INTERVENTION MODEL OF MALARIA

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Abstract. Every year up to about 300 million people are infected by malaria, an infectious disease caused by *Plasmodium* species parasites. Consequently, nearly 660,000 deaths occur. Infected female *Anophele* mosquitoes transmit the parasite to humans through their salivary glands. Although there are other species that cause malaria, *P. falciparum* is the most dangerous type that infects and is transmitted by humans. Mosquito elimination, avoidance of mosquitoes, sleeping nets, and spraying insecticides are a few methods to retard the spread of malaria. My project focused on the impact of sleeping nets in sub-saharan countries in Africa. A mathematical model was created and simulated by using eight differential equations. Among a number of results, a set of inequalities were derived that give necessary and sufficient conditions under which the disease would become endemic in a population. These inequalities highlight the role that the use of sleeping nets plays in supressing or diminishing a malaria outbreak.

Introduction

Half of the world's population, about 3.3 billion people, are at risk for becoming infected with malaria. This infectious disease is endemic to 106 countries and territories. In 2010, it was estimated that there were 216 million cases of malaria. Consequently, 655,000 people died during that particular year (**?**). According to Mahamadou and Plowe, malaria "is thought to have killed more humans throughout history than any other single cause (**?**)." Parts of Central and South America, Asia, and sub-saharan Africa struggle with malaria. Much focus has been directed towards countries in the sub-saharan African areas because they contribute to about 91% of malaria mortality each year (**?**).

Malaria is transmitted in a criss cross process, involving two different species: *Anopheles* mosquitoes and humans. The mosquitoes behave as vectors that transmit parasites into the human body, which acts as the host (**?**). Female mosquitoes are exclusively interested in blood because it nourishes their eggs. There are four *Plasmodium* parasitic species that can be transmitted: *P. vivax*, *P. ovale*, *P. malariae*, and

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P. falciparum. An additional species, *P. knowlesi* was mostly found in nonhuman primates, however, it has been found in humans as well(**?**).

The transmission cycle begins when a female *Anopheles* mosquito takes a blood meal from a human and injects sporozoites into the human blood. These sporozoites travel to the liver, where they invade the liver cells and multiply to form tens of thousands of merozoites. The merozoites are stored in a single hepatocyte until they become too populous, causing the hepatocyte to bursts. The released merozoites invade erythrocytes and reproduce asexually. Again, the erythrocytes become too dense and burst. After about 2 days, the cycle begins again as the merozoites reinvade the cells. Sexual forms, or male and female gametocytes, develop from this stage. As the mosquito takes another blood meal from the human, the gametocytes enter the mosquito. Later, they grow into gametes, or mature sex cells. The gametes enter a haploid stage where they form oocysts that travel from the gut to the salivary glands of the mosquito. Each oocyst contains about $1,000$ infectious sporozoites. The mosquito will then take another blood meal from the human and the sporozoites will leave the salivary glands into the human blood. These descriptions represent one complete transmission cycle, and this process repeats continuously (**?**).

One may begin to experience repetitive cycles of malaria symptoms after being bitten by an infectious mosquito. The most common description of the symptoms are characterized as flu-like, involving fever, headaches, chills, sweating, and muscle pains. These symptoms typically occur every one to three days. Others my experience nausea, vomiting, diarrhea, and cough. Certain patients may develop jaundice, whites of the eyes, or a rash. More severe cases of malaria may cause bleeding difficulties, shock, liver or kidney failure, central nervous system problems, coma, and/or death (**?**).

Children, pregnant women, and people with weak immune systems have a higher risk of contacting malaria. With developing immune systems, these groups of people make up majority of the people that die from the disease. Women who are pregnant lose their protected immunity due to placenta-specific cytoadherence proteins. Healthy adults generally do not become ill nor develop clinical malaria disease. The cause of this deals with the number of times one has been infected. After several years of being infected with malaria, partial immunity increases. However, without exposure to the parasite, the immunity decreases, and the risk of becoming susceptible to the disease increases (**?**).

Fortunately, there are medications available to cure malaria, and they are distributed depending on whether the patient has a mild or

very severe case. A few types of drugs that are commonly used to treat malaria patients are intravenous or intramuscular quinine, artemisinin derivative artesunate, mefloquine, and choloroquine (**?**). In Nigeria in particular, it is common for doctors to use a standard treatment called artemisinin-based combination therapy (ACT) (**?**). Additionally, intermittent preventive treatment for pregnant women (IPTp) has a big impact on reducing the symptoms and effects of malaria for women and their fetuses. They are given a minimum of two doses of sulfadoxine-pyrimethamine (SP) (**?**).

Although there are several known medications to cure this disease, no form of vaccination exists. However, due to the intense effort being applied to the problem, it seems likely that a vaccine for malaria will eventually be introduced. A pre-erythrocyctic vaccine, RTS,S/AS01 has reached phase III trial. It targets the circumsporozoite protein (CSP) of *P. falciparum*. RTS,S was given to children and infants, resulting in a 66% protection percentage against the infection. After promising results, the vaccine moved to phase II and several trials were experimented on $1,465$ Mozambican children. The reduction of contacting the infection, protection from only one clinical malaria episode, and protection against clinical malaria were $26\%, 32\%$, and 38% lower, respectively.

Eradication and elimination programs fight a continuous battle to develop efficient malaria control medications, strategies, and vaccines. The difficulty arises when the size and plasticity of the *P. falciparum* genome is understood. It has 23 million bases of DNA that are organized into 14 chromosomes. There are about $5,000$ genes that are expressed at different times as the parasite goes through various life cycles from the vector to the host.

Medications help cure the disease, however, there are other ways to prevent transmission from mosquito to human. On average, a person receives 300 infectious bites per year where there is a high risk for contracting malaria (**?**). Studies have shown that using sleeping/bed nets reduce malaria transmission, however, in certain regions in Nigeria, net usage can range from 20% to about 63% (**?**). A sleeping net is a net that can be used to hang over someone while sleeping. An ever-treated net is a net that has been treated at least once with insecticides. An insecticide-treated net (ITN) is a net that has been treated with insecticide before acquiring or purchasing the net (**?**). It is essential that ITNs be retreated about every six months, and after this point the net become less efficient (**?**). With the use of ITNs there has been up to 90% reduced malaria transmission (**?**). A long-lasting insecticide-treated net (LLIN) is a net that has been treated with insecticide and

lasts for at least 12 months (**?**). LLINs are the most cost-effective intervention method because it is designed to last longer than any other net (**?**). Baby nets are also used, which are untreated, umbrella-like nets that protect an infant from flies during the day and mosquitoes during the night (**?**).

Besides using physical barriers between the vector and host, environmental advances have been made to significantly lower the mosquito population. Indoor Residual Spraying (IRS) is used to kill mosquitoes that collect on walls inside houses (**?**). Other methods may involve spraying insect repellents and draining standing water (**?**).

My project focused on the impact of sleeping nets in sub-saharan countries in Africa. Africa is responsible for a large percentage of malaria deaths in the world, therefore, it is vital to try to improve these statistics. There were several biological questions that could give insight as to better understanding the mechanics of the disease and the best way to approach preventing it. The overarching question determined whether malaria can be eliminated solely by the use of sleeping nets. Other technical questions arose as I further investigated this question.

Biological Questions

1. What proportion of the population needs to use sleeping nets for an infected population to reach an equilibrium of 0?
2. How does female mosquitoes living longer than 2 weeks effect the infectious populations?
3. How would humans having a longer or shorter period to recover effect the infectious populations?
4. What is the minimum efficiency level for a sleeping net (50% and 100% net usage) that keeps the infectious populations at 0?

With the help of mathematical modeling, these questions were evaluated.

Model Development

When developing this model, it was important to understand the transmission process of malaria. It is common when mathematically modeling infectious diseases to use the following denotations:

$$S := \text{Susceptible (people who can become infectious)}$$
$$I := \text{Infectious (people with the disease)}$$
$$R := \text{Recovered (people recently cured)}$$

The total mosquito population (N_M) was split into two sub-populations, S_M and I_M. The total human population (N_H), was divided into two sub-populations as well. For simplicity, the two divisions are written below in the form of equations.

$$N_H = H_1 + H_2$$
$$H_1 = S_1 + I_1 + R_1$$
$$H_2 = S_2 + I_2 + R_2$$

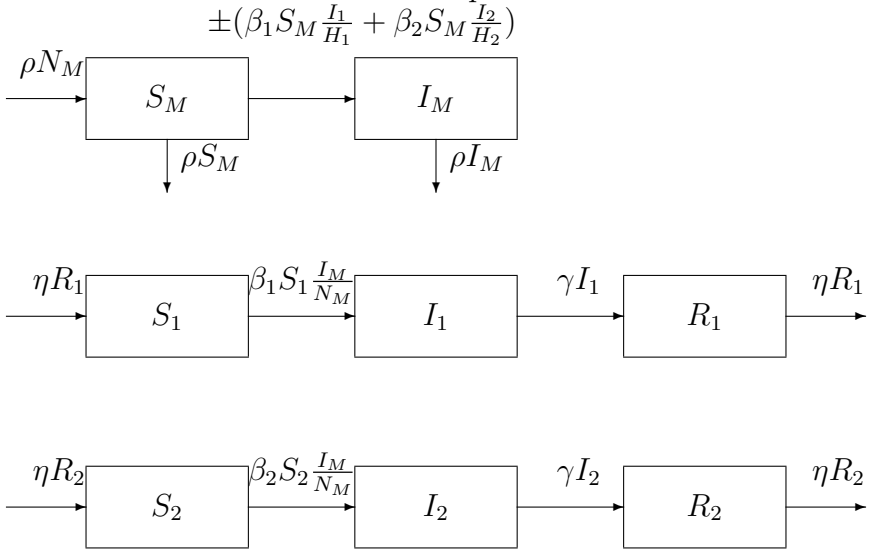
H_1 represents the number of people in the human population that uses sleeping nets while sleeping. Likewise, H_2 represents the number of people in the human population that does not use sleeping nets while sleeping.

There were 8 compartments involved in this model, and the diagram for this model can be found at Figure 1. The parameters displayed in the diagram represent the rates at which one person moves from one class to the other.

Model Assumptions

1. The human population had a constant population size.
2. The primary net used was an ITN.
3. The data used are all equivalent to data from Africa.

FIGURE 1. Nets vs. No Nets Compartmental Model for Malaria



After constructing the model, differential equations were generated for each compartment. Below are the differential equations corresponding to the mosquito population.

$$S'_M = -\beta_1 S_M \tfrac{I_1}{H_1} - \beta_2 S_M \tfrac{I_2}{H_2} + \rho N_M - \rho S_M$$

$$I'_M = \beta_1 S_M \tfrac{I_1}{H_1} + \beta_2 S_M \tfrac{I_2}{H_2} - \rho I_M$$

These were the H_1 differential equations.

$$S'_1 = -\beta_1 S_1 \tfrac{I_M}{N_M} + \eta R_1$$

$$I'_1 = \beta_1 S_1 \tfrac{I_M}{N_M} - \gamma I_1$$

$$R'_1 = \gamma I_1 - \eta R_1$$

These were the H_2 differential equations.

$$S'_2 = -\beta_2 S_2 \tfrac{I_M}{N_M} + \eta R_2$$

$$I'_2 = \beta_2 S_2 \tfrac{I_M}{N_M} - \gamma I_2$$

$$R'_2 = \gamma I_2 - \eta R_2$$

Each of these equations enabled the possibility of simulating the model and interpreting given information.

Methods

The first preliminary step consisted of non-dimensionalizing each differential equation. In this particular model, this step simplified the number of equations and indicated the relevancy of variables. Thus, S_M, R_1 and R_2 were substituted in terms of the other known variables. The revised equations are listed below.

$$I'_M = \beta_1 \frac{I_1}{H_1}(N_M - I_M) + \beta_2 \frac{I_2}{H_2}(N_M - I_M) - \rho I_M$$

$$S'_1 = -\beta_1 S_1 \frac{I_M}{N_M} + \eta(H_1 - S_1 - I_1)$$

$$S'_2 = -\beta_2 S_2 \frac{I_M}{N_M} + \eta(H_2 - S_2 - I_2)$$

After non-dimensionalizing the equations, the determinant of the Jacobian matrix was generated. This method identified the characteristic polynomial. Because it is difficult to find the eigenvalues of a fifth root polynomial, Routh Hurwitz conditions were applied. This method tested stability by checking to ensure the determinants of a specific sequence of matrices were all positive. Also, it determined whether all roots of the characteristic polynomial had negative real parts. The Hurwitz conditions for the polynomial in my particular model hold true, indicating further research efforts could be made. The equations were placed into mathematica and it was used for extracting results. The parameters from the model were manipulated to help answer the biological questions listed above. For example, the proportion of the population that used and did not use nets were defined as α_1 and α_2, respectively. α_1 ranged from 0 to 1, and α_2 was defined to be $1 - \alpha_1$.

Results

Among a number of results, a set of inequalities were derived using Routh Hurwitz conditions. All of the inequalities were satisfied except the one below. The quantity was generated from the requirement that the constant term in the characteristic polynomial from the Jacobian matrix, evaluated at the disease-free state, be positive.

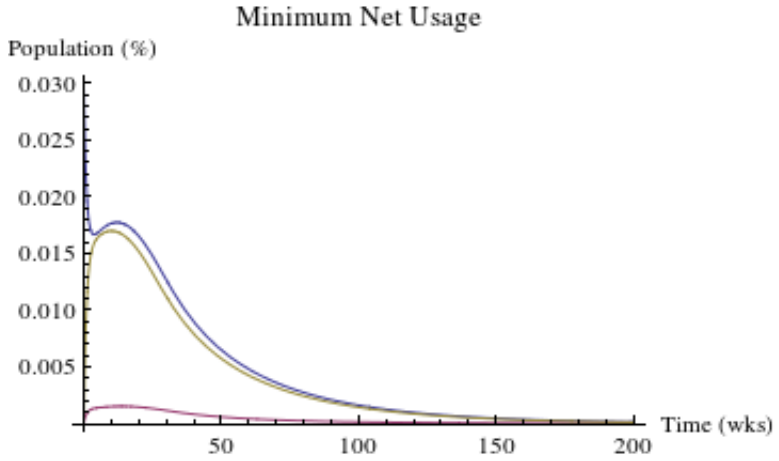
$$\frac{\beta_2^2\alpha_2 + \beta_1^2\alpha_1}{\rho\gamma} < 1$$

In modeling infectious diseases, finding the standard R_0 value is a complicated concept to understand if more than one infectious class exists. Instead, this quantity was determined, and it gives necessary and sufficient conditions in a disease free state under which the disease would not become endemic in a population. The parameters in this inequality can be manipulated to either predict or prevent an epidemic from

happening, hence its usefulness. The data used for each parameter (see Appendix) were adjusted to answer the biological questions.

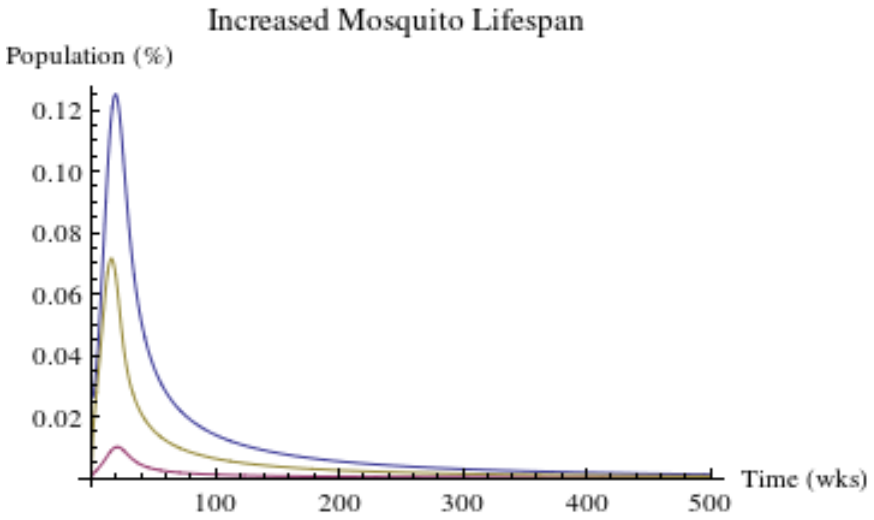
Question 1

The parameters α_1 and α_2 were altered to see the minimum net usage needed to make i_m, i_1 and $i_2 \to 0$. Only 20% net usage was needed to satisfy these inequalities. The infectious populations are shown below in the graph. The blue line represents i_m, the red line represents i_1, and the gold line represents i_2. It was important to observe the behavior of each line. In the graph they peak at $0.001\%, 1.6\%$ and 1.7%, then, each population reached equilibrium of 0 as t $\to \infty$.



Question 2

This question involved changing the value of ρ. Initially ρ equaled 0.5, but under these conditions, it was evaluated at 0.25. The original 20% was not enough to make i_m, i_1 and $i_2 \to 0$. In this scenario, 57% net usage was required. Again, the graph below represents these three infectious populations.



Question 3

In the situation where it takes a longer time for humans to recover, γ was modified to be 0.25. Increasing γ required that there be at least 60% net usage. The requirement must be satisfied in order for i_m, i_1 and $i_2 \to 0$. In the shorter period condition, γ was set to be $\frac{5}{8}$. Even with 0% net usage, i_m, i_1 and $i_2 \to 0$.

Question 4

For this scenario, α_1 was set to be 50%. One must use a sleeping net with at least a 12% reduction rate for i_m, i_1 and $i_2 < 0$. In the event that α_1 reached 100%, its effects were evaluated. With no reduction rate, or $\beta_1 = \beta_2$, there remained a difference in the net efficiency between i_1 and i_2. With the two β rates equaling each other, $i_1 > 0$ and $i_2 < 0$. There must be at least a 6% net reduction for i_1 and i_m to eventually reach 0.

Discussion

The exciting results show that it is possible to eliminate malaria by only using sleeping nets as an intervention method. According to the model, there must be at least 20% net usage to ensure that the infectious populations die out. Under conditions in which mosquitoes live longer, a greater net usage would be vital. One key aspect to understand is that although the infectious populations die out, they peak at different points before they go to 0. If this is the case, this means that a lot of people will become ill before the infectious populations die out. Also, in the scenario that humans recover in a month, 60% net usage would be required to make the infectious populations die out.

If we can lower the recovery period to one week and a half, nets are not needed at all. This verifies the idea that malaria can be eliminated even without the use of nets. Lastly, the effectiveness of nets greatly depended on the percentage of net usage.

Overall, my model simulated useful results that can be used towards eradication applications in the future. This model would be more useful if it specified one country or general area that has an intense transmission rate for malaria. Additionally, I would obtain more realistic results if birth and death rates (non-constant population) were taken into account in the model. This would better represent what actually happens in nature. Because a new malaria vaccine has had promising protection results, it would be interesting to test how effective the vaccine would be in terms of eradicating the disease. Once I introduce vaccination into the model, combining it with the sleeping net model could show vital results. Also, evaluating which intervention methods are more cost-efficient could help organizations such as the Who Health Organization or the Center for Disease Control.

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Appendix

Data

$\beta_1 := 0.0082\beta_2$
$\beta_2 := 0.53$
Source: **?**

$\gamma := 0.5$
Source: www. drugs.com/health-guide/malaria.html

$\eta := 0.25$
Source: boards.straightdope.com/sdmb/showthread.php?t=577636

$\rho := 0.5$
Source: en.wikipedia.org/wiki/Anopheles

Initial Conditions

$s_1[0] = 1.0$

$s_2[0] = 1.0$

$i_m[0] = 0.03$

$i_1[0] = 0$

$i_2[0] = 0$