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A Mathematical Model for Anti-Malarial Drug Resistance

by

© Amanda Matthews

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School of Graduate Studies
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Master of Science

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Abstract

Despite the array of medical advances of our modern day society, infectious diseases still plague millions of people worldwide. Malaria, in particular, causes substantial suffering and death throughout both developed and developing countries. Aside from the socioeconomic challenges presented by the disease's prevalence in impoverished nations, one of the major difficulties scientists have encountered while attempting to eradicate the disease is the parasite's ability to become resistant to new drugs and methods of treatment. In an effort to better understand the dynamics of malaria, we analyze a mathematical model that accounts for both the treatment aspect as well as the drug resistance that accompanies it. Simulations demonstrating the effects of treatment rates and the level of resistance are studied and discussed in hopes of shedding additional light on the characteristics of this devastating epidemic.

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Chapter 1

Introduction

1.1 History

The word epidemic comes from the Greek *epi* and *demos* and means *upon people*. Epidemic diseases have often changed the course of history. Even early history records use the term. The Bible tells us that lepers were cast away from society to be quarantined and to avoid transmission to the rest of the population. Some periods of history revolve entirely around the epidemics that occurred like the Bubonic Plague, Smallpox, Typhoid Fever and Influenza to name a few. The possibility of an outbreak these days would cause many people to shudder at the mention of such terrible afflictions. For instance, Polio was one of the most dreaded maladies in the 1950s that left many children crippled. The pain and agony that this disease caused was well known to many people. We tend not to think of modern diseases as plagues that could ransack an entire population, yet there are some diseases that are considered to be at epidemic levels even in our modern society. One such infection is malaria.

While instances of malaria were mentioned in some of the earliest texts, it continues to be problematic for many parts of the world, particularly those with tropical environments. Malaria comes from the Italian term *mal' aria* meaning *bad air*, due to the common belief that malaria was an air-borne disease associated with swamps and marshes. Ague was another term that was used in the 14th century to describe the symptoms that accompany a malarial infection, coming specifically from the acute intervals of chills, fever, and sweating induced by the parasite's rapid multiplication within the human host. The French refer to malaria as paludisme which originated from *paludis*, Latin for swamp. Whatever the name, it remains that malaria is an epidemic that should be eliminated.

1.2 The Extensive Reach of Malaria

Although our modern society recognizes the importance of disease control, oftentimes malaria is overlooked due to its transparency within the media. Since malaria occurs within rural areas, most public figures do not experience malaria, and so it is difficult to raise awareness even though it afflicts many people.

“The figures are staggering, though perhaps constant repetition is preventing some of us from fully grasping the implications: although over the centuries malaria has been eradicated from many parts of the world simply by draining swamps and marshes, and more deliberate malaria eradication programs have further enabled many hundreds of millions to free themselves from the disease, there are still approximately 350 million people in the world living in areas where the infection is endemic and where no

organized antimalarial measures have yet been undertaken. The human suffering caused by the disease alone is catastrophic enough, but when it is remembered that the effects are often compounded by chronic under-nutrition, economic underdevelopment, growing environmental stress and pollution, together with social and political conflicts, the result virtually amounts to an almost unrelieved state of disaster [2].”

The World Health Organization (WHO) estimates that approximately 50% of the world is at risk for malaria. The people most at risk are children under five years of age in the poorest countries in the world. There are reportedly near a billion cases of malaria [10] every year with over 1 million of those cases resulting in death [16]. It is estimated that Sub-Saharan Africa accounts over 90% of malaria fatalities [3], with the majority of cases being undocumented due to their occurrence in rural areas. Due to the lack of transportation and the rural location, many people suffer without treatment. Many of these people are too poor to afford access to hospitals and pharmacies even if they were within walking distance. These percentages should be motivation enough for a global fight to end malaria as it continues to be one of the most devastating diseases afflicting mankind. “Malaria is ranked among the most frequent causes of morbidity and mortality among children and is often the leading identifiable cause [3].”

Affected areas are illustrated by the shaded region shown in Figure 1.1. This map shows that malaria occurs most often in tropical environments where conditions for mosquito populations are ideal.



Figure 1.1: Regions affected by malaria: The dark gray shows regions of the world that are affected by malaria, with sub-Saharan Africa experiencing the largest portion of this burden [3].

Chapter 2

Malaria

2.1 Symptoms

Malaria infection is accompanied by a suite of symptoms including waves of fever and coldness, vomiting, anemia, and convulsions. Because it can be accompanied by various symptoms that may resemble the common cold or other illnesses, malaria is often misdiagnosed leading to incorrect treatment. Treatment options are generally dictated by the region in which the infection occurs. Oftentimes treatment options are not available due to the rural location and the lack of resources. Other times drugs are administered incorrectly due to lack of education or misdiagnoses.

Chloroquine, the main drug used to combat malaria is inexpensive and was, at one time, effective. Recent observations confirm that certain strains of the parasite that causes malaria are becoming resistant to many drugs that have been widely used in the past. This evolving resistance poses new obstacles when trying to control the spread of malaria. Research is being conducted to explore the options that are available

including combination therapy, mosquito (or vector) control, and vaccines. Some of the most promising successes have been achieved using combination therapies in which several different drugs are administered. The downfall of combination therapy is that the cost is often too great for infected individuals to afford.

2.2 Causes and Pathogenesis

Malaria is caused by protozoan parasites of the genus *Plasmodium*. Within this genus, five of over one hundred existing species are found to infect humans: *P. falciparum*, *P. malariae*, *P. ovale*, *P. vivax*, and *P. knowlesi*. The most common variant in Africa is *Plasmodium falciparum*, which accounts for more than 50% of malaria attacks [14] and most of the malaria fatalities. Malaria is transmitted to humans by female *Anopheles* mosquitoes which obtain infection by biting an infected person. The mosquito then carries the parasites within their salivary glands and transmits them to a susceptible individual through a successive bite when the sporozoites are injected from the mosquito's salivary glands. The sporozoites then travel through the human's bloodstream and enter the liver and begin to multiply into merozoites for several days.

Latent parasites of some species can dwell in the liver for a period of days or even years, sometimes causing chronic cases of malaria. During these periods of latency, the human is infected but would not be able to transmit the disease to other mosquitoes. The individual does not experience the symptoms associated with infection at this time. After multiplying, the merozoites migrate into red blood cells where they continue to multiply, rupture red blood cells, and contaminate new red blood cells.

Due to the fact that malaria stays within both the liver and the red blood cells, it is difficult for the human immune system to detect and overcome the parasite.

2.3 Preventative Measures

Preventative measures such as mosquito control have proven to be very successful. Many countries have banded together via the WHO to provide insecticide-treated nets (ITNs) to impoverished areas that cannot afford them. These nets are effective, but due to the level of poverty within these areas, the nets often become a trade resource or a source of income for the people that receive them, since the nets can be sold or used as fishing nets. Another preventative measure includes spraying pesticides within the home, referred to as Indoor Residual Spraying (IRS), but mosquitoes can then develop resistance to the pesticides as well. Some research has focused on genetically engineering mosquitoes that are resistant to malaria infection. Although much attention has been given to the research that focuses on developing a vaccine, no vaccine exists to date.

2.4 Treatment

With documented cases of malaria as early as the fifth century BC [2], it is clear that this parasite has endured many changes despite civilizations' best efforts to eradicate the epidemic. Some successful measures used in early times to counteract the spread of malaria are still being exploited today. One commonly prescribed drug used to treat malarial infections is Quinine which was isolated from the tree *Cinchona*. The

Peruvian Indians started this practice by chewing the bark from the *Cinchona* tree [2].

Another method to attempt to prevent malaria involves draining nearby swamps and marshes, thereby reducing mosquito populations. It is unclear whether people realized initially that by draining the marshes they were effectively reducing the mosquitoes' breeding grounds and thereby controlling the mosquitoes that carry the disease.

Eventually the importance of mosquito control was realized in the 1930s and 1940s with the introduction of Dichloro-Diphenyl-Trichloroethane (DDT), a powerful synthetic insecticide. At first, this pesticide proved to be a useful deterrent for the mosquitoes, but over time the mosquito population began to develop resistance to DDT. In the 1950s, the eradication of malaria was the focus of WHO as they continued their efforts to prevent and treat the disease with a global campaign. These efforts were successful at the time and many countries were able to effectively eradicate the disease. Unfortunately, malaria continues to have a devastating presence in Africa where drug resistance and insecticide resistance makes controlling outbreaks more difficult. Another challenge is that many of the drugs that are available in Africa are used incorrectly due to misdiagnoses. Even when used correctly, it is believed that one of the main drugs, Chloroquine, has lost much of its effectiveness as a result of overuse in some areas [3].

2.5 Drug Resistance

Drug resistance is defined to be the ability of disease-causing organisms to adapt in order to survive exposure to a drug that was at one time able to effectively kill the organisms. Drug resistance occurs due to a random genetic mutation that allows the organism to survive treatment. During replication, an organism sometimes experiences a random mutation. If this mutation somehow combats the effectiveness of treatment, these mutated organisms will continue to replicate and survive as their non-mutated cousins will die during treatment [7]. The new drug resistant organisms will continue growing regardless of human intervention.

Improper use of drugs aggravates the rise in drug resistance. For instance, if a family has two children diagnosed with malaria, they may try to split the recommended treatment between their two children if they cannot afford to buy more than one treatment regimen. Taking smaller than recommended doses allows the pathogens to be exposed to treatment without most of the organisms dying. A large number of the organisms survive treatment increasing the likelihood that the surviving pathogens have developed resistance to the drug. In fact, misuse of drugs is arguably the leading contributor to the expansion of drug resistance [7].

Due to the appearance and prevalence of drug resistant malaria, many scientists have devoted time to exploring new treatment plans to counter the disease. Combination therapy has been used successfully, as it is unlikely that the parasite can become resistant to two or more drugs at one time. However, combination therapy is more expensive which can negate much of its effectiveness.

Although we are constrained by drug resistance, we are not defeated entirely in

our efforts to cure diseases. Research is constantly being updated to account for new developments in drugs and vaccines. In addition, educating the public about the importance of the correct use of medicine can help reduce this development of resistance from occurring as frequently.

2.6 Effects of Poverty

One of the major difficulties in the fight to overcome drug resistance is poverty. Poor conditions make it difficult to correctly diagnose and treat the disease consistently. To make matters worse, many of the people in desperate need of treatment simply cannot afford it [8].

“It is estimated that a single bout of malaria costs a sum equivalent to over 10 working days in Africa. The cost of treatment is between \$0.08 USD and \$5.30 USD according to the type of drugs prescribed as determined by local drug resistance [8].”

Many researchers believe this cycle of illness continues to hinder the people’s ability to advance. Poverty induces conditions that will cause them to obtain and retain the disease.

“Beyond the human toll, malaria wreaks significant economic havoc in high-rate areas, decreasing Gross Domestic Product (GDP) by as much as 1.3% in countries with high levels of transmission. Over the long-term, these aggregated annual losses have resulted in substantial differences in GDP between countries with and without malaria (particularly in Africa).

Malaria's health costs include both personal and public expenditures on prevention and treatment. In some heavy-burden countries, the disease accounts for: up to 40% of public health expenditures, 30% to 50% of inpatient hospital admissions, and up to 60% of outpatient health clinic visits. Malaria disproportionately affects poor people who cannot afford treatment or have limited access to health care, and traps families and communities in a downward spiral of poverty [9].”

Illness causes individuals to lose valuable days of school or work, which only restricts their ability to develop further. The lack of education also inhibits their ability to fully understand the disease and the importance of using treatment only when they are infected as well as for the correct amount of time. In the end, malaria is one of the major culprits for children missing school and adults missing work which translates to loss of education and lower wages.

Chapter 3

Mathematical Models

3.1 Background

Mathematical models have been used for centuries to develop a better understanding of systems in order to control or optimize results. A wide range of applications include everything from radar development to production rates within factories to the spread of disease. Mathematical models concerned with the spread of infectious diseases are referred to as epidemic models. Models are created to study treatment and infection rates in order to optimize our ability to predict, quarantine and control disease.

3.2 Kermack and McKendrick's SIR Model

One of the first epidemic models, the SIR model, was a result of the work of O. Kermack and Anderson Gray McKendrick [4]. The SIR model studied the movement of populations between the *susceptible* class, the *infected* class, and the *recovered* class, hence the name, SIR model. Kermack and McKendrick proposed a nonlinear,

compartmental model with a constant total population, N [4]. Though relatively simple, this model proved to be useful in providing a resource that allows one to predict and hopefully mitigate the results of an epidemic.

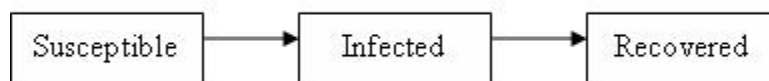


Figure 3.1: Susceptible-Infected-Recovered Flowchart

To begin studying the movement between the classes, we will lay out a system of differential equations that represent the status of infection. The rate of change of susceptible people is proportional to the product of the number of people in the susceptible and infected classes. This rate is negative since the number of people in this class is decreasing.

κ is the constant of proportionality. In this case, κ represents the contact rate, or the likelihood that a susceptible person would become infected through interaction with an infectious person.

$$\frac{dS}{dt} = -\kappa IS \quad (3.1)$$

The rate of change of the infected population grows at the same rate the susceptible class decreases. The recovery rate, λ , is the likelihood that an infected person would recover, with $\frac{1}{\lambda}$ being the time it takes to recover.

$$\frac{dI}{dt} = \kappa IS - \lambda I \quad (3.2)$$

The recovered population is growing proportional to the product of the infected

class and the recovery rate, λ .

$$\frac{dR}{dt} = \lambda I \tag{3.3}$$

Equations 3.1, 3.2, and 3.3 are defined such that

$$\frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0 \tag{3.4}$$

and

$$S + I + R = N, \tag{3.5}$$

where N represents the total population. This means that we are assuming the total population is constant.

3.3 An SIR Model with Vital Dynamics

Many other variables and parameters can be considered when creating an epidemic model. Other models that are in use today include variables that account for latency, temporary immunity, drug resistance, multiple infections, and vaccination. The trade off remains a balance between creating a more accurate model that affords the ability to study details or a model that is easier to work with functionally omitting some of the facts [4]. The following model accounts for vital dynamics, or changes within the population size due to birth and death rates.

This model is a revised form of the previously mentioned SIR model to account for birth, represented by β , as well as death, represented by μ [4]. We modify Equations 3.1, 3.2, and 3.3 to get the following system.

$$\frac{dS}{dt} = -\kappa IS - \mu S + \beta N \quad (3.6)$$

$$\frac{dI}{dt} = \kappa IS - \lambda I - \mu I \quad (3.7)$$

$$\frac{dR}{dt} = \lambda I - \mu R \quad (3.8)$$

such that

$$\mu = \beta \quad (3.9)$$

to keep a constant total population.

The susceptible population grows in accordance with the birth rate, β , which is proportional to the total population, N . The susceptible population decreases as a result of infection, $-\kappa IS$, or death, $-\mu S$.

The infected population grows in proportion to the product of the infected population, the susceptible population, and the contact rate, κIS . The infected class decreases due to recovery, $-\lambda I$, and death, $-\mu I$.

The recovered population grows in accordance with the recovery rate, which is proportional to the size of the infected population, λI , and decreases due to the death rate which is proportional to the recovered population, $-\mu R$.

3.4 Ross MacDonald Malaria Model

With a variety of books and published works including [11], [12], and [13]. Ronald Ross was one of the first to conduct breakthrough research on malaria due to his discovery that malaria is transmitted to human hosts via bites from mosquitoes. With his first book published in 1902, Ross was a pioneer of malaria research. His studies

afforded him countless honors and awards, including the Nobel Prize for Medicine. Ross reported in his observations in Mauritius, an island off the coast of Africa, that several elements contribute to the spread of malaria. Some elements include details about the human population while others are concerned with the mosquito population.

The Ross MacDonald Malaria Model is different from the previous models in that it takes into account two different species and the interactions that take place between them. Previous models were only concerned with tracking the population changes within a single species. A clever simplification affords the ability to track both the infectious and the susceptible populations of two species while only using two equations. He assumes that a human or mosquito that is not infected is susceptible to the disease.

The Ross MacDonald Malaria Model is comprised of two components: the proportion of infectious humans, x , and the proportion of the female mosquito population that is infected, y . These populations are affected by several parameters that include the rate of infection passed to humans by the mosquitoes, α , the average duration of a human infection, $\frac{1}{r}$, the average lifetime of a mosquito, $\frac{1}{\mu}$, and the rate of infection of mosquitoes by humans, β .

Let

$$\frac{dx}{dt} = \alpha y(1 - x) - rx \tag{3.10}$$

$$\frac{dy}{dt} = \beta x(1 - y) - \mu y \tag{3.11}$$

where the total human and mosquito populations remain constant [4].

The infected class of humans increases due to the contact rate, α , which is pro-

portional to the number of susceptible humans, $1 - x$, and infected mosquitoes, y . This growing population of infected humans is then reduced by the recovery rate, r , proportional to the number of infected humans, x .

The infected class of mosquitoes increases due to the contact rate, β , which is proportional to the number of infected humans and susceptible mosquitoes. The infected mosquitoes are then reduced by the natural death rate, μy , proportional to the number of infected mosquitoes, y .

This model was published initially by Ross in 1908 and further explorations and refinements were mentioned subsequently through 1916. The model did not experience significant updates until 1952 when Dr. George MacDonald discovered some interesting results as he studied the endemic equilibria of the model. MacDonald also made advances in his studies of the reproductive number, a ratio that determines whether or not the epidemic will sustain or fail. Ross and MacDonald's work continue to be the foundation for epidemic models today.

Chapter 4

A Model for Drug Resistant Malaria

4.1 Drug Resistance

As drug resistance becomes increasingly common, it is necessary to study the effects resistance has on treatment regimens. The World Health Organization defined three levels of resistance to be:

- RI: recrudescence following parasite clearance (at least 2 consecutive days with no detectable asexual parasites within 7 days after start of treatment)
- RII: no clearance and asexual parasitaemia below 25% of initial parasitemia 48 hours after start of treatment
- RIII: no clearance and asexual parasitaemia above 25% of initial parasitemia 48 hours after start of treatment [15]

By addressing drug resistance within a mathematical model, we can identify patterns of interest. Different scenarios can be studied by simulating what happens in the real world and analyzing the results. We could study the effects of treatment by changing the treatment rate or the effects of preventative measures by reducing the contact rate. The results provide health care professionals the information they need to make informed and more appropriate decisions. As we will see in the following sections, drug resistance is tied very closely to the percentage of the population that is treated. Therefore reducing the effects of malaria is not as simple as merely increasing treatment.

4.2 Classifications

This model is partitioned into eleven classes that interact with each other. There are two main categories of populations: the human population and the mosquito population. The human population has eight classes that account for Sensitive: S_h , Latent: L_h , Infected: I_h , Treated: T_h , Withdrawn: W_h , and Resistant Classes RI: R_{h1} , RII: R_{h2} , and RIII: R_{h3} . Individuals fall into the sensitive category when they have never been infected with malaria, or when they have recovered completely without any residual immunity from the prior infection. The latent class includes all humans that have experienced a bite from an infected mosquito, prior to experiencing symptoms. This stage will include humans that have the parasite multiplying in their liver, but the parasites have not yet progressed into the red blood cells.

The infected class includes all humans that are experiencing symptoms of malaria which are brought on by the replication of parasites within the red blood cells. The

treated class includes all humans that have received treatment regardless of outcome. An individual will progress to the withdrawn class when they experience temporary immunity due to recovery from malaria. To enter the resistance classes, a human must undergo treatment without successful results. The level of resistance is determined by the reduction in asexual parasitemia, as discussed in Section 4.1. Movement within the class structure of the human population can be studied via the flowchart depicted in Figure 4.1.

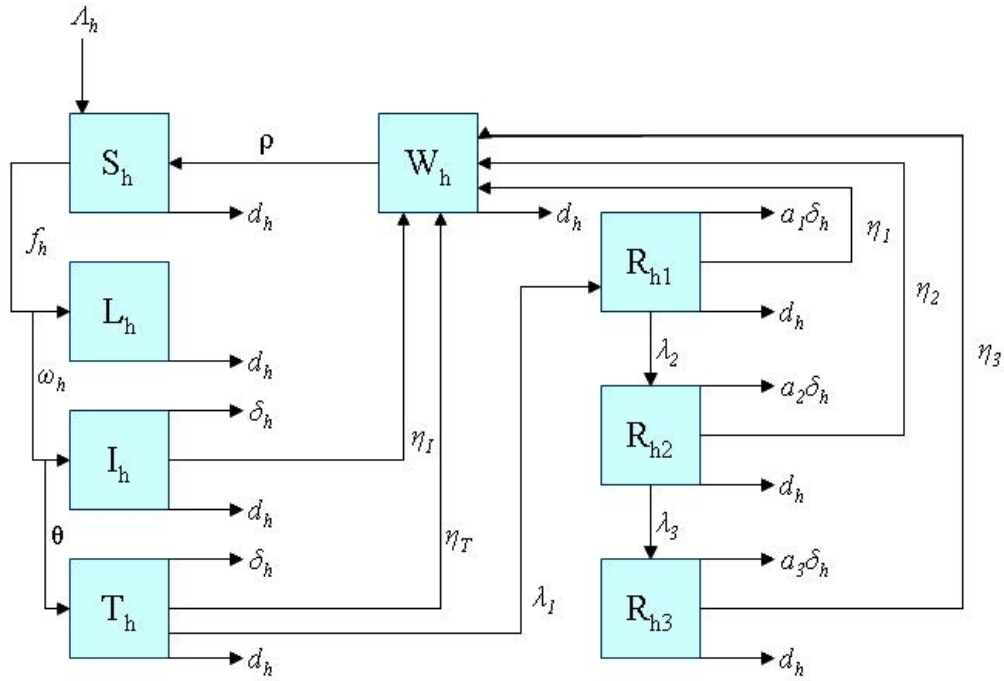


Figure 4.1: Flowchart Detailing Movement Between the Human Population Classes

There are three classes used to identify the mosquito population. They include the Sensitive, Latent, and Infected mosquitoes, with the definitions being similar to those for the human population. Refer to Figure 4.2 for more details.

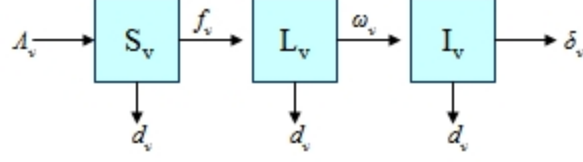


Figure 4.2: Flowchart Detailing Movement Between the Vector Population Classes

4.3 Model Formulation and Assumptions

Although malaria incidences rise and fall depending on factors such as rainfall and temperature, we assume that malaria infections are uniformly transmitted throughout the year for modeling purposes. An important component of this model is drug resistance which is compartmentalized into three classes. Drug resistance develops as a result of genetic mutations or it can be caused by natural selection due to low level exposure to a drug that does not fully kill the parasite. Drug resistance may arise due to an ineffective treatment regimen.

$$\begin{aligned}
\frac{dS_h(t)}{dt} &= \Lambda_h - f_h(t)S_h(t) + \rho W_h(t) - d_h S_h(t), \\
\frac{dL_h(t)}{dt} &= f_h(t)S_h(t) - (\omega_h + d_h)L_h(t), \\
\frac{dI_h(t)}{dt} &= \omega_h L_h(t) - (\theta + \eta_I + d_h + \delta_h)I_h(t), \\
\frac{dT_h(t)}{dt} &= \theta I_h(t) - (\eta_T + \lambda_1 + d_h)T_h(t), \\
\frac{dR_{h1}(t)}{dt} &= \lambda_1 T_h(t) - (\eta_1 + \lambda_2 + d_h + a_1 \delta_h)R_{h1}(t), \\
\frac{dR_{h2}(t)}{dt} &= \lambda_2 R_{h1}(t) - (\eta_2 + \lambda_3 + d_h + a_2 \delta_h)R_{h2}(t), \\
\frac{dR_{h3}(t)}{dt} &= \lambda_3 R_{h2}(t) - (\eta_3 + d_h + a_3 \delta_h)R_{h3}(t), \\
\frac{dW_h(t)}{dt} &= \eta_I I_h(t) + \eta_T T_h(t) + \eta_1 R_{h1}(t) + \eta_2 R_{h2}(t) + \eta_3 R_{h3}(t)
\end{aligned}$$

$$\begin{aligned}
& -(\rho + d_h)W_h(t), \\
\frac{dS_v(t)}{dt} &= \Lambda_v - f_v(t)S_v(t) - d_vS_v(t), \\
\frac{dL_v(t)}{dt} &= f_v(t)S_v(t) - (\omega_v + d_v)L_v(t), \\
\frac{dI_v(t)}{dt} &= \omega_vL_v(t) - (d_v + \delta_v)I_v(t),
\end{aligned}$$

with

$$f_h(t) = \beta_h c \frac{I_v(t)}{N_h(t)} \quad (4.1)$$

and

$$f_v(t) = \beta_v c \frac{I_h(t) + \eta_I T_h(t) + \eta_1 R_{h1}(t) + \eta_2 R_{h2}(t) + \eta_3 R_{h3}(t)}{N_h(t)}. \quad (4.2)$$

Infection is passed from mosquitoes to humans in proportion to the contact rate, β_h , much like κ mentioned in Section 3.2. The magnitude of the contact rate, β_h , defined in f_h is affected by several factors, including the proportion of infected mosquitoes relative to the total human population, $\frac{I_v(t)}{N_h(t)}$, as well as the size of the susceptible human class, S_h .

Infection can also be passed from humans to mosquitoes via β_v , contained in the function f_v . A mosquito can obtain infection by biting a human in any of the infectious classes which include: I_h , T_h , R_{h1} , R_{h2} , or R_{h3} . Thus the proportion of the populations within these classes relative to the total human population is taken into account, along with the size of the susceptible mosquito subpopulation, S_v .

The susceptible class grows in accordance with the birth rate, Λ_h , and the recovery rate proportional to the withdrawn subpopulation, $\rho W_h(t)$. The susceptible class decreases due to the contact rate proportional to the susceptible population, $-f_h(t)S_h(t)$, or due to the natural death rate, $-d_h S_h(t)$.

The latent class will become larger by introducing humans that have been bitten by an infected mosquito, $f_h(t)S_h(t)$. The latent class is reduced by the proportion of people experiencing symptoms of malaria, $-\omega_h L_h(t)$, or by the death rate, $-d_h L_h(t)$.

The infected class increases proportional to the decrease experienced within the latent population, $\omega_h L_h(t)$. There are several decreasing rates of change within the infected class: the treatment rate, $-\theta I_h(t)$, the recovery rate, $-\eta I_h(t)$, the natural death rate, $-d_h I_h(t)$, and the infection-induced death rate, $-\delta_h I_h(t)$, with all rates used in proportion to the infected class.

The treated class is increasing due to the treatment rate proportional to the infected population, $\theta I_h(t)$. Treated humans experience a decreasing rate of change due to recovery, $-\eta_T T_h(t)$, the appearance of RI-level drug resistance, $-\lambda_1 T_h(t)$, or due to the natural death rate, $-d_h T_h(t)$. The outcome of treatment will determine whether or not the infection is sensitive or resistant to drugs.

The RI class of humans experiencing the first level of drug resistance grows after treatment failure, $\lambda_1 T_h(t)$. Humans can either recover, $-\eta_1 R_{h1}(t)$, progress to RII resistance class, $-\lambda_2 R_{h1}(t)$, or they die, $-(d_h + a_1 \delta_h) R_{h1}(t)$.

The RII class grows as people move from the RI resistance class, $\lambda_2 R_{h1}(t)$. Humans can then either recover, $-\eta_2 R_{h2}(t)$, progress to RIII resistance class, $-\lambda_3 R_{h2}(t)$, or they die, $-(d_h + a_2 \delta_h) R_{h2}(t)$.

Additions to RIII resistance class are a result of humans experiencing RII resistance failing to recover or respond to treatment, $\lambda_3 R_{h2}(t)$. At this stage, humans can recover, $-\eta_3 R_{h3}(t)$, or they die, $-(d_h + a_3 \delta_h) R_{h3}(t)$.

The withdrawn population includes all humans that have recovered and are temporarily immune regardless of which class they come from. Thus W_h is increasing due

to the following rates of change: $\eta_I I_h(t) + \eta_T T_h(t) + \eta_1 R_{h1}(t) + \eta_2 R_{h2}(t) + \eta_3 R_{h3}(t)$. Humans leave the withdrawn class after losing immunity, and thus W_h also has a decreasing rate of change to account for losing immunity, $-\rho W_h(t)$, or dying, $-d_h W_h(t)$. After a period of time, specifically $\frac{1}{\rho}$, an individual will lose temporary immunity to re-enter the susceptible class. These individuals are fully susceptible to re-infection.

Similarly, the mosquito population is adjusted based on their infection status. The susceptible mosquito population increases due to their birth rate, Λ_v . Susceptible mosquitoes are decreasing via the contact rate, β_v contained in the function f_v or by the natural death rate, $-d_v S_v(t)$, both of which are proportional to the susceptible mosquito class. The latent mosquito population experiences an increasing rate of change proportional to the susceptible class, $f_v(t) S_v(t)$. Latent mosquitoes can then either obtain the infection, $-\omega_v L_v(t)$, or die, $-d_v L_v(t)$. While the infectious mosquito class will become larger due to the rate at which latent mosquitoes obtain infections, $\omega_v L_v(t)$, the infectious mosquitoes will eventually die without recovering from infection, $-(d_v + \delta_v) I_v(t)$.

Chapter 5

Results

5.1 Parameters

In this section, we examine the effects of treatment rates and drug resistance rates on the subpopulation sizes. Many of the parameter values used are based on values found in [6]. See Table 5.1. In this study, they found two sets of parameter values based on high and low transmission areas depending on the force of infection and contact rates between humans and mosquitoes. The parameters were derived using data from various sources such as the Central Intelligence Agency, field studies, and long term data collection through observation. We chose parameter values from their model that functioned similarly to our parameters.

We made a few assumptions with regard to the parameters in [6]. The death rate was split into two parameter values accounting for a density independent death rate as well as a density dependent death rate that was multiplied by the total population. For our model, we chose to use only the density independent death rate.

Table 5.1: Parameter Values

Parameter	Dimension	Value
Λ_h	Humans \times Day $^{-1}$	5.533
ρ	Day $^{-1}$	0.00055
d_h	Day $^{-1}$	0.000016
ω_h	Day $^{-1}$	0.1
δ_h	Day $^{-1}$	9.0×10^{-5}
β_h	Day $^{-1}$	0.022
Λ_v	Mosquitoes \times Day $^{-1}$	39000
d_v	Day $^{-1}$	0.033
ω_v	Day $^{-1}$	0.091
β_v	Day $^{-1}$	0.48
δ_v	Day $^{-1}$	0.0165

Another modification was made regarding Λ_h . In [6], they accounted for birth as well as immigration, with the birth rate depending upon the size of the total population. In order to account for both values, we combined them by adding their immigration rate with the product of the birth rate and the initial population. We made similar modifications when using the parameter values for mosquitoes.

Some parameter values were not available in [6]. These include η_T , η_I , η_1 , η_2 , η_3 , a_1 , a_2 , a_3 , and c , which can enhance the contact rate as well as the malaria induced death rate. The η_i values were estimated to be 0.05. We approximated the time an individual spends in the infected or resistance classes to be about three weeks. Similarly, the time spent to treat an infection could last about a week. So, η_T is $\frac{1}{0.14} \approx 7$ days.

a_1 , a_2 , a_3 enhance the malaria induced death rate experienced at each resistance level. It is feasible that the death rate could be higher if an infection is not sensitive to treatment, but for simplification, our simulations set these values equal to one.

The parameter c incorporates the bite rate, which can enhance the transmission of infections between humans and mosquitoes. Although slight changes to c can create large differences in the results, this parameter is set equal to one for simplification. However, studying the effects of c could provide insight into prevention programs mentioned such as mosquito control by simulating the reduction in the bite rate due to ITNs.

5.2 Numerical Results

We conducted numerical simulations using a simple forward Euler scheme and varied both the percentage of people that were treated as well as the resistance rates. We assumed a human population size of 50,000 and a mosquito population size of 390,000. Also, we assumed that initially there was no treatment occurring with approximately 6% of the population being latent and approximately 24% of the population being infected. Table 5.2 has the number of people (rounded normally) in T_h , R_{h1} , R_{h2} , and R_{h3} . The values shown represent the number of people that had the parasite in their system after 1,000 days since the treatment started, which is about 3 years. These values are near the steady state values of the system.

Resistance rates vary from place to place. One of the “hot spots” for resistance is near the Thailand-Myanmar border, where they see rates of resistance from 4.5% to 21.9% [5]. Since we are interested in drug resistance, we decided to vary parameters that would affect the level of resistance experienced by the human population. For the remainder of the discussion, we refer to low resistance as 4.5%, medium resistance as 13.2%, and high resistance as 21.9%, where this percentage controls the likelihood that a person would become resistant.

We partition our exploration of treatment and resistance into two categories. First, we focus on how increasing the percentage of people that receive treatment affects the number of people in each class. We will also speak of the changes to the infectious group as a whole, which is the sum of I_h , T_h , R_{h1} , R_{h2} , and R_{h3} . Then, we investigate the effects of drug resistance by comparing low, medium, and high levels of resistance.

5.2.1 Varying the Treatment Rate at Each Level of Resistance

As we survey the results, we discover that the old adage “less is more” holds true with respect to treatment rates. We will walk through each subpopulation speaking of the change that is experienced as we double the treatment rate starting with a 10% level. The biggest decrease in the infectious subpopulation is seen when comparing 10% to 20% treatment rates. By the time 80% is attained, the results are much less significant. Thus, increasing treatment alone is not a valid solution. It is clear that our approach must be more sophisticated than merely providing antimalarial drugs to endemic regions. Refer to Table 5.2 for details.

The latent class experiences almost no change during these manipulations. The steadiness of the latent group makes sense due to the fact that the parameters affecting the entrance or exit from the latent class were not changed.

The infected class, however, does change. As treatment increases from 10% to 20% the infected group drops 40%. Doubling treatment from 20% to 40% treatment rate provides a decrease of 44%. Comparing the 40% to 80% treatment rate, the decrease in the infected class is 47%. This large and consistent reduction is to be expected, since the goal of administering treatment is to shrink the infected subpopulation.

The treated class grows steadily as we increase treatment. The treated class increases 20% as we double the treatment rate from 10% to 20%. As we double the treatment rate again to achieve 40% treatment, we witness only an 11% increase in the treated class. Doubling treatment a final time to attain 80% treatment yields an even smaller increase in the treated group at 6%. Thus, treating 20% as opposed to

Table 5.2: Long Term Population Values - High Transmission Case

θ	$\lambda_{h1}, \lambda_{h2}, \lambda_{h3}$	L_h	I_h	T_h	R_{h1}	R_{h2}	R_{h3}
10%	4.5%	341	227	123	58	27	25
20%	4.5%	341	136	147	70	33	30
40%	4.5%	340	76	163	77	37	33
80%	4.5%	340	40	173	82	39	35
10%	13.2%	342	228	84	61	44	116
20%	13.2%	342	137	100	73	53	139
40%	13.2%	341	76	112	81	59	154
80%	13.2%	341	40	118	86	62	163
10%	21.9%	342	228	63	52	42	183
20%	21.9%	342	137	76	62	50	220
40%	21.9%	342	76	85	69	56	244
80%	21.9%	342	40	90	73	59	259

10% yields a formidable change while doubling the treatment rate thereafter produces increasingly smaller changes. It is important to note that managing a treatment rate of 40% or more would be expensive as well as difficult. Thus, the most “bang for your buck” may be achieved at a lower level of treatment.

R_{h1} follows a similar pattern to the one noted for the treated class as it increases steadily as treatment is increased. Beginning with a 10% treatment rate and doubling treatment produces a 20% increase in R_{h1} . Doubling treatment again to obtain 40% treatment, we see a 10% increase. Doubling the treatment once more to 80% gives us a 6% increase in the subpopulation size.

R_{h2} follows a similar pattern of increasing size. Comparing the 10% treatment rate to the 20% treatment rate, we witness a 22% increase. As we move from 20% to 40% treatment, there is an additional 12% increase. Increasing treatment to 80% yields an extra 5% of people in the R_{h2} class.

R_{h3} has the same percentage of increase as R_{h1} . Moving from 20% to 10% to 6% growth as we double the treatment rate moving from 10% to 80% treatment rates.

The contact rate β_v is affected by the magnitude of all infectious people which include I_h , T_h , R_{h1} , R_{h2} , and R_{h3} . As we double the treatment rate from 10% to 20%, the sum of all infectious people decreases 10% in a low resistance case. This response to treatment, however, diminishes at the higher levels of resistance. When treatment is increased from 10% to 20% at the high resistance level, the change within the infectious group is only 4%; less than half of the change seen at the low resistance level.

5.2.2 Varying the Level of Resistance at Each Treatment Rate

Table 5.3: Long Term Population Percentage of Change due to Resistance

Change in Resistance	T_h	R_{h1}	R_{h2}	R_{h3}	All Infectious
10% Treatment					
Low to Med	-32%	5%	63%	364%	16%
Med to High	-25%	-15%	-5%	58%	7%
20% Treatment					
Low to Med	-32%	4%	61%	363%	21%
Med to High	-24%	-15%	-6%	58%	9%
40% Treatment					
Low to Med	-31%	5%	59%	367%	25%
Med to High	-24%	-15%	-5%	58%	10%
80% Treatment					
Low to Med	-32%	5%	59%	366%	27%
Med to High	-24%	-15%	-5%	59%	11%

Now we will alter the resistance rates to examine the effects on the population. To simplify, we will refer to changes within the resistance levels at a 10% treatment rate unless otherwise stated. It should be noted that the percentage of change is similar within each treatment group.

As we will see in the following section, varying the resistance rates produces a

much larger increase in the infectious group when studying the 80% treatment rate versus the 10% treatment rate. This result tells us that we are much more likely to experience a higher level of drug resistance when treatment is easily accessible to a large proportion of the population. The greatest change can be seen in the R_{h3} class, with an explosive increase in size as we compare the low and medium levels of resistance.

T_h decreases from 123 people to 84 people moving from low to medium resistance, a change of 32%. While, moving from medium to high resistance produces a 25% decrease in the treated class. Due to the fact that we are increasing resistance to treatment, we would expect more people to end up in a resistance class instead of the treated class.

As we increase the resistance from low to medium, R_{h1} increases 5%. As we increase resistance from medium to high, however, R_{h1} decreases 15%. So, changing from low to medium resistance causes R_{h1} to increase in size slightly, while moving from medium to high resistance causes a considerable 15% drop in the size of R_{h1} .

R_{h2} behaves similarly, with a more dramatic increase at 63% followed by a smaller 5% decrease.

R_{h3} behaves in an opposite fashion. Instead of increasing and decreasing, R_{h3} more than triples its size and then only continues to increase. R_{h3} experiences a 364% increase from low to medium resistance and an additional 58% increase as we progress to high resistance.

Consider the effects of resistance on the infectious group: I_h , T_h , R_{h1} , R_{h2} , and R_{h3} . We see a 16% increase in the infectious class as we compare the low and medium levels of resistance. The increase as we move from medium to high levels of resistance

is 7%. It is worth noting that the infectious subpopulation still increases even if at a lesser rate.

5.2.3 Increasing and Decreasing Resistance Rates

All of the results that have been discussed assume that the resistance rates, λ_1 , λ_2 , and λ_3 are equal. We will now examine how using different resistance rates affects the population. When we refer to *Increasing Resistance* we mean that $\lambda_1 = 4.5\%$, $\lambda_2 = 13.2\%$, and $\lambda_3 = 21.9\%$. In this case, we are simulating the possibility that it is less likely that you will obtain resistance in the first place, but if you do become RI resistant, then you are more likely to progress to RII and even more likely to become RIII resistant.

In the increasing resistance case, the latent, infected, and treated classes behave in much the same way as the constant resistance rates. We will therefore focus our attention to the changes within the resistance classes.

R_{h1} increases from 30 to 36 people as we increase treatment from 10% to 20%. This results in a 20% increase. As we progress to 40%, we see an additional 11% increase to a total of 40 people. Doubling treatment a final time yields 43 people for a 6% change.

R_{h2} and R_{h3} follow a similar progression as their percentage of change as we increase treatment goes from 20% to 11% and finally 6%. This behavior is much like the changes observed when using constant resistance.

When we refer to *Decreasing Resistance*, we are examining the opposite scenario. Thus, we will assume that it is easier to obtain RI resistance than RII resistance

Table 5.4: Long Term Population Values - Increasing and Decreasing Resistance Rates

θ	L_h	I_h	T_h	R_{h1}	R_{h2}	R_{h3}
Increasing						
10%	341	227	123	30	15	65
20%	341	136	147	36	18	78
40%	340	76	163	40	20	86
80%	340	40	173	43	21	91
Decreasing						
10%	342	228	63	76	106	95
20%	342	137	76	92	127	114
40%	342	76	85	102	141	126
80%	342	40	90	108	149	134

and even less likely that you will become RIII resistant. We achieve this by setting $\lambda_1 = 21.9\%$, $\lambda_2 = 13.2\%$, and $\lambda_3 = 4.5\%$.

Behavior for L_h , I_h , and T_h is the same as in the constant resistance rates. R_{h1} , R_{h2} , and R_{h3} experience the same percentage of change as the constant resistance rates, but the actual number of people in each is slightly different. Thus, all of the resistance classes increase 20%, 11%, and then 6% as we increase treatment. This percentage of change is identical to both the constant resistance rates as well as the increasing resistance case.

5.3 Areas of Low Transmission

Simulations for areas of low transmission were also analyzed by adjusting the resistance levels and the treatment rate. The baseline values for the low transmission parameters are shown in Table 5.5.

When comparing the high transmission case with the low transmission case, an interesting result appears. The progression through the treatment rates and the resistance levels yield near identical percentages of change. However, the subpopulation sizes for the low transmission case within L_h , I_h , T_h , R_{h1} , R_{h2} , and R_{h3} are significantly larger than those subpopulations in the high transmission case. For instance, the infected class at a 10% treatment rate in the high transmission case is 227 people. The same value in the low transmission case is 853 people, an increase of 276%. Every instance of comparing like numbers moving from areas of high transmission to low transmission yields a similar increase that ranges between 271% and 283%.

Comparing areas of high and low transmission, the parameters that were adjusted

Table 5.5: Parameter Values

Parameter	Dimension	Value
Λ_h	Humans \times Day $^{-1}$	2.791
ρ	Day $^{-1}$	0.0027
d_h	Day $^{-1}$	0.0000088
ω_h	Day $^{-1}$	0.1
δ_h	Day $^{-1}$	1.8×10^{-5}
β_h	Day $^{-1}$	0.022
Λ_v	Mosquitoes \times Day $^{-1}$	39000
d_v	Day $^{-1}$	0.033
ω_v	Day $^{-1}$	0.083
β_v	Day $^{-1}$	0.24
δ_v	Day $^{-1}$	0.0165

include the recovery rate: ρ , the human birth rate: Λ_h , the human death rate: d_h , the malaria-induced death rate for humans: δ_h , the bite rate for mosquitoes: β_v , and the infection rate for mosquitoes: ω_v . In the low transmission case, the amount of people recovering, ρ , increased 80%. The human birth rate, Λ_h , was reduced 98% for the low transmission case. The human death rate, d_h , was reduced by 82%, while δ_h is reduced by 400%. The mosquito population was affected by the 100% reduction in the bite rate, β_v , as well as the 10% reduction in the infection rate, ω_v .

Although the human birth rate decreased, the human death rates are even smaller in comparison which accounts for some of the difference between high and low transmission. The major change, however, is the recovery rate with is more than tripled.

This increased recovery rate allows people to move back into the susceptible class much faster, thereby obtaining new infections. In the high transmission case, once a person is withdrawn, they sustain temporary immunity for nearly five years. However, in the low transmission case, temporary immunity lasts just over a year. This single change almost doubles the amount of people within the susceptible class which allows a greater proportion of people to become infected. β_v is also reduced, but notice that this parameter is then multiplied by the proportion of infectious people which has been increased a significant amount.

Table 5.6: Long Term Population Values - Low Transmission Case

θ	$\lambda_{h1}, \lambda_{h2}, \lambda_{h3}$	L_h	I_h	T_h	R_{h1}	R_{h2}	R_{h3}
10%	4.5%	1280	853	461	218	103	93
20%	4.5%	1279	511	553	262	124	111
40%	4.5%	1276	284	613	290	137	123
80%	4.5%	1275	150	648	307	145	131
10%	13.2%	1281	854	314	228	165	435
20%	13.2%	1281	512	377	273	198	522
40%	13.2%	1281	285	418	303	220	580
80%	13.2%	1281	151	443	321	233	614
10%	21.9%	1281	854	238	194	158	689
20%	21.9%	1281	512	285	232	189	827
40%	21.9%	1281	285	317	258	210	919
80%	21.9%	1281	151	336	273	222	973

5.4 Conclusions

As we have seen, the infectious population is responsive to both changes in treatment as well as changes in the levels of drug resistance that are experienced. Increasing the percentage of people receiving treatment causes the infectious population to drop. However, this decrease in the infectious group becomes much less significant as we move from low to high levels of resistance. In other words, treatment can be effective in reducing the number of people that are sick if the drug resistance is not too high. On the other hand, once drug resistance becomes prevalent, treatment is less likely to be successful. As we study the high resistance case, we see that increasing treatment leads to a major increase in the drug resistant population with minimal reduction in the infectious group as a whole. In this case, mathematical models such as this one can help suggest thresholds in which treatment would be effective and when treatment should be used conservatively to avoid creating more problems by aggravating drug resistance.

A cost-benefit analysis of treatment rates can be analyzed using mathematical simulations. In our study, we discovered that increasing treatment yields a smaller decrease of infectious individuals. In other words, doubling the treatment rate may produce significant changes in the size of the infectious subpopulation, but this effectiveness decays as we continue to increase treatment. A balance can be found such that treating a certain percentage of people would yield optimal effectiveness per dollar spent.

Varying constant levels of resistance provided insight by the differences of growth in the resistance classes, R_{h1} , R_{h2} , and R_{h3} . Moving from low to medium resistance,

R_{h1} increases slightly. Increasing from medium to high resistance, R_{h1} actually becomes smaller. Similarly for R_{h2} , the same progression from low to medium to high resistance induces an increase in R_{h2} followed by a decrease. R_{h3} , however, grows dramatically from low to medium resistance with another increase as we progress from medium to high. Thus, more individuals will acquire RIII resistance as resistance to treatment becomes more prevalent. Several components are at work in this case. As we increase resistance by increasing λ_i , we are not only allowing more people to move in to the resistance classes, but we are also moving them through the resistance classes at a faster pace since $\frac{1}{\lambda_i}$ is the time a person is in the resistance class. Throughout our parameter manipulations, we do not change the recovery rate and thus the proportion of people recovering becomes fewer in comparison to those obtaining drug resistant malaria.

As a result of our research, we are painfully aware of the implications that treatment has on drug resistance. All of our simulations have reinforced the strong cause and effect relationship that exists between resistance and treatment. Innately, we desire to aid those that suffer by administering antimalarial drugs, but as a result we are reducing the effectiveness of the drugs. Although treatment cures some cases of malaria, the cost of an influx of drug resistant strains of the parasite must be considered.

From the simulations that were conducted, we continue to gain confidence that our model acts similarly to real world scenarios. Using our knowledge of malaria and drug resistance, further studies can refine the selections that were made for the parameter values and the initial conditions. Many more areas of the model can and should be explored to better understand the implications of treatment and how it

affects drug resistance. Ongoing research and analysis will hopefully help the world get closer to eliminating the burden of infectious diseases. The trade off, however, must be made between treating symptoms and creating a more volatile and resistant disease. Care must be taken when evaluating treatment plans, which is one of the most useful ways to leverage mathematical models.

Appendix A

Parameter Descriptions and Initial Conditions

Table A.1: Human Parameter Descriptions

Parameter	Description
Λ_h	Rate at which new recruits enter the susceptible human population
β_v	Rate at which a human receives a successful bite from an infected mosquito
c	A constant that will increase or decrease the frequency of bites
ρ	Rate at which humans lose partial immunity
d_h	Natural death rate for humans
δ_h	Malaria-induced death rate for humans
ω_h	Rate that humans become infectious after they have been exposed
θ_h	Treatment rate for humans
η_I	Rate that humans acquire partial immunity prior to treatment
η_T	Rate that treated humans acquire partial immunity
η_1	Rate that humans in the first resistance class acquire partial immunity
η_2	Rate that humans in the second resistance class acquire partial immunity
η_3	Rate that humans in the third resistance class acquire partial immunity
λ_1	Rate that humans become RI resistant after receiving treatment
λ_2	Rate that humans become RII resistant after receiving treatment
λ_3	Rate that humans become RIII resistant after receiving treatment
a_1	Rate that the malaria-induced death rate increases due to RI resistance
a_2	Rate that the malaria-induced death rate increases due to RII resistance
a_3	Rate that the malaria-induced death rate increases due to RIII resistance

Table A.2: Vector Parameter Descriptions

Parameter	Description
Λ_v	Rate at which new recruits enter the susceptible mosquito population
β_h	Rate at which a susceptible mosquito successfully bites an infected human
δ_v	Malaria-induced death rate for mosquitoes
d_v	Natural death rate for mosquitoes
Ω_v	Rate that mosquitoes become infectious after they have been exposed

Table A.3: Initial Conditions - High Transmission

Parameter	Value
Λ_h	5.533
β_v	0.48
ρ	0.00055
d_h	0.000016
δ_h	0.00009
ω_h	0.1
η_I	0.05
η_T	0.14
η_1	0.05
η_2	0.05
η_3	0.05
Λ_v	39000
β_h	0.022
δ_v	0.0165
d_v	0.033
Ω_v	0.091

Table A.4: Initial Conditions - Low Transmission

Parameter	Value
Λ_h	2.791
β_v	0.24
ρ	0.0027
d_h	0.0000088
δ_h	0.000018
ω_h	0.1
η_I	0.05
η_T	0.14
η_1	0.05
η_2	0.05
η_3	0.05
Λ_v	39000
β_h	0.022
δ_v	0.0165
d_v	0.033
Ω_v	0.083

Appendix B

Graphical Results

Results previously discussed focus on population sizes after an outbreak, once the changes in population sizes become less drastic. The following graphs depict how an outbreak of malaria would affect the population within the various classes, assuming an area of high transmission.

B.1 High Resistance

Comparing Figures B.1 and B.2, it is clear that increasing treatment increases the population in R_{h3} by comparing the peak of the blue curve. A result that was mentioned when studying the populations after they settle.

B.2 Medium Resistance

Although the treatment rate affects the height of the peak in population size, qualitatively the results are the same. T_h and R_{h3} have approximately the same population

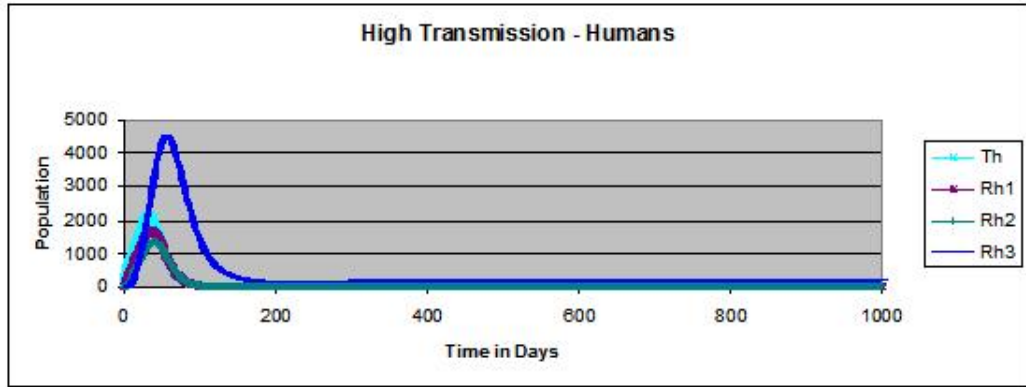


Figure B.1: T_h , R_{h1} , R_{h2} , and R_{h2} Classes with High Resistance Levels and a 10% Treatment Rate

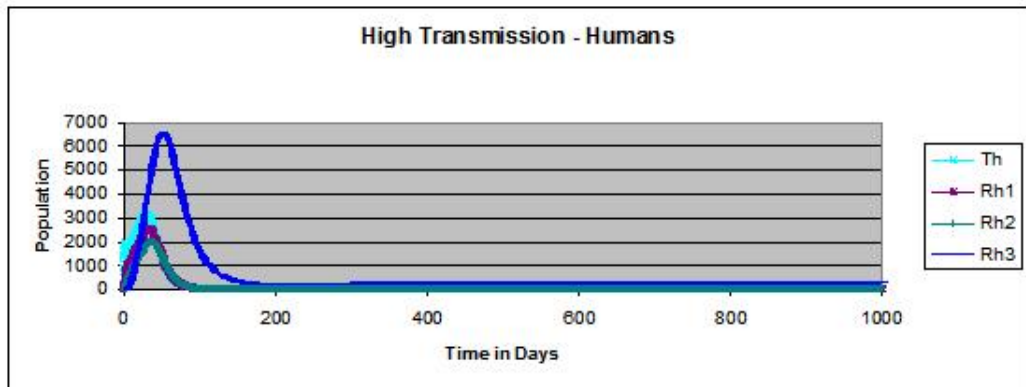


Figure B.2: T_h , R_{h1} , R_{h2} , and R_{h2} Classes with High Resistance Levels and a 80% Treatment Rate

size, with the peak in T_h arriving prior to R_{h3} . See Figure B.3.

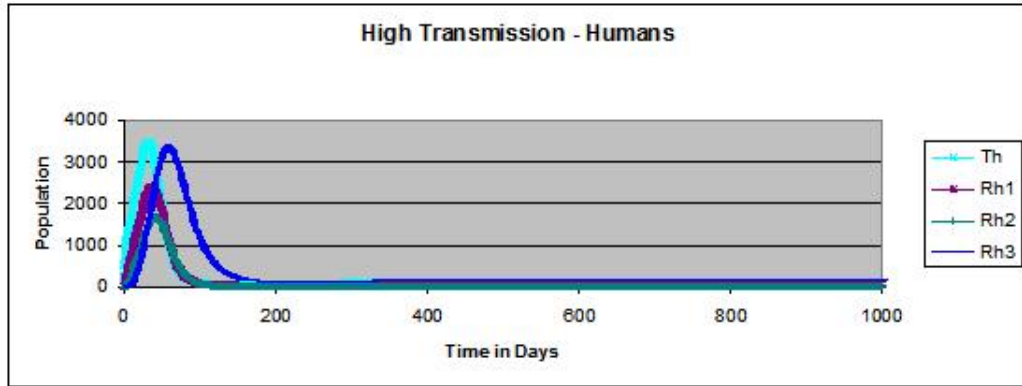


Figure B.3: T_h , R_{h1} , R_{h2} , and R_{h2} Classes with Medium Resistance Levels and a 20% Treatment Rate

B.3 Low Resistance

We will continue examining outbreaks as they occur in the low resistance case. Figures B.4 and B.5 show the difference between 20% and 40% treatment rates within the low resistance case. Moving from 20% to 40% treatment rates, demonstrates a large difference in the R_{h3} class. In the 20% treatment case, the population that has the largest peak is T_h , but when we double treatment R_{h3} becomes the population with the largest increase. This illustrates an example where keeping treatment rates lower may actually help the population overcome malaria with less resistance.

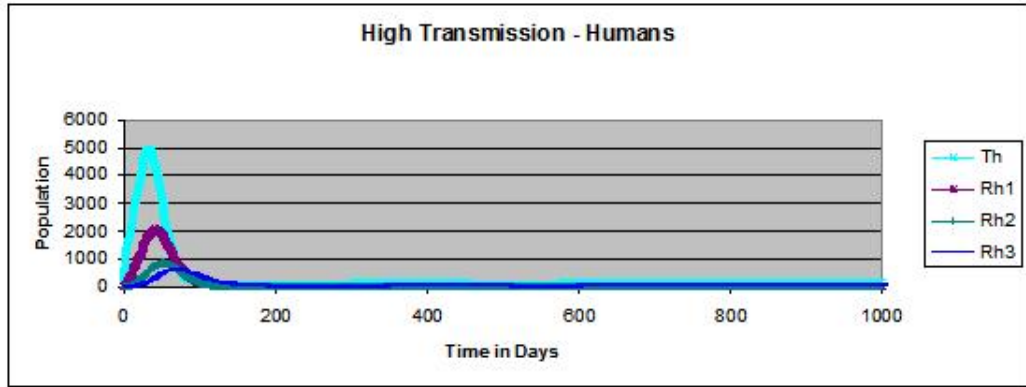


Figure B.4: T_h , R_{h1} , R_{h2} , and R_{h2} Classes with Low Resistance Levels and a 20% Treatment Rate

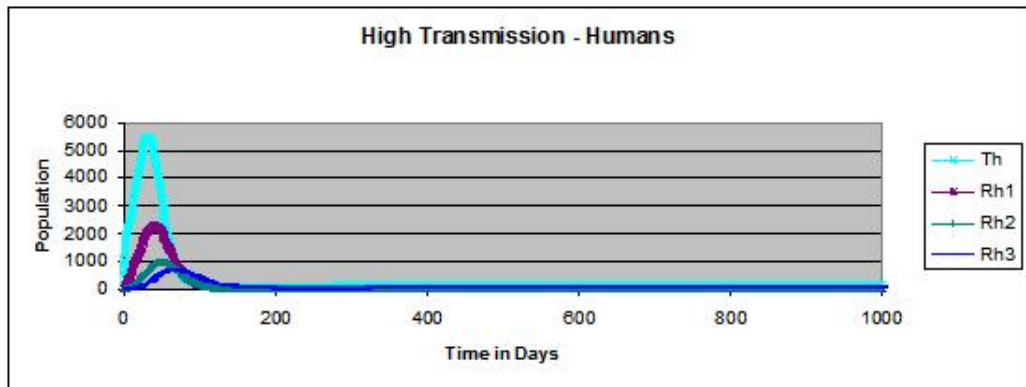


Figure B.5: T_h , R_{h1} , R_{h2} , and R_{h2} Classes with Low Resistance Levels and a 40% Treatment Rate

B.4 The Mosquito Population

Figure B.6 shows the change in the mosquito population as an outbreak occurs assuming a 10% treatment rate with low resistance. Notice the proportion of infected and latent mosquitoes compared to the number of susceptible mosquitoes.

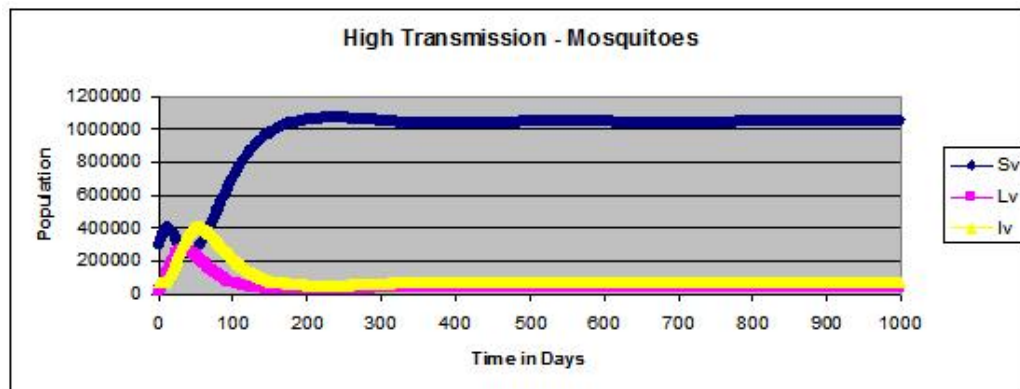


Figure B.6: The Mosquito Population with Low Resistance Levels and a 10% Treatment Rate

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