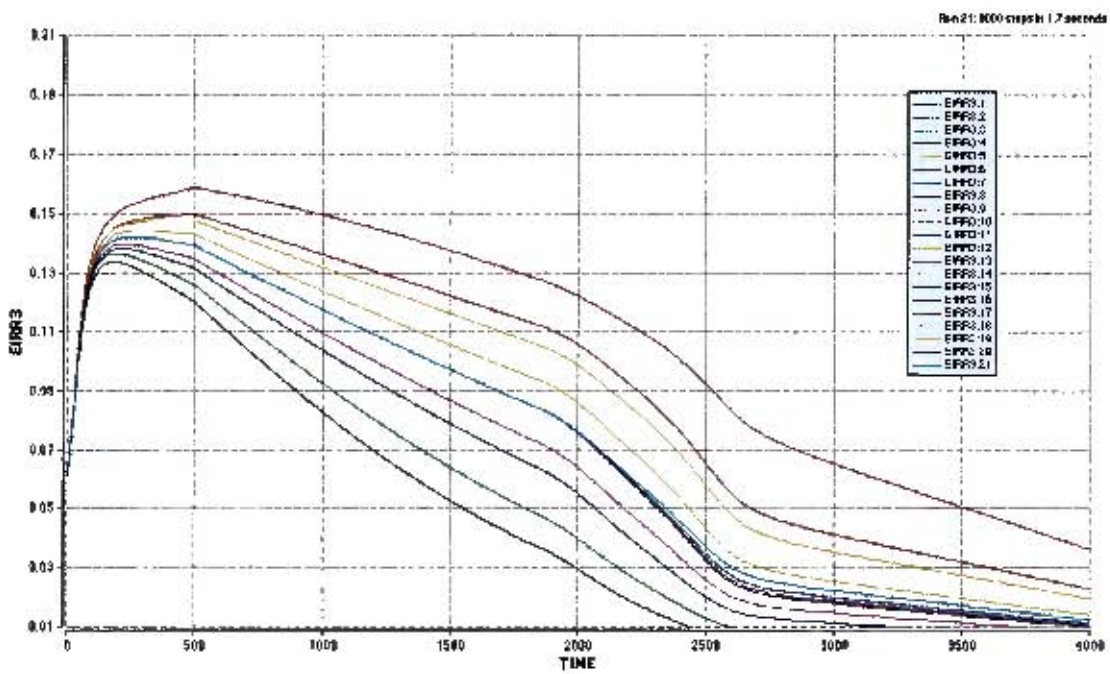
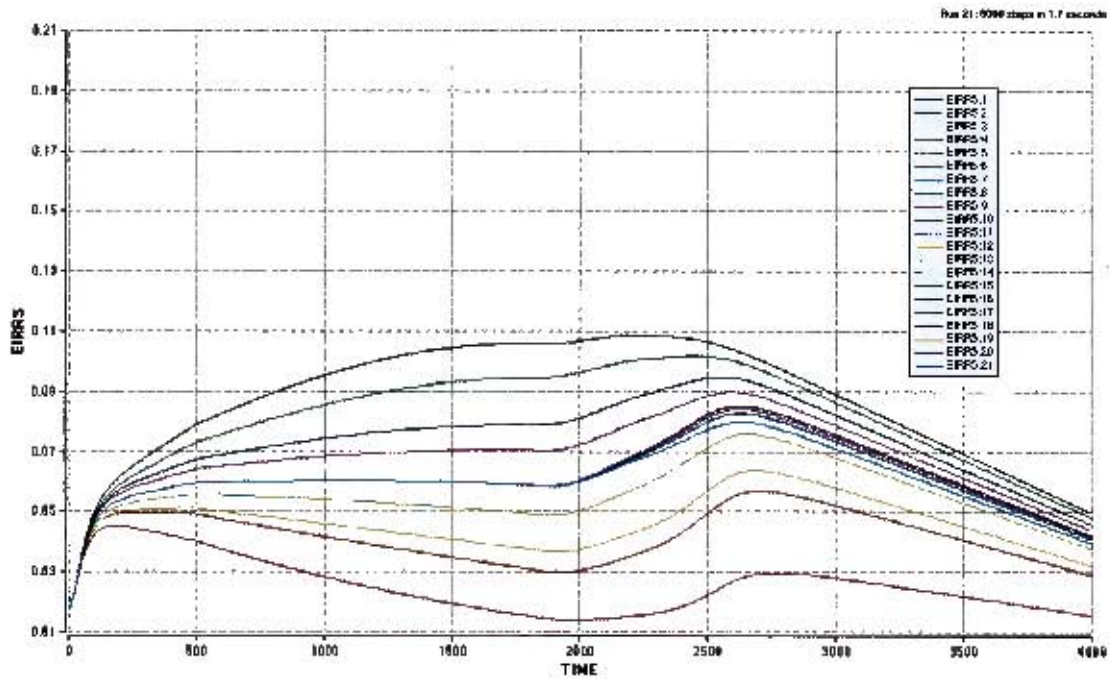


Figure B.4: Sensitivity Testing: Time to failure

Appendix C

Model Extension equations and output

C.1 Model Equations

The equations underlying Figure 5.9 follow.

$$\frac{dSus}{dt} = \delta + NewRec + NewSus + NewSusA - NewInfS - NewInfR3 - NewInfR5 - \delta Sus \quad (C.1)$$

$$\frac{dInfS}{dt} = NewInfS - SSusR5 - SSusR5A - SETF - SETFA - SLTF - SLTFA - \delta InfS \quad (C.2)$$

$$\begin{aligned} \frac{dInfR5}{dt} = & NewInfR5 - R5SusR5 - R5SusR5A - R5ETF - R5ETFA \\ & - R5LTF - R5LTFA - \delta InfR5 \end{aligned} \quad (C.3)$$

$$\begin{aligned} \frac{dInfR3}{dt} = & NewInfR3 - R3SusR5 - R3SusR5A - R3ETF - R3LTF \\ & - R3ETFA - R3LTFA - \delta InfR3 \end{aligned} \quad (C.4)$$

$$\frac{dSusR5}{dt} = SSusR5 + R3SusR5 + R5SusR5 - SSusR3 - \delta SusR5 \quad (C.5)$$

$$\frac{dSusR3}{dt} = SSusR3 + SETFSusR3 + R5ETF SusR3 + R3ETF SusR3 - NewSus - \delta SusR3 \quad (C.6)$$

$$\frac{dSusR5A}{dt} = SSusR5A + R3SusR5A + R5SusR5A - SSusR3A - \delta SusR5A \quad (C.7)$$

$$\frac{dSusR3A}{dt} = SSusR3A - NewSusA - \delta SusR3A \quad (C.8)$$

$$\begin{aligned} \frac{dSusRes3LTF}{dt} = & SLTFSusR3LTF + R5LTF SusR3LTF \\ & + R3LTF SusR3LTF - NewRec \\ & - \delta SusR3LTF \end{aligned} \quad (C.9)$$

$$\frac{dFailuresSETF}{dt} = SETF + SETFA - SETFSusR3 - \delta FailuresSETF \quad (C.10)$$

$$\frac{dFailuresSLTF}{dt} = SLTF + SLTFA - SLTFSusR3LTF - \delta FailuresSLTF \quad (C.11)$$

$$\frac{dFailuresR5ETF}{dt} = R5ETF + R5ETF A - R5ETF SusR3 - \delta FailuresR5ETF \quad (C.12)$$

$$\frac{dFailuresR5LTF}{dt} = R5LTF + R5LTF A - R5LTF SusR3LTF - \delta FailuresR5LTF \quad (C.13)$$

$$\frac{dFailuresR3ETF}{dt} = R3ETF + R3ETF A - R3ETF SusR3 - \delta FailuresR3ETF \quad (C.14)$$

$$\frac{dFailuresR3LTF}{dt} = R3LTF + R3LTF A - R3LTF SusR3LTF - \delta FailuresR3LTF \quad (C.15)$$

The equations underlying Figure 5.10 follow.

$$\begin{aligned} \frac{dSus}{dt} = & \delta + NewRec + NewSus + NewSusA - NewInfS \\ & - NewInfR3 - NewInfR5 - \delta Sus \end{aligned} \quad (C.16)$$

$$\begin{aligned} \frac{dInfS}{dt} = & NewInfS - SSusR5 - SSusR5A - SSusR5A - SETF - SETFA \\ & - SLTF - SLTFA - \delta InfS \end{aligned} \quad (C.17)$$

$$\begin{aligned} \frac{dRes5}{dt} = & NewInfR5 - R5SusR5 - R5SusR5A - R5ETF \\ & - R5ETFA - R5LTF - R5LTFA + ReinR5SusR5 \\ & + ReinR5SusR3 + ReinR5SusR5A \\ & + ReinR5SusR3A + ReinR5SusR3LTF - \delta Res5 \end{aligned} \quad (C.18)$$

$$\begin{aligned} \frac{dRes3}{dt} = & NewInfR3 - R3SusR5 - R3SusR5A - R3ETF \\ & - R3LTF - R3ETFA - R3LTFA + ReinR3SusR3 \\ & + ReinR3SusR3A + ReinR3SusR3LTF - \delta Res3 \end{aligned} \quad (C.19)$$

$$\begin{aligned} \frac{dSusR5}{dt} = & SSusR5 + R3SusR5 + R5SusR5 - SSusR3 - ReinR5SusR5 - \delta SusRes5 \end{aligned} \quad (C.20)$$

$$\begin{aligned} \frac{dSusR3}{dt} = & SSusR3 + SETFSusR3 + R5ETFsusR3 + R3ETFsusR - NewSus \\ & - ReinR5SusR3 - ReinR3SusR3 - \delta SusRes3 \end{aligned} \quad (C.21)$$

$$\begin{aligned} \frac{dSusR5A}{dt} = & SSusR5A + R3SusR5A + R5SusR5A \\ & - SSusR3A - ReinR5SusR5A - \delta SusRes5A \end{aligned} \quad (C.22)$$

$$\frac{dSusR3A}{dt} = SSusR3A - NewSusA - ReinR5SusR3A - ReinR3SusR3A - \delta SusRes3A \quad (C.23)$$

$$\begin{aligned} \frac{dSusR3LTF}{dt} = & SLTFSusR3LTF + R5LTFSusR3LTF + R3LTFSusR3LTF \\ & - NewRec - ReinR5SusR3LTF - ReinR3SusR3LTF \\ & - \delta SusRes3LTF \end{aligned} \quad (C.24)$$

$$\frac{dFailuresSETF}{dt} = SETF + SETFA - SETFSusR3 - \delta FailuresSETF \quad (C.25)$$

$$\frac{dFailuresSLTF}{dt} = SLTF + SLTFA - SLTFSusR3LTF - \delta FailuresSLTF \quad (C.26)$$

$$\frac{dFailuresR5ETF}{dt} = R5ETF + R5ETF A - R5ETF SusR3 - \delta FailuresR5ETF \quad (C.27)$$

$$\frac{dFailuresR5LTF}{dt} = R5LTF + R5LTF A - R5LTF SusR3LTF - \delta FailuresR5LTF \quad (C.28)$$

$$\frac{dFailuresR3ETF}{dt} = R3ETF + R3ETF A - R3ETF SusR3 - \delta FailuresR3ETF \quad (C.29)$$

$$\frac{dFailuresR3LTF}{dt} = R3LTF + R3LTF A - R3LTF SusR3LTF - \delta FailuresR3LTF \quad (C.30)$$

where δ is the birth/death rate and those stocks and flows ending in 'A' refer to the ACT treatment arm.

C.2 Stocks, Flows and Parameters

Table C.1 summarises all the parameters used in the model. The column headed 'Type' classifies parameter values as sourced from References (R), Data (D) or Assumptions (A).

Table C.1: Summary of Model Parameters

Name	Description	Value	Unit	Range	Type	Source
Drug Parameters						
r	Period of Chemoprophylaxis for SP	$r_0 = 7$ $r_1 = 8$ $r_2 = 37$	day	(5,9) (6, 10) (33, 41)	R	Watkins and Mosobo [1993], Prudhomme-O'Meara et al. [2006]
r_{2LTF}	Period of Chemoprophylaxis for SP for late treatment failures	$r_{2LTF} = 24$	day	(21, 27)	D	
b_{1S}	Infectiousness of humans to mosquitoes (R0)	SP=0.04; ACT=0.002	prob	(0.035,0.045) (0.0015,0.0025)	D	
b_{1R5}	Infectiousness of humans to mosquitoes (R5)	SP=0.18; ACT=0.056	prob	(0.1, 0.28) (0.045,0.07)	D	
b_{1R3}	Infectiousness of humans to mosquitoes (R3)	SP=0.13; ACT=0.04	prob	(0.1, 0.16) (0.035, 0.045)	D	
p_{R5}	Probability of Reinfection with Res5 infection	SP = 0.0265 ACT = 0.0238	prob	(0.02, 0.031) (0.018, 0.028)	D	

Continued on Next Page...

Table C.1 – Continued

Name	Description	Value	Unit	Range	Type	Source
<i>PR3</i>	Probability of Reinfection with Res3 infection	SP = 0.0244 ACT = 0.0238	prob	(0.019, 0.03) (0.018, 0.028)	D	

Table C.2: Description of Flows in the model

	Flow	Value
FailuresSETF → SusR3	SETFSusR3	$\frac{1}{q} \times FailuresSETF$
FailuresSLTF → SusR3LTF	SLTFSusR3LTF	$\frac{1}{q} \times FailuresSLTF$
FailuresR5ETF → SusR3	R5ETFSusR3	$\frac{1}{q} \times FailuresR5ETF$
FailuresR3LTF → SusR3LTF	R5LTFSusR3LTF	$\frac{1}{q} \times FailuresR5LTF$
FailuresR3ETF → SusR3	R3ETFSusR3	$\frac{1}{q} \times FailuresR3ETF$
FailuresR3LTF → SusR3LTF	R3LTFSusR3LTF	$\frac{1}{q} \times FailuresR3LTF$
InfS → SusR5	SSusR5	$f \times psACPR \times \frac{1}{r_0} \times InfS$
InfS → SusR5A	SSusR5A	$(1 - f) \times psACPRA \times \frac{1}{r_0} \times InfS$
InfR3 → SusR5	R3SusR5	$f \times pR3ACPR \times \frac{1}{r_0} \times InfR3$
InfR3A → SusR5A	R3SusR5A	$(1 - f) \times pR3ACPRA \times \frac{1}{r_0} \times InfR3$
InfR5 → SusR5	R5SusR5	$f \times pR5ACPR \times \frac{1}{r_0} \times InfR5$
InfR5A → SusR5A	R5SusR5A	$(1 - f) \times pR5ACPRA \times \frac{1}{r_0} \times InfR5$
SusR5 → SusR3	SSusR3	$(1 - pR5) \times \frac{1}{r_1} \times SusR5$
SusR5A → SusR3A	SSusR3A	$(1 - pR5A) \times \frac{1}{r_1} \times SusR5A$
SusR3 → Sus	NewSus	$(1 - pR5 - pR3) \times \frac{1}{r_2} \times SusR3$
SusR3A → Sus	NewSusA	$(1 - pR5A - pR3A) \times \frac{1}{r_2} \times SusR3A$
SusR3LTF → Sus	NewRec	$(1 - pR3 - pR5) \times \frac{1}{r_{2LTF}} \times SusR3LTF$
SusR5 → InfR5	ReinR5SusR5	$pR5 \times hInfR5 \times SusR5$
SusR5A → InfR5	ReinR5SusR5A	$pR5A \times hInfR5 \times SusR5A$
SusR3 → InfR5	ReinR5SusR3	$pR5 \times hInfR5 \times SusR3$
SusR3A → InfR5	ReinR5SusR3A	$pR5A \times hInfR5 \times SusR3A$
SusR3 → InfR3	ReinR3SusR3	$pR3 \times hInfR3 \times SusR3$

Continued on Next Page...

Table C.2 – Continued

	Flow	Value
SusR3A → InfR3	ReinR3SusR3A	$p_{R3A} \times h_{InfR3} \times SusR3A$
SusR3LTF → InfR5	ReinR5SusR3LTF	$p_{R5} \times h_{InfR5} \times SusR3LTF$
SusR3LTF → InfR3	ReinR3SusR3LTF	$p_{R3} \times h_{InfR3} \times SusR3LTF$
	SusR5d	$\delta \times SusR5A$
	SusR5Ad	$\delta \times SusR5$
	SusR3d	$\delta \times SusR3A$
	SusR3Ad	$\delta \times SusR3$
	SusR3LTFd	$\delta \times SusR3LTF$

All flows ending in 'd' are rates of death.

C.3 PK Model Results

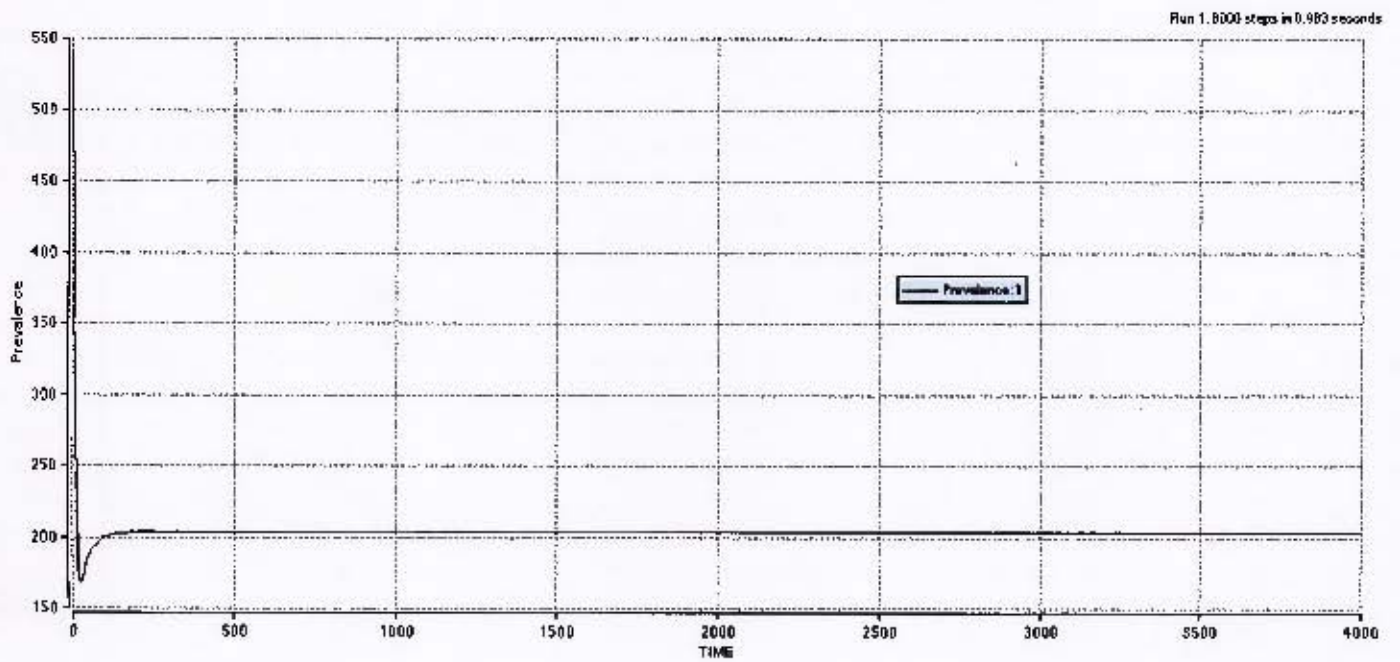
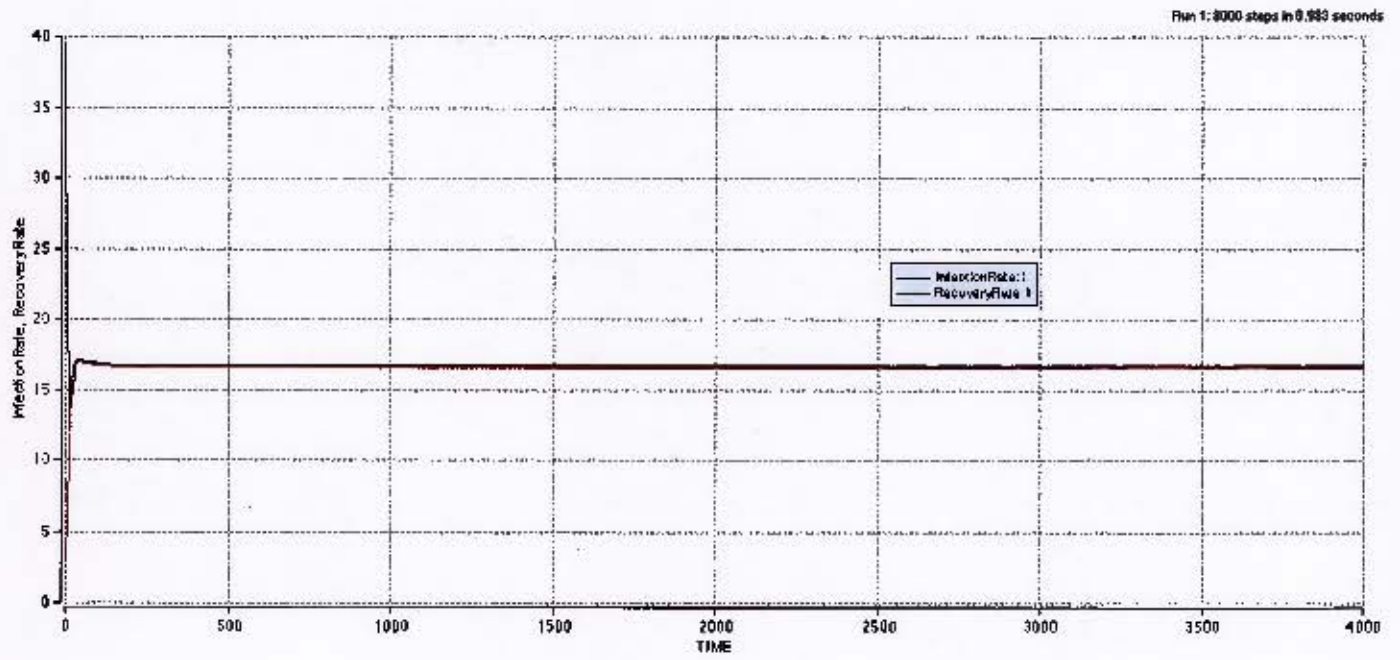


Figure C.1: Steady state conditions: 1 (PK model)

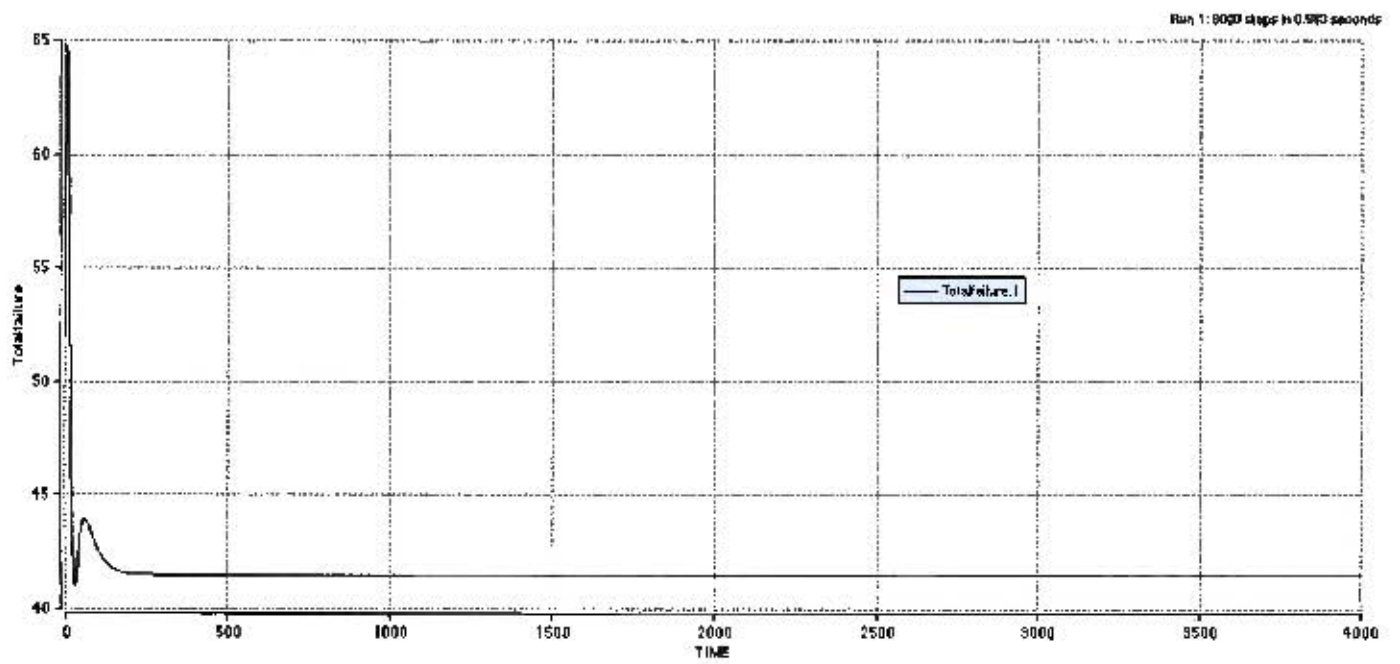
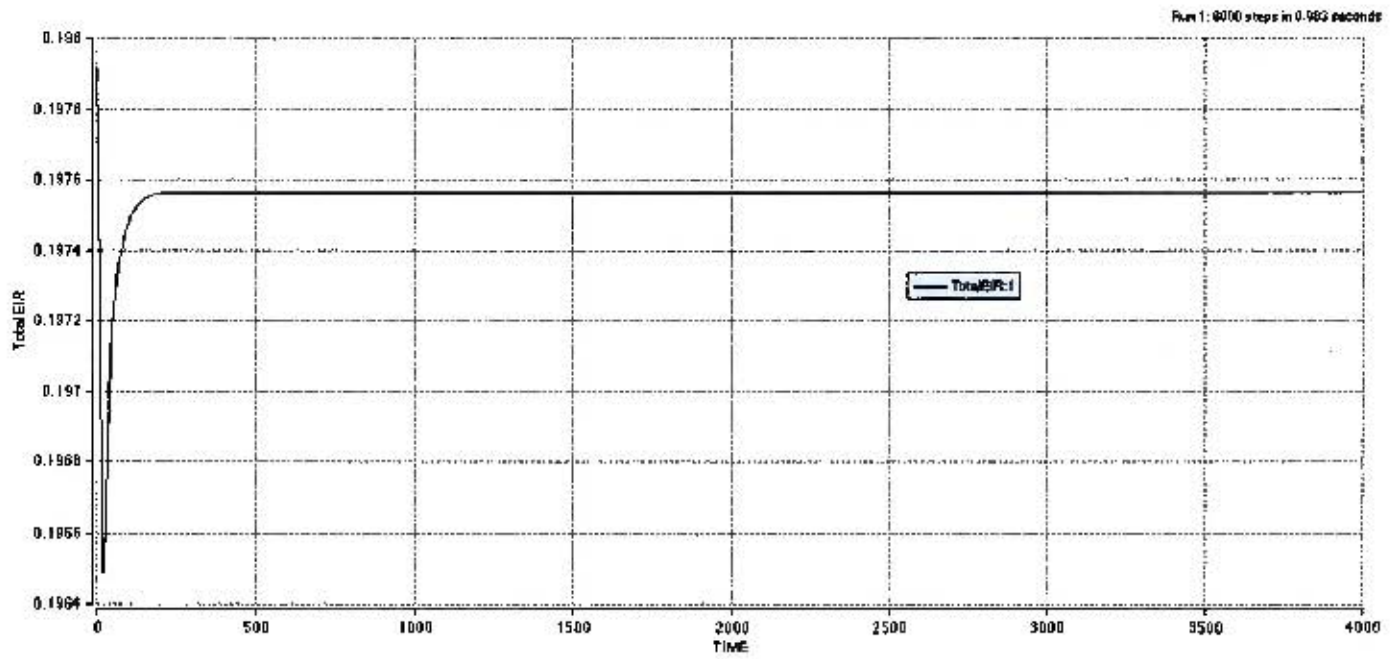


Figure C.2: Steady state conditions: 2 (PK model)

C.4 Sensitivity Testing of PK model

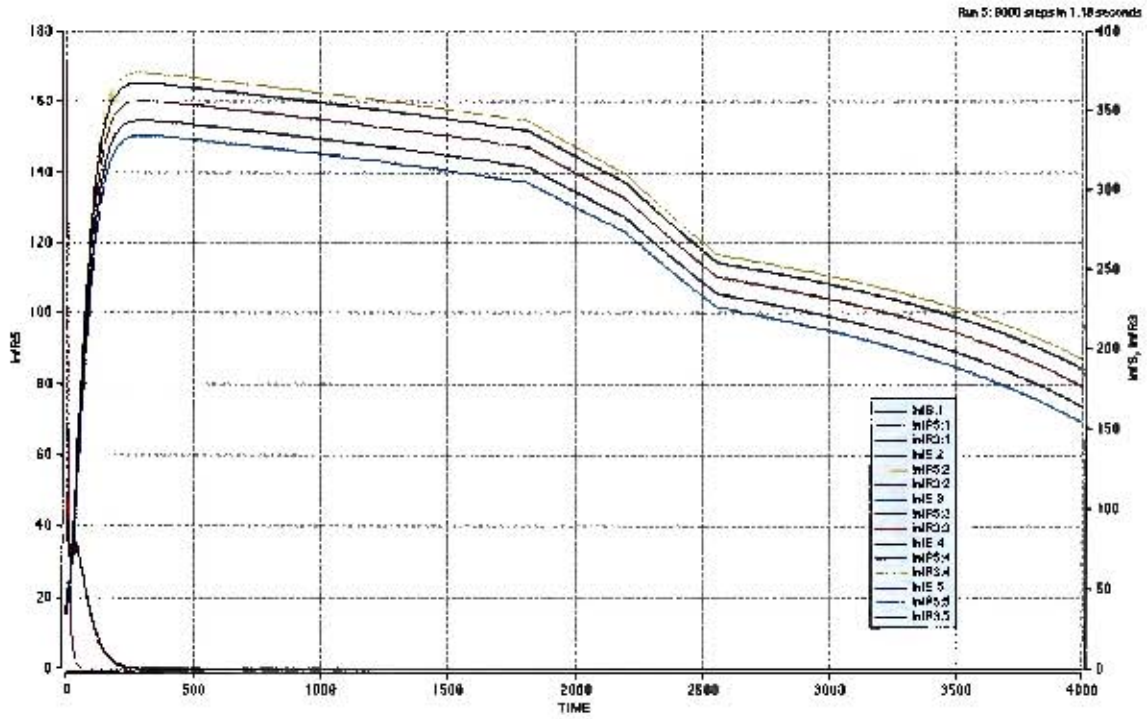


Figure C.3: Sensitivity Testing: Mosquito density m (PK model)

Run 7: 8000 steps in 1.3 seconds

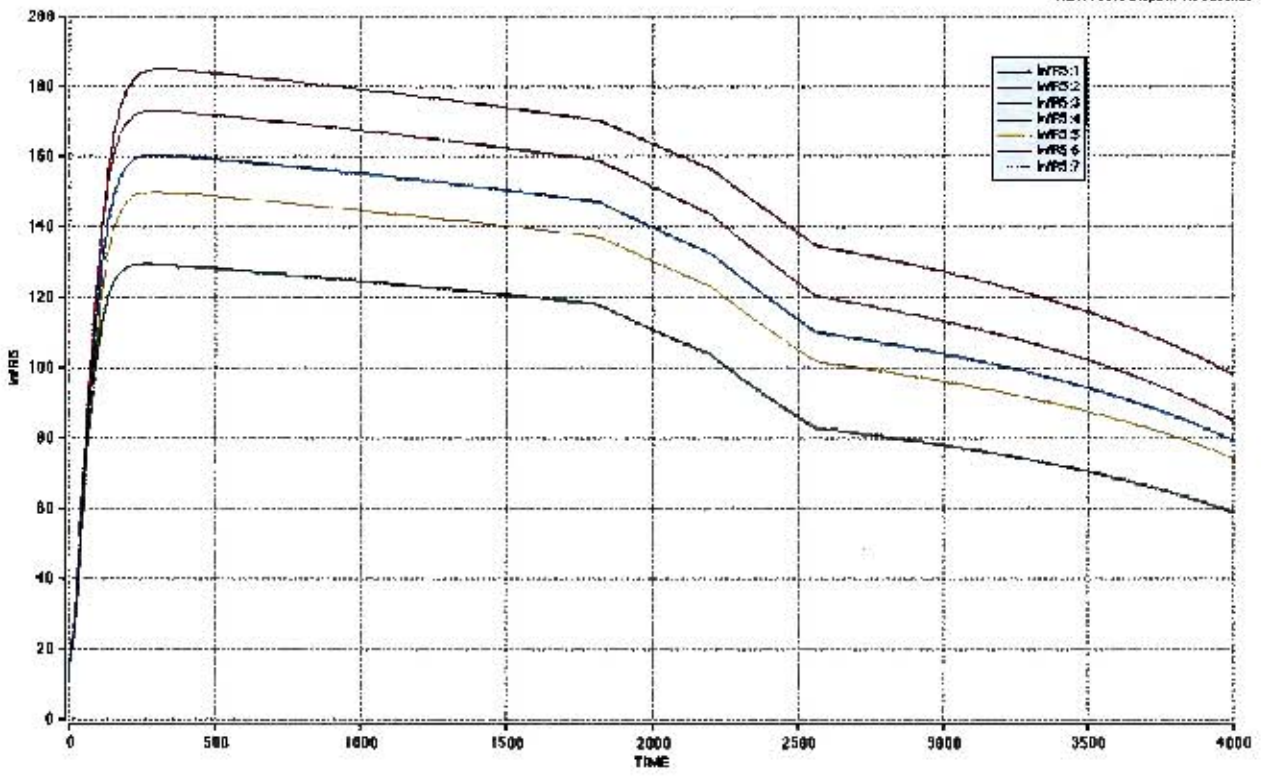


Figure C.4: Sensitivity Testing: r_0 and r_3 (PK model)

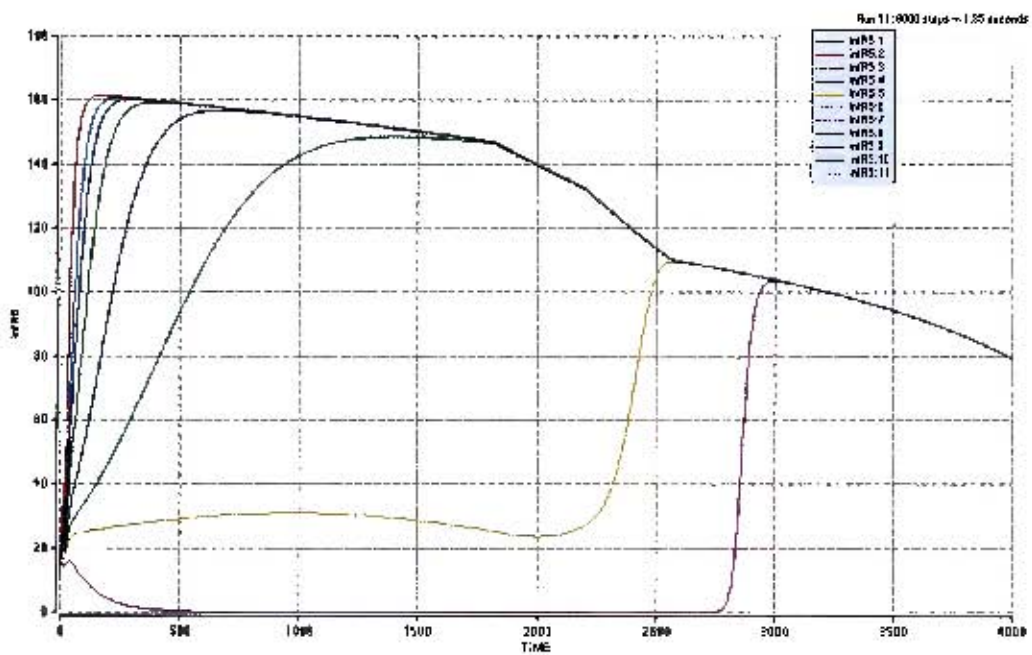
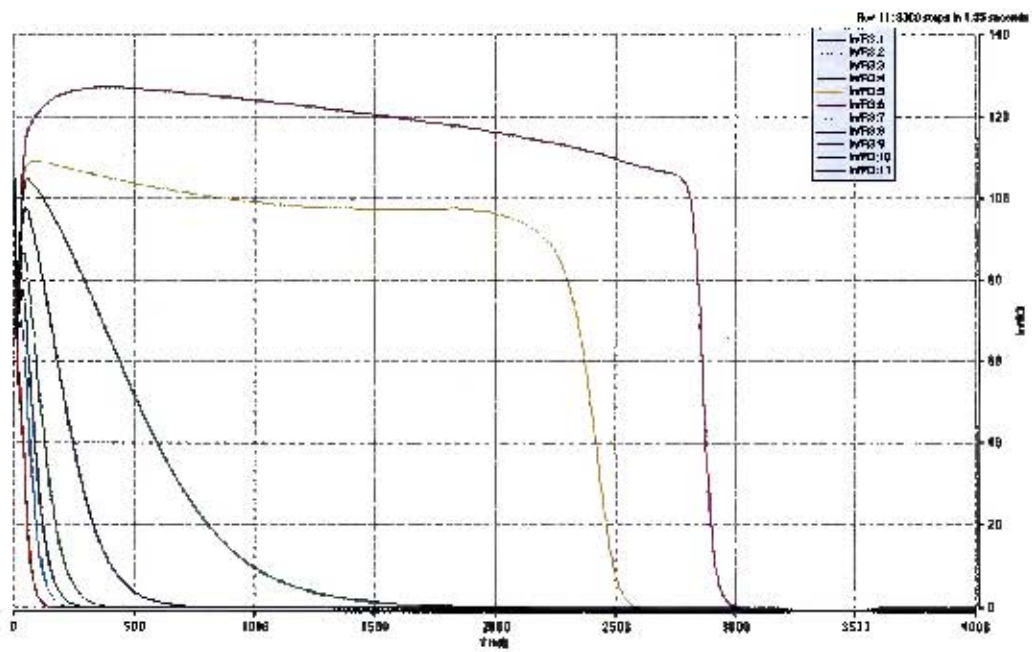


Figure C.5: Sensitivity Testing: Human Infectiousness parameter b_1 (PK model)

Appendix D

Model Code

D.1 Base Model Code

METHOD RK4

STARTTIME = 0
STOPTIME = 4000
DT = 0.5

{Differential Equations}

d/dt (Sus) = Susb - New_InfS - New_Infr2 - New_Infr1 + New_Rec + New_RecA
+ New_RecS +New_RecSA + New_RecR5 +New_SusSETF+New_SusSLTF
+New_RecR5A + New_RecR3 +New_RecR3A + New_SusR2ETF + New_SusR2LTF
+ New_SusR1ETF + New_SusR1LTF - Susd
INIT Sus = 250

d/dt (InfS) = New_InfS - InfectiousS - InfectiousSA - S_Rec - S_RecA - InfSd
-SETF-SETFA-SLTF-SLTF
INIT InfS = 328

d/dt (Infr5) = New_Infr2 - R2ETF - R2LTF - R2ETFA - R2LTFA - R2_Rec
- R2_RecA - InfectiousR5 - InfectiousR5A - Infr2d
INIT Infr5 = 4

d/dt (Infr3) = New_Infr1 - R1_Rec - R1_RecA -R1ETF - R1LTF - R1ETFA
- R1LTFA - InfectiousR3 - InfectiousR3A - Infr1d
INIT Infr3 = 53

$d/dt (\text{InfectS}) = \text{InfectiousS} - \text{InfectS_Rec} - \text{InfectSd}$
INIT InfectS = 200

$d/dt (\text{InfectSA}) = \text{InfectiousSA} - \text{InfectS_RecA} - \text{InfectSAd}$
INIT InfectSA = 0

$d/dt (\text{InfectR5}) = \text{InfectiousR5} - \text{InfectR2_Rec} - \text{InfectR5d}$
INIT InfectR5 = 4

$d/dt (\text{InfectR5A}) = \text{InfectiousR5A} - \text{InfectR2_RecA} - \text{InfectR5Ad}$
INIT InfectR5A = 0

$d/dt (\text{InfectR3}) = \text{InfectiousR3} - \text{InfectR1_Rec} - \text{InfectR3d}$
INIT InfectR3 = 50

$d/dt (\text{InfectR3A}) = \text{InfectiousR3A} - \text{InfectR1_RecA} - \text{InfectR3Ad}$
INIT InfectR3A = 0

$d/dt(\text{Rec}) = \text{S_Rec} + \text{R2_Rec} + \text{R1_Rec} - \text{New_Rec} - \text{Recd}$
INIT Rec = 20

$d/dt(\text{RecA}) = \text{S_RecA} + \text{R2_RecA} + \text{R1_RecA} - \text{New_RecA} - \text{RecAd}$
INIT RecA = 0

$d/dt(\text{RecS}) = \text{InfectS_Rec} - \text{New_RecS} - \text{RecSd}$
INIT RecS = 10

$d/dt(\text{RecSA}) = \text{InfectS_RecA} - \text{New_RecSA} - \text{RecSAd}$
INIT RecSA = 0

$d/dt(\text{RecR5}) = \text{InfectR2_Rec} - \text{New_RecR5} - \text{RecR5d}$
INIT RecR5 = 4

$d/dt(\text{RecR5A}) = \text{InfectR2_RecA} - \text{New_RecR5A} - \text{RecR5Ad}$
INIT RecR5A = 0

$d/dt(\text{RecR3}) = \text{InfectR1_Rec} - \text{New_RecR3} - \text{RecR3d}$
INIT RecR3 = 23

d/dt(RecR3A) = InfectR1_RecA - New_RecR3A - RecR3Ad
 INIT RecR3A = 0

d/dt (FailuresSETF) = SETF + SETFA - New_SusSETF - FailuresSETFd
 INIT FailuresSETF = 1

d/dt (FailuresSLTF) = SLTF + SLTFA - New_SusSLTF - FailuresSLTFd
 INIT FailuresSLTF = 1

d/dt (FailuresR5ETF) = R2ETF + R2ETFA - New_SusR2ETF - FailuresR5ETFd
 INIT FailuresR5ETF = 2

d/dt (FailuresR5LTF) = R2LTF + R2LTFA - New_SusR2LTF - FailuresR5LTFd
 INIT FailuresR5LTF = 16

d/dt (FailuresR3ETF) = R1ETF + R1ETFA - New_SusR1ETF - FailuresR3ETFd
 INIT FailuresR3ETF = 13

d/dt (FailuresR3LTF) = R1LTF + R1LTFA - New_SusR1LTF - FailuresR3LTFd
 INIT FailuresR3LTF = 21

{Explicit terms}

Susb = deltab*1000

New_InfS = hInfS*Sus

New_Infr2 = hInfr2*Sus

New_Infr1 = hInfr1*Sus

$$hInfS = (m*a^2*b2*EXP(-mu*tau)*b1S*(InfectS+InfectSA+FailuresSETF+FailuresSLTF))/$$

$$(a*(b1S*(InfectS+InfectSA+FailuresSETF+FailuresSLTF)+b1R2*(InfectR5+InfectR5A$$

$$+FailuresR5ETF +FailuresR5LTF)+b1R1*(InfectR3+ InfectR3A +FailuresR3ETF$$

$$+FailuresR3LTF)) + mu)$$

$$hInfr2 = (m*a^2*b2*EXP(-mu*tau)*b1R2*(InfectR5+InfectR5A+FailuresR5ETF$$

$$+FailuresR5LTF))/ (a*(b1S*(InfectS+InfectSA+FailuresSETF+FailuresSLTF)$$

$$+b1R2*(InfectR5+InfectR5A +FailuresR5ETF +FailuresR5LTF)+b1R1*(InfectR3$$

$$+ InfectR3A +FailuresR3ETF +FailuresR3LTF)) + mu)$$

$$hInfr1 = (m*a^2*b2*EXP(-mu*tau)*b1R1*(InfectR3+ InfectR3A +FailuresR3ETF$$

$$+FailuresR3LTF)) / (a*(b1S*(InfectS+InfectSA+FailuresSETF+FailuresSLTF))$$

$$+b1R2*(\text{InfectR5}+\text{InfectR5A} +\text{FailuresR5ETF} +\text{FailuresR5LTF})+b1R1*(\text{InfectR3} \\ + \text{InfectR3A} +\text{FailuresR3ETF}+\text{FailuresR3LTF})) + \mu)$$

$$\begin{aligned} \text{New_SusSETF} &= 1/q\text{SETF}*\text{FailuresSETF} \\ \text{New_SusSLTF} &= 1/q\text{SLTF}*\text{FailuresSLTF} \\ \text{New_SusR2ETF} &= 1/q\text{R2ETF}*\text{FailuresR5ETF} \\ \text{New_SusR2LTF} &= 1/q\text{R2LTF}*\text{FailuresR5LTF} \\ \text{New_SusR1ETF} &= 1/q\text{R1ETF}*\text{FailuresR3ETF} \\ \text{New_SusR1LTF} &= 1/q\text{R1LTF}*\text{FailuresR3LTF} \end{aligned}$$

$$\begin{aligned} \text{New_Rec} &= 1/r1*\text{Rec} \\ \text{New_RecA} &= 1/r1A*\text{RecA} \end{aligned}$$

$$\begin{aligned} \text{New_RecS} &= 1/r1S*\text{RecS} \\ \text{New_RecSA} &= 1/r1SA*\text{RecSA} \end{aligned}$$

$$\begin{aligned} \text{New_RecR5} &= 1/r1R5*\text{RecR5} \\ \text{New_RecR5A} &= 1/r1R5A*\text{RecR5A} \end{aligned}$$

$$\begin{aligned} \text{New_RecR3} &= 1/r1R3*\text{RecR3} \\ \text{New_RecR3A} &= 1/r1R3A*\text{RecR3A} \end{aligned}$$

$$\begin{aligned} \text{InfectR2_Rec} &= f*1/\text{gamedurR5}*\text{InfectR5} \\ \text{InfectR2_RecA} &= (1-f)*1/\text{gamedurR5A}*\text{InfectR5A} \end{aligned}$$

$$\begin{aligned} \text{InfectS_Rec} &= f*1/\text{gamedurS}*\text{InfectS} \\ \text{InfectS_RecA} &= (1-f)*1/\text{gamedurSA}*\text{InfectSA} \end{aligned}$$

$$\begin{aligned} \text{InfectR1_Rec} &= f*1/\text{gamedurR3}*\text{InfectR3} \\ \text{InfectR1_RecA} &= (1-f)*1/\text{gamedurR3A}*\text{InfectR3A} \end{aligned}$$

$$\begin{aligned} \text{InfectiousS} &= f*p\text{SACPR}*p\text{InfS}*1/\text{gamestartS}*\text{InfS} \\ \text{InfectiousSA} &= (1-f)*p\text{SACPRA}*p\text{InfSA}*1/\text{gamestartSA}*\text{InfS} \end{aligned}$$

$$\begin{aligned} \text{InfectiousR5} &= f*p\text{R2ACPR}*p\text{InfR5}*1/\text{gamestartR5}*\text{InfR5} \\ \text{InfectiousR5A} &= (1-f)*p\text{R2ACPRA}*p\text{InfR5A}*1/\text{gamestartR5A}*\text{InfR5} \end{aligned}$$

$$\begin{aligned} \text{InfectiousR3} &= f*p\text{R1ACPR}*p\text{InfR3}*1/\text{gamestartR3}*\text{InfR3} \\ \text{InfectiousR3A} &= (1-f)*p\text{R1ACPRA}*p\text{InfR3A}*1/\text{gamestartR3A}*\text{InfR3} \end{aligned}$$

$R2_Rec = f * pR2ACPR * (1 - pInfr5) * 1 / r0 * Infr5$
 $R2_RecA = (1 - f) * pR2ACPRA * (1 - pInfr5A) * 1 / r0A * Infr5$

$R1_Rec = f * pR1ACPR * (1 - pInfr3) * 1 / (r0) * Infr3$
 $R1_RecA = (1 - f) * pR1ACPRA * (1 - pInfr3A) * 1 / r0A * Infr3$

$S_Rec = f * pSACPR * (1 - pInfS) * 1 / r0 * InfS$
 $S_RecA = (1 - f) * pSACPRA * (1 - pInfSA) * 1 / r0A * InfS$

$SETF = f * pSETF * 1 / SETFday * InfS$
 $SLTF = f * pSLTF * (1 / SLTFday) * InfS$
 $R2ETF = f * pR2ETF * 1 / R2ETFday * Infr5$
 $R2LTF = f * pR2LTF * (1 / R2LTFday) * Infr5$
 $R1ETF = f * pR1ETF * 1 / R1ETFday * Infr3$
 $R1LTF = f * pR1LTF * 1 / R1LTFday * Infr3$
 $SETFA = f * pSETFA * 1 / SETFAday * InfS$
 $SLTFA = f * pSLTFA * (1 / SLTFAday) * InfS$
 $R2ETFA = (1 - f) * pR2ETFA * 1 / R2ETFAday * Infr5$
 $R2LTFA = (1 - f) * pR2LTFA * 1 / R2LTFAday * Infr5$
 $R1ETFA = (1 - f) * pR1ETFA * 1 / R1ETFAday * Infr3$
 $R1LTFA = (1 - f) * pR1LTFA * 1 / R1LTFAday * Infr3$

$Susd = deltad * Sus$
 $InfSd = deltad * InfS$
 $Infr2d = deltad * Infr5$
 $Infr1d = deltad * Infr3$
 $FailuresSETFd = deltad * FailuresSETF$
 $FailuresSLTFd = deltad * FailuresSLTF$
 $FailuresR5ETFd = deltad * FailuresR5ETF$
 $FailuresR5LTFd = deltad * FailuresR5LTF$
 $FailuresR3ETFd = deltad * FailuresR3ETF$
 $FailuresR3LTFd = deltad * FailuresR3LTF$
 $InfectSd = deltad * InfectS$
 $InfectSAd = deltad * InfectSA$
 $InfectR5d = deltad * InfectR5$
 $InfectR5Ad = deltad * InfectR5A$
 $InfectR3d = deltad * InfectR3$
 $InfectR3Ad = deltad * InfectR3A$
 $Recd = deltad * Rec$

RecAd=deltad*RecA
 RecSd = deltad*RecS
 RecSAd = deltad*RecSA
 RecR5d = deltad*RecR5
 RecR5Ad = deltad*RecR5A
 RecR3d = deltad*RecR3
 RecR3Ad = deltad*RecR3A

Totdeaths = Susd + InfSd +Infr2d + Infr1d + InfectSd +InfectSAd +InfectR5d
 +InfectR5Ad + InfectR3d +InfectR3Ad + Recd +RecAd +RecSd + RecSAd +RecR5d
 +RecR5Ad +RecR3d +RecR3Ad + FailuresR5ETFd +FailuresR5LTFd +FailuresR3ETFd
 +FailuresR3LTFd + FailuresSETFd + FailuresSLTFd

Total = Sus + InfS+Infr5+Infr3 + FailuresR5ETF +FailuresR5LTF +FailuresR3ETF
 +FailuresR3LTF + FailuresSETF + FailuresSLTF + InfectS +InfectSA +InfectR5
 +InfectR5A + InfectR3 +InfectR3A + Rec + RecA +RecS + RecSA +RecR5
 +RecR5A +RecR3 +RecR3A

TotRec = Rec +RecA +RecS + RecSA +RecR5 +RecR5A +RecR3 +RecR3A
 Prevalence = InfS+Infr5+Infr3 +FailuresR5ETF +FailuresR5LTF +FailuresR3ETF
 +FailuresR3LTF +FailuresSETF +FailuresSLTF + InfectS +InfectSA +InfectR5
 +InfectR5A + InfectR3 +InfectR3A

R5toR3= Infr5/Infr3
 Total35 = Infr3+Infr5 +Totalfailure
 Unity=R5toR3/R5toR3
 EIRS=hInfS/b2
 EIRR5=hInfr2/b2
 EIRR3=hInfr1/b2
 InfectionRate = New_InfS +New_Infr2 +New_Infr1
 RecoveryRate = New_Rec + New_RecA+ New_RecS +New_RecSA + New_RecR5
 +New_SusSETF+New_SusSLTF+New_RecR5A + New_RecR3 +New_RecR3A +
 New_SusR2ETF + New_SusR2LTF + New_SusR1ETF + New_SusR1LTF
 TotalEIR=EIRS +EIRR3 +EIRR5
 Totalfailure = FailuresR5ETF +FailuresR5LTF +FailuresR3ETF +FailuresR3LTF
 +FailuresSETF +FailuresSLTF
 TotalEIR35 = EIRR3 +EIRR5

AnnualEIR = TotalEIR*365

TotInfS = InfS +InfectS +InfectSA+FailuresSETF+FailuresSLTF
TotInfr5 = Infr5 +InfectR5 +InfectR5A+FailuresR5ETF+FailuresR5LTF
TotInfr3 = Infr3 +InfectR3 +InfectR3A+FailuresR3ETF+FailuresR3LTF
TotFailuresETF = FailuresR5ETF +FailuresR3ETF +FailuresSETF
TotFailuresLTF = FailuresR5LTF +FailuresR3LTF +FailuresSLTF

{Parameters}

deltab = 0.038/365

deltad = 0.038/365

m = IF TIME<500 THEN mstart ELSE mstart*(1.105-0.00021*time)

a = 0.3

mu = 0.1

tau = 11

mstart=2

b1S = f*b1SSP+(1-f)*b1SACT

b1R2 = f*b1R2SP+(1-f)*b1R2ACT

b1R1 = f*b1R1SP+(1-f)*b1R1ACT

b1SSP = 0.2

b1R2SP = 0.3

b1R1SP = 0.24

b1SACT = 0.2

b1R2ACT = 0.2

b1R1ACT = 0.2

gamestartS = 7

gamestartSA = 14

gamedurS = 21

gamedurSA = 14

gamestartR5 = 7

gamestartR5A = 10

gamedurR5 = 21

gamedurR5A = 14

gamestartR3 = 14

gamestartR3A = 17

gamedurR3 = 21

gamedurR3A = 11

pInfS = 0.2
pInfSA = 0.1
pInfR5 = pInfS*2.6
pInfR5A = pInfSA*2.2
pInfR3 = pInfS*2.5
pInfR3A = pInfSA*2

b2 = 0.8
r0 = 7
r0A = 4
r1 = 45
r1A = 48
r1S = 24
r1SA = 24
r1R5 = 24
r1R5A = 28
r1R3 = 17
r1R3A = 24
q = 7
qSETF = q + 43
qSLTF = q + 24
qR2ETF = q + 43
qR2LTF = q + 24
qR1ETF = q + 43
qR1LTF = q + 35

SETFday = 2
SLTFday = 21
R2ETFday = 3
R2LTFday = 21
R1ETFday = 2
R1LTFday = 10
SETFaday = 3
SLTFaday = 21
R2ETFaday = 3
R2LTFaday = 21
R1ETFaday = 3
R1LTFaday = 21

```
pSETF =0.02
pSLTF = 0.01
pSACPR = 1-pSETF - pSLTF
```

```
pSETFA = 0.02
pSLTFA = 0.01
pSACPRA = 1-pSETFA - pSLTFA
```

```
pR2ETF = pSETF*3
pR2LTF = pSLTF*35
pR2ACPR = 1-pR2ETF - pR2LTF
```

```
pR1ETF = pSETF*3
pR1LTF = pSLTF*25
pR1ACPR = 1-pR1ETF - pR1LTF
```

```
pR2ETFA = pSETFA*2
pR2LTFA = pSLTFA*2
pR2ACPRA = 1-pR2ETFA - pR2LTFA
```

```
pR1ETFA = pSETFA*2
pR1LTFA = pSLTFA*2
pR1ACPRA = 1-pR1ETFA - pR1LTFA
```

```
f = (IF TIME< 1825 THEN 1 ELSE (IF TIME>=1825 AND TIME<2190 THEN
(-0.000822*time+2.4874) ELSE (IF TIME >=2190 AND TIME<2555 THEN
(-0.00188*time+4.8076) ELSE 0)))
```

D.2 PK Model Code

```
METHOD RK4
```

```
STARTTIME = 0
STOPTIME = 4000
DT = 0.5
```

{Differential Equations}

d/dt (Sus) = Susb - New_InfS - New_Infr2 - New_Infr1 + New_Rec + New_Sus
+ New_SusA - Susd
INIT Sus = 250

d/dt (InfS) = New_InfS - S_SusR2 - S_SusR2A -SETF-SETFA-SLTF-SLTFA - InfSd
INIT InfS = 380

d/dt (Infr5) = New_Infr2 - R2ETF - R2LTF - R2ETFA - R2LTFA - R2_SusR2 - R2_SusR2A
+ ReinR2_SusR2 + ReinR2_SusR1 + ReinR2_SusR2A + ReinR2_SusR1A
+ ReinR2_SusR1LTF - Infr2d
INIT Infr5 = 11

d/dt (Infr3) = New_Infr1 - R1_SusR2 - R1_SusR2A - R1ETF - R1LTF - R1ETFA - R1LTFA
ReinR1_SusR1+ ReinR1_SusR1A + ReinR1_SusR1LTF - Infr1d
INIT Infr3 = 97

d/dt (FailuresSETF) = SETF + SETFA - SETF_SusR1 - FailuresSETFd
INIT FailuresSETF = 1

d/dt (FailuresSLTF) = SLTF + SLTFA - SLTF_SusR1LTF - FailuresSLTFd
INIT FailuresSLTF = 1

d/dt (FailuresR2ETF) = R2ETF + R2ETFA - R2ETF_SusR1 - FailuresR2ETFd
INIT FailuresR2ETF = 2

d/dt (FailuresR2LTF) = R2LTF + R2LTFA -R2LTF_SusR1LTF - FailuresR2LTFd
INIT FailuresR2LTF = 16

d/dt (FailuresR1ETF) = R1ETF + R1ETFA - R1ETF_SusR1 - FailuresR1ETFd
INIT FailuresR1ETF = 13

d/dt (FailuresR1LTF) = R1LTF + R1LTFA - R1LTF_SusR1LTF - FailuresR1LTFd
INIT FailuresR1LTF = 21

d/dt (SusR5) = S_SusR2 + R1_SusR2 +R2_SusR2 - ReinR2_SusR2 - S_SusR1 - SusR2d
INIT SusR5 = 95

d/dt (SusR3) = S_SusR1 + SETF_SusR1 +R2ETF_SusR1 + R1ETF_SusR1 - ReinR2_SusR1
- ReinR1_SusR1 - New_Sus - SusR1d

INIT SusR3 = 111

d/dt (SusR5A) = S_SusR2A + R1_SusR2A + R2_SusR2A - ReinR2_SusR2A
- S_SusR1A - SusR2Ad
INIT SusR5A = 0

d/dt (SusR3A) = S_SusR1A - ReinR2_SusR1A - ReinR1_SusR1A - New_SusA - SusR1Ad
INIT SusR3A = 0

d/dt (SusR3LTF) = SLTF_SusR1LTF + R2LTF_SusR1LTF + R1LTF_SusR1LTF
- ReinR2_SusR1LTF - ReinR1_SusR1LTF - New_Rec - SusR1LTFd
INIT SusR3LTF = 2

{Explicit terms}

Susb = deltab*1000

New_InfS = hInfS*Sus

New_InfR2 = hInfR2*Sus

New_InfR1 = hInfR1*Sus

$$hInfS = (m*a^2*b2*EXP(-mu*tau)*b1S*(InfS+FailuresSETF+FailuresSLTF))/$$
$$(a*(b1S*(InfS+FailuresSETF+FailuresSLTF)+b1R2*(InfR5+FailuresR2ETF$$
$$+FailuresR2LTF)+b1R1*(InfR3 +FailuresR1ETF +FailuresR1LTF)) + mu)$$

$$hInfR2 = (m*a^2*b2*EXP(-mu*tau)*b1R2*(InfR5+FailuresR2ETF +FailuresR2LTF))/$$
$$(a*(b1S*(InfS+FailuresSETF+FailuresSLTF)+b1R2*(InfR5+FailuresR2ETF$$
$$+FailuresR2LTF)+b1R1*(InfR3 +FailuresR1ETF +FailuresR1LTF)) + mu)$$

$$hInfR1 = (m*a^2*b2*EXP(-mu*tau)*b1R1*(InfR3 +FailuresR1ETF +FailuresR1LTF)) /$$
$$(a*(b1S*(InfS+FailuresSETF+FailuresSLTF)+b1R2*(InfR5+FailuresR2ETF$$
$$+FailuresR2LTF)+b1R1*(InfR3 +FailuresR1ETF +FailuresR1LTF)) + mu)$$

S_SusR2 = f*pSACPR*1/r0*InfS

S_SusR2A = (1-f)*pSACPRA*1/r0*InfS

R2_SusR2 = f*pR2ACPR*1/r0*InfR5

R2_SusR2A = (1-f)*pR2ACPRA*1/r0*InfR5

R1_SusR2 = f*pR1ACPR*1/r0*InfR3

R1_SusR2A = (1-f)*pR1ACPRA*1/r0*InfR3

SETF = f*pSETF*1/SETFday *InfS

$SLTF = f * pSLTF * (1/SLTFday) * InfS$
 $R2ETF = f * pR2ETF * 1/R2ETFday * InfR5$
 $R2LTF = f * pR2LTF * (1/R2LTFday) * InfR5$
 $R1ETF = f * pR1ETF * 1/R1ETFday * InfR3$
 $R1LTF = f * pR1LTF * 1/R1LTFday * InfR3$
 $SETFA = f * pSETFA * 1/SETFAday * InfS$
 $SLTFA = f * pSLTFA * (1/SLTFAday) * InfS$
 $R2ETFA = (1-f) * pR2ETFA * 1/R2ETFAday * InfR5$
 $R2LTFA = (1-f) * pR2LTFA * 1/R2LTFAday * InfR5$
 $R1ETFA = (1-f) * pR1ETFA * 1/R1ETFAday * InfR3$
 $R1LTFA = (1-f) * pR1LTFA * 1/R1LTFAday * InfR3$

$S_SusR1 = (1-hInfR2 * pR2) * 1/r1 * SusR5$
 $S_SusR1A = (1-hInfR2 * pR2A) * 1/r1 * SusR5A$

$SETF_SusR1 = 1/q * FailuresSETF$
 $SLTF_SusR1LTF = 1/q * FailuresSLTF$
 $R2ETF_SusR1 = 1/q * FailuresR2ETF$
 $R2LTF_SusR1LTF = 1/q * FailuresR2LTF$
 $R1ETF_SusR1 = 1/q * FailuresR1ETF$
 $R1LTF_SusR1LTF = 1/q * FailuresR1LTF$

$ReinR2_SusR2 = pR2 * hInfR2 * SusR5$
 $ReinR2_SusR2A = pR2A * hInfR2 * SusR5A$

$ReinR2_SusR1 = pR2 * hInfR2 * SusR3$
 $ReinR2_SusR1A = pR2A * hInfR2 * SusR3A$

$ReinR1_SusR1 = pR1 * hInfR1 * SusR3$
 $ReinR1_SusR1A = pR1A * hInfR1 * SusR3A$

$ReinR2_SusR1LTF = pR2 * hInfR2 * SusR3LTF$
 $ReinR1_SusR1LTF = pR1 * hInfR1 * SusR3LTF$

$New_Rec = (1-pR2 * hInfR2 - pR1 * hInfR1) * 1/r2R1LTF * SusR3LTF$
 $New_Sus = (1-hInfR2 * pR2 - hInfR1 * pR1) * 1/r2 * SusR3$
 $New_SusA = (1-hInfR2 * pR2A - hInfR1 * pR1A) * 1/r2 * SusR3A$

$Susd = \text{deltad} * Sus$
 $InfSd = \text{deltad} * InfS$
 $InfR2d = \text{deltad} * InfR5$
 $InfR1d = \text{deltad} * InfR3$
 $SusR2d = \text{deltad} * SusR5$
 $SusR1d = \text{deltad} * SusR3$
 $SusR2Ad = \text{deltad} * SusR5A$
 $SusR1Ad = \text{deltad} * SusR3A$
 $SusR1LTFd = \text{deltad} * SusR3LTF$
 $FailuresSETFd = \text{deltad} * FailuresSETF$
 $FailuresSLTFd = \text{deltad} * FailuresSLTF$
 $FailuresR2ETFd = \text{deltad} * FailuresR2ETF$
 $FailuresR2LTFd = \text{deltad} * FailuresR2LTF$
 $FailuresR1ETFd = \text{deltad} * FailuresR1ETF$
 $FailuresR1LTFd = \text{deltad} * FailuresR1LTF$

$Totdeaths = Susd + InfSd + InfR2d + InfR1d + SusR2d + SusR1d + SusR2Ad + SusR1Ad$
 $+ SusR1LTFd + FailuresSETFd + FailuresSLTFd + FailuresR2ETFd + FailuresR2LTFd$
 $+ FailuresR1ETFd + FailuresR1LTFd$

$Total = Sus + InfS + InfR5 + InfR3 + SusR5 + SusR5A + SusR3 + SusR3A + SusR3LTF$
 $+ FailuresSETF + FailuresSLTF + FailuresR2ETF + FailuresR2LTF$
 $+ FailuresR1ETF + FailuresR1LTF$

$TotSus = Sus + SusR5 + SusR5A + SusR3 + SusR3A + SusR3LTF$
 $Prevalence = InfS + InfR5 + InfR3 + FailuresSETF + FailuresSLTF + FailuresR2ETF$
 $+ FailuresR2LTF + FailuresR1ETF + FailuresR1LTF$
 $EIRS = hInfS / b2$
 $EIRR5 = hInfR2 / b2$
 $EIRR3 = hInfR1 / b2$
 $TotalEIR = EIRS + EIRR5 + EIRR3$
 $TotalEIR35 = EIRR5 + EIRR3$
 $InfectionRate = New_InfS + New_InfR1 + New_InfR2$
 $RecoveryRate = New_Rec + New_Sus + New_SusA$
 $Res3reinfections = ReinR1_SusR1 + ReinR1_SusR1A + ReinR1_SusR1LTF$
 $Res5reinfections = ReinR2_SusR2 + ReinR2_SusR1 + ReinR2_SusR2A$
 $+ ReinR2_SusR1A + ReinR2_SusR1LTF$
 $Totalfailure = FailuresR2ETF + FailuresR2LTF + FailuresR1ETF + FailuresR1LTF$
 $+ FailuresSETF + FailuresSLTF$

TotETFFailure= FailuresR2ETF +FailuresR1ETF +FailuresSETF
TotLTFFailure= FailuresR2LTF +FailuresR1LTF +FailuresSLTF

{Parameters}

deltab = 0.038/365

deltad = 0.038/365

m = IF TIME < 150 THEN mstart ELSE mstart*(1.0315-0.00021*time)

a = 0.3

mu = 0.1

tau = 11

mstart=2

b1S = f*b1SSP+(1-f)*b1SACT

b1R2 = f*b1R2SP+(1-f)*b1R2ACT

b1R1 = f*b1R1SP+(1-f)*b1R1ACT

b1SSP = 0.04

b1R2SP =0.18

b1R1SP = 0.13

b1SACT = 0.002

b1R2ACT = 0.056

b1R1ACT = 0.04

b2 = 0.8

r0 = 7

r1 = 8

r2 =37

q = 7

r2R1LTF=24

SETFday = 2

SLTFday = 21

R2ETFday = 3

R2LTFday = 21

R1ETFday = 2

R1LTFday = 10

SETFaday = 3

SLTFaday = 21

R2ETFaday = 3

R2LTFaday = 21

R1ETFAday = 3
R1LTFAday = 21

pSETF = 0.02
pSLTF = 0.01
pSACPR = 1-pSETF - pSLTF

pSETFA = 0.02
pSLTFA = 0.01
pSACPRA = 1-pSETFA - pSLTFA

pR2ETF = pSETF*3
pR2LTF = pSLTF*35
pR2ACPR = 1-pR2ETF - pR2LTF

pR1ETF = pSETF*3
pR1LTF = pSLTF*25
pR1ACPR = 1-pR1ETF - pR1LTF

pR2ETFA = pSETFA*2
pR2LTFA = pSLTFA*2
pR2ACPRA = 1-pR2ETFA - pR2LTFA

pR1ETFA = pSETFA*2
pR1LTFA = pSLTFA*2
pR1ACPRA = 1-pR1ETFA - pR1LTFA

pR2 = 0.0265
pR1 = 0.0244
pR2A = 0.0238
pR1A = 0.0238

f = (IF TIME < 1825 THEN 1 ELSE (IF TIME >= 1825 AND TIME < 2190 THEN
(-0.000822*time+2.4874) ELSE (IF TIME >= 2190 AND TIME < 2555 THEN
(-0.00188*time+4.8076) ELSE 0)))