# Impact of Indoor Residual Spraying and Insecticide-treated Bed Nets on Malaria Transmission in Sub-Saharan Africa Using Mathematical Modelling

**Andrew Tomayer**

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## Abstract

**Background:** Malaria causes over 400,000 estimated deaths annually worldwide, with about 90% in sub-Saharan Africa. Long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) are two vector-control interventions proven to reduce malaria transmission, but their use together compared to separate has shown mixed results.

**Methodology:** We used a mathematical model to examine the impact of LLINs and IRS on malaria transmission. Time-series analyses and basic reproductive numbers ($R_0$) were developed using MATLAB. We also assessed IRS timing and performed a sensitivity analysis on $R_0$.

**Results:** Modelling scenarios combining LLINs with IRS were similar to those with LLINs alone. Shorter IRS impulses had greater reductions in mosquito populations. The LLIN feeding-inhibition rate was a key parameter with a negative correlation to $R_0$.

**Discussion/Conclusion:** We developed an understanding of the effect of vector-control strategies on malaria transmission. IRS, when paired with LLINs, showed only small improvements in reducing malaria transmission compared to LLINs alone. These results can assist vector-control programmes.

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# 1. INTRODUCTION AND OVERVIEW

## 1.1. MALARIA

### 1.1.A. THE HISTORY OF MALARIA

Malaria is a disease that has existed for centuries, dating back to 2700 BC (Centers for Disease Control and Prevention [CDC], 2012a; Cox, 2010). The first antimalarial was discovered around the 17th century, where a type of tree bark was used as a treatment of malarial fever. The medicinal ingredient found within it, quinine, became one of the first medications against the disease (CDC, 2012a). In 1880, Charles Louis Alphonse Laveran found the *Plasmodium* parasite within a malaria patient's blood (Cox, 2010). Further research by Camillo Golgi found differing forms of the parasite, along with the replication process of the disease through merozoites (CDC, 2012a).

In 1897, Ronald Ross discovered that mosquitoes could transmit the infection (CDC, 2012a; Cox, 2010). Laveran and his colleague Patrick Manson had originally hypothesized the disease was spread by mosquitoes and, through examining birds, Ross demonstrated that mosquitoes would become infected after taking blood meals from infected birds and then pass the *Plasmodium* parasite to susceptible birds upon taking further blood meals (CDC, 2012b; Cox, 2010). Ross and Lavaran earned Nobel prizes for their respective works in the greater understanding of malaria (CDC, 2012a).

### 1.1.B. PATHOPHYSIOLOGY AND LIFE-CYCLE OF MALARIA

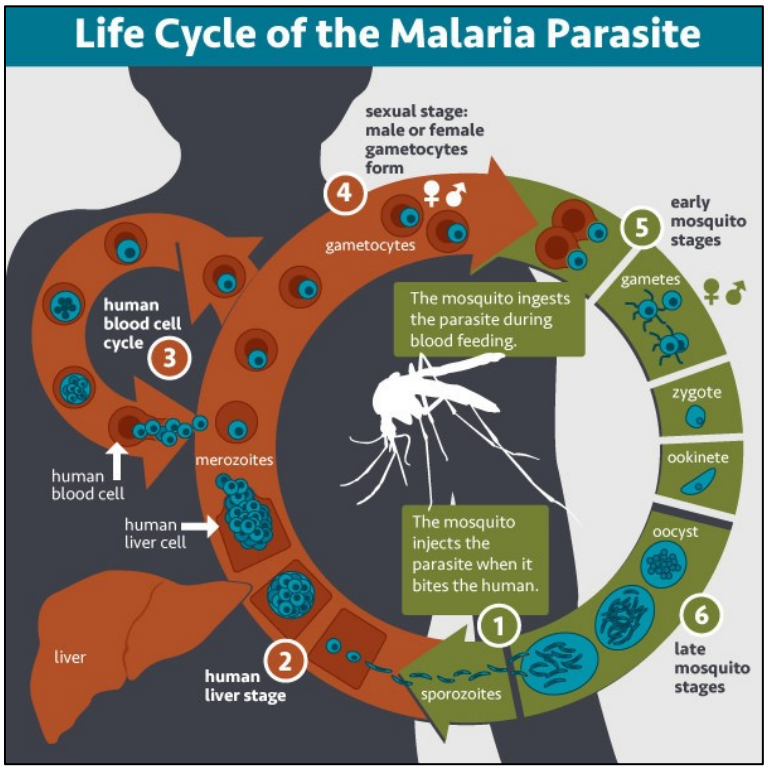
The protozoan parasite *Plasmodium* is the cause of malaria and includes the various strains of the parasite that affect humans, such as *Plasmodium falciparum*, *P. vivax*, *P. malariae* and *P. ovale* (Black, 2008). There is also the zoonotic strain of malaria, *P. knowlesi*, found in monkeys specific to environments of South-east Asia (World Health Organization [WHO], 2016a).

*Plasmodium falciparum* causes the greatest incidence of the illness and highest mortality in humans as it affects all types of red blood cells while *P. vivax* leads to fewer cases due to reticulocytes (early stage blood cells) having a greater vulnerability to this strain (de Almeida e Val, Montiero, & de Lacerda, 2013). As well, the *P. vivax* parasites are detectable in the blood in the early stages of infection, while *P. falciparum* parasites are detectable in the blood in later stages after a human demonstrates symptoms (de Almeida e Val et al., 2013). *P. falciparum* and *P. vivax* cause the majority of human cases, while *P. ovale* and *P. malariae* are much less prominent.

A human can contract the parasite through the bite of an infected female *Anopheles* mosquito, for the *Anopheles* species that are competent vectors, and the taking of a blood meal is much more likely to occur during the night (WHO, 2016a). Uninfected mosquitoes can pick up the parasite by taking a blood meal from an infected human. There are greater levels of malaria incidence and prevalence in environments that can sustain *Anopheles* mosquito habitats, such as wetland-like areas, including swamps, rice fields and other humid environments. Rainfall can also account for potential increases in parasite transmission as the water accumulation and humidity can develop an ideal environment for mosquito breeding and proliferation (Mandal, Sarkar, & Sinha, 2011).

The life cycle of malaria in humans and mosquitoes has a cyclical presentation (see Figure 1). When an infected female *Anopheles* mosquito takes a blood meal from an uninfected human, the *Plasmodium* parasite can get injected into the bloodstream of the human (Black, 2008; National Institute of Allergy and Infectious Diseases [NIAID], 2016). Once the parasite is in the human, the sporozoites of the disease enter into the liver, where they multiply into merozoites. This can occur over a few days to one or two weeks or can remain dormant for months within the

liver before further replication occurs (Black, 2008; NIAID, 2016). Once multiplied into thousands of merozoites, the parasite then leaves the liver and begins attacking red blood cells by invading the blood cells and performing further replication of merozoites (NIAID, 2016). This leads to a continuous cycle of asexual replication of the parasite. This develops many symptoms of the disease within humans, including fever and headaches, and can then lead to sepsis, shock, renal failure, respiratory distress and even death (Black, 2008; NIAID, 2016; WHO, 2016a; Heymann, 2008). Some merozoite-infected blood cells can leave the replication phases, and the merozoites become male or female gametocytes, the sexual stage of the parasite, which can be picked up by uninfected mosquitoes (NIAID, 2016).




Courtesy: National Institute of Allergy and Infectious Diseases (2015)

**Figure 1: Malaria Life Cycle**

Once the uninfected mosquito ingests the gametocytes, the blood cells then release the parasites, which develop into gametes, and then fuse into zygotes, which eventually become oocysts of the parasite. The oocysts then further mature in their midgut and develop many

sporozoites that then enter into the mosquito's salivary gland (Black, 2008; NIAID, 2016). This cycle of infection from infected mosquitoes to susceptible humans, then infected humans to susceptible mosquitoes leads to further spread of the illness to others in the human and mosquito populations. In order to develop an appropriate model of malaria, the cycle of infection must be appropriately understood.

### 1.1.C. IMPACT OF MALARIA IN SUB-SAHARAN AFRICA

In 2015, the WHO stated that malaria led to an estimated 438,000 deaths globally, with the heaviest burden occurring in sub-Saharan Africa, where an estimated 90% of deaths occurred (WHO, 2015a). Significant increases in global malaria-control strategies have in part led to a 48% decline in mortality within sub-Saharan Africa since 2000, along with a 58% reduction in the mortality rate among children under 5 years of age (WHO, 2015a). Several strategies to combat malaria transmission within Africa include those devised by programs such as the Global Malaria Action Plan's Roll-Back Malaria Partnership and the President's Malaria Initiative (President's Malaria Initiative [PMI], 2015; WHO, 2015a). Some objectives set forth through the Roll-Back Malaria Partnership included a reduction of deaths from malaria to almost none by 2015 while reducing incidence of the disease by 75% in 2015 from year 2000 estimates (WHO, 2015a). In 2015, the WHO reported globally that 57 endemic countries were able to meet the 75% reduction target, while the number of countries considered endemic fell from 106 in 2000 to 95 by 2015 (WHO, 2015a). Newer goals to reach by 2030 have also been set with even greater declines, such as a 90% reduction of global cases and deaths due to malaria (WHO, 2015a).

## 1.2. THERAPEUTIC AND VECTOR-CONTROL INTERVENTIONS

There are several methods for prevention and/or control of malaria transmission. These include use of vector-control interventions such as insecticide-treated nets (ITNs) and long-

lasting insecticidal nets (LLINs), indoor residual spraying (IRS) as well as use of medication treatments and potential vaccinations.

Through provision of a protective barrier, as well as reducing the volume of mosquitoes through insecticidal activity, ITNs and LLINs have been effective in reducing malaria transmission. Pyrethroids are a commonly used treatment within the netting, and country-wide distribution programmes have occurred across Africa to protect the human population (WHO, 2015a). Such elements regarding ITNs and LLINs, along with their efficacy, are discussed in Section 1.3.

IRS is an effective method of spraying insecticide to the walls of one's home. IRS reduces disease transmission through repelling and killing the vector once it enters the home and rests on the treated wall after taking a blood meal. The type of insecticide used depends upon the regulations of the nation distributing the IRS and the level of mosquito resistance to the insecticide in the respective areas (WHO, 2015a). This, along with its efficacy, is explored further in Section 1.4.

There have been various pharmacotherapies developed against malaria. Medications like chloroquine and aminoquinoline were originally used due to their efficacy and inexpensiveness; however, parasite resistance to these drugs has grown in recent years (Sinha, Medhi, & Sehgal, 2014). Even antimalarials under the class of sulfoamides and sulfones are increasing in resistance from the parasite; the median failure rate of sulfadoxine-pyrimethamine in eastern Africa was reported at 52.8% (WHO, 2010). Artemisinin-combination therapies (ACTs) are antimalarial interventions of various derivatives of artemisinin combined with other effective antimalarials such as dihydroartemisinin-piperaquine, artesunate-pyronaridine and artemether-lumefantrine (Visser et al., 2014). The use of ACTs is also supported by the WHO; it is recommended to

combine artemisinin with a second active medication to reduce the potential for malaria resistance from a single artemisinin drug (WHO, 2015b). ACTs are suggested for *P. falciparum*, but chloroquine is recommended for *P. vivax* unless malaria resistance exists in the area of drug administration, in which case ACT is also then recommended for use against *P. vivax* (WHO, 2015b; Visser et al., 2014).

As of 2016, the RTS,S malaria vaccine received positive evaluation by the European Medicine's Agency and is in the final phase of clinical trials (WHO, 2016b). Results from Phase 3 trials, however, show only partial efficacy among 5–17 month old children receiving a shot at months 0, 1, 2 and 20, with a vaccine efficacy of 36.3% (95% CI 31.8–40.5%) (RTS,S Clinical Trials Partnership, 2015). With efficacy well below 100%, and with months to years until this and other potential vaccinations are widely available and distributed to the world, vector-control methods will continue to be necessary and must be used well in the control and prevention of malaria transmission.

Along with antimalarial treatment and the RTS,S vaccine, there are other malaria and vector-control interventions, including chemoprophylaxis for pregnant women (known as intermittent preventative treatment), larval control and carbamate-treated plastic sheeting (WHO, 2015a; Corbel et al., 2012).

The focus in this thesis is on IRS and ITNs/LLINs as vector-control interventions and their respective impact on reducing the spread of the disease, as these are the two most common vector-control interventions in use by malaria-control programmes around the world.

## 1.3. INSECTICIDE-TREATED NETS AND LONG-LASTING INSECTICIDAL NETS

### 1.3.A. HISTORY OF ITNS AND LLINS

Bed nets protect humans by providing a barrier from the vector and were originally tested with materials such as wire mesh or muslin (MacGregor et al., 1901). This simple level of prevention leads to a reduction in the spread of parasites from infected humans to susceptible mosquitoes and vice versa (WHO, 2007).

Curtis et al. stated that, during World War II, some countries' armed forces' fatigues and bed nets were treated with insecticides to maintain the health of individuals (as cited in Lengeler, 2004, p. 2). Pyrethroids were being used on nets by the late 1970s due to their high effectiveness against mosquitoes and the fact that they provided little harm to humans (Lengeler, 2004).

The addition of insecticide to the netting material, creating an ITN, increases the likelihood that the mosquito does not come in contact with a human. This occurs through the insecticide's ability to repel the mosquito, as well as increasing the chance of mosquito mortality from contact with the insecticide in the netting (WHO, 2007).

LLINs were created to combat the potential threat of reduced effectiveness of insecticides in ITNs and reduce the need for repeated treatments. LLINs have the insecticide infused into the fibres during the manufacturing process, and the insecticide remains in the bed netting for much longer than traditional application of the insecticide after manufacturing the net (WHO, 2007).

There has also been the increasing threat of mosquito resistance to the insecticides in bed netting. Through the addition of synergists, like Piperonyl Butoxide (PBO), the insecticide-resistant mosquitoes' ability to metabolize the net's insecticide is reduced (Metcalf, 1967). This method has led to greater mortality of the mosquito population and has shown greater levels of

effectiveness than insecticide-only LLINs in areas of pyrethroid resistance (N'Guessan et al., 2010; Pennetier et al., 2013).

The focus of this thesis is LLINs, reflecting their use in current malaria-prevention programmes and evidence from the most recent randomized controlled trials of vector-control interventions available (Corbel et al., 2012; Pinder et al., 2015; West et al., 2014). These randomized controlled trials, further discussed in Section 1.5 and the Methodology chapter, are the basis of the analyses herein.

Net-distribution campaigns, supported by the National Malaria Control Programme, have occurred around the world, including in the most malaria-prevalent countries in sub-Saharan Africa (WHO, 2015a). Based on results from the WHO, in 2015 about 55% of those at risk in sub-Saharan Africa were sleeping under an ITN, compared to less than 2% in 2000 (WHO, 2015a).

In some of the affected countries, such as Benin, access to bed netting today is significantly greater than it was 10 years ago, where there was an increase in access to ITNs or LLINs from below 20% in 2006 to above 60% in 2012 (WHO, 2015a). Benin saw a slight rise in deaths due to malaria from about 15 per 100,000 in 2006 to just above 17 per 100,000 in 2014 (WHO, 2015a). The Gambia saw a similar rise in estimated bed-net access from under 40% in 2006 to over 80% in 2014. The number of deaths due to malaria fell slightly from about 11 per 100,000 in 2006 to about 9 per 100,000 in 2014 (WHO, 2015a). Kenya and Tanzania both experienced a rise in estimated bed-net coverage, from about 20% of their population in 2005 to about 30% in Tanzania and above 70% in Kenya in 2014 (WHO, 2015a). Tanzania had a sharp decline in malaria-related deaths, from about 53 per 100,000 in 2005 to about 12 per 100,000 in 2014. Kenya saw a greater reported decline, with close to 160 deaths per 100,000 in 2003 to near zero

reported in 2013 and 2014 (WHO, 2015a). Overall, preventative methods like ITNs and LLINs have greatly increased in use since 2000, and countries all across sub-Saharan Africa have seen a varied but overall decline in malaria-related deaths.

### 1.3.B. EFFICACY OF ITNS AND LLINS

ITNs and LLINs are effective vector-control strategies. In early studies, Alonso et al. (1991) reviewed insecticide-impregnated nets in a Gambian village to understand the intervention's effect on malaria-transmission reduction. This study looked at bed nets treated with permethrin at the start of the malaria transmission season and recorded bed net usage and malaria-related mortality in areas with and without a primary healthcare facility (Alonso et al., 1991). One important finding was in the villages with a healthcare facility where there was a considerable drop in malaria-related deaths among infants and neonates when comparing a time before and after implementation of ITNs (Alonso et al., 1991). Comparing pre-intervention to post-intervention timeframes, the neonates (age < 1 year) had a decrease in malaria-related mortality from 19.5 deaths per 1000 live births to 3.6, while infant (ages 1 to 4) mortality rate fell from 20.6 deaths per 1000 per year to 3.4 deaths per 1000 per year (Alonso et al., 1991).

Many other studies on ITNs also show the intervention as an effective strategy in reducing the impact of malaria on the human population. A systematic review by Lengeler (2004) discussed the results of many studies that examined ITNs and assessed different insecticides such as permethrin, cyfluthrin, alphacypermethrin, deltamethrin and lambdacyhalothrins. Overall, they concluded that proper use of ITNs could lead to about 370,000 lives saved among African children under 5 years of age annually (Lengeler, 2004).

More recently, Moiroux et al. (2014) demonstrated the overall level of protection that can be provided by LLINs from studying two different villages in Benin. Their study examined the

biting behaviour of *An. funestus* mosquitoes and the impact of LLINs, along with level of true personal protection; i.e. the percentage of all mosquito bites that can be reduced through use of an LLIN (Moiroux et al., 2014). The investigators noted greater than 80% protection from mosquito exposure through nightly use of LLINs within both villages (Moiroux et al., 2014).

A field trial evaluating Icon®Life LLINs was conducted in Uttar Pradesh, India, by Mittal, Sood, Kapoor, Razdan and Dash (2012). The evaluation occurred in 2008–2009 and involved three study villages: one with the LLINs, one with nets that were not treated with insecticides, and one village with no nets as a control (Mittal et al., 2012). Mittal et al. (2012) noted that there was a significantly lower parasite index (number of cases per 1000 humans) among the LLIN group (4.34) compared to control (13.46). During post-intervention, there was a significant reduction in the parasite index in the LLIN group (from 7.96 to 4.34), while the untreated net group experienced an increase (from 3.8 to 4.94), as did the control group (from 5.23 to 13.46) (Mittal et al., 2012). This study demonstrated that LLINs have a greater impact in reducing malaria transmission than untreated nets.

Kweka et al. (2011) examined the durability of LLINs over a timeframe of five years and reported that holes can develop due to wear-and-tear and that the number of washes that the bed net has gone through can lower the amount of active ingredient on an LLIN. Therefore, one must be wary of an LLIN's condition with extended use over time in order to receive complete and proper protection.

Bed netting can be used to prevent other vector-borne illnesses as well. The ability to prevent the mosquito from transmitting other pathogens was shown in a randomized-control trial in Haiti by Lenhart and colleagues (2008). The investigators explored the effects of LLIN use on dengue fever transmission and noted a significant reduction in the main vector of transmission

(*Aedes aegypti*) post-intervention compared to a control (Lenhart et al., 2008). The reduction of this flavivirus due to LLINs can also support LLIN use against other flaviviruses transmitted by mosquitoes, including the Zika virus (Petersen, Jamieson, Powers, & Honein, 2016). LLINs can therefore be an effective vector-control method against other vector-borne diseases and provide a benefit to the health of humans in many malaria-affected areas of the world.

### 1.4. INDOOR RESIDUAL SPRAYING

Indoor residual spraying is another key vector-control intervention. The strategy involves utilizing a WHO-approved insecticide at appropriate concentrations (such as pyrethroids and carbamates) and spraying the interior walls of the home with the insecticide to deter or eliminate the mosquito vector after it has taken a blood meal (WHO, 2015a).

Various studies on IRS investigated the impact of this vector-control method. Misra, Webber, Lines, Jaffar and Bradley (1999) assessed use of deltamethrin IRS compared to a control. When considering IRS as one arm of a three-arm trial in India — reviewing IRS, ITNs and a control group — there was a lower incidence of malarial fever within those living in households receiving IRS (43.3 per 1000 person-years) when compared to the control group (61.5 per 1000 person-years) (Misra et al., 1999). Since the time of this study, mosquitoes have developed extensive resistance to this type of insecticide. Many countries that previously used pyrethroid insecticides for IRS have begun shifting to non-pyrethroid insecticides (WHO, 2015a).

An experimental hut study conducted by Agossa et al. (2014) examined the efficacy of various types of insecticides, including one carbamate, two organophosphates and one pyrethroid within Benin. Their study examined the effect of each type of insecticide on the mosquitoes and noted that some types produced different results from others (Agossa et al., 2014). Pyrethroid

resistance within the study area was determined based on the low mosquito mortality rate and from reviewing susceptibility of *An. gambiae* mosquitoes against deltamethrin and permethrin (Agossa et al., 2014). The investigators also noted that there was susceptibility of the mosquitoes to carbamates, with an average mortality rate of 100% on exposure to bendiocarb and susceptibility to organophosphates with mean mortality rates of 98.53% and 100% after exposure to fenitrothion and pirimiphos methyl, respectively (Agossa et al., 2014). This study shows great potential for fairly high mosquito mortality through use of appropriately chosen IRS insecticide.

Other studies have found that IRS has significant potential to reduce malaria transmission and prevalence. Aikpon et al. (2014) examined the use of pirimiphos methyl IRS compared to a control group, examining the human biting rate, sporozoite rate (percent of infected mosquitoes) and entomological inoculation rate (EIR) (infectious bites per person per month within this study). The investigators noted a significantly lower human biting rate in the treated group (0.55 bites per person per night) compared to control (9.56 bites per person per night), a lower sporozoite rate in the treated group (0.03%) compared to control (0.22%) and a significantly lower EIR in the treated group (0.48 infectious bites/person/month) compared to control (63.3 infectious bites/person/month) (Aikpon et al., 2014). This study established that IRS use may be effective in the reduction of malaria transmission.

Pluess, Tanser, Lengeler and Sharp (2010) performed a systematic review of IRS studies, including Misra et al. (1999). The investigators assessed studies in areas with stable malaria (EIR > 1) and unstable malaria (EIR < 1) (Pluess et al., 2010). Within studies assessing IRS compared to no IRS, Pluess et al. (2010) stated that different levels of protective efficacy occurred based on type of surveillance (active compared to passive), where the study happened and the time of year in which it occurred.

IRS must be repeated every few months to assure complete protection among humans. It is also important to consider the rate of the insecticide degrading over time, as it can vary based on level of coverage and type of interior walls. Although studies have demonstrated varied levels of IRS efficacy, it is a viable vector-control intervention (Pluess et al., 2010).

From the effectiveness of reducing malaria transmission as exhibited by ITNs/LLINs and IRS individually, combining the two methods to provide even greater control of the disease is understandable. The following delves further into the trials and studies that consider both interventions together compared to their separate efficacy.

## 1.5. COMBINED EFFICACY OF LLINS AND IRS

Various studies have shown mixed results when comparing combined intervention efficacy to each method's individual efficacy. A randomized controlled trial in Tanzania examined *An. gambiae* mosquitoes and the effect of Olyset bed nets and carbamate (bendiocarb) IRS on vectors and malaria prevalence (West et al., 2014). West et al. (2014) examined three time points throughout the course of the trial and found a statistically significant result only in their second survey, after the long rainy season. The results of this second survey suggested that LLINs and IRS had a greater effect on reducing malaria transmission compared to LLINs alone (West et al., 2014). This also led to an overall result when combining the three surveys showing LLINs coupled with IRS had a statistically significant protective effect compared to LLINs alone (West et al., 2014).

Pinder et al. (2015) performed a randomized controlled trial within The Gambia and tested Olyset bed nets and dichlorodiphenyltrichloroethane (DDT) IRS in areas with *An. gambiae* mosquitoes. By comparing the efficacy of the LLINs to the efficacy of the LLINs with IRS on

the populations, the overall malaria incidence rate ratio was not statistically significant, at 1.08 (95% CI 0.80–1.46) (Pinder et al., 2015).

A non-randomized study by Bekele, Belyhun, Petro, and Deressa (2012) in Ethiopia also assessed the impact of the vector-control methods by comparing three villages: one that used ITNs and IRS, one that used ITNs alone and one village that did not use either. Both the villages with ITNs and IRS as well as ITNs alone were statistically different from the control group in levels of malaria prevalence, showing 1.7% and 5.4% respectively, compared to 10.4% in the control group ($P<0.05$) (Bekele et al., 2012). Using chi-square values with 95% confidence intervals, it appears there were lower prevalence rates of malaria with the ITNs and IRS village compared to that of ITNs alone. However, further studies within Ethiopia would be needed to review and further justify their evidence (Bekele et al., 2012).

A cluster randomized controlled trial by Corbel et al. (2012) in Benin in areas with *An. gambiae* and *An. funestus* mosquitoes had four study arms: targeting LLINs to the most vulnerable population (pregnant women and children), universal coverage of LLINs (entire population receiving the intervention), LLIN with IRS coverage on the vulnerable population, and universal LLIN coverage with carbamate-treated plastic sheeting. The investigators found the difference between the EIRs was not significant when examining the odds ratio comparing the LLIN with IRS group to the LLINs-alone group in the vulnerable populations (0.78 with 95% CI of 0.32–1.91) (Corbel et al., 2012). The clinical incidence densities among groups were also not significant, with a ratio between the LLIN with IRS group and the LLINs-alone group of 1.32 (95% CI 0.90–1.93) (Corbel et al., 2012).

Overall, the many studies examining the impact of the interventions combined and separate show results that are mixed; this can be based on many other factors that cannot be controlled or

are difficult to measure (West et al., 2014; Pinder et al., 2015; Bekele et al., 2012; Corbel et al., 2012; Hamel et al., 2011; Kleinschmidt et al., 2009; Okumu et al., 2013). Level of mosquito resistance to insecticides, climate and weather, differing landscapes and environments for mosquito habitat, and even complete mosquito volumes, can differ among populations. The country itself, those reporting disease status appropriately and other confounders in the methods can potentially develop skewed results and possible observed variations. These factors and many others are important to consider. Some are included in the mathematical model in this thesis.

These interventions directly affect the natural flow of malaria and transmission between the human and mosquito states of being susceptible, infected and recovered. In order to directly reduce the flow between susceptible and infected states, subsequently reducing the infected populations, the interventions must show a large enough reduction of malaria transmission through its vector-control measures. Randomized controlled trials have provided some evidence of the significance of combining interventions compared to individual use (West et al., 2014; Corbel et al., 2012; Pinder et al., 2015). Further evidence can be developed through the unique perspective of mathematical modelling and numerical simulations that estimate the impact of malaria reduction that can occur with these interventions.

## 1.6. MATHEMATICAL MODELLING OF MALARIA

Different mathematical models have been developed to assess the efficacy of interventions on malaria incidence and prevalence. The aspect of mathematical modelling that must be understood is that, to paraphrase Box and Draper (1987), no model can exactly predict the flow of malaria infection in human and mosquito populations, but, through use of appropriate variables and parameters, there can be greater accuracy in understanding the disease. There are different ways to model disease within a population, including generalized linear modelling,

logistic regression analysis and differential equations. We used ordinary and impulsive differential equations.

Ordinary and impulsive differential equations can be used to model malaria transmission and intervention strategies. Ordinary differential equation models calculate the different states of populations, such as humans that are susceptible to an illness or infected with a disease, and the rate of change of these states over time using derivatives (Bolton, 1994). Impulses can be added to the ordinary differential equations at specified points in time to approximate an instantaneous increase or decrease in a population based on, for example, a reaction to an intervention such as IRS (Smith? & Hove-Musekwa, 2008). These ordinary differential equations combined with impulses create a mathematical model of impulsive differential equations to understand the behaviour of a disease like malaria (Bolton, 1994). Smith? and Hove-Musekwa (2008) demonstrated these methods through examination of effective spraying periods for insecticide using their mathematical model based on the level of efficacy of IRS and parameters affecting their set of impulsive differential equations. The investigators' results led to understanding the spraying intervals effects for both scheduled and unscheduled sprayings (Smith? & Hove-Musekwa, 2008). An understanding of LLIN and IRS efficacy can be achieved through modelling ordinary and impulsive differential equation models.

Okumu and Moore (2011) studied and reviewed the use of IRS and ITNs for malaria control and examined the various models of mosquitoes transmitting malaria to humans as well as the many interventions available. They illustrated the disease-transmission process through a diagrammatic model displaying the varying ways in which mosquitoes can factor into disease transmission. This included mosquitoes that do not enter the home due to the repellant nature of

the insecticides, die due to the insecticides in either nets or IRS, or mosquitoes that enter the home but are deterred due to the insecticides and leave quickly (Okumu & Moore, 2011).

Griffin et al. (2010) also developed a modelling approach to understanding vector-borne transmission of malaria within human populations and the effect of IRS, LLINs, ACT, mass drug administration and pre-erythrocytic vaccines. Their study developed a model to examine the disease's flow through the human population. They included humans who are susceptible, develop malaria and treated successfully, those successfully treated and taking prophylaxis, those who fail treatment but recover, those recovering from a failed treatment who are asymptomatic and those who are a reservoir for the illness (Griffin et al., 2010). The authors found a significant decline in malaria prevalence through combined use of these interventions (Griffin et al., 2010).

Yakob, Dunning and Yan (2011) looked at an important element in mathematical modelling of malaria, the basic reproductive ratio ($R_0$), and reviewed the effect that interventions have on the $R_0$ value over time. The basic reproductive ratio is the number of secondary infections spread from a currently infected individual and can provide an understanding of how quickly a disease can become an epidemic and potentially remain with sustainable transmission in a population (if $R_0 > 1$) or how quickly the disease can die out and disappear in a population (if $R_0 < 1$) (Smith?, 2008). The investigators developed their own mathematical model in assessing the impact of IRS, ITNs and their combined effect on malaria (Yakob et al., 2011). The investigators examined varying levels of insecticide efficacies among the interventions and found that ITNs alone or combining ITNs and IRS gave an $R_0$ value falling below 1 over the first 200 days of intervention, while IRS alone showed very little change in reducing the $R_0$ value (Yakob et al., 2011).

Chitnis, Schapira, Smith and Steketee (2010) also created a mathematical model to assess the combined effectiveness of ITNs and IRS. Their study looked at the feeding cycle of the mosquito, reviewing the various states between feeding rates and probability of infection such as the states of host-seeking, host-encountered, fed, resting and laying eggs (Chitnis et al., 2010). These aspects of the mosquito feeding cycle then lead to a greater understanding of the infection rates within humans and mosquitoes and the various rates to consider, such as the EIR and sporozoite rate (Chitnis et al., 2010).

Agusto, Marcus and Okosun (2012) used ordinary differential equations to examine the movement of humans from susceptible to exposed to infectious to recovered/temporarily immune states, and change of states among mosquitoes, from susceptible to exposed to infectious states. The study's model examined different factors in malaria transmission among the two populations and tested the effectiveness of ITNs, IRS and antimalarial treatment on the disease (Agusto et al., 2012). Simulations showed varying levels of optimal control of the disease with use of the interventions over time based on differing combinations of the interventions (Agusto et al., 2012).

Mathematical models can provide assistance in predicting the state of malaria and its persistence among human and mosquito populations. With this in mind, decision-support strategies and tools can be developed not only to reduce the affliction of malaria but also to examine cost-effectiveness. A program that uses stochastic modelling simulations, assessing probabilities of movement between states, is OpenMalaria, which includes different interventions to assess malaria transmission (Swiss Tropical and Public Health Institute, 2016). The software was developed by the Swiss Tropical and Public Health Institute and Liverpool School of Tropical Medicine (Swiss Tropical and Public Health Institute, 2016). One notable study that

used OpenMalaria was by Stuckey et al. (2014), investigating vector-control methods in Kenya (Stuckey et al., 2014). Through various simulations, using populations of 100,000 individuals, the investigators examined LLIN use at 56% and 80% coverage and compared it with and without IRS use at 70% and 90% coverage along with other elements such as screening populations for malaria infection, ACTs, as well as the ability to access care and the overall cost of performing testing (Stuckey et al., 2014). The investigators found that the current strategy in place (lower LLIN and IRS coverage) was the most cost effective in their model, while little change was seen in disability-adjusted life years when tested at other coverage levels (Stuckey et al., 2014). However, as with most tools like this, there are limitations, such as no spatial element in OpenMalaria, so experimental evidence would be further needed to support the results developed from the model (Stuckey et al., 2014). Overall, through use of mathematical models, decision-support tools can be developed that can assist in better understanding of the cost and spread of malaria.

In order to further develop such tools for understanding the spread of the disease and the effect of the interventions, there needs to be consideration of other, more deterministic mathematical models to develop another perspective of the illness, outside of stochastic-modelling programs. The models explored here and developed in this thesis all have potential to be used as evidence to guide the decision-making processes and assist in the development of these tools.

We provided a new perspective on the illness through the use of a simple epidemic mathematical model that takes into account use of LLINs and disease transmission through ordinary differential equations, alongside examination of IRS use at different spraying intervals through the inclusion of impulse equations, developing a set of impulsive differential equations.

## 1.7. RESEARCH STATEMENT

### 1.7.A. PURPOSE AND SUMMARY OF RESEARCH

The focus of this thesis is on the following research question: what is the combined efficacy of using long-lasting insecticidal nets and indoor residual spraying in the control and reduction of malaria transmission in sub-Saharan Africa compared to each intervention's separate efficacy using mathematical modelling? The main objective of this thesis was to determine if a distinct difference exists between combined interventions to individual strategies. This thesis examined the impact of each modelling parameter on the basic reproductive number among the ordinary differential equations and the interventions' impact on the volume of infected humans and mosquitoes through time. The time-series and sensitivity analyses were based on specific trials and published statistics.

The assessment of these interventions was performed through use of a deterministic mathematical model and applied LLIN parameters in an overall set of impulsive differential equations. These differential equations and the assessment of the mathematical model are further described in the Methodology section. Time-series and sensitivity analyses along with their implications are shown in the Results chapter. A summary of these results — along with the strengths, weaknesses, opportunities and threats of this research — are explored in the Discussion and Conclusion chapters. Overall, this thesis examined the efficacy of the interventions on malaria control through use of mathematical modelling, in order to better understand and control this illness.

### 1.7.B. SIGNIFICANCE OF RESEARCH

Recent randomized controlled trials evaluating LLINs and IRS have demonstrated mixed results, which could cause confusion in determining the most appropriate course of action for

malaria transmission-prevention campaigns (West et al., 2014; Corbel et al., 2012; Pinder et al., 2015). Through unique research, applying a mathematical model to examine LLINs and IRS, a pared-down version of events over time can be shown. We compared parameters from studies on LLINs with IRS use (combined vector-control methods) compared to LLINs alone. The evidence developed from this thesis can aid in decision support of strategies and the choice of vector-control interventions. The results developed herein, subject to the assumptions and limitations of the model, can guide appropriate practices to assist in malaria-transmission reduction. Such conclusions can help remove some of the confusion surrounding the current mixed set of results stemming from recent trials and place attention on using these vector-control measures in a more effective manner.

# 2. METHODOLOGY

## 2.1. THE MATHEMATICAL MODEL

### 2.1.A. COMPARTMENTS AND PARAMETERS

For this thesis, we adapted the compartmental model and differential equations of Smith? and Hove-Musekwa (2008), as shown in Figure 2 and Section 2.1.B., respectively. The human population consists of individuals who are not yet infected with malaria and are susceptible (*S*), humans who are infected with malaria (*I*) and humans who have recovered from a malaria infection and become temporarily immune (*R*). This model also includes mosquitoes that are susceptible (*M*) and infected with malaria (*N*). In this model, it is assumed once a mosquito becomes infected, it remains infected for the course of its short life.

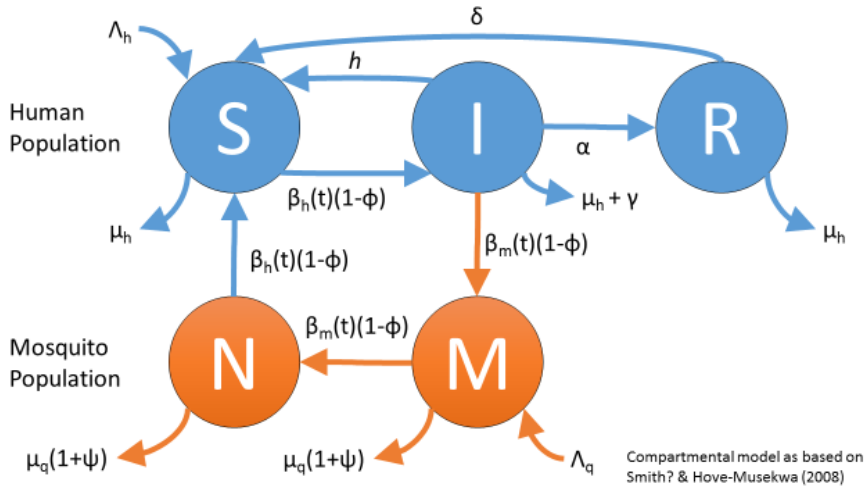



**Figure 2: Compartmental Model of Malaria Transmission among Humans and Mosquitoes**

To understand disease transmission and how it moves through these different states of the populations, there are various parameters in the cycle of infection. These include the infection rate (overall rate of malaria transmission) from humans to mosquitoes ($\beta_m(t)$) and the infection rate from mosquitoes to humans ($\beta_h(t)$). The infection rate for a mosquito is based on susceptible mosquitoes becoming infected through taking of a blood meal from an infected human. The

infection rate for a human is based on susceptible humans becoming infected through bites from infected mosquitoes. There are other rates to consider in the model as well, such as the infected humans becoming susceptible without immunity ($h$), infected humans recovering and becoming temporarily immune ($\alpha$) and the temporarily immune humans becoming susceptible again ($\delta$).

Calculation of the overall rate of infection in humans ($\beta_h(t)$) and mosquitoes ($\beta_m(t)$) requires the average transmission of the infection ($b_0$ and $b_2$, respectively), and seasonal fluctuation in each population is also considered ($b_1$ and $b_3$, respectively). The overall infection rates include seasonality through assuming peak time points in the year and applying a cosine wave as a proxy. Therefore, the following overall infection rates were considered in this mathematical model using a phase difference ($\rho$) to determine the initial peak in the wave of infection after a specific number of days from time 0:

$$\beta_h(t) = b_0(1 + b_1 \cos(2\pi t + \rho))$$

$$\beta_m(t) = b_2(1 + b_3 \cos(2\pi t + \rho)).$$

We also consider the natural birth and death rates for humans ($\Lambda_h$ and $\mu_h$, respectively) and mosquitoes ($\Lambda_q$ and $\mu_q$, respectively). The natural human and mosquito birth rates in this model only affect the susceptible classes ($S$ and $M$, respectively), while the natural human and mosquito mortality rates affect all classes within this model specific to humans and mosquitoes. There is also additional human mortality from malaria ($\gamma$) in the infected human class.

From these factors, the appropriate metrics to consider the LLIN components were added to the model. This included additional daily proportion of mosquito mortality ($\psi$) and the proportion of mosquitoes that can be deterred and reduced ($\phi$). In the case of mosquito netting, the reduced proportion of mosquitoes was based on published feeding-inhibition rates by the type of LLIN. The additional daily proportion of mosquito mortality is specific to the mosquito population whereas the feeding-inhibition rates that led to mosquito reduction ($\phi$) affected the

malaria transmission rates between the humans (specifically the *S* and *I* states) and the mosquitoes (*M* and *N*).

### 2.1.B. DIFFERENTIAL EQUATIONS

These elements all combine into an overall set of impulsive differential equations using standard incidence in the absence of IRS:

$$\frac{dS(t)}{dt} = \Lambda_h - (1-\phi)\beta_h(t)\frac{SN}{M+N} + hI + \delta R - \mu_h S \quad (1)$$

$$\frac{dI(t)}{dt} = (1-\phi)\beta_h(t)\frac{SN}{M+N} - hI - \alpha I - (\mu_h + \gamma)I \quad (2)$$

$$\frac{dR(t)}{dt} = \alpha I - \delta R - \mu_h R \quad (3)$$

$$\frac{dM(t)}{dt} = \Lambda_m - \mu_q(1+\psi)M - (1-\phi)\beta_m(t)\frac{MI}{S+I+R} \quad (where\ t \neq t_k) \quad (4)$$

$$\frac{dN(t)}{dt} = -\mu_q(1+\psi)N + (1-\phi)\beta_m(t)\frac{MI}{S+I+R} \quad (where\ t \neq t_k). \quad (5)$$

To consider the effect of IRS, difference equations were then included in the model, with the addition of the proportion of mosquitoes that survive the IRS insecticide and are assumed resistant (*c*) and the potential proportion of mosquitoes reduced due to IRS (*r*) at the k$^{th}$ moment of spraying. This required the following difference equations to be developed with the limits of $()^+$ and $()^-$ at $t_k$ examining directly before and after each impulse of spraying:

$$M^+ = (1 - r + rc)M^- \quad (where\ t = t_k) \quad (6)$$

$$N^+ = (1 - r + rc)N^- \quad (where\ t = t_k). \quad (7)$$

### 2.1.C. ASSUMPTIONS OF THE MATHEMATICAL MODEL

Several assumptions exist in this mathematical model. An initial assumption was the cosine wave in the human and mosquito infection rates that assumed a similar pattern to actual seasonal fluctuations. This is an assumption that commonly exists in such seasonality calculations (Grassly & Fraser, 2006). Another assumption was that the model did not consider immigration or emigration among the populations. Birth and death rates were the only measures of populations entering and leaving the mathematical model. A third assumption was that the human population did not receive antimalarial treatments or any potential vaccines.

With the exception of seasonality, a fourth assumption of this model was that environmental factors related to mosquito habitat were constant. This included type of land cover, temperature and level of precipitation. These factors can all play an important role in the ability to better predict the habitats of mosquito populations and determine greater risk areas of malaria (Kulkarni, Desrocher, & Kerr, 2010). This model then assumed that the land areas under review remained the same for mosquito habitat suitability and did not account for any environmental differences.

Other than the variability in overall infection rates over time, the parameters were for a deterministic model and the rates applied were static and unchanging. This fifth assumption also involved the IRS difference equations that used the same level of insecticide coverage that is assumed to occur for each specific household and remained at the same concentration for each IRS application. Through use of a sensitivity and uncertainty analysis, we examined the effects of most parameters.

We assumed that there was no wear occurring with the nets over time. This included the assumption that the level of insecticide remained the same through the course of time. This assumption was addressed through assessing parameters for new nets versus nets washed 20 times (used nets), along with the sensitivity and uncertainty analysis that examined varied parameter values.

This model also included the assumption that the bed nets were used by each member of the human population. Although this is only sometimes the case (WHO, 2015a), this model sought to provide accurate results as based on the ideal scenario for LLIN usage. This assumed LLINs were used in the same correct manner, with the same set up for each individual every night.

Our mathematical model considered mosquitoes taking blood meals from humans who were asleep over the course of the night within the household. This did not incorporate other environments in which one can receive the infectious bite, such as outdoors. Although the bed netting can provide greater than 80% of one's overall protection from malaria, a human could still be infected by malaria elsewhere (Moiroux et al., 2014).

This mathematical model also assumed that all mosquitoes are susceptible to the insecticides used in the LLINs. This element is further explored in the Discussion chapter as a weakness, as well as an opportunity for future modelling.

One final assumption was that the impulses assumed a near-instantaneous reduction in mosquitoes at each IRS occurrence. This proxy was close in replicating the overall reductions over time, but the shortest possible intervals of spraying would lead to potentially inaccurate results due to overlap between reductions and recoveries of the mosquito population.

Overall, there are assumptions of this model that must be acknowledged. Some assumptions are addressed in the sensitivity and uncertainty analysis, while some are potential limitations in this model that are further examined in the Discussion chapter.

## 2.2. THE BASIC REPRODUCTIVE RATIO

### 2.2.A. DESCRIPTION OF $R_0$ AND CALCULATION METHODS

The basic reproductive ratio ($R_0$) is an important threshold parameter that measures the number of secondary infections that can occur from a disease based on a single infected individual (Smith?, 2008). Essentially, the basic reproductive ratio can indicate whether the malaria-control method assessed in the ordinary differential equations can reduce the impact of the illness to the population so there is a reduction of the epidemic rather than an expansion.

There are various ways one can determine the $R_0$ value; one method is through developing the Jacobian matrix of the ordinary differential equations (a matrix of partial derivatives of each ordinary differential equation relative to each state of the examined populations to determine a linear approximation of the model), assessing the determinant at the disease-free equilibrium and finding the largest eigenvalue (Smith?, 2008). Other methods include calculating the endemic equilibrium and reviewing the infected population value at endemic equilibrium, examining the survival function or through using the next-generation method to determine the threshold (Smith?, 2008).

For this malaria model, we used the next-generation method. The use of the next-generation method was chosen due to the fact that the human and mosquito populations become infected in separate classes (Smith?, 2008). This meant the $R_0$ value was derived from the largest eigenvalue related to those elements of the model.

**2.2.B. BASIC REPRODUCTIVE RATIO CALCULATION**

The $R_0$ value for this model was determined using the next-generation method. We calculated $F_i(\bar{X})$, the rate at which new infections move into the infected states, along with $V_i(\bar{X}) = V_i^-(\bar{X}) - V_i^+(\bar{X})$, where $V_i^+$ were the human or mosquito cases that moved into an infected state through all methods of infection while $V_i^-$ were the cases that moved out of an infected state through recovery or death (Smith?, 2008). From these elements, the next-generation matrix was then developed to create $FV^{-1}$, which was developed based on the matrices of the partial derivatives of $F_i$ and $V_i^{-1}$ (Smith?, 2008).

The following ordinary differential equations from this model were considered in the $R_0$ development based on their elements related to specific populations becoming infected:

$$\frac{dI}{dt} = (1 - \phi)\beta_h(t)\frac{SN}{M+N} - hI - \alpha I - (\mu_h + \gamma)I$$

$$\frac{dN}{dt} = -\mu_q(1+\psi)N + (1-\phi)\beta_m(t)\frac{MI}{S+I+R}.$$

The development of the basic reproductive number using the next-generation method is shown below, where t = 0.

Development of $F_i(\bar{X})$:

$$\mathcal{F}_1 = (1-\phi)\beta_h\frac{SN}{M+N}, \mathcal{F}_2 = (1-\phi)\beta_m\frac{MI}{S+I+R}$$

$$\mathrm{F} = \begin{bmatrix} \frac{\partial\mathcal{F}_1}{\partial I} & \frac{\partial\mathcal{F}_2}{\partial I} \\ \frac{\partial\mathcal{F}_1}{\partial N} & \frac{\partial\mathcal{F}_2}{\partial N} \end{bmatrix}$$

$$\mathrm{F} = \begin{bmatrix} 0 & \frac{(1-\phi)\beta_m M(S+R)}{(S+I+R)^2} \\ \frac{(1-\phi)\beta_h SM}{(M+N)^2} & 0 \end{bmatrix}$$

Development of $V_i(\bar{X})^{-1}$:

$$V_1 = (h+\alpha+\mu_h+\gamma)I, V_2 = (\mu_q(1+\psi)N)$$

$$\mathrm{V} = \begin{bmatrix} \frac{\partial V_1}{\partial I} & \frac{\partial V_2}{\partial I} \\ \frac{\partial V_1}{\partial N} & \frac{\partial V_2}{\partial N} \end{bmatrix}$$

$$\mathrm{V} = \begin{bmatrix} h+\alpha+\mu_h+\gamma & 0 \\ 0 & \mu_q(1+\psi) \end{bmatrix}$$

$$\mathrm{V}^{-1} = \frac{1}{(h+\alpha+\mu_h+\gamma)(\mu_q(1+\psi))}\begin{bmatrix} \mu_q(1+\psi) & 0 \\ 0 & h+\alpha+\mu_h+\gamma \end{bmatrix}$$

$$\mathrm{V}^{-1} = \begin{bmatrix} \frac{1}{h+\alpha+\mu_h+\gamma} & 0 \\ 0 & \frac{1}{\mu_q(1+\psi)} \end{bmatrix}$$

Development of $FV^{-1}$:

$$\mathrm{FV}^{-1} = \begin{bmatrix} 0 & \frac{(1-\phi)\beta_m M(S+R)}{(S+I+R)^2} \\ \frac{(1-\phi)\beta_h SM}{(M+N)^2} & 0 \end{bmatrix}\begin{bmatrix} \frac{1}{h+\alpha+\mu_h+\gamma} & 0 \\ 0 & \frac{1}{\mu_q(1+\psi)} \end{bmatrix}$$

$$= \begin{bmatrix} 0 & \frac{(1-\phi)\beta_m M(S+R)}{(S+I+R)^2\mu_q(1+\psi)} \\ \frac{(1-\phi)\beta_h SM}{(M+N)^2(h+\alpha+\mu_h+\gamma)} & 0 \end{bmatrix}$$

Determining the eigenvalues:

$$\det(\mathrm{FV}^{-1} - \lambda I) = \begin{bmatrix} -\lambda & \frac{(1-\phi)\beta_m M(S+R)}{(S+I+R)^2\mu_q(1+\psi)} \\ \frac{(1-\phi)\beta_h SM}{(M+N)^2(h+\alpha+\mu_h+\gamma)} & -\lambda \end{bmatrix}$$

$$0 = \lambda^2 - \frac{(1-\phi)^2\beta_h\beta_m SM^2(S+R)}{(h+\alpha+\mu_h+\gamma)(M+N)^2(S+R)^2\mu_q(1+\psi)}$$

$$\lambda = \pm\sqrt{\frac{(1-\phi)^2\beta_h\beta_m SM^2(S+R)}{(h+\alpha+\mu_h+\gamma)(M+N)^2(S+I+R)^2\mu_q(1+\psi)}}.$$

Therefore, based on the greater eigenvalue:

$$R_0 = \sqrt{\frac{(1-\phi)^2\beta_h(0)\beta_m(0)S(0)M(0)^2(S(0)+R(0))}{(h+\alpha+\mu_h+\gamma)(M(0)+N(0))^2(S(0)+I(0)+R(0))^2\mu_q(1+\psi)}}.$$

This $R_0$ value can show either how quickly the disease can die out or if the epidemic increases with time. With respect to results, for each set of parameter values used, the $R_0$ was calculated alongside the time-series and sensitivity analyses. The time-series analyses were useful in determining the effect of IRS, since the impulses could not be incorporated into the basic reproductive ratio calculation.

## 2.3. DATA FOR THE MODEL

In this thesis, three randomized controlled trials formed the basis of the interventions tested in the mathematical model, looking at the parameters related to the country, LLINs tested, IRS methods examined and other necessary parameters used within each study. These trials are described by West et al. (2014) in Tanzania, Corbel et al. (2012) in Benin and Pinder et al. (2015) in The Gambia.

We used a large initial population of 10,000 humans and 10,000 mosquitoes for each scenario in order to develop comparable results. The volume of infected humans was based on malaria prevalence at baseline from each study, while the rest were susceptible humans at t=0. The volume of infected mosquitoes was based on the sporozoite rate from each study, while the rest were deemed susceptible mosquitoes at t=0.

Through data mining of the published literature, factors for the mathematical model were obtained for use within the time-series analyses. The first key measures necessary for the model were the various different rates of movement among states within the populations (both human and mosquito). For the humans moving from a susceptible to an infected state ($\beta_h(t)$), there was the average transmission rate of malaria from mosquitoes to humans ($b_0$) along with seasonality ($b_1$) and consideration of the phase difference ($\rho$) characterized by a cosine wave. Seasonality of malaria among humans was based on values used within a study by Childs and Boots (2010) while the phase-difference values were measured from 0 days to 180 days as West et al. (2014) states two different rainy seasons occur throughout the year within their Tanzania study, leading to an estimated potential phase difference value of about 6 months.

The average infection/transmission rate of malaria from mosquitoes to humans was determined from the EIR, the average number of infected mosquito bites occurring per person per day, among each study reviewed (West et al., 2014; Corbel et al., 2012; Pinder et al., 2015). This value provided an accurate estimate of the potential volume of infections per human per day that could cause illness at baseline (see Table 1).

Birth and death rates for human populations were based on national statistics specific to the country of each trial. We used the 2013 crude birth rates for each country from the United Nations International Children's Emergency Fund (UNICEF), estimated to a population of

10,000 humans based on the time-series simulations conducted for a daily estimated number of births per day (UNICEF, 2015). For the natural death rate, the adjusted life expectancies from each country as reported by the Institute for Health Metrics and Evaluation (2013) were used; for the sensitivity analysis, the same range of life expectancies among the three countries were tested based on The World Bank Group (2016) data looking at maximum and minimum life expectancies between the three countries from 1960 to 2013 as an estimated range of values. Malaria-specific mortality rates within humans can vary and so the rate was based on the under-five mortality rate assessed by Arudo et al. (2003) and a range of possible malaria mortality rates from Chitnis, Hyman and Cushing (2008). The sensitivity analysis utilizes an estimated range from 0 to 150 deaths per 1000 per year to evaluate the influence of changes in the malaria mortality rate on the mathematical model (Chitnis et al., 2008). Malaria prevalence among humans was determined from baseline metrics of each study (West et al., 2014; Corbel et al., 2012; Pinder et al., 2015).

Recovery rates were not directly available from the examined trials, so we considered values from other models in the literature. In 2010, Ermert, Fink, Jones and Morse (2011) estimated a general daily human recovery rate ($day^{-1}$) of 0.005 with values ranging from 0.0015 to 0.0385. A review by Nedelman (1984) discussed a recovery rate based from Earle, Pérez, Rió and Arzola ranging from 0.00024 to 0.005 (as cited in Nedelman, 1984, p. 224). Within Nedelman (1984)'s article, there is also a constant rate on the infected moving to recovered state, which was a value that was a ten times the rate of humans moving from an infected to a susceptible state. This rate is also used in this thesis. With use of Nedelman (1984)'s recovery rates, supported by Ermert et al. (2011)'s recovery rates, we assessed a wide range of values through the sensitivity and uncertainty analysis.

The rate of loss of immunity must also be considered for the recovered/temporarily immune population. A model developed by Childs and Boots (2010) used a time span of two years to develop their rate of immune individuals returning to a susceptible state. This was the same rate used in the simulations developed by Agusto et al. (2012). The range of values for the loss of immunity for the sensitivity analysis was based on Chitnis et al.'s (2008) tested loss of immunity rates.

Mosquito parameters such as the average infection/transmission rate were determined based on calculating the average number of infections of previously uninfected mosquitoes that bite infected humans and assumed similar mosquito densities to number of humans (West et al., 2014; Corbel et al., 2012; Pinder et al., 2015). Mosquito death rates were based on the median life expectancies of gravid and non-gravid mosquitoes and used the average life expectancy between the two medians of 27 days as an estimated life expectancy (Govoetchan et al., 2013). Mosquito birth rates were estimated from the calculations of Smith? and Hove-Musekwa (2008). Seasonality of mosquitoes was based on Massad, Coutinho, Lopez and da Silva (2011), who estimated seasonal volumes of mosquitoes.

Parameters related to LLIN and IRS efficacy such as the average reduction in transmission and additional mosquito mortality rate were derived from the literature. Studies by Pennetier et al. (2013) and N'Guessan et al. (2010) tested LLINs as new (0 wash) and used (20-times washed) to determine the full scope of LLIN efficacy. Matowo et al. (2015) determined the proportion surviving bendiocarb IRS while Pinder et al. (2015) determined the percentage of mosquitoes that survived DDT IRS. For the proportion of mosquitoes reduced due to IRS, the maximum rates from studies by Ossè et al. (2012) and Ratovonjato et al. (2014) were used for bendiocarb and DDT efficacy, respectively. The maximum potential for reduction was used to

test whether IRS added any potential effect when paired with LLINs. The level of IRS efficacy can vary and so these set levels were used in the time-series analyses. A summarized set of parameters tested is available in Table 1 and Appendix A.

| Table 1: Tested Parameter Values[1] | Tanzania Study | | Benin Study | | The Gambia Study | | References |
|---|---|---|---|---|---|---|---|
| **Human Parameters** | Group 1 (LLINs Alone) | Group 2 (LLINs with IRS) | Group 1 (LLINs Alone) | Group 2 (LLINs with IRS) | Group 1 (LLINs Alone) | Group 2 (LLINs with IRS) | |
| Natural Birth Rate ($\Lambda_h$ – births per day) | 1.07 | | 0.997 | | 1.17 | | UNICEF, 2015 |
| Natural Mortality Rate ($\mu_h$ – days$^{-1}$) | 0.000044 | | 0.000043 | | 0.000044 | | Institute for Health Metrics and Evaluation, 2013 |
| Malaria Mortality Rate ($\gamma$ – days$^{-1}$) | 0.00009 | | 0.00009 | | 0.00009 | | Arudo et al., 2003; Chitnis et al., 2008 |
| Average Malaria Transmission/Infection Rate ($b_0$ – infections per day) | 0.0341 | 0.044 | 0.0254 | 0.02 | 0.016 | 0.007 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |
| Seasonality ($b_1$ - percent) | 0.355 | | 0.355 | | 0.355 | | Childs & Boots, 2010 |
| Phase Difference ($\rho$ - days) | 0 to 180 | | 0 to 180 | | 0 to 180 | | West et al., 2014 |
| Infected to Susceptible Recovery Rate (h – days$^{-1}$) | 0.00262 | | 0.00262 | | 0.00262 | | Nedelman, 1984; Ermert et al., 2011 |
| Infected to Recovered/Immune Recovery Rate ($\alpha$ – days$^{-1}$) | 0.0262 | | 0.0262 | | 0.0262 | | Nedelman, 1984; Ermert et al., 2011 |
| Loss of Immunity Rate ($\delta$ – days$^{-1}$) | 0.0014 | | 0.0014 | | 0.0014 | | Childs & Boots, 2010 |
| **Bed Net Parameters** | | | | | | | |
| LLINs – Feeding-Inhibition Rate ($\phi$ - percent) | New=82%, Used=60% | | New=14%, Used=10% | | New=82%, Used=60% | | Pennetier et al., 2013; N'Guessan et al., 2010 |
| LLINs - Mosquito Mortality Rate ($\psi$ – percent) | New=42%, Used=36% | | New=44%, Used=29% | | New=42%, Used=36% | | Pennetier et al., 2013; N'Guessan et al., 2010 |
| **Indoor Residual Spraying Parameters** | | | | | | | |
| IRS - Proportion of Mosquitoes Reduced (r – percent) | 93.2% | | 93.2% | | 94.0% | | Ratovonjato et al., 2014; Ossè et al., 2012 |
| IRS - Proportion of Mosquitoes Resistant to IRS (c – percent) | 25.7% | | 25.7% | | 9.5% | | Pinder et al., 2015; Matowo et al., 2015 |
| **Mosquito Parameters** | | | | | | | |
| Natural Birth Rate ($\Lambda_q$ – births per day) | 10.56 | | 10.56 | | 10.56 | | Smith? & Hove-Musekwa, 2008; Govoetchan et al., 2013 |
| Natural Mortality Rate ($\mu_q$ – days$^{-1}$) | 0.037 | | 0.037 | | 0.037 | | Govoetchan et al., 2013 |
| Average Malaria Transmission/Infection Rate ($b_2$ - infections per day) | 0.316 | 0.181 | 0.223 | 0.226 | 0.696 | 0.617 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |
| Seasonality ($b_3$ - percent) | 0.065 | | 0.065 | | 0.065 | | Massad et al., 2011 |
| Phase Difference ($\rho$ - days) | 0 to 180 | | 0 to 180 | | 0 to 180 | | West et al., 2014 |

1. Further details of parameters, values and each population size tested at time 0 available in Appendix A

## 2.4. MATLAB AND TIME-SERIES ANALYSES (SIMULATIONS)

The time-series, sensitivity and uncertainty analyses, along with the calculations of the basic reproductive ratios, were done using MATLAB version 8.5. MATLAB, developed by the MathWorks, Inc., is a program that can be used for numerically solving differential equations (The MathWorks, Inc., 2015). The ordinary differential equations, along with the infection rate calculations, were defined in an initial m-file that set up the equations and parameters. Additional m-files were developed to apply the parameters for each specific study. Multiple m-files were created, with some specific to just the ordinary differential equations, examining the effects of only LLINs. Other m-files assessed the complete set of impulsive differential equations to explore the effects of LLINs and IRS together on malaria transmission. The m-files used the ode45 function, which is programmed to develop robust solutions from the ordinary and impulsive differential equations. The MATLAB code used in the m-files for the mathematical model's time-series analyses is available in Appendix C.

In each assessed trial, there were at least two groups: the LLINs-alone group and the LLINs with IRS group. The LLINs-alone group included the study arm where only LLINs were applied, while the LLINs with IRS group included the study arm that combined the two interventions. Baseline values, or the closest values available, determined the average transmission/infection rates from each group and define each group's parameter values for each study. This led to two sets of parameters for each assessed study. The LLINs-alone group parameters are referred to as Group 1 in the Results and the LLINs with IRS group parameters are referred to as Group 2.

We performed time-series analyses for each trial's Group 1 and Group 2 parameters to show the population movement between states over time in the following scenarios: no

interventions, LLINs alone, IRS alone and LLINs with IRS. We analyzed the LLINs with IRS group parameters without IRS impulses as well. Separate analyses occurred for new LLINs (0 washed nets) and used LLINs (after 20 washes).

The time-series analyses examined a range of parameter values. Low infection rates were based on the minimum of the range among human and mosquito infection rates. Middle infection rates were the average mid-point of infection rates (as shown in Table 1) while high infection rates were the maximum infection rates. Similar analyses were explored for low, middle and high human recovery rates, including recovery without immunity and recovery with temporary immunity.

**2.5. SENSITIVITY AND UNCERTAINTY ANALYSIS**

A Monte Carlo sensitivity analysis using Latin Hypercube sampling with Partial Rank Correlation Coefficients (PRCCs) was performed. Latin Hypercube Sampling is a method similar to stratified sampling without replacement, where there is a specified set of probability intervals from the metrics and populations reviewed (Marino, Hogue, Ray & Kirschner, 2008). A random method was applied to each parameter in the model, and a value was selected only once without replacement among each strata (Marino et al., 2008).

The sensitivity of these sampled values was then examined in the Latin Hypercube Sampling matrix involving a column for each parameter in the model alongside rows for each sample within the population size (Marino et al., 2008). PRCCs determined the correlation between the input metrics and the basic reproductive number (Marino et al., 2008). A PRCC is similar to that of a Spearman's Rank correlation coefficient; the latter is a rank-transformed correlation coefficient, while a PRCC develops nonlinear but individual relationships between

input variables and the basic reproductive ratio with very little correlations between the input parameters themselves (Marino et al., 2008).

The sensitivity of the variables and the robustness of the data were then analyzed using this method (Marino et al., 2008). In an article by Blower and Dowlatabadi (1994), the steps developed to perform a sensitivity and uncertainty analysis using Latin Hypercube Sampling and PRCCs are stated within an examination of a mathematical model for HIV transmission. These steps include gathering the probability-density functions for each metric in the model along with the appropriate variable values, finding the number of simulations to perform, parsing each parameter into appropriate strata of values, developing the Latin Hypercube sampling matrix, providing the values for the input parameters and the number of simulations and examining the results of the uncertainty and sensitivity analyses (Blower & Dowlatabadi, 1994).

These methods were performed through MATLAB code that calculated each necessary step, assuming uniform distribution for 1000 simulations with each parameter. The Latin Hypercube Sampling and PRCC MATLAB code was adapted from code developed by Smith?, Cloutier, Harrison and Desforges (2012). As the sensitivity analysis was specific to each metric and their effect on $R_0$, this provided evidence for only ordinary differential equation metrics.

## 2.6. EXAMINATION OF INDOOR RESIDUAL SPRAYING

We used impulsive differential equations (1)–(7) to apply an instantaneous reduction to the population of mosquitoes at the kth time interval, based on the state of the mosquito population directly before each impulse occurrence. The use of IRS assumes that, at the moment of spraying the insecticide, an expected proportion ($r$) of mosquitoes is removed from the population while a proportion survive due to resistance to the insecticide ($c$).

The effect of mosquito reduction is assumed to be instant. Every home receives insecticide at the same time to determine the best estimate of the mosquito reduction. In realistic scenarios, spraying cannot happen at every home at the same time and the reduction in the mosquito population does not occur instantly, but the use of impulsive differential equations provides an estimate that approximates reality.

Different timings of IRS were tested. Initial examinations were performed at three-month intervals, similar to that of Smith? and Hove-Musekwa (2008). This was done to determine whether LLINs with IRS were more significant than LLINs alone. The three-month intervals were chosen initially to look at a general application of spraying and to compare similar intervals between the examined studies despite differing levels of IRS efficacy. The timing of IRS sprayings, once tests demonstrated whether there was a great difference or not, were then explored using two-month intervals, monthly intervals and weekly intervals to develop proof-of-concept of the model and to understand IRS's impact on reducing mosquito populations and controlling the transmission of the vector.

## 2.7. METHODOLOGY SUMMARY

Mathematical modelling is an important approach to determine the state of the infected humans and mosquitoes and malaria transmission over time using a model with appropriate compartments and parameters. Through a set of impulsive differential equations, this thesis examines combining LLINs and IRS interventions compared to LLINs and IRS on their own, to see if combined methods are more effective than when used individually. By evaluating the LLINs and IRS methods from published randomized controlled trials, this thesis develops a robust set of time-series analyses using MATLAB. As well, a sensitivity and uncertainty analysis using Latin Hypercube Sampling and development of index values using PRCCs provided a

robust set of results that determined the full scope of the ordinary differential equations. Although the basic reproductive number and sensitivity analyses were able to assess only the effect of LLINs, the effect of IRS was compared within the time-series analyses that were developed. The basic reproductive ratio and sensitivity analysis explored whether LLINs on their own were able to potentially eradicate the disease.

# 3. RESULTS

## 3.1. TIME-SERIES ANALYSES (SIMULATIONS)

### 3.1.A. NO INTERVENTIONS

The different sets of parameters tested are referred to as each specific country's study in this thesis. Among the simulations developed when no interventions were applied, close to all of the calculated basic reproductive numbers were above 1. A low infection rate in humans and mosquitoes, along with greater rates of humans moving out of the infectious state, was likely to develop a lower $R_0$ value, which fell below 1 among certain sets of parameters. Among the three studies' parameters, each assessment of low human and mosquito infection rates with low human recovery rates resulted in an epidemic with sustained malaria transmission over time. Higher human and mosquito infection rates with similar recovery rates resulted in epidemics as well. These epidemics were much quicker and on a larger scale to humans and mosquitoes than with lower infection rates.

The basic reproductive numbers for simulations with 0-day phase difference are shown in Table 2. In some scenarios, the low infection rates result in $R_0$ values below 1 when coupled with middle to higher recovery rates. In all other scenarios, the basic reproductive number rises above 1, indicating an epidemic. For comparison, below are time-series analyses with a middle-level set of recovery rates that displays an eradication of malaria-infected humans in Figures 3a and 4a with low infection rates as well as a small epidemic occurring in Figure 5a. Epidemics with sustained malaria transmission occurred in Figures 3b, 4b and 5b with high infection rates. The following figures were specific to the Group 1 parameters, but similar results were shown among the Group 2 values.

When different phase difference values were tested, slight changes were found. At a phase difference of 0 days, each test performed had the largest $R_0$ in comparison to phase differences of 90 days and 180 days. For example, as seen in Appendix B for the Tanzania study parameters, testing at the lowest infection rate and lowest rate of humans leaving the infected state led to $R_0$ values for phase differences of 0 days, 90 days and 180 days of 3.01, 2.26 and 2.18, respectively. There were also very few differences found among the time-series analyses, all showing similar patterns regardless of the phase differences.

**Table 2: Basic Reproductive Numbers – No Use of LLINs or IRS[1]**

| Infection Rates[2] | Human Recovery Rates[3] | Tanzania Study Parameters | | Benin Study Parameters | | The Gambia Study Parameters | |
|---|---|---|---|---|---|---|---|
| | | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 |
| Low | Low | 3.01 | 1.81 | 3.34 | 2.38 | 6.58 | 3.56 |
| | Middle | 0.93 | 0.56 | 1.03 | 0.74 | 2.04 | 1.10 |
| | High | 0.67 | 0.41 | 0.75 | 0.53 | 1.48 | 0.80 |
| Middle | Low | 10.91 | 9.50 | 6.48 | 4.83 | 10.61 | 6.49 |
| | Middle | 3.38 | 2.94 | 2.00 | 1.50 | 3.29 | 2.01 |
| | High | 2.45 | 2.13 | 1.45 | 1.08 | 2.38 | 1.46 |
| High | Low | 38.06 | 46.29 | 11.71 | 8.86 | 14.65 | 9.42 |
| | Middle | 11.78 | 14.33 | 3.63 | 2.74 | 4.53 | 2.91 |
| | High | 8.54 | 10.38 | 2.63 | 1.99 | 3.29 | 2.11 |

1. Table based a 0 day phase difference. For 90 and 180 days phase difference results, see Appendix B.

2. Low, middle and high malaria infection rates were based on the minimum tested range value, the value in Table 1 and the maximum tested range value, respectively, for the average malaria infection/transmission rates for humans ($b_0$) and mosquitoes ($b_2$) from Table 1 and Appendix A for each specific study's Group 1 and Group 2 parameter values. Further details are available in Appendix A.

3. Low, middle and high human recovery rates were based on the minimum tested range value, the value in Table 1 and the maximum tested range value, respectively, for the infected to susceptible recovery rate (h) and the infected to recovered/immune recovery rate ($\alpha$) from Table 1 and Appendix A for each specific study's Group 1 and Group 2 parameter values. Further details are available in Appendix A.

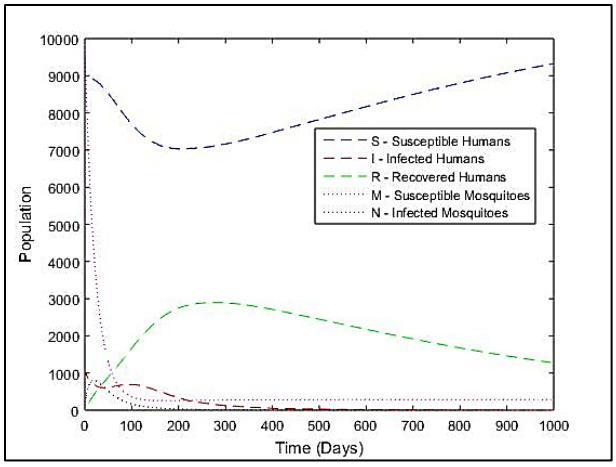



**Figure 3a**: Tanzania Study, No Interventions, Group 1, Low Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.93$

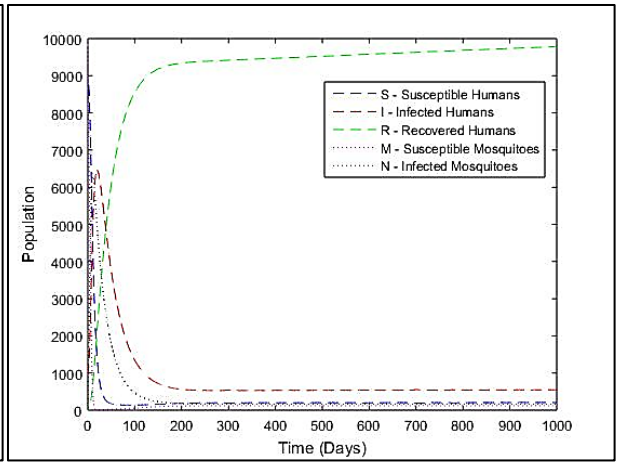



**Figure 3b**: Tanzania Study, No Interventions, Group 1, High Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 11.78$

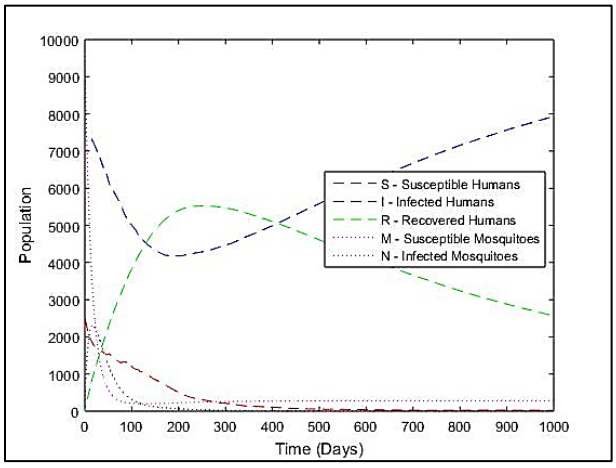



**Figure 4a**: Benin Study, No Interventions, Group 1, Low Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.03$

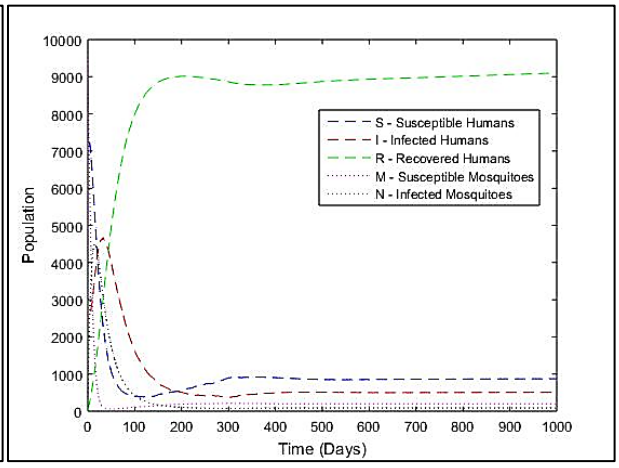



**Figure 4b**: Benin Study, No Interventions, Group 1, High Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 3.63$

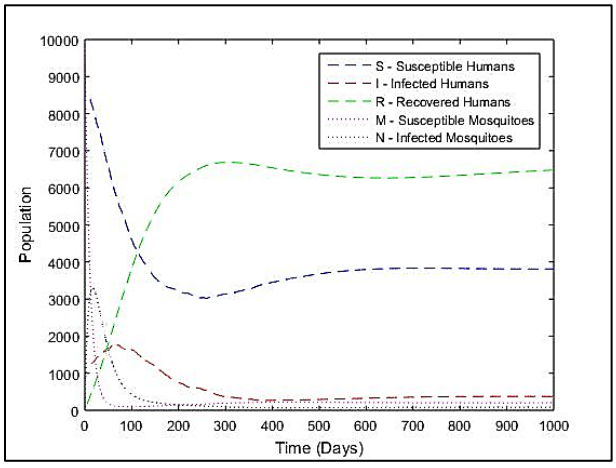



**Figure 5a**: The Gambia Study, No Interventions, Group 1, Low Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 2.04$

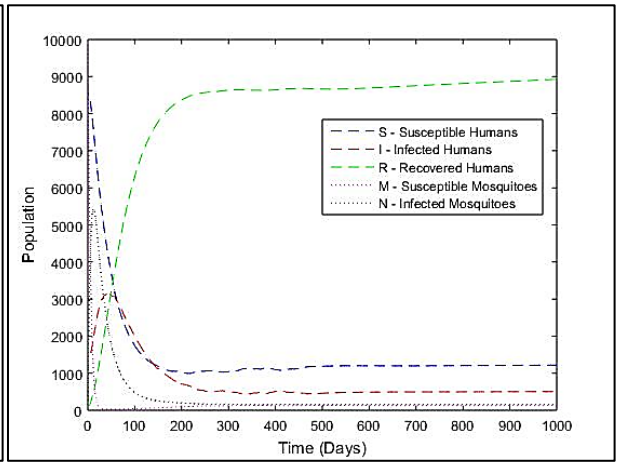



**Figure 5b**: The Gambia Study, No Interventions, Group 1, High Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 4.53$

The results indicate that malaria would easily spread in the populations without involvement of interventions, showing a need to use an intervention to reduce potential spread. The ability of LLINs to protect humans while they sleep, along with reduction of mosquitoes through use of IRS, were important to examine as malaria outbreaks and subsequent sustained transmission may occur without any interventions. The disease could possibly be eradicated from the population without assistance as long as the transmission rate is low; otherwise an epidemic with sustained transmission would likely occur.

### 3.1.B. EFFICACY OF ONLY IRS

In order to maintain comparative results, three-month IRS intervals were applied across all three sets of study parameters despite different possible optimal intervals due to differing levels of IRS efficacy. Assessment of the effect of IRS use on its own demonstrated a difference when testing each study's Group 2 with and without IRS use, comparing only IRS use to no interventions. Once again, different phase difference values had very little changes to the respective time-series analyses and only slightly lower basic reproductive ratios with each increase in phase difference. The basic reproductive ratios assessed with the IRS parameters were similar to use of no interventions, which is expected because the impulses do not apply to the $R_0$ calculations.

The time-series analyses showed that addition of IRS resulted in reduced malaria transmission and lowered infected population levels; however, the infected human and mosquito populations remained in most scenarios. At middle to high levels of human recovery when examined against low infection rates, the infected populations leave the system well before 500 days.

Among each of the three tested sets of parameters, the recovery rates of humans greatly influences the infected population. The results showed that higher recovery rates resulted in fewer infected humans and mosquitoes. As expected, epidemics were much greater with higher infection rates when compared to lower infection rates. An epidemic and subsequent sustained transmission occur in each scenario, but the volume of infected people and mosquitoes in most scenarios was lower with each increased set of human recovery rates. A drop in the population of infected individuals occurred in some cases when the mosquitoes were reduced at three-month intervals.

In comparison to no application of interventions with each set of study parameters, there is very little improvement in the reduction of malaria transmission among humans when IRS is applied initially, while small improvements happened with time. For the Tanzania study, as illustrated in Figure 6, the difference between the two time-series analyses was with the later time periods, where at day 500 the number of infected humans in the no-intervention analysis and the IRS-alone analysis was 437 and 327, respectively. In Figure 7, the number of infected mosquitoes in the analyses at day 500 was 46 and 24, respectively.

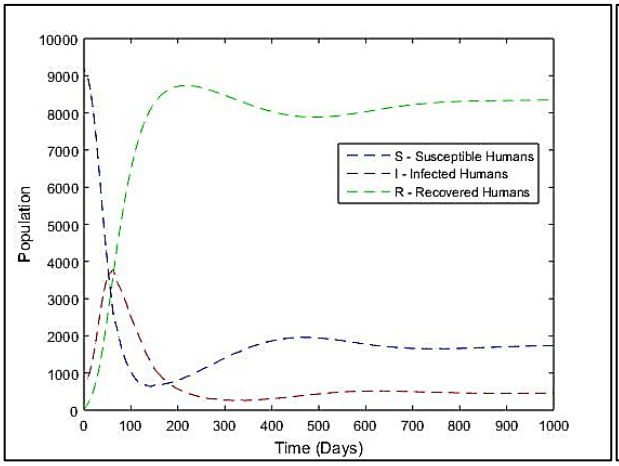



**Figure 6a**: Tanzania Study, Group 2, Human Population, No Interventions, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 2.94$

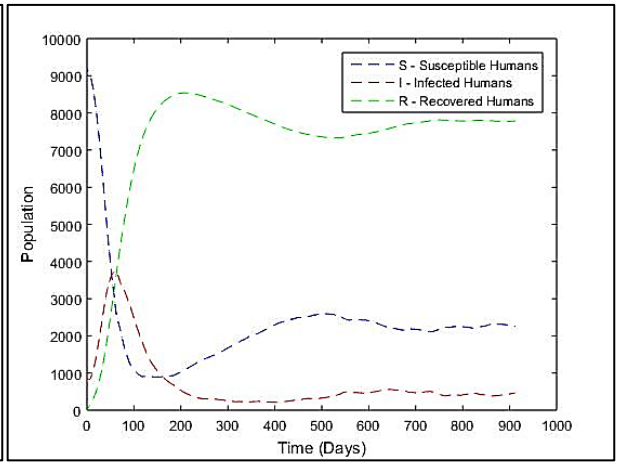



**Figure 6b**: Tanzania Study, Group 2, Human Populations, 3 month IRS Intervals, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 2.94$

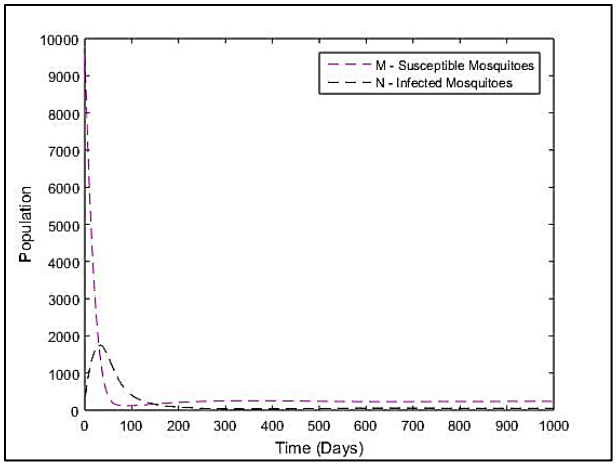



**Figure 7a**: Tanzania Study, Group 2, Mosquito Population, No Interventions, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 2.94$

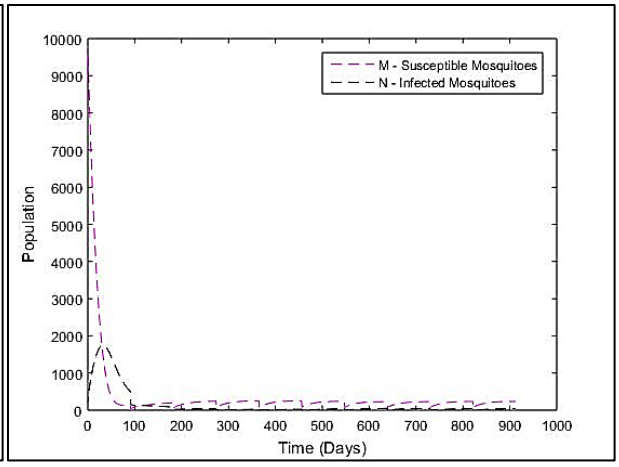



**Figure 7b**: Tanzania Study, Group 2, Mosquito Populations, 3 month IRS Intervals, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 2.94$

The effect of bendiocarb IRS on the human and mosquito populations was also noted through analyses with the Benin study parameters. From the observed results, showing no intervention use and use of only IRS, the differences also occurred over the long term with a slightly lower volume of infected individuals over time. At day 500, comparing no interventions to IRS alone, the number of infected humans was 222 and 121, respectively, and number of infected mosquitoes was 32 and 12, respectively. However, a removal of the malaria-infected populations did not occur in most of the performed simulations. The results are shown in Figures 8 and 9.

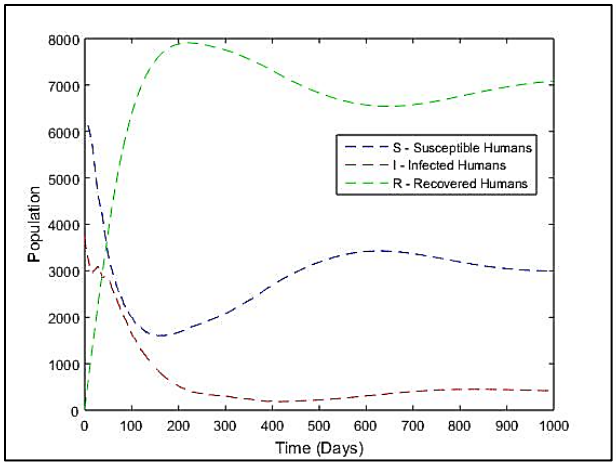



**Figure 8a**: Benin Study, Group 2, Human Population, No Interventions, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.50$

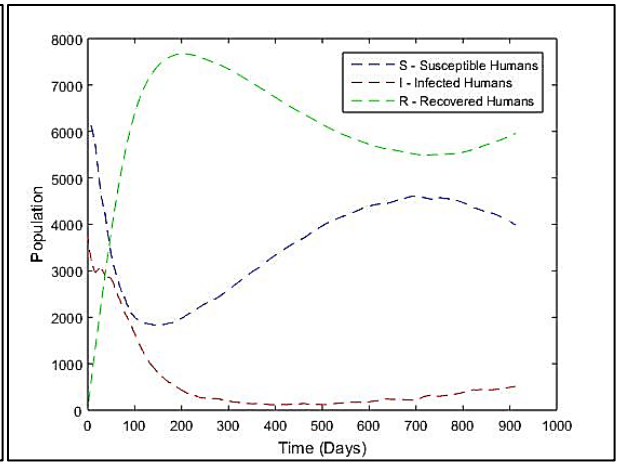



**Figure 8b**: Benin Study, Group 2, Human Populations, 3 month IRS Intervals, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.50$

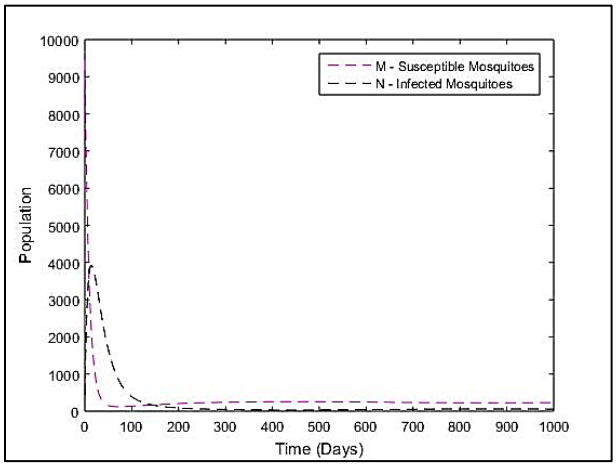



**Figure 9a**: Benin Study, Group 2, Mosquito Population, No Interventions, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.50$

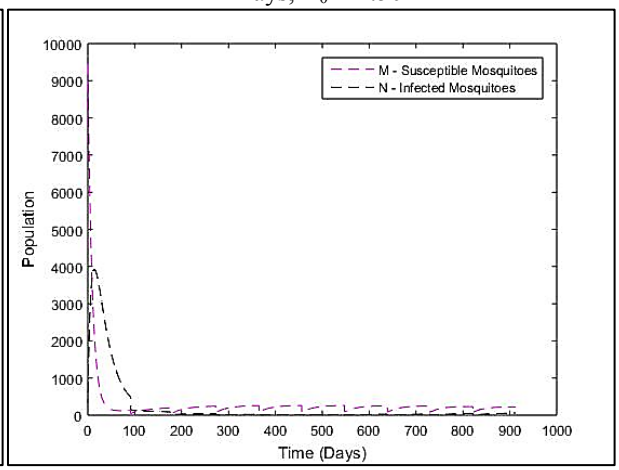



**Figure 9b**: Benin Study, Group 2, Mosquito Populations, 3 month IRS Intervals, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.50$

Time-series analyses with The Gambia study parameters had less pronounced differences between the two groups. The effect of IRS on the infected populations can be seen in Figures 10 and 11, noting the change among the infected human and mosquito populations with time. The slight differences between IRS use and no interventions were seen with later time periods, where at day 500 the number of infected humans in the no-intervention analysis compared to IRS-alone analysis was 291 and 198, respectively, while the number of infected mosquitoes was 91 and 45, respectively.

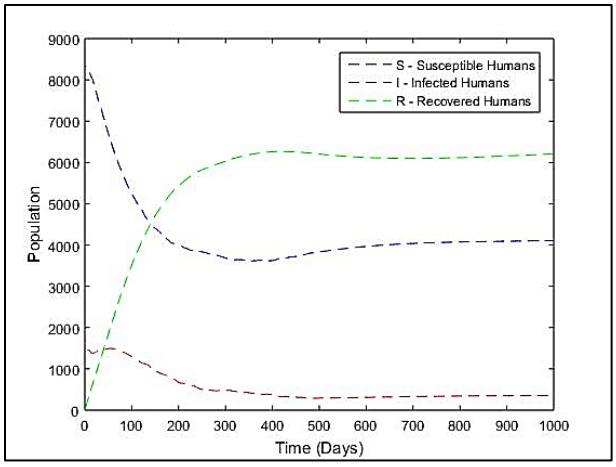



**Figure 10a**: The Gambia Study, Group 2, Human Population, No Interventions, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 2.01$

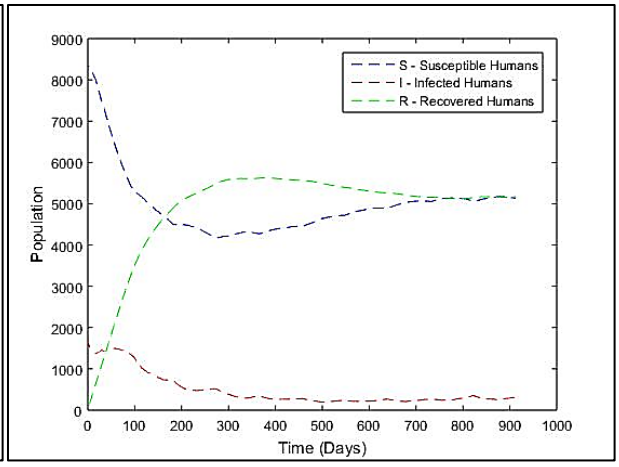



**Figure 10b**: The Gambia Study, Group 2, Human Populations, 3 month IRS Intervals, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 2.01$

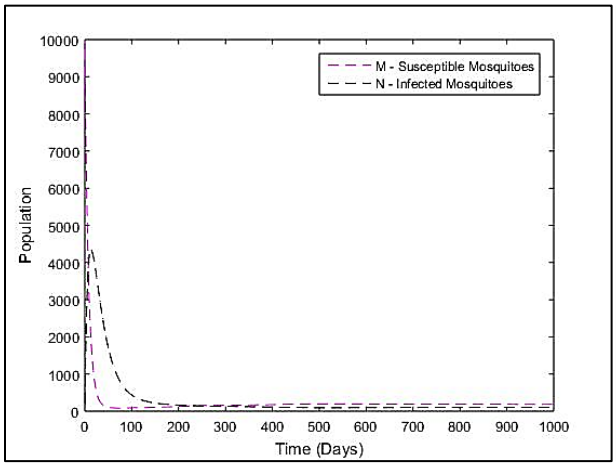



**Figure 11a**: The Gambia Study, Group 2, Mosquito Population, No Interventions, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 2.01$

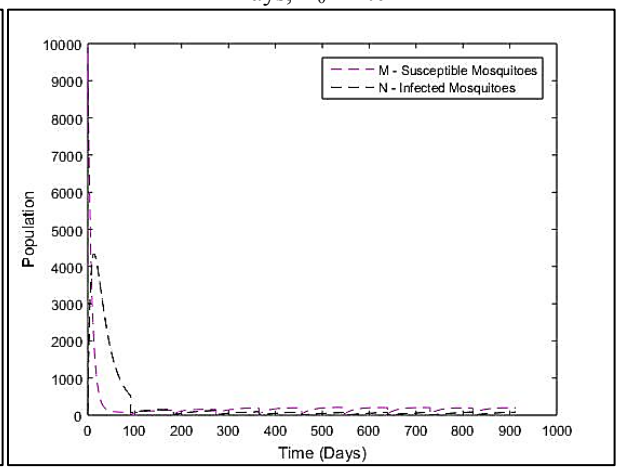



**Figure 11b**: The Gambia Study, Group 2, Mosquito Populations, 3 month IRS Intervals, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 2.01$

Each set of study parameters had different time-series analyses tested at different levels of human recovery and malaria infection rates. The important elements to note from each set of results when IRS was used alone was the IRS spraying intervals of three months exhibited only small changes to the infected human populations.

The implications of the results where IRS is used are that IRS has the possibility of reducing malaria but still illustrates only small changes to the overall reduction of transmission. The three-month intervals of spraying show that a reduction in mosquito populations can occur if

the insecticide is used and the efficacy is high, but an epidemic among humans would likely happen in most cases before the interval of spraying occurred. If the efficacy is low, the results would likely show an even milder reduction in the spread of malaria. These implications are important to consider as the spread of disease can vary and the efficacy of IRS can also change. From using parameters related to maximum potential to reduce malaria spread, this demonstrated IRS as an important intervention on its own when examined at its greatest possible efficacy. However, from the results showing an epidemic occurring in most simulations, as well as the potential of increasing mosquito resistance to insecticides overall, the potential effectiveness of IRS could be threatened (WHO, 2015a; Matowo et al., 2015).

### 3.1.C. EFFICACY OF ONLY LLINS

#### 3.1.C.1. EFFICACY OF ONLY LLINS – NEW LLINS

The use of new LLINs compared to no use of interventions shows a great drop in the infected populations. In most scenarios, where the basic reproductive number is above 1 without interventions, applying bed-net parameters led to a distinct drop in the $R_0$ values among each of the three studies' sets of parameters. Some scenarios with bed-net parameters led to $R_0$ values below 1. Overall, there is a change from sustained malaria transmission in no-intervention scenarios to eradication or near eradication of infected populations with the addition of bed-net parameters. The sets of parameters where net efficacy was high had a greater decline in the $R_0$ values (as seen in Table 3) and much less infected populations compared to the parameter sets that included lower net efficacy values. The time-series analyses in Figures 12, 13 and 14 show either the infected populations dissipating with time or dropping to a level that is much lower than the analyses without interventions.

When middle-level infection rates were examined with the lowest rates of human recovery, assessing sets of parameters that used Olyset net metrics (i.e. The Gambia and Tanzania studies), majority of basic reproductive numbers were above 1. A somewhat lesser decline in infectious populations was seen in examinations of the Benin study parameters (Permanet 2.0 metrics). At higher rates of humans leaving the infectious state when paired with middle-level infection rates, $R_0$ drops below 1. For all three studies tested at the highest infection rate, the basic reproductive number was above 1 for most of the time-series analyses, signifying an epidemic that does not greatly dissipate. The exception to this was with the highest rates of humans leaving the infectious state for The Gambia study parameters and the 90 and 180 days phase-difference values for the Tanzania study. The basic reproductive values for 90 and 180 days phase differences can be seen in Appendix B.

**Table 3: Basic Reproductive Numbers – Use of New LLINs[1]**

| Infection Rates[2] | Human Recovery Rates[3] | Tanzania Study Parameters | | Benin Study Parameters | | The Gambia Study Parameters | |
|---|---|---|---|---|---|---|---|
| | | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 |
| Low | Low | 0.45 | 0.27 | 2.39 | 1.71 | 0.99 | 0.54 |
| | Middle | 0.14 | 0.08 | 0.74 | 0.53 | 0.31 | 0.17 |
| | High | 0.10 | 0.06 | 0.54 | 0.38 | 0.22 | 0.12 |
| Middle | Low | 1.65 | 1.43 | 4.64 | 3.46 | 1.60 | 0.98 |
| | Middle | 0.51 | 0.44 | 1.44 | 1.07 | 0.50 | 0.30 |
| | High | 0.37 | 0.32 | 1.04 | 0.78 | 0.36 | 0.22 |
| High | Low | 5.75 | 6.99 | 8.40 | 6.35 | 2.21 | 1.42 |
| | Middle | 1.78 | 2.16 | 2.60 | 1.97 | 0.68 | 0.44 |
| | High | 1.29 | 1.57 | 1.88 | 1.42 | 0.50 | 0.32 |

1. Table based a 0 day phase difference. For 90 and 180 days phase difference results, see Appendix B.

2. Low, middle and high malaria infection rates were based on the minimum tested range value, the value in Table 1 and the maximum tested range value, respectively, for the average malaria infection/transmission rates for humans ($b_0$) and mosquitoes ($b_2$) from Table 1 and Appendix A for each specific study's Group 1 and Group 2 parameter values. Further details are available in Appendix A.

3. Low, middle and high human recovery rates were based on the minimum tested range value, the value in Table 1 and the maximum tested range value, respectively, for the infected to susceptible recovery rate (h) and the infected to recovered/immune recovery rate ($\alpha$) from Table 1 and Appendix A for each specific study's Group 1 and Group 2 parameter values. Further details are available in Appendix A.

Figure 12 displays the large change that occurs between using no interventions to using new LLINs with the Tanzania set of parameters. In the scenario where no interventions occurred, the number of infected humans and mosquitoes on day 500 was 469 and 207, respectively. Once new LLINs were added, there were 0 infected mosquitoes and humans on day 500 and later.

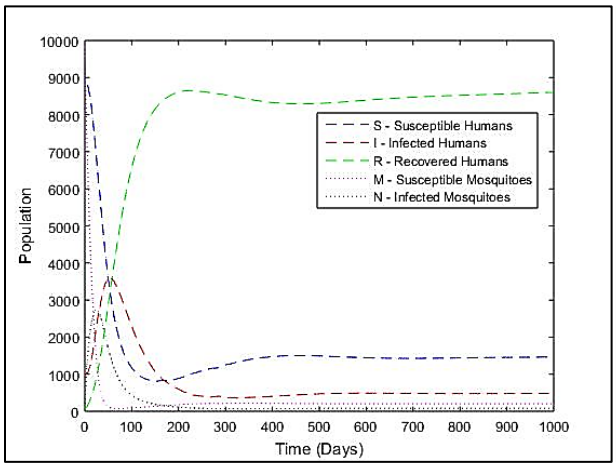



**Figure 12a**: Tanzania Study, Group 1, No Interventions, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 3.38$

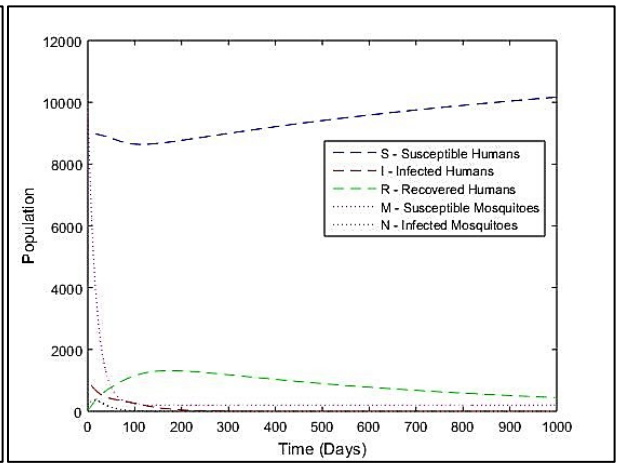



**Figure 12b**: Tanzania Study, Group 1, New LLINs, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.51$

For the Benin study parameters, upon comparison with no use of interventions, an improvement is also seen, although it is much smaller than the results from the sets of parameters that examined Olyset LLINs. The number of infected humans and mosquitoes on day 500 without interventions were 293 and 244, respectively, while with new LLINs those volumes fell to 90 and 6, respectively.

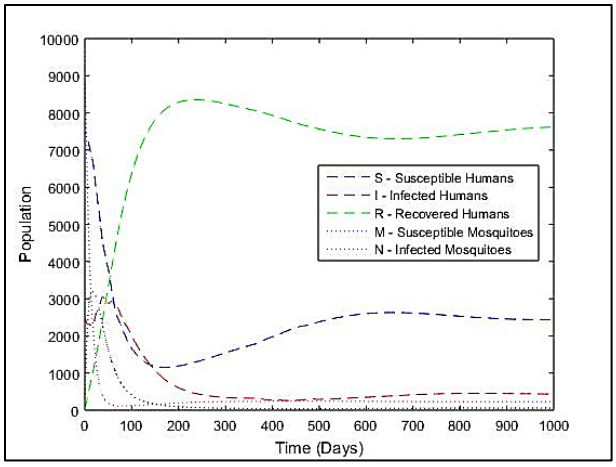



**Figure 13a**: Benin Study, Group 1, No Interventions, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 2.00$

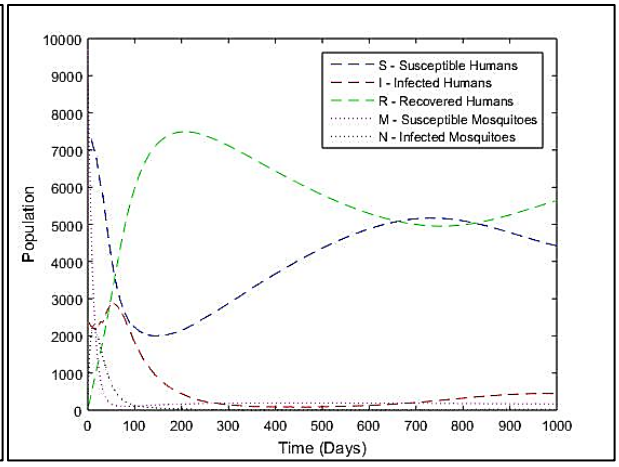



**Figure 13b**: Benin Study, Group 1, New LLINs, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.44$

For The Gambia study, as mentioned above, the Olyset bed net study parameters had greater improvement than no use of interventions. At day 500 in Figure 14, comparing no interventions to new LLINs, the number of infected humans fell from 448 to 0 and the infected mosquito population decreased from 129 to 0 as well.

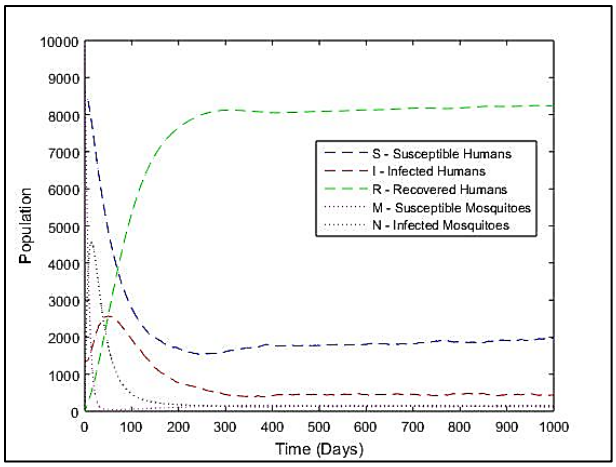



**Figure 14a**: The Gambia Study, Group 1, No Interventions, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 3.29$

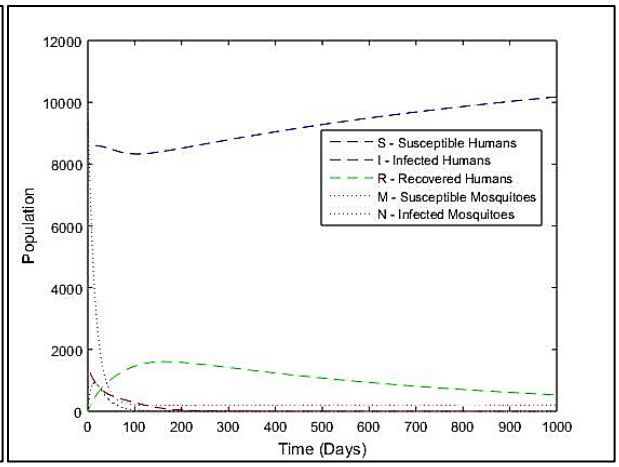



**Figure 14b**: The Gambia Study, Group 1, New LLINs alone, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.50$

The time-series analyses with LLINs differed in the Benin study compared to the Tanzania and The Gambia study parameters due to different types of LLINs used. The results developed from the Tanzania and The Gambia study parameters both individually showed the ability for the basic reproductive number to be greatly reduced.

The Benin study used Permanet 2.0 LLINs and analysis of feeding-inhibition and mosquito mortality rates were based on N'Guessan et al. (2010). These efficacy rates were much lower than the Olyset LLIN metrics from Pennetier et al. (2013). The Benin study parameters that were examined led to only certain opportunities where the basic reproductive number could be brought below 1 and also develop eradication of the disease.

Mosquitoes resistant to insecticides in LLINs is a concern in the endemic areas of the world. Examining time-series analyses using N'Guessan et al. (2010) parameters in the model showed the effects of lower mosquito mortality and feeding-inhibition rates of LLINs. A possible increase in mosquito resistance could make LLINs more ineffective in protecting humans and reducing overall transmission. This is addressed further in the strengths and weaknesses section of the Discussions chapter, but it is also an implication that can affect the human population.

New LLINs could reduce malaria transmission as long as the LLIN has a high enough level of feeding inhibition. Using the values tested in this thesis, this would mean that the Olyset bed nets have a greater potential for reduction of malaria transmission compared to Permanet 2.0 bed nets. This is solely based on the parameters tested for each type of LLIN and does not mean that one specific type of LLIN will work better than another in practice every time, depending on vector population characteristics in a given location. The level of malaria transmission reduction requires the consideration of the mosquito-resistance levels existing in the population and therefore depends on the actual protection the LLIN can provide against malaria transmission.

These results are specific to LLINs without inclusion of PBO or other synergists. These additives to LLINs have shown greater efficacy of LLINs in reducing malaria transmission in areas with mosquito resistance to pyrethroids (Pennetier et al., 2013; N'Guessan et al., 2010).

Future assessment of these types of interventions in time-series and sensitivity analyses are recommended.

### 3.1.C.2. EFFICACY OF ONLY LLINS – USED LLINS

The simulations with 20-times washed LLINs also produce similar outcomes to that of the new LLINs but with a lesser effect. Table 4 shows basic reproductive ratios for the 20-times washed LLINs and can be compared to situations that would display an $R_0$ below 1 when new LLINs are used in Table 3 but an $R_0$ above 1 with 20-times washed LLINs. For example, from the results for the Tanzania study with middle-level infection and recovery rates, $R_0$ was 0.51 using new LLINs but 1.16 using LLINs after 20 washes.

**Table 4: Basic Reproductive Numbers – Use of LLINs after 20 Washes**

| Infection Rates | Human Recovery Rates | Tanzania Study Parameters | | Benin Study Parameters | | The Gambia Study Parameters | |
|---|---|---|---|---|---|---|---|
| | | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 |
| Low | Low | 1.03 | 0.62 | 2.65 | 1.89 | 2.26 | 1.22 |
| | Middle | 0.32 | 0.19 | 0.82 | 0.58 | 0.70 | 0.38 |
| | High | 0.23 | 0.14 | 0.59 | 0.42 | 0.51 | 0.27 |
| Middle | Low | 3.74 | 3.26 | 5.13 | 3.83 | 3.64 | 2.23 |
| | Middle | 1.16 | 1.01 | 1.59 | 1.19 | 1.13 | 0.69 |
| | High | 0.84 | 0.73 | 1.15 | 0.86 | 0.82 | 0.50 |
| High | Low | 13.05 | 15.88 | 9.28 | 7.02 | 5.02 | 3.23 |
| | Middle | 4.04 | 4.91 | 2.87 | 2.17 | 1.56 | 1.00 |
| | High | 2.93 | 3.56 | 2.08 | 1.57 | 1.13 | 0.72 |

1. Table based a 0 day phase difference. For 90 and 180 days phase difference results, see Appendix B.

2. Low, middle and high malaria infection rates were based on the minimum tested range value, the value in Table 1 and the maximum tested range value, respectively, for the average malaria infection/transmission rates for humans ($b_0$) and mosquitoes ($b_2$) from Table 1 and Appendix A for each specific study's Group 1 and Group 2 parameter values. Further details are available in Appendix A.

3. Low, middle and high human recovery rates were based on the minimum tested range value, the value in Table 1 and the maximum tested range value, respectively, for the infected to susceptible recovery rate (h) and the infected to recovered/immune recovery rate (α) from Table 1 and Appendix A for each specific study's Group 1 and Group 2 parameter values. Further details are available in Appendix A.

Such behaviour is also seen when comparing the time-series analyses of the 20-times washed LLINs to the new LLINs. Figure 15 shows the difference that occurs with greater usage of LLINs using Tanzania study parameters. The difference between LLINs washed 20 times to

new LLINs is similar among studies tested with the exception of scenarios such as Figure 15, where the epidemic does not occur in Figure 15a but does in Figure 15b. In Figure 15a, at day 500, the number of infected humans and mosquitoes were both 0, while in Figure 15b, there were 68 infected humans and 4 infected mosquitoes at that point in time. For time-series analyses related to Benin and The Gambia parameters, see Appendix D.

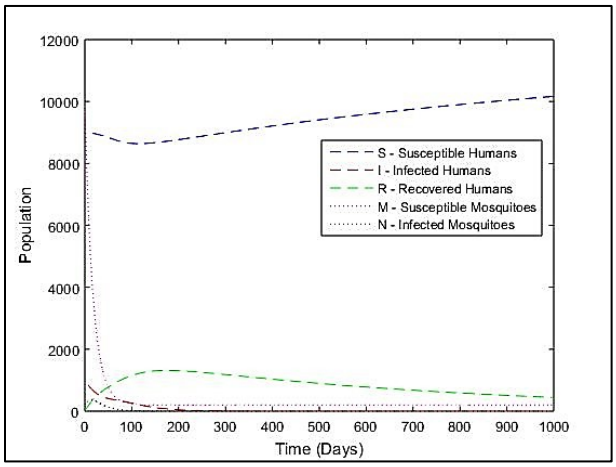



**Figure 15a**: Tanzania Study, Group 1, New LLINs, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.51$

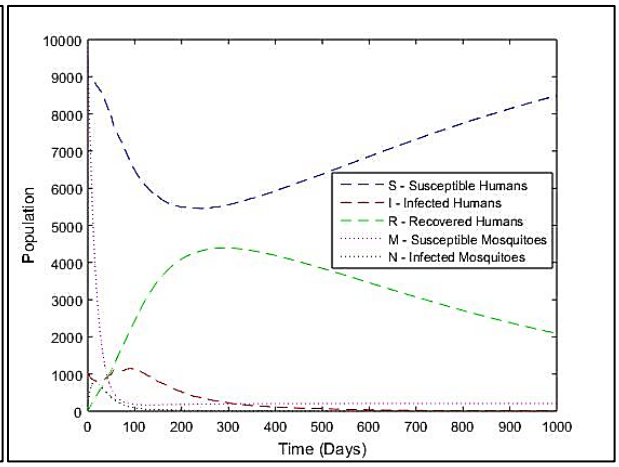



**Figure 15b**: Tanzania Study, Group 1, LLINs after 20 washes, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.16$

Through testing the various levels of efficacy against no use of interventions, greater levels of reduction from feeding inhibition and mosquito mortality in LLINs show a higher decrease in malaria transmission among humans and mosquitoes. These effects on the $R_0$ value were further assessed using sensitivity and uncertainty analysis.

In reality, LLINs will not always be new. LLINs washed 20 times were able to reduce malaria transmission but to a lower extent. In comparison to used LLINs assessed in the Benin study, the Olyset parameters developed a much greater impact on malaria transmission with a much larger reduction than the Permanet 2.0 parameters.

The results with LLINs used after 20 washes provide greater perspective on the LLINs' ability to reduce malaria transmission. The more the LLINs are used, the less effective they become. Whether it is Olyset or Permanet 2.0 LLINs, it has been shown that the feeding-

inhibition rate and mosquito mortality proportion can decline with continued usage (Pennetier et al., 2013; N'Guessan et al., 2010). Lower net efficacy showed that well-used LLINs can still reduce the spread of malaria. The reduction in malaria transmission may not be as great as using new nets, but a reduction in transmission can still occur and, in some cases, lead to an eradication of the disease from the populations.

### 3.1.D. EFFICACY OF LLINS WITH IRS

#### 3.1.D.1. EFFICACY OF LLINS WITH IRS – NEW LLINS

The combined effect of LLINs with IRS is potentially more effective in reducing malaria transmission with time and has been assessed in various studies showing mixed results (West et al., 2014; Corbel et al., 2012; Pinder et al., 2015). At low infection rates with parameters related to LLINs after 0 washes, the infected populations are reduced to 0 at any of the tested human recovery rates. The higher recovery rates led to the infected populations dissipating much sooner.

At greater infection rates, looking at the lowest rate of humans leaving the infectious state, a sustained level of malaria transmission among populations occurs even with IRS involvement. Higher rates of human recovery led to the infected human population decreasing to zero when tested at the middle-level infection rate in most scenarios and nearly dissipating at the highest infection rate. This occurred among the three sets of study parameters. At the highest infection rate with LLINs and IRS involvement, the time-series analyses show the different states of the population with time as well and while a malaria epidemic and sustained transmission happens, it was more muted with each increased set of human recovery rates.

There were very small differences found between the results of LLINs alone compared to LLINs with IRS. The observable differences were the infected and susceptible mosquitoes' respective population reductions at the time intervals of spraying as well as slight changes in the

number of infected humans at later time periods with fewer infected humans in the LLINs with IRS analysis compared to LLINs alone over time. The difference among results with Olyset net parameters (i.e. The Gambia and Tanzania studies) exists but does not appear pronounced between intervention groups regardless of the examined IRS efficacy. The difference between LLINs with IRS and LLINs alone results with the less efficacious Permanet 2.0 LLIN parameter values (i.e. the Benin study) appeared slightly greater with less infected humans in the LLINs with IRS group, but it only appeared among later time periods in the time-series analyses.

Below in Figure 16a based on the Tanzania study parameters with LLINs alone, there were 0 infected humans and mosquitoes on day 500. The same result happened at day 500 in Figure 16b showing LLINs with IRS. For comparative figures of Group 1 parameters to Group 2 parameters, see Appendix E.

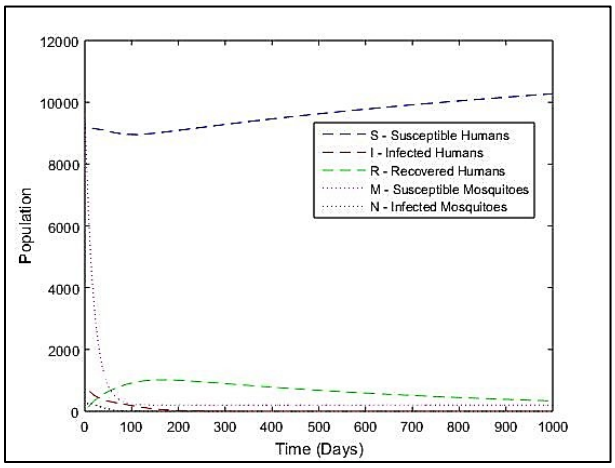



**Figure 16a**: Tanzania Study, Group 2, New LLINs only, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.44$

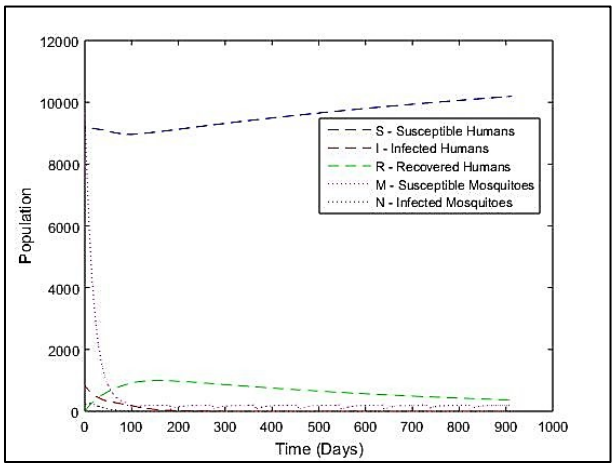



**Figure 16b**: Tanzania Study, Group 2, New LLINs with 3 Month IRS Intervals, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.44$

In Figure 17a, based on the Benin study parameters with LLINs alone, the number of infected humans and mosquitoes were 75 and 5 at day 500, respectively. In Figure 17b, showing LLINs with IRS, this volume was 28 infected humans and 2 infected mosquitoes. For comparative time-series analyses between Group 1 and Group 2 parameters as well, see Appendix E.

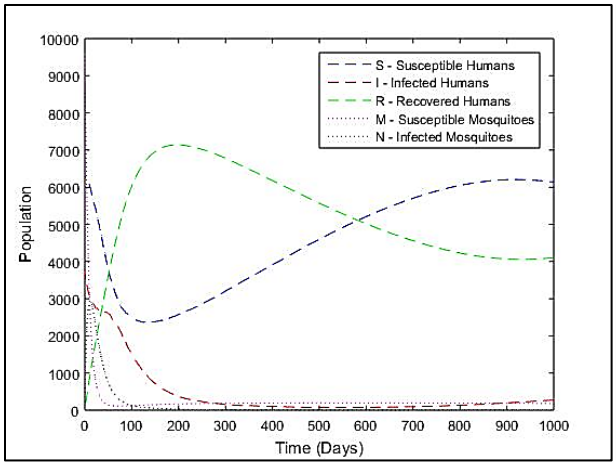



**Figure 17a**: Benin Study, Group 2, New LLINs only, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.07$

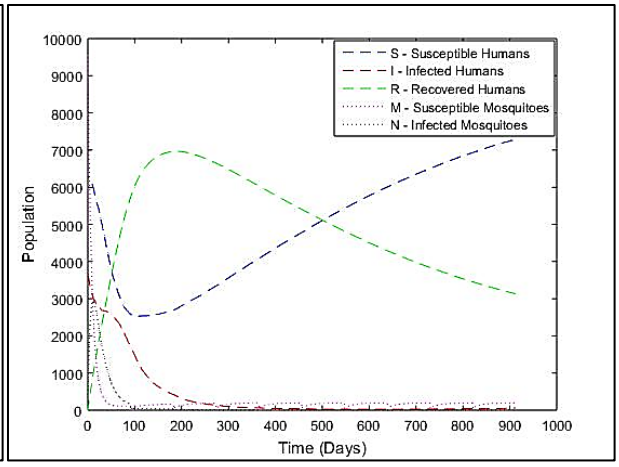



**Figure 17b**: Benin Study, Group 2, New LLINs with 3 Month IRS Intervals, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.07$

Among the analyses of new LLINs with The Gambia study parameters, the disease eventually dies out among the low malaria infection rates. Once again, when comparing the new LLINs between LLINs with IRS to LLINs alone, the differences were not distinct. In Figure 18a and 18b at day 500, both had no infected humans or mosquitoes. The same can be seen when comparing Group 1 parameters to Group 2 parameters in Appendix E.

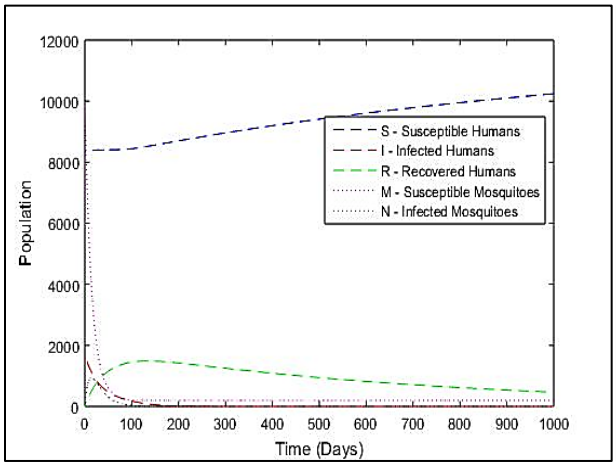



**Figure 18a**: The Gambia Study, Group 2, New LLINs only, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.30$

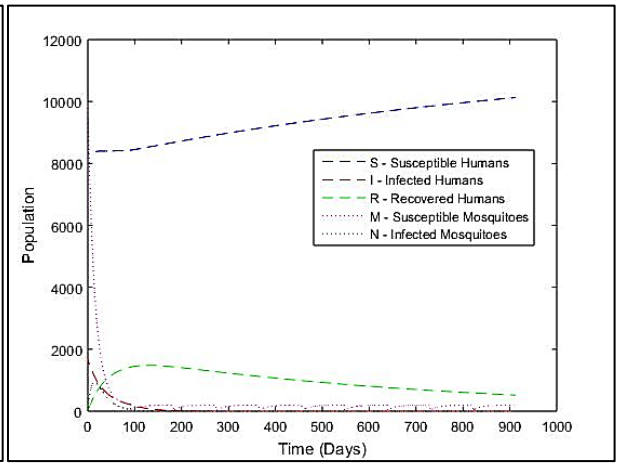



**Figure 18b**: The Gambia Study, Group 2, New LLINs with 3 Month IRS Intervals, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.30$

The methods tested among the Tanzania study parameters and The Gambia study parameters showed very little differences between the combined use of LLINs with IRS interventions and LLINs alone when comparing infected humans over time. Some differences

were seen but were not great enough to declare that adding IRS to the model at three-month spraying intervals provided a distinct effect. The Benin study parameters had lower effective LLIN parameters, which displayed a slightly greater difference when IRS was added, but one that was still not as pronounced among the infected human populations over time.

Simulations where the basic reproductive ratio fell below 1 meant that malaria transmission would be eradicated based on the parameters tested in the ordinary differential equations, especially those related to the LLINs. As IRS involvement is not included in the $R_0$, those situations would mean that the LLIN interventions would be sufficient to reduce the epidemic and possibly eradicate the disease from the population.

The implications of these results mean that there does not appear to be a greater reduction in malaria transmission values when using LLINs with IRS compared to using LLINs alone in certain scenarios. The effect of the interventions together compared to separate shows that the influence of LLINs with IRS may only be of great importance when the LLINs have low efficacy or when combatting possible sustained transmission over time. Limitations and assumptions of the model and analyses considered, the results of the model show there is some effect on the total number of infected individuals when the LLINs are combined with IRS. However, in comparison to LLINs on their own, combined interventions do not show a distinct improvement. Various factors outside of the elements in the tested model need to be further considered in the determination of the interventions to use in most scenarios and are discussed in the strengths, weaknesses, opportunities and threats in the Discussion chapter.

### 3.1.D.2. EFFICACY OF LLINS WITH IRS – USED LLINS

The assessment of LLINs with IRS using LLINs after 20 washes showed similar results to new LLINs when comparing LLINs alone to LLINs with IRS. Among the three sets of study

parameters, and as discussed above, lower infection rates when coupled with higher human recovery rates produced a much lesser epidemic and sustained transmission and, in some cases, produced an $R_0 < 1$. These scenarios led to eradication of the disease in the human and mosquito populations. The opposite situation occurred when increasing infection rates were coupled with decreasing recovery rates.

The differences were slightly greater with less effective LLIN parameter values. Figure 19 demonstrates the difference between LLINs with IRS to LLINs alone using 20-times washed LLINs from the Benin study values. The differences among the infected population of humans is reduced slightly more when IRS is added than LLINs on their own. This may reflect on the efficacy of the net when used in the models. At day 500 in Figure 19a, the populations of infected humans and mosquitoes were 90 and 8, respectively. When IRS was added in Figure 19b, the volumes of infected humans and mosquitoes at day 500 were 46 and 3, respectively. For comparisons of the Tanzania study and The Gambia study parameters, see Appendix F.

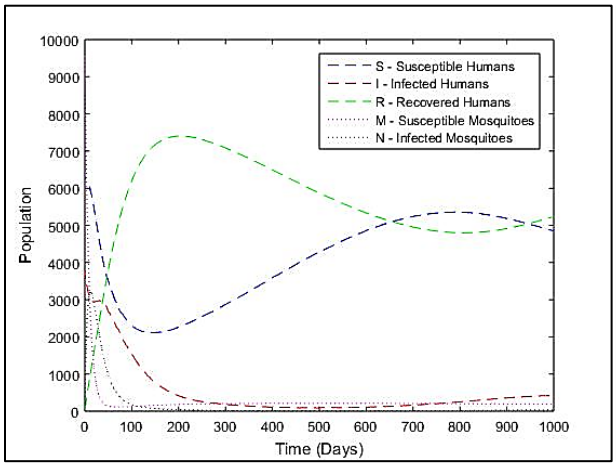



**Figure 19a**: Benin Study, Group 2, Used LLINs only, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.19$

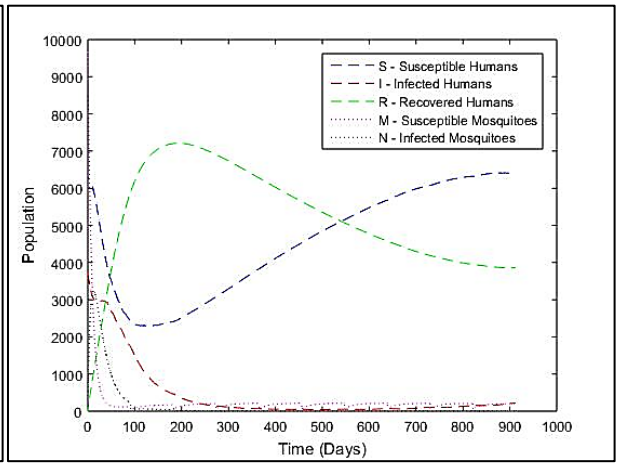



**Figure 19b**: Benin Study, Group 2, Used LLINs with 3 Month IRS Intervals, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.19$

LLINs after 20 washes still show potential for effective impact in reducing malaria transmission. Situations where the basic reproductive number was below 1 prior to IRS use indicated that there would not be a distinctly greater benefit with inclusion of IRS. If the LLIN

efficacy was low, there would be a greater need for IRS, as low LLIN efficacy would lead to a greater potential for a malaria epidemic and subsequent sustained transmission.

The inclusion of IRS can assist in some scenarios, but if the efficacy of the LLINs is at an adequate level, then there is little added benefit seen with adding IRS alongside the LLIN intervention. Overall, in testing the parameters among the LLINs used after 20 washes, the differences are visibly small and support the thought that IRS could assist LLINs, but not to a great degree.

### 3.1.E. – ASSESSMENT OF IRS SPRAYING INTERVALS

Using the three-month spraying intervals after the epidemic begins showed some effect, but one that was not pronounced, on infected humans. As proof-of-concept, shorter spraying intervals of every two months, every month and every week were explored to understand whether each shorter interval resulted in greater reductions on the infected human and mosquito populations.

The first tests were performed with IRS alone, and, as the intervals decreased in time, a greater reduction occurred in both infected human and infected mosquito populations. Similar reductions then occurred among the combination of IRS with LLINs using shorter intervals of spraying. The Gambia study results in Figure 20 depicted the decreasing infected human population with shorter intervals while Figure 21 showed greater diminutions in mosquitoes with shorter intervals. At day 93 (after the first IRS for three month intervals), when comparing IRS intervals of three months, two months, once a month and once a week, the number of infected humans in Figure 20 slowly fell at volumes of 200, 177, 150 and 120, respectively. At day 93 as well, the number of infected mosquitoes in Figure 21 for these same intervals were 7, 11, 1 and 0, respectively. The increase at day 93 with two month IRS intervals was due to mosquito births

increasing the mosquito population before the next interval of spraying. Figure 20 and 21 both show infected humans and mosquitoes dissipating with time when paired with new LLINs. Similar results were seen with the Tanzania and Benin study and are found in Appendix G. Used LLINs also had similar results and can be found in Appendix H.

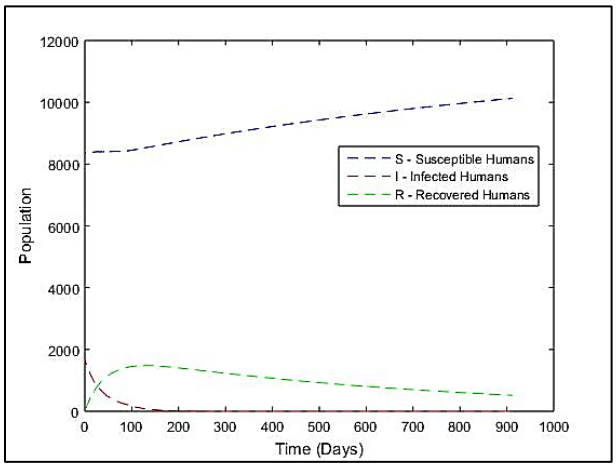



**Figure 20a**: The Gambia Study, Group 2, New LLINs, 3 Month IRS Intervals, Humans, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.30$

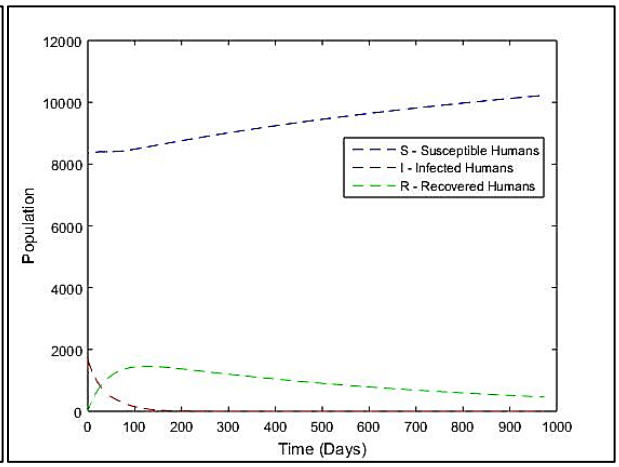



**Figure 20b**: The Gambia Study, Group 2, New LLINs, 2 Month IRS Intervals, Middle Infection Rates, Humans, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.30$

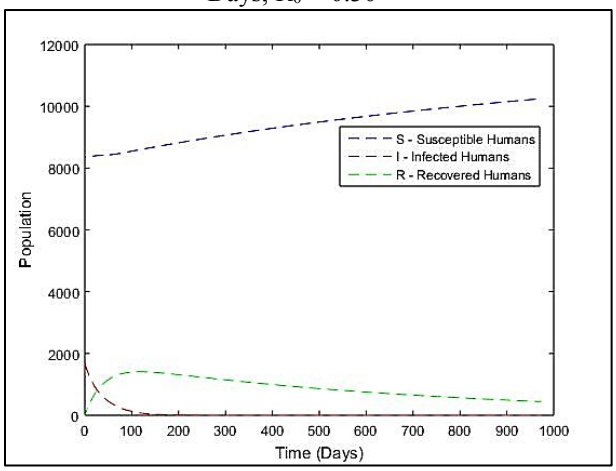



**Figure 20c**: The Gambia Study, Group 2, New LLINs, 1 Month IRS Intervals, Human Population, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.30$

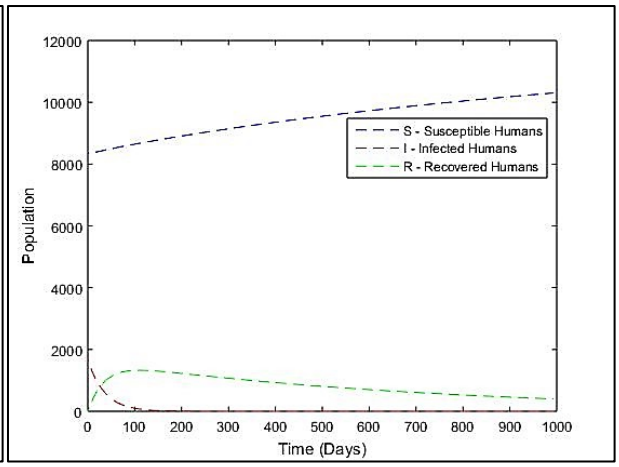



**Figure 20d**: The Gambia Study, Group 2, New LLINs, 1 Week IRS Intervals, Human Population, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.30$

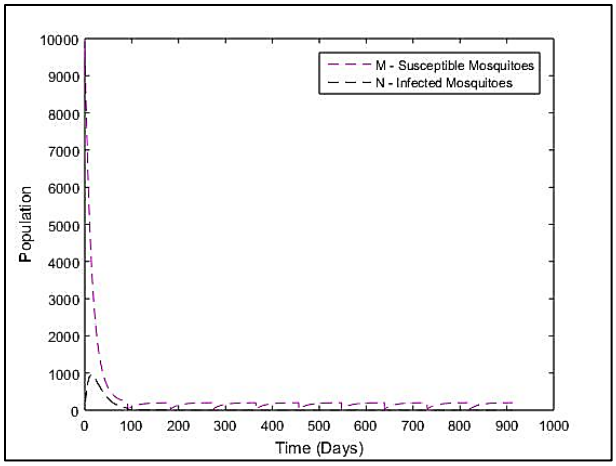



**Figure 21a**: The Gambia Study, Group 2, New LLINs, 3 Month IRS Intervals, Mosquito Population, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.30$

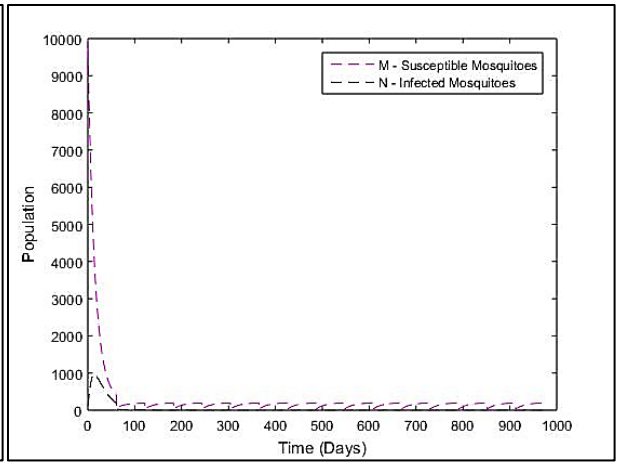



**Figure 21b**: The Gambia Study, Group 2, New LLINs, 2 Month IRS Intervals, Mosquito Population, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.30$

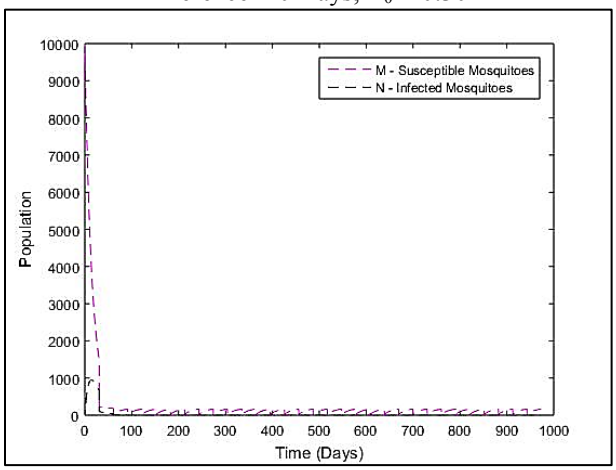



**Figure 21c**: The Gambia Study, Group 2, New LLINs, 1 Month IRS Intervals, Mosquito Population, Middle Infection Rates, Middle Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.30$

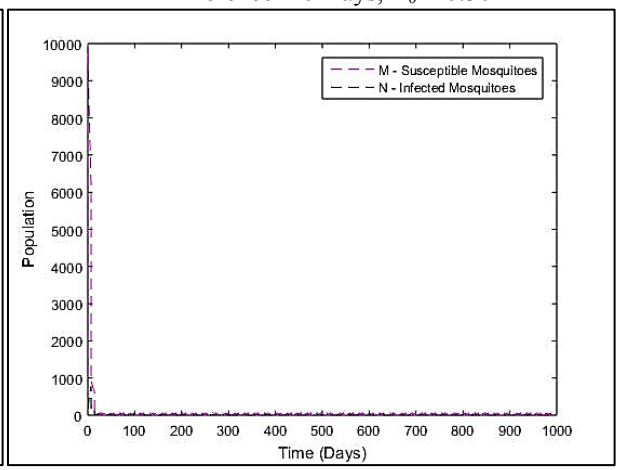



**Figure 21d**: The Gambia Study, Group 2, New LLINs, 1 Week IRS Intervals, Mosquito Population, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.30$

The effects of decreasing the IRS spraying intervals had the greatest visible outcomes when coupled with the lowest LLIN efficacy parameters from the Benin study. Feasibility aside, shorter intervals led to a greater reduction in the infected mosquitoes and infected humans from each of the three sets of study parameters.

The assumption of the impulses approximating very short intervals must also be considered, as there is greater likelihood of a breakdown of the impulse assumptions compared to the actual reductions of the mosquito population. The instant reductions due to the impulses

would become more affected by the shorter intervals as less recovery and more reductions in the mosquito population would occur in much shorter time periods of IRS. This would lead to inaccurate depictions of malaria movement between populations at the shortest IRS intervals due to an overlap between the proxies of near-instant mosquito reductions compared to realistic IRS scenarios.

When the scenarios were tested with shorter and shorter IRS intervals with new LLINs included, the differences between LLINs with IRS to LLINs alone became much greater, showing more favourably towards using the two interventions together rather than separate. Similar results were seen with used LLINs. The problem with the shorter intervals then resides on the feasibility of the measures happening in such shortened intervals (every two months, every month and every week), the impulse assumption of short intervals and the potential lack of resources and capacity to implement IRS appropriately at shorter intervals. As proof-of-concept, however, the two interventions produce significantly improved results compared to their individual reductions of malaria transmission when used with shorter intervals of spraying. Further research is recommended to assess varied levels of IRS reduction capabilities.

### 3.2. SENSITIVITY AND UNCERTAINTY ANALYSIS

The previous section provided results in terms of the time-series analyses performed. To further examine the effect that each parameter had on the basic reproductive number and, in turn, the presence of a malaria epidemic and subsequent sustained transmission in the populations over time, the Monte Carlo sensitivity analysis through the use of Latin Hypercube Sampling and PRCCs assessed the parameters most sensitive to the basic reproductive number. The analyses were specific to the ordinary differential equations as the basic reproductive number was derived from these differential equations.

An examination of the ranges of each parameter values was performed for each set of study parameters. The parameter ranges are found in Appendix A. From the review of the ordinary differential equations, similar PRCCs were developed among the three studies when tested against the basic reproductive number. For the full scope of results, see Appendix I. Figure 22 is specific to the Tanzania study parameters but is similar to that of The Gambia study set of parameters with respect to parameters of greatest positive and negative influence. The Benin study parameters also show similar parameters of greatest influence with exception of the feeding-inhibition rate of the LLINs as the Permanet 2.0 parameters examined a lower range of efficacy.

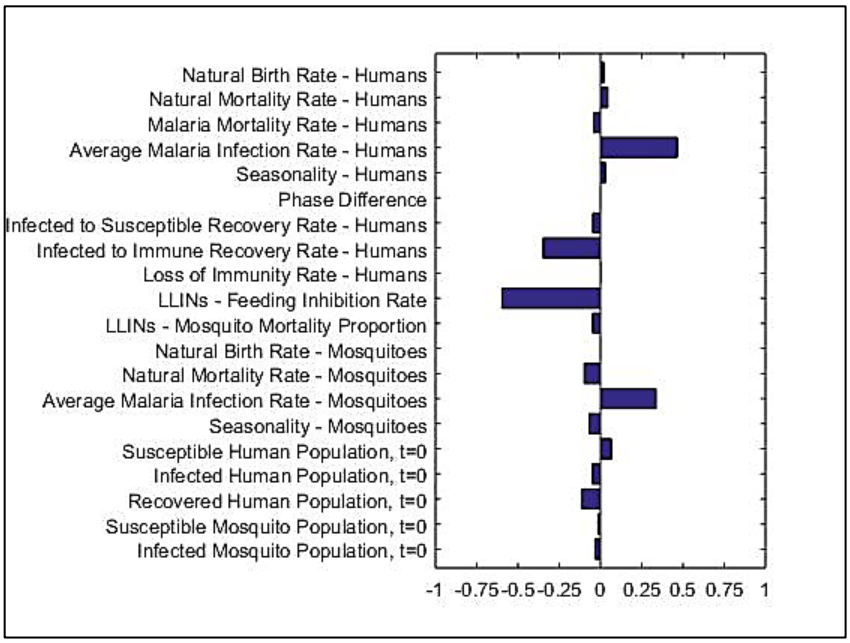


Figure 22: Tanzania Study, Group 1, Partial Rank Correlation Coefficients

The first noticeable negatively correlated parameter was that of the rate of humans moving from an infected state to recovered and temporarily immune state. The Tanzania set of parameters demonstrated a correlation coefficient for this parameter around -0.4, showing a relative effect of decreasing the $R_0$ with increasing recovery rates. Essentially, fewer malaria infections would happen if this recovery rate was higher. The Monte Carlo simulations in Figure

23 show a declining trend in the $R_0$ with an increasing infected to recovered/temporarily immune rate among humans. This negative correlation to the rate of recovery was also seen in the PRCC results for the Benin study and The Gambia study set of parameters.

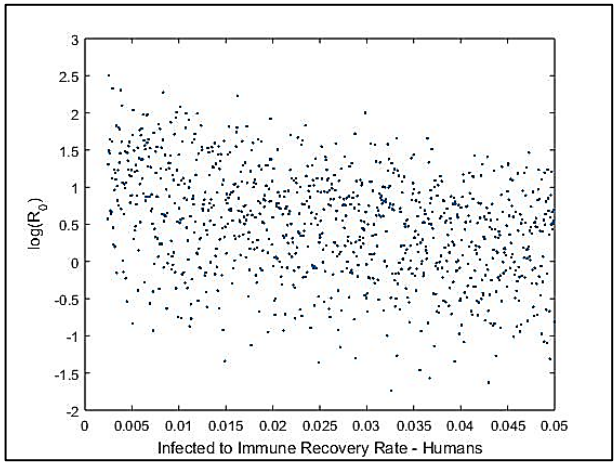



Figure 23: Tanzania Study, Group 1, Infected to Recovered/Immune Recovery Rate Sensitivity Analysis

The second parameter with a high negative correlative effect was that of the feeding-inhibition proportion of the LLINs. This parameter, when tested with the Tanzania study set of parameters, had a much greater negative correlation with a coefficient value below -0.5 and a distinctly negative slope among its sensitivity analysis, as seen in Figure 24. This shows that the basic reproductive number falls as the feeding-inhibition rate increases.

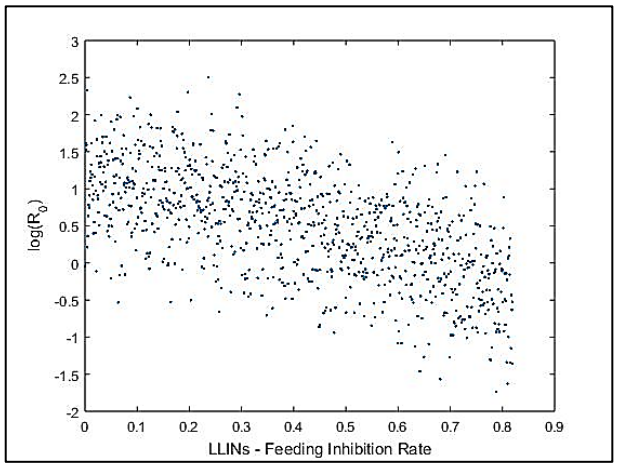



Figure 24: Tanzania Study, Group 1, LLIN – Feeding-Inhibition Rate Sensitivity Analysis

A lower net efficacy showed the LLIN as having less potential to reduce the $R_0$. The Benin study results demonstrated its low feeding-inhibition rates did not develop a substantial negative correlation. There does not appear to be a distinct slope in the Monte Carlo simulations when assessing the parameter in this study, as displayed in Figure 25.

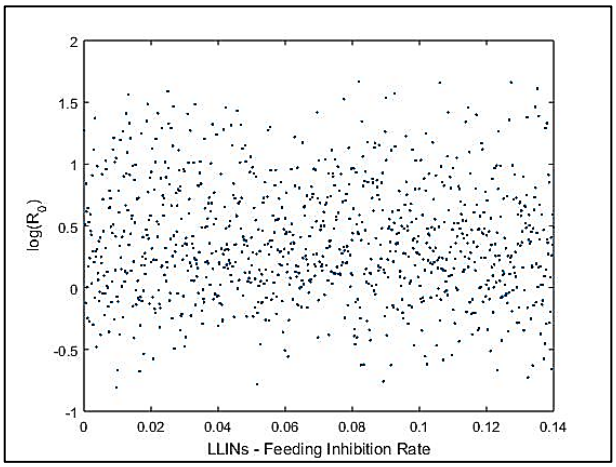



Figure 25: Benin Study, Group 1, LLIN – Feeding-Inhibition Rate Sensitivity Analysis

The parameters with a positive correlation to $R_0$ were the average malaria infection/transmission rates among humans and mosquitoes. These rates had strong positive PRCCs, falling between 0.35 and 0.5 from the Tanzania set of parameters. There is some difference among the other study parameters with respect to the infection rate, but a positive correlation does exist with the Benin and The Gambia study parameters as well. The Monte Carlo simulations exhibited a noticeable upward trend showing that, as the infection rates increase, so too would the value of $R_0$.

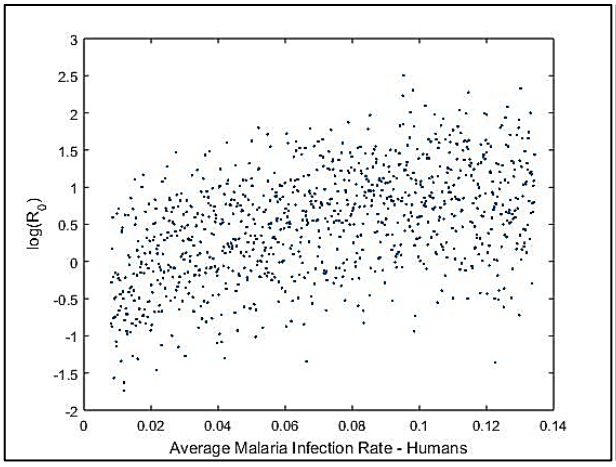



Figure 26a: Tanzania Study, Group 1, Average Malaria Infection Rate – Humans, Sensitivity Analysis

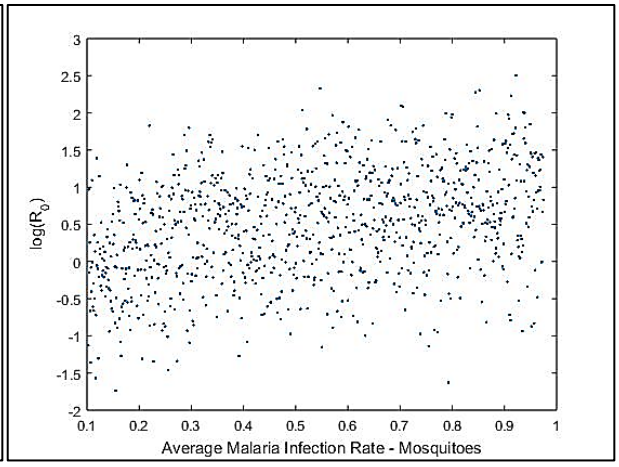



Figure 26b: Tanzania Study, Group 1, Average Malaria Infection Rate – Mosquitoes, Sensitivity Analysis

From the sensitivity and uncertainty analysis of the parameters relevant to the basic reproductive numbers, it can be seen that a lower $R_0$ value occurs with higher infected-to-recovered/temporarily immune rates among humans and a greater LLIN feeding-inhibition rate. Greater average infection/transmission rates among both humans and mosquitoes can be associated with greater volumes of infected populations. From the overall uncertainty and sensitivity analysis among both groups, when testing variations of the $R_0$ values for the Tanzania study and Benin Study, over 75% of the iterations led to an $R_0$ value that was greater than 1. The Gambia set of parameters showed that over 75% had an $R_0$ below 1 when examining Group 2 parameter values, while about half were above 1 testing Group 1 parameter values.

Overall, there were key parameters in the ordinary differential equations that should be considered when reducing $R_0$ and attempting to eliminate malaria transmission. As the impulses of IRS do not affect $R_0$, the time-series analyses displayed the evidence for its use and efficacy towards reducing malaria transmission.

# 4. DISCUSSIONS

## 4.1. SUMMARY OF COMBINING LLINS WITH IRS COMPARED TO LLINS ALONE

There are various motives for including IRS alongside LLINs. One possible benefit is that different multiple insecticides when used at the same time could provide a much lengthier timeframe of toxicity to mosquitoes than using just LLINs alone. Okumu and Moore (2011) assessed multiple studies on this topic that were developed before the trials reviewed in this thesis and stated that the effects of malaria transmission reduction lasted much longer in combined scenarios than LLINs alone. This is advantageous to preventing greater volumes of insecticide resistance in mosquitoes through combining different insecticides at the same time too. Bekele et al. (2012) mentioned that, with the increasing urbanization of African homes, leading to more replastering of walls, that combined vector-control efforts need to occur more frequently due to these changes in habitable environments as well.

Improper maintenance of the LLINs could lead to wear occurring and holes developing and, although the insecticide in the LLIN could kill some mosquitoes, a gap in malaria-transmission reduction would exist (Kweka et al., 2011). The five-year assessment of LLINs by Kweka et al. (2011) noted that holes as well as burns in the netting can happen with time. The level of detectable insecticide can also decrease with time (Kweka et al., 2011). Both of these occurrences with net usage can lead to ineffective vector-control methods. IRS could assist these problems that may happen with continued use of LLINs if replacement does not occur on a regular basis. This, as well as low distribution of LLINs among human populations noted in some sub-Saharan African countries, can also provide reasoning to using IRS with LLINs (WHO, 2015a).

Overall, what has been summarized by Okumu and Moore (2011) is that combining LLINs with IRS is thought to increase the control of the vector in circumstances where one method lags in efficacy as well as develop low enough mosquito levels so transmission does not happen (or occurs at extremely low levels). As well, the deterioration of both interventions' insecticide levels with time and threat of increasing mosquito resistance to many different insecticides provides scenarios that can theoretically push combined use of these methods as necessary practices.

There are also reasons behind not using IRS with LLINs. The resource utilization of using LLINs and IRS separately was assessed by Yukich et al. (2008). Through cost evaluation of IRS methods, it was stated out of two IRS trials that the cost per person-year protected among entire populations was $3.27 and $3.90 USD, and cost per person-year for children under five years was $21.63 and $23.96 USD (Yukich et al., 2008). While the cost per death averted was high in each trial examining IRS use, the element to consider is the cost of using IRS alongside another effective method (Yukich et al., 2008). If LLINs can provide a sufficient amount of protection and can reduce malaria transmission and epidemics without further assistance, then the costs of using IRS can be saved.

The cost and resource requirements, as well as the increased amount of research on efficacy of combining LLINs and IRS has led to trends of less IRS use over recent years among African populations (WHO, 2015a). The evidence from some trials demonstrate no significant difference between combining interventions to LLINs alone in certain scenarios, providing evidence that has led to declining trends of including IRS in malaria vector-control strategies (Corbel et al., 2012; Pinder er al., 2015). The appropriateness of combining methods may also be based on access to these interventions. The WHO (2015a) stated that the combined proportion of

the African population with access to either LLINs or IRS was about 59% in 2014. In sub-Saharan Africa, it was stated that nine countries had access levels >80% (WHO, 2015a). Considering efficacy and access to LLINs, if the proportion of the population with access is great and coverage is sufficient, LLINs may be the only intervention required.

As stated, insecticide resistance and overall access are important factors in decisions made on using LLINs and IRS together or using LLINs alone. These elements, as well as convenience of humans not requiring frequent IRS of one's home and reducing the potential for IRS scheduling conflicts, are reasons that can be stated towards only requiring LLINs over combining interventions.

LLINs and IRS are well-regarded measures to control the *Anopheles* vector and reduce malaria transmission. The environment, infrastructure and decisions made by high-level stakeholders in one's government as well as malaria control programmes that are implemented in populations all affect what is utilized and the level of access to vector-control interventions. Evidence provided through research involving randomized controlled trials, observational studies, cost-benefit analyses and, like this thesis, mathematical modelling can all aide in the decisions made on implementation of these interventions (Okumu & Moore, 2011).

The randomized controlled trials evaluating LLINs and IRS have varied with respect to their results on effectiveness of combining these methods compared to LLINs alone (Pinder et al., 2015; Corbel et al., 2012; West et al., 2014). The studies that have demonstrated no significant difference between LLINs with IRS to LLINs alone are in line with the results of this thesis (Pinder et al., 2015; Corbel et al., 2012). The trials and non-randomized studies that have shown a significant difference between intervention groups demonstrate the opposite conclusions of this thesis (West et al., 2014; Bekele et al., 2012). The differences among examined studies

and the results herein could relate to differing methodologies. This includes level of ITN/LLIN coverage, where less protection from low levels of ITN/LLIN distribution would be compensated by adding IRS, as well as differences between the intervention groups' human and mosquito populations. Mathematical modelling of malaria using other sensitivity analyses have also shown similar key parameters of influence akin to the developed results, including the rate of human recovery to a temporarily immune state and the infection/transmission rates among mosquitoes and humans (Chitnis et al., 2008).

The development of time-series and sensitivity analyses led to a wide range of results with a fairly consistent theme. Overall, there is very little benefit to combining LLINs and IRS if the protective efficacy of LLINs alone is of a sufficient level. The mathematical modelling of three studies in differing areas of sub-Saharan Africa and their respective parameter values showed only certain situations required combining LLINs with IRS. These situations occurred when either the efficacy of the LLIN is low, due to higher insecticide resistance in the area or loss of insecticide efficacy with time and use, or the coverage of LLINs in an environment is low among the population. These scenarios would show that IRS may provide assistance to fill this gap in malaria-transmission protection.

The infection and recovery rates of the populations also influenced malaria transmission. Varied levels of infection and recovery may also lead to a greater understanding of the interventions' respective efficacies among specific populations.

The overall implications with new and used LLINs showed very little difference between examining parameters combining interventions, testing IRS at three-month intervals, compared to LLINs alone when the LLIN efficacy is at a level that can greatly protect the human population on its own. The scenarios discussed above can lead to the opportunity to combine

LLINs with IRS as long as the IRS efficacy is of an adequate level. However, there is a dependency seen with respect to the timing of IRS. The findings support the conclusion that there is no distinct improvement in malaria reduction when LLINs were paired with three-month IRS intervals. Therefore, the addition of IRS at greater time intervals would not experience a distinct effect in reducing malaria transmission as well.

## 4.2. STRENGTHS, WEAKNESSES, OPPORTUNITIES AND THREATS

### 4.2.A. STRENGTHS OF METHODS AND RESULTS

The model was adapted from Smith? and Hove-Musekwa (2008), which was a variation of other historically significant mathematical models that each originated from Ronald Ross' well-known initial malaria model of susceptible to infected to susceptible humans and susceptible to infected mosquitoes (as cited by Mandal et al., 2011, p. 5).

The parameter values in this thesis were mostly from reported metrics. The randomized controlled trials among three separate populations in Africa gave relevant infection rates and malaria-prevalence values for appropriate baseline parameters (Pinder et al., 2015; West et al., 2014; Corbel et al., 2012). The other parameter values tested were from journals and national statistics that are displayed in Table 1 and Appendix A. The analyses performed in this thesis used reported metrics, either measured or appropriately estimated, to determine the applied metrics in the time-series and sensitivity analyses, which further strengthen the results.

The effect that LLINs and IRS had on the human and mosquito populations in the design of the model appropriately reflected each interventions' respective effects on reducing malaria transmission. For the LLIN parameters, we used feeding-inhibition rates to determine the proportion of mosquitoes that could be reduced from the netting's insecticide. IRS was also

applied to reflect the biting rate from mosquitoes that would be reduced, as well as the proportion that would be resistant to the IRS insecticide.

Another strength was the sensitivity and uncertainty analysis that assessed a range for each metric and provided robustness to the ordinary differential equations and its parameters' influences on the basic reproductive number. The basic reproductive number cannot account for the impulses from the IRS, which is a possible weakness, but the sensitivity and uncertainty analysis found an influence of the LLIN metrics and the effect of other model parameters on reducing malaria transmission. A partial understanding of the interventions could be seen from the sensitivity and uncertainty analysis and a full scope of all parameters not related to the IRS intervention occurred. Through performing multiple analyses over 1000 iterations from a range of values for each parameter in the ordinary differential equations, there is much credence to the results and greater knowledge of the most sensitive metrics in the model.

Contrasting LLIN metrics by type of net led to a robust set of results as well. The comparisons between new and used LLINs gave greater perspective to answering the research question. The N'Guessan et al. (2010) study showed that Permanet 2.0 LLIN efficacy could be low and was contrasted against greater feeding-inhibition proportions and mosquito mortality proportions of Olyset LLINs from Pennetier et al. (2013). Although there has been some time since their studies concluded and potential for increases in mosquito resistance to the insecticides, the difference between LLINs with high and low effect against mosquitoes as well as reviewing new and used LLINs develops a wide scope for understanding bed net efficacy.

The examination of using different levels of LLIN efficacy against the maximum efficacy of the IRS also displayed potential results in seeing if IRS, when combined with LLINs, can lead to the addition of IRS as having any distinct effect from LLINs alone. The varied levels of net

efficacy are ideal and give greater strength to the results developed in this thesis. The contrasting parameter values used for Olyset LLINs and Permanet 2.0 LLINs does not necessarily mean one type of net is more effective than the other. The type of LLIN, when utilized in different parts of the world, can have different levels of effectiveness due to different levels of possible mosquito resistance (WHO, 2015a).

### 4.2.B. WEAKNESSES OF METHODS AND RESULTS

One weakness of this mathematical model and its results is that the model used was but one of many different models that have examined malaria spread within human and mosquito populations. Mandal et al. (2011) reviewed several different models that have been developed, and similarities could be noted between the various different models such as the susceptible and infected humans and susceptible and infected mosquitoes. There were also extensions to the model seen, such as the addition of a time delay and exposed class for humans and mosquitoes when moving from a susceptible to an infected state (Mandal et al., 2011). The model used to examine use of interventions on reducing malaria transmission was based on Smith? and Hove-Musekwa (2008) and includes a set of impulsive differential equations to assess LLINs and IRS with specific impulses for IRS. This is discussed as one of its strengths; however, there is potential to consider other elements in the model, so the model is also prone to that same weakness. The element of a time between exposure to malaria and onset of infection is not evaluated in the model but could be considered negligible. The results from this thesis' model to other models with an exposed class for each population may likely develop similar conclusions when also examining use of LLINs with IRS compared to LLINs alone. The weakness would relate to the timing of the populations moving between states and could show greater accuracy

than without the exposed class. Other models have an exposed class and developed respectable results on malaria transmission among populations (Mandal et al., 2011; Agusto et al., 2012).

The parameters chosen for the model include potential for bias due to the lack of consideration regarding certain measurements. Parameters not considered in this thesis' mathematical model include age, socio-economic status, immigration and environment.

Age has a bearing on the infected population, where adults living in malaria-endemic areas are more likely to have experienced the disease before and develop temporary immunity compared to children (Mandal et al., 2011). Socio-economic status also has an effect that was not considered, where those of a lower socio-economic status may be more likely to develop the illness compared to individuals of a higher socio-economic status (Mandal et al., 2011). Immigration, similar to birth rate, is another factor that can increase the number of humans through new individuals entering the population. The same can be said with emigration rates as being similar to mortality rates, where individuals leave their populations over time. There was also no consideration of environment in the thesis's model. For example, *Anopheles* mosquitoes live in lower altitudes and wetter climates and therefore humans that live in such areas are more likely to be exposed to the disease (Mandal et al., 2011). There is a possible bias among the simulations conducted, as the scenarios assume the same environment, same age, same socio-economic status and that immigration and emigration rates are equal and therefore not needed. This could misrepresent the populace; however, the purpose and focus was intervention assessment.

Another weakness in the results is the birth rate measurement addressed in the mathematical model; more specifically, the birth rates of mosquitoes. Some models address birth rate as a per capita rate ($days^{-1}$) rather than how it was considered herein as number of births per

day (Chitnis et al., 2008). The birth rate among both humans and mosquitoes could pose as a weakness with respect to the populations entering and further research into type of birth rate used in mathematical modelling may be desired.

Another potential weakness is the static nature of the parameters. The parameter values, such as mortality rates and birth rates, have changed over time (UNICEF, 2015; The World Bank Group, 2016). The deterministic model parameters used only initial static values, with the exception of the human and mosquito overall infection rates. Variable rates over time could also be used. The variability that exists with parameters can provide opportunities for future studies. The mathematical model's static nature and potential bias was reduced due to the use of the sensitivity and uncertainty analysis. From consideration of the parameter values used in the thesis and sensitivity analysis that was done, there is some weakness that must be acknowledged when examining the results.

Although the initial parameters are based on published articles and trials, the simulations developed do not dictate what can happen in real scenarios. The randomized controlled trials had differing results on combining methods compared to LLINs alone (West et al., 2014; Pinder et al., 2015; Corbel et al., 2012). The use of a deterministic mathematical model develops predictions that review the outcomes over time. There are scenarios that exist where the epidemic declines quickly and dissipates, while other situations lead to the epidemic becoming sustained. The simulations demonstrate the simple nature of the outbreak and sensitivity analyses, through use of uniform distribution scenarios, depict the possible spread that can occur. It is recognized that the simulations do not experience the nuances of reality, but the results provide further evidence to the research question.

### 4.2.C. OPPORTUNITIES FROM METHODS AND RESULTS

An opportunity of this mathematical model is the ability to predict malaria spread within endemic regions of the world. Testing parameter values related to the interventions and malaria transmission can predict effective use of LLINs and IRS. A mathematical model such as the one used in this thesis can help create future decision-support tools and other health-system and intervention-distribution program improvements. Stochastic models are already being used and improved upon through tools like OpenMalaria (Swiss Tropical and Public Health Institute, 2016). A deterministic model like the one developed here can also assist in decision-support tool development. The simple malaria model examined in this thesis could be applied, along with future enhancements, to develop more accurate analysis through inclusion of other parameters.

Future enhancements to this model could include applying socio-economic status, age and other relevant factors (Mandal et al., 2011). These can also provide an opportunity for further model improvements in future research such as the inclusion of various metrics to assist in the predictions of malaria transmission. An example of such improvements could be through adding parameters or components to include elements like mosquito resistance to LLINs.

The potential for mosquito resistance to nets was not considered in the main analyses, leading to the possibility for future research with more accurate mathematical modelling. As based on the model discussed in this thesis, as altered from Smith? and Hove-Musekwa (2008), two additional components would be required in the mosquito population to assess four classes of mosquitoes: susceptible to malaria and not resistant to LLINs ($M$), susceptible to malaria and resistant to LLINs ($P$), infected with malaria and not resistant to LLINs ($N$), and infected with malaria and resistant to LLINs ($Q$). This can change the mathematical model to develop a more

complex examination of malaria transmission. Figure 27 shows the updated compartmental model based on the updated mathematical model.

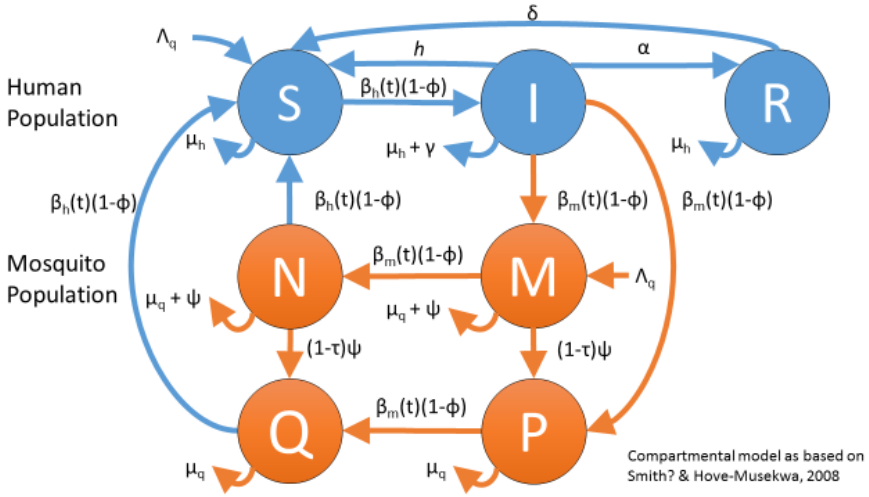



**Figure 27: Compartmental Model of Malaria Transmission among Humans and Mosquitoes with Mosquito Classes Resistant to LLIN Insecticides**

This altered model would lead to an overall set of impulsive differential equations, using the same parameters as before, with the alteration of LLIN mortality ($\psi$) into a rate, the additions of the new mosquito compartments and consideration of the proportion of mosquitoes susceptible to the LLINs that would be expected to expire due to the insecticide ($\tau$):

$$\frac{dS(t)}{dt} = \Lambda_h - (1-\phi)\beta_h(t)\left(\frac{SN}{M+N+P+Q}\right) - \beta_h(t)\left(\frac{SQ}{M+N+P+Q}\right) + hI + \delta R - \mu_h S \quad (8)$$

$$\frac{dI(t)}{dt} = (1-\phi)\beta_h(t)\left(\frac{SN}{M+N+P+Q}\right) + \beta_h(t)\left(\frac{SQ}{M+N+P+Q}\right) - hI - \alpha I - (\mu_h+\gamma)I \quad (9)$$

$$\frac{dR(t)}{dt} = \alpha I - \delta R - \mu_h R \quad (10)$$

$$\frac{dM(t)}{dt} = \Lambda_q - \mu_q M - \psi M - (1-\phi)\beta_m(t)\left(\frac{MI}{S+I+R}\right) \ (where\ t \neq t_k) \quad (11)$$

$$\frac{dN(t)}{dt} = -\mu_q N - \psi N + (1-\phi)\beta_m(t)\left(\frac{MI}{S+I+R}\right) \quad (where\ t \neq t_k) \quad (12)$$

$$\frac{dP(t)}{dt} = -\mu_q P + (1-\tau)\psi M - \beta_m(t)\left(\frac{PI}{S+I+R}\right) \quad (where\ t \neq t_k) \quad (13)$$

$$\frac{dQ(t)}{dt} = -\mu_q Q + (1-\tau)\psi N + \beta_m(t)\left(\frac{PI}{S+I+R}\right) \quad (where\ t \neq t_k). \quad (14)$$

The effects on the mosquitoes using the IRS intervention can be described by the following difference equations in this altered model:

$$M^{+} = (1 - r + rc)M^{-} \quad (where\ t = t_k) \tag{15}$$
$$N^{+} = (1 - r + rc)N^{-} \quad (where\ t = t_k) \tag{16}$$
$$P^{+} = (1 - r + rc)P^{-} \quad (where\ t = t_k) \tag{17}$$
$$Q^{+} = (1 - r + rc)Q^{-} \quad (where\ t = t_k). \tag{18}$$

This is just one of many potential alterations to the mathematical model, which can provide even more opportunity for greater accuracy of results.

The extent to which the mathematical model can be adjusted is based on the appropriate selection and use of parameters. As mentioned, some models use an exposed class for mosquitoes and humans to represent the time between the parasite entering the host and the development of an infected state (Agusto et al., 2012; Mandal et al., 2011). This is another possibility to consider with future mathematical modelling of this disease.

Including more parameters — like socio-economic status, age, immigration, emigration and others — can be addressed for greater accuracy. Development of trials to assess LLINs and IRS have occurred to understand the appropriateness of using these interventions together and separately and have developed parameters used in this thesis that can also be used in future analyses (West et al., 2014; Corbel et al., 2012; Pinder et al., 2015). The mathematical model in this thesis shows the potential to further examine data in a simulated nature as the cost can be quite extensive with implementing further randomized controlled trials.

Another opportunity of this mathematical model is through applying the model to other vector-borne illnesses. In assessment of other vector-borne diseases, with emphasis on mosquito-related diseases, the modelling in this thesis could also be altered to reflect other illnesses. This may include such diseases as chikungunya, dengue fever and other vector-borne illnesses that can be considered based on this thesis' model, alongside other published models (Erickson, Presley, Allen, Long, & Cox, 2010; Dumont, Chiroleu, & Domerg, 2008). The use of this model

can be applied to the transmission of many other illnesses, and this is another opportunity to apply the methods conducted in this thesis.

### 4.2.D. THREATS FROM METHODS AND RESULTS

There are some unknowns that exist regarding this model, the results developed and strategies against malaria transmission in populations that pose as possible threats. One threat to combatting malaria transmission is increasing resistance of mosquitoes to the insecticides in LLINs and IRS (WHO, 2015a; Matowo et al., 2015). There is potential for the resistance levels to increase and cause problems such as ineffective vector-control interventions. Pyrethroid resistance is of most concern in LLINs due to few options available outside of the differing forms of this family of insecticides. Synergists, such as PBO, are being used in newer LLINs and have shown a greater effect to malaria-transmission reduction (N'Guessan et al., 2010; Pennetier et al., 2013). IRS has a wide variety of effective insecticides that should be changed frequently to prevent mosquito resistance (Agossa et al., 2014). Without use of such methods, insecticide resistance could make LLINs and IRS potentially obsolete in their insecticidal activity.

The vector-control methods used by countries may also differ from the types of LLINs and IRS examined from the three randomized controlled trials (West et al., 2014; Corbel et al., 2012; Pinder et al., 2015). The three trials assessed were from three of the many countries of sub-Saharan Africa. Each country could potentially have different types of approved LLINs or IRS based on the malaria-control programmes in place. This is also a potential threat in that the generalization of results in this thesis may not be able to be considered in other areas of sub-Saharan Africa if different methods are being used.

The actual rates examined in this thesis may not reflect other malaria-endemic areas of Africa which also poses as a threat due to this unknown element and its ability to affect the

generalization of the results. The actual rates among other populations could be a threat, as it may fall outside the values examined in the sensitivity analysis. This is not certain and so future research is recommended on this specific subject.

A final threat to consider in this model is the extent to which this model reflects reality. It has been mentioned as a possible weakness of the model, but the unknown elements that exist in reality pose possible threats to the model and its results. Additional parameters were discussed in the opportunities section, including age, environment and socio-economic status. However, the overall aspects that can lead to increases or decreases in malaria transmission could be far more complex and be due to immeasurable parameters. Predictions from mathematical models can generalize to an extent. The threat of other, more complex parameters can pose as a threat to both the mathematical model and results, along with future opportunities to mathematical modelling of vector-control strategies on malaria transmission.

# 5. CONCLUSION

## 5.1. SUMMARY OF THESIS

Malaria is one of the most dangerous illnesses in the world, and, even with ambitious goals and numerous protective and preventative measures put in place, over 400,000 individuals were estimated to have perished in 2015 globally (WHO, 2015a). Studies have assessed the combined effects of using LLINs/ITNs and IRS to reduce malaria transmission and note if there was a significant difference between the use of interventions together and separately. These studies had mixed results (West et al., 2014; Corbel et al., 2012; Pinder et al., 2015). Through a new perspective on these interventions using mathematical modelling of an overall set of impulsive differential equations, evidence was developed from time-series and sensitivity analyses to assess whether there was a distinct difference between combining these interventions compared to their separate effects.

Using MATLAB and data from published trials in sub-Saharan Africa, alongside related journal articles and statistics, time-series model simulations were conducted on the use of no interventions, IRS alone, LLINs alone and the combined effect of LLINs with IRS. The key results showed that the addition of three-month IRS intervals alongside LLINs did not drastically change the pattern of malaria transmission compared to using LLINs alone. The lower efficacy LLIN parameters in the Benin study exhibited IRS having a slightly greater effect when paired with LLINs, but the effect on the number of infected humans was small.

The evidence in this thesis is not without its limitations, which were mostly related to the assumptions placed upon the mathematical model. While future research will help to support the results of the analyses, the results herein through qualitative analysis support that IRS in

combination with LLINs compared to LLINs alone does not provide a great improvement in reducing transmission of malaria.

The addition of IRS in conjunction with LLINs depends on the level of effectiveness of the LLINs and their proper use and overall distribution by the population. As discussed, situations of high mosquito resistance to LLINs or low distribution and/or improper use of LLINs among humans could result in the need to add an IRS strategy to decrease the potential gaps in malaria transmission reduction. Overall, the results indicated that LLINs alone appeared just as effective as LLINs with IRS as a vector-control strategy against malaria.

## 5.2. FUTURE RESEARCH

Future studies are recommended to develop further clarity on this topic. A proposal was released by Deressa et al. (2016) and is in the preparatory phases to perform a randomized control trial on this subject in Ethiopia. This study will develop further evidence towards these practices in a new environment, looking at LLINs with IRS compared to LLINs alone, IRS alone and a control (Deressa et al., 2016). Further assessment of mathematical modelling is also recommended, including examination of the expanded model provided in the Opportunities section. Overall, there are numerous potential opportunities that can be put forth through future research, which can assist in providing greater knowledge on optimal use of vector-control interventions to lower the burden of malaria in sub-Saharan Africa. The continued efforts to reduce the fatal consequences of this disease are vast, and greater knowledge on malaria can significantly benefit the world.

# 6. APPENDICES

## APPENDIX A

| Appendix A.1. Tanzania Study – Related Parameter Values | Parameter Values Tested in Time-Series Analyses | | Range Tested in Sensitivity Analysis | | References |
|---|---|---|---|---|---|
| | Group 1 (LLINs Alone) | Group 2 (LLINs with IRS) | Group 1 (LLINs Alone) | Group 2 (LLINs with IRS) | |
| **Human Parameters** | | | | | |
| Natural Birth Rate ($\Lambda_h$) | 1.07 | | 1.07–1.32 | | UNICEF, 2015 |
| Natural Mortality Rate ($\mu_h$) | 0.000044 | | 0.000042586–0.000085451 | | Institute for Health Metrics and Evaluation, 2013; The World Bank Group, 2016 |
| Malaria Mortality Rate ($\gamma$) | 0.00009 | | 0–0.00041 | | Arudo et al., 2003; Chitnis et al., 2008 |
| Average Malaria Transmission/Infection Rate ($b_0$) | 0.0341 | 0.044 | 0.008–0.1344 | 0.007–0.2548 | West et al., 2014 |
| Seasonality ($b_1$) | 0.355 | | 0.11–0.6 | | Childs & Boots, 2010 |
| Phase Difference ($\rho$) | 0 to 180 | | 0–180 | | West et al., 2014 |
| Infected to Susceptible Recovery Rate (h) | 0.00262 | | 0.00024–0.005 | | Nedelman, 1984; Ermert et al., 2011 |
| Infected to Recovered/Immune Recovery Rate ($\alpha$) | 0.0262 | | 0.0024–0.05 | | Nedelman, 1984; Ermert et al., 2011 |
| Loss of Immunity Rate ($\delta$) | 0.0014 | | 0.000055–0.011 | | Childs & Boots, 2010; Chitnis et al., 2008 |
| **Bed Net Parameters** | | | | | |
| LLINs – Feeding-Inhibition Rate ($\phi$) | 0 Washes = 82%, 20 Washes = 60% | | 0–0.82 | | Pennetier et al., 2013 |
| LLINs - Mosquito Mortality Rate ($\psi$) | 0 Washes = 42%, 20 Washes = 36% | | 0–0.42 | | Pennetier et al., 2013 |
| **Indoor Residual Spraying Parameters** | | | | | |
| IRS - Proportion of Mosquitoes Reduced (r) | 93.2% | | Not applicable | | Ossè et al., 2012 |
| IRS - Proportion of Mosquitoes Resistant to IRS (c) | 25.7% | | Not applicable | | Matowo et al., 2015 |
| **Mosquito Parameters** | | | | | |
| Natural Birth Rate ($\Lambda_q$) | 10.56 | | 8.6–12.5 | | Smith? & Hove-Musekwa, 2008; Govoetchan et al., 2013 |
| Natural Mortality Rate ($\mu_q$) | 0.037 | | 0.03125–0.04545 | | Govoetchan et al., 2013 |
| Average Malaria Transmission/Infection Rate ($b_2$) | 0.316 | 0.181 | 0.102–0.975 | 0.041–0.743 | West et al., 2014 |
| Seasonality ($b_3$) | 0.065 | | 0.06–0.07 | | Massad et al., 2011 |
| Phase Difference ($\rho$) | 0 to 180 | | 0–180 | | West et al., 2014 |

| **Tested Populations at t=0 (out of 10000 Humans and 10000 Mosquitoes)** | | | | |
|---|---|---|---|---|
| Susceptible Human Population | 8970 | 9160 | 5770–9550 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |
| Infected Human Population | 1030 | 840 | 450–4230 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |
| Recovered/Temporarily Immune Population | 0 | 0 | 0–10000 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |
| Susceptible Mosquito Population | 9860 | 9800 | 9530–9981 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |
| Infected Mosquito Population | 140 | 200 | 19–470 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |

| Appendix A.2. Benin Study – Related Parameter Values | Parameter Values Tested in Time-Series Analyses | | Range Tested in Sensitivity Analysis | | References |
|---|---|---|---|---|---|
| | Group 1 (LLINs Alone) | Group 2 (LLINs with IRS) | Group 1 (LLINs Alone) | Group 2 (LLINs with IRS) | |
| **Human Parameters** | | | | | |
| Natural Birth Rate ($\Lambda_h$) | 0.997 | | 0.997–1.28 | | UNICEF, 2015 |
| Natural Mortality Rate ($\mu_h$) | 0.000043 | | 0.000042586–0.000085451 | | Institute for Health Metrics and Evaluation, 2013; The World Bank Group, 2016 |
| Malaria Mortality Rate ($\gamma$) | 0.00009 | | 0–0.00041 | | Arudo et al., 2003; Chitnis et al., 2008 |
| Average Malaria Transmission/Infection Rate ($b_0$) | 0.0254 | 0.02 | 0.0101–0.055 | 0.007–0.045 | Corbel et al., 2012 |
| Seasonality ($b_1$) | 0.355 | | 0.11–0.6 | | Childs & Boots, 2010 |
| Phase Difference ($\rho$) | 0 to 180 | | 0–180 | | West et al., 2014 |
| Infected to Susceptible Recovery Rate (h) | 0.00262 | | 0.00024–0.005 | | Nedelman, 1984; Ermert et al., 2011 |
| Infected to Recovered/Immune Recovery Rate ($\alpha$) | 0.0262 | | 0.0024–0.05 | | Nedelman, 1984; Ermert et al., 2011 |
| Loss of Immunity Rate ($\delta$) | 0.0014 | | 0.000055–0.011 | | Childs & Boots, 2010; Chitnis et al., 2008 |
| **Bed Net Parameters** | | | | | |
| LLINs – Feeding-Inhibition Rate ($\phi$) | 0 Washes = 14%, 20 Washes = 10% | | 0–0.14 | | N'Guessan et al., 2010 |
| LLINs - Mosquito Mortality Rate ($\psi$) | 0 Washes = 44%, 20 Washes = 29% | | 0–0.44 | | N'Guessan et al., 2010 |
| **Indoor Residual Spraying Parameters** | | | | | |
| IRS - Proportion of Mosquitoes Reduced (r) | 93.2% | | Not applicable | | Ossè et al., 2012 |
| IRS - Proportion of Mosquitoes Resistant to IRS (c) | 25.7% | | Not applicable | | Matowo et al., 2015 |
| **Mosquito Parameters** | | | | | |
| Natural Birth Rate ($\Lambda_q$) | 10.56 | | 8.6–12.5 | | Smith? & Hove-Musekwa, 2008; Govoetchan et al., 2013 |
| Natural Mortality Rate ($\mu_q$) | 0.037 | | 0.03125–0.04545 | | Govoetchan et al., 2013 |
| Average Malaria Transmission/Infection Rate ($b_2$) | 0.223 | 0.226 | 0.148–0.335 | 0.149–0.339 | Corbel et al., 2012 |
| Seasonality ($b_3$) | 0.065 | | 0.06–0.07 | | Massad et al., 2011 |
| Phase Difference ($\rho$) | 0 to 180 | | 0–180 | | West et al., 2014 |

| **Tested Populations at t=0 (out of 10000 Humans and 10000 Mosquitoes)** | | | | |
|---|---|---|---|---|
| Susceptible Human Population | 7470 | 6270 | 5770–9550 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |
| Infected Human Population | 2530 | 3730 | 450–4230 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |
| Recovered/Temporarily Immune Population | 0 | 0 | 0–10000 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |
| Susceptible Mosquito Population | 9720 | 9680 | 9530–9981 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |
| Infected Mosquito Population | 280 | 320 | 19–470 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |

| Appendix A.3. The Gambia Study – Related Parameter Values | Parameter Values Tested in Time-Series Analyses | | Range Tested in Sensitivity Analysis | | References |
|---|---|---|---|---|---|
| | Group 1 (LLINs Alone) | Group 2 (LLINs with IRS) | Group 1 (LLINs Alone) | Group 2 (LLINs with IRS) | |
| **Human Parameters** | | | | | |
| Natural Birth Rate ($\Lambda_h$) | 1.17 | | 1.17–1.38 | | UNICEF, 2015 |
| Natural Mortality Rate ($\mu_h$) | 0.000044 | | 0.000042586–0.000085451 | | Institute for Health Metrics and Evaluation, 2013; The World Bank Group, 2016 |
| Malaria Mortality Rate ($\gamma$) | 0.00009 | | 0–0.00041 | | Arudo et al., 2003; Chitnis et al., 2008 |
| Average Malaria Transmission/Infection Rate ($b_0$) | 0.016 | 0.007 | 0.00976–0.0217 | 0.00386–0.0102 | Pinder et al., 2015 |
| Seasonality ($b_1$) | 0.355 | | 0.11–0.6 | | Childs & Boots, 2010 |
| Phase Difference ($\rho$) | 0 to 180 | | 0–180 | | West et al., 2014 |
| Infected to Susceptible Recovery Rate (h) | 0.00262 | | 0.00024–0.005 | | Nedelman, 1984; Ermert et al., 2011 |
| Infected to Recovered/Immune Recovery Rate ($\alpha$) | 0.0262 | | 0.0024–0.05 | | Nedelman, 1984; Ermert et al., 2011 |
| Loss of Immunity Rate ($\delta$) | 0.0014 | | 0.000055–0.011 | | Childs & Boots, 2010; Chitnis et al., 2008 |
| **Bed Net Parameters** | | | | | |
| LLINs – Feeding-Inhibition Rate ($\phi$) | 0 Washes = 82%, 20 Washes = 60% | | 0–0.82 | | Pennetier et al., 2013 |
| LLINs - Mosquito Mortality Rate ($\psi$) | 0 Washes = 42%, 20 Washes = 36% | | 0–0.42 | | Pennetier et al., 2013 |
| **Indoor Residual Spraying Parameters** | | | | | |
| IRS - Proportion of Mosquitoes Reduced (r) | 94.0% | | Not applicable | | Ratovonjato et al., 2014 |
| IRS - Proportion of Mosquitoes Resistant to IRS (c) | 9.5% | | Not applicable | | Pinder et al., 2015 |
| **Mosquito Parameters** | | | | | |
| Natural Birth Rate ($\Lambda_q$) | 10.56 | | 8.6–12.5 | | Smith? & Hove-Musekwa, 2008; Govoetchan et al., 2013 |
| Natural Mortality Rate ($\mu_q$) | 0.037 | | 0.03125–0.04545 | | Govoetchan et al., 2013 |
| Average Malaria Transmission/Infection Rate ($b_2$) | 0.696 | 0.617 | 0.432–0.961 | 0.338–0.895 | Pinder et al., 2015 |
| Seasonality ($b_3$) | 0.065 | | 0.06–0.07 | | Massad et al., 2011 |
| Phase Difference ($\rho$) | 0 to 180 | | 0–180 | | West et al., 2014 |

| **Tested Populations at t=0 (out of 10000 Humans and 10000 Mosquitoes)** | | | | |
|---|---|---|---|---|
| Susceptible Human Population | 8580 | 8330 | 5770–9550 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |
| Infected Human Population | 1420 | 1670 | 450–4230 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |
| Recovered/Temporarily Immune Population | 0 | 0 | 0–10000 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |
| Susceptible Mosquito Population | 9968 | 9981 | 9530–9981 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |
| Infected Mosquito Population | 32 | 19 | 19–470 | West et al., 2014; Corbel et al., 2012; Pinder et al., 2015 |

# Appendix A.4. Description of Metrics in Appendix A and Table 1

### Human Parameters

| |
|---|
| **Natural Birth Rate – $\Lambda_h$ (births per day) –** The analyses used UNICEF's 2013 daily crude birth rate for each respective country (birth rate/(1000 times 365.25)) multiplied to 10,000 humans for an appropriate estimated birth rate with the range of birth rates for each respective country's 1970 to 2013 rates for the sensitivity analyses (UNICEF, 2015). |
| **Natural Mortality Rate – $\mu_h$ (days$^{-1}$) –** The analyses used 2010's life expectancies (1/(Life Expectancy times 365.25)) to develop a per day value for each respective country (all three compared within one *Global Burden of Diseases Profile* for Benin) (Institute for Health Metrics and Evaluation, 2013). Range of death rates were based on the maximum and minimum life expectancies among Tanzania, Benin, and The Gambia together from The World Bank Group (2016) life expectancy data. |
| **Malaria mortality rate – $\gamma$ (days$^{-1}$) –** The analyses used metrics reported by Arudo et al. (2003) reporting a malaria mortality rate among children under 5 years of age of 32.9 per 1000 per year and range of malaria mortality rates assessed by Chitnis et al. (2008). Although population is assumed as mixed ages in the simulations, the malaria mortality rate tested provides an appropriate consideration in the analysis along with a range tested with a minimum of 0 based on Chitnis et al. (2008). |
| **Average Malaria Transmission/Infection Rate – $b_0$ (infections per day) –** The analyses used each respective study's baseline or initial reported entomological inoculation rate, the number of infective bites on humans from mosquitoes per day (West et al., 2014; Corbel et al., 2012; Pinder et al., 2015). Range of values was based on multiplying the minimum of the 95% confidence interval of the sporozoite rate with the minimum of the 95% confidence interval of the biting rate to the maximum of the 95% confidence interval of the sporozoite rate multiplied with the maximum of the 95% confidence interval of the biting rate of each study. If a confidence interval was not available on either the biting rate or the sporozoite rate, the overall rate of one metric was multiplied with the maximum and minimum of the 95% confidence interval of the other metric for a suitable range in the sensitivity analysis. |
| **Seasonality – $b_1$ (percent) –** The analyses used tested values from a previous report on varying levels of seasonal forcing that was also applied to the sensitivity analysis (Childs & Boots, 2010). |
| **Phase Difference – $\rho$ (days) –** The analyses used coverage of possible time delays within human malaria incidence rates. West et al. (2014) states two rainy seasons in Tanzania throughout the year, stating a short rainy season prior to February and a second longer rainy season prior to June. As well, based on a report by Childs & Boots (2010), when testing seasonality of malaria, there was no inclusion of a phase difference. As such a sensitivity analysis using a phase difference range of 0 to 180 days (about 6 months) was used. |
| **Infected to susceptible recovery rate – h (days$^{-1}$) –** The analyses used rates discussed by Earle et al. (as cited in Nedelman, 1984, p. 224). As rates differ, a sensitivity analysis took place to examine the rate of humans returning to a susceptible state after malaria infection per day (Nedelman, 1984). As well, a recovery rate from Ermert et al. (2011) was 0.005 and also supports the range of reviewed rates. |
| **Infected to Recovered/Immune Recovery Rate – $\alpha$ (days$^{-1}$) –** The analyses also used rates discussed by Earle et al. (as cited in Nedelman, 1984, p. 224). This rate was developed from the rate placed by Nedelman (1984) of (Rate of Humans becoming susceptible after infection)*10. A sensitivity analysis took place to examine the rate of humans going to a recovered/temporarily immune state after infection per day (Nedelman, 1984). As well, a recovery rate from Ermert et al. (2011) was 0.005 and also supports the range of reviewed rates. |
| **Loss of immunity rate – $\delta$ (days$^{-1}$) –** The analyses used a two year period for loss of malaria immunity in humans (Childs & Boots, 2010). Range was based on values assessed by Chitnis et al. (2008). |
| **Human Malaria Prevalence (percent) –** The analyses used the proportion of humans with a positive result for a *Plasmodium* parasite from each assessed trial based on baseline or initial survey of study (West et al., 2014; Corbel et al., 2012; Pinder et al., 2015). |

### Bed Net Parameters

| |
|---|
| **LLIN – Feeding-inhibition rate – $\phi$ (percent) –** The analyses applied an Olyset bed net efficacy based on a study by Pennetier et al. (2013) and was used for the Tanzania and The Gambia study parameters. The Permanet 2.0 bed net efficacy for the Benin study parameters was based on a study by N'Guessan et al. (2010). For both types of bed nets, percent feeding inhibition was based on average reduction in mosquito to human transmission for nets that have been washed 0 and 20 times (Pennetier et al., 2013; N'Guessan et al., 2010). |
| **LLIN - Mosquito mortality rate – $\psi$ (percent) –** The analyses used additional mortality rate (%) for Olyset and Permanet 2.0 bed nets after 0 and 20 washes from studies by Pennetier et al. (2013) and N'Guessan et al. (2010), respectively. |

**Indoor Residual Spraying Parameters**

| |
|---|
| **IRS - Proportion of mosquitoes reduced – r (percent)**. Proportion of mosquitoes reduced was based on the maximum proportional reduction of the biting rates found in Ossè et al. (2012), which assessed bendiocarb IRS, and Ratovonjato et al. (2014), which assessed DDT IRS. Both reduction rates were tested at maximum levels to note if any distinct change would occur in LLINs with IRS analyses compared to LLINs-alone analyses. |
| **IRS - Proportion of mosquitoes resistant to IRS – c (percent) –** The analyses used values derived from Matowo et al.'s study (2015) and Pinder et al.'s (2015) study, applying the proportion of mosquitoes that did not die due to the IRS method (1 - Mosquito Mortality). |

**Mosquito Parameters**

| |
|---|
| **Natural Birth Rate – $\Lambda_q$ (births per day) –** The analyses applied calculations of estimated mosquito birth rates from Smith? and Hove-Musekwa (2008). The estimation calculation from their study was about 1000 mosquito births per year from mosquitoes with life expectancies of 7 days (Smith? & Hove-Musekwa, 2008). Using the mosquito life expectancies tested herein, an estimated birth rate was calculated. |
| **Natural Mortality Rate – $\mu_q$ (days$^{-1}$) –** The analyses used the average of the two median life expectancies for gravid and non-gravid mosquitoes as examined in Govoetchan et al. (2013). |
| **Average malaria transmission/infection rate – $b_2$ (infections per day) –** The analyses used calculated values from each respective study from baseline or overall data, using the following calculation: ((Human Biting Rate - EIR) * Malaria Prevalence in Humans) (West et al., 2014; Corbel et al., 2012; Pinder et al., 2015). Range of values were based on the maximum and minimum confidence interval ranges from each study's EIR and Human Biting Rate values. Where a confidence limit was not available with one metric, the other metric's confidence limit was still applied to develop a reasonable range of values. |
| **Seasonality – $b_3$ (percent) –** The analyses used seasonal variation values estimated for mosquito birth seasons from Massad et al. (2011). |
| **Phase Difference – ρ (days) –** Similar to phase difference among humans, the mosquito population's phase difference was also based on West et al.'s (2014) two rainy seasons in Tanzania throughout the year. As well, based on a report by Childs & Boots (2010), when testing seasonality of malaria, there was no inclusion of a phase difference. As such, a sensitivity analysis using a phase difference range of 0 to 180 days (about 6 months) was used. |

**Population Values**

| |
|---|
| **Susceptible Human Population** for the initial time-series analyses used the following estimate from the 10,000 humans, 10,000 - (10,000*Human Malaria Prevalence Rate (%)). This calculation was applied for each study's respective Group 1 and Group 2. The range of values were based on the overall highest and lowest possible susceptible population among the three studies combined based off of the maximum and minimum confidence limit of baseline human malaria prevalence and using the calculation (10,000 - (10,000*Human Malaria Prevalence Rate (%) )) to develop a maximum and minimum range of possible susceptible populations among 10,000 individuals. |
| **Infected Human Population** for the initial time-series analyses used the following estimate from the 10,000 humans, 10,000*Human Malaria Prevalence Rate (%). This calculation was applied for each study's respective Group 1 and Group 2. The range of values were based on the overall highest and lowest possible infected population among the three studies combined based on the maximum and minimum confidence limit of baseline human malaria prevalence and using the calculation (10,000*Human Malaria Prevalence Rate (%)) to develop a maximum and minimum range of possible infected populations among 10,000 individuals. |
| **Recovered/Temporarily Immune Human Population** was set at 0 for the initial time-series analyses and assumed none of the population was infected and subsequently recovered at time 0. For the range of values for the sensitivity and uncertainty analysis, a range from 0 to 10,000 individuals were tested to see if there was any level of effect to the basic reproductive number based on the volume of recovered individuals. |
| **Susceptible Mosquito Population** for the initial time-series analyses used the following estimate from the 10,000 mosquitoes, 10,000 - (10,000*Mosquito sporozoite rate (%)). This calculation was applied for each study's respective Group 1 and Group 2. The range of values were based on the overall highest and lowest possible sporozoite rates among the three studies combined and using the calculation (10,000 - (10,000*Mosquito sporozoite rate (%))) to develop a maximum and minimum range of possible susceptible mosquitoes among 10,000 mosquitoes. |
| **Infected Mosquito Population** for the initial time-series analyses used the following estimate from the 10,000 mosquitoes, 10,000*Mosquito sporozoite rate (%). This calculation was applied to each study's respective Group 1 and Group 2. The range of values were based on the overall highest and lowest possible sporozoite rates among the three studies combined and using the calculation 10,000*Mosquito sporozoite rate (%) to develop a maximum and minimum range of possible infected mosquitoes among 10,000 mosquitoes. |

## APPENDIX B. Basic Reproductive Numbers Developed from Time-Series Analyses

| Basic Reproductive Numbers | | | Tanzania Study-Related Parameters | | | | | | Benin Study-Related Parameters | | | | | | Gambia Study-Related Parameters | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Infection Rates Level[1] | Phase Difference | Recovery Rates Level[2] | Group 1 (LLINs Alone) | | | Group 2 (LLINs with IRS) | | | Group 1 (LLINs Alone) | | | Group 2 (LLINs with IRS) | | | Group 1 (LLINs Alone) | | | Group 2 (LLINs with IRS) | | |
| | | | No Nets | New Nets | Used Nets | No Nets | New Nets | Used Nets | No Nets | New Nets | Used Nets | No Nets | New Nets | Used Nets | No Nets | New Nets | Used Nets | No Nets | New Nets | Used Nets |
| Low | 0 Days | Low | 3.01 | 0.45 | 1.03 | 1.81 | 0.27 | 0.62 | 3.34 | 2.39 | 2.65 | 2.38 | 1.71 | 1.89 | 6.58 | 0.99 | 2.26 | 3.56 | 0.54 | 1.22 |
| | | Middle | 0.93 | 0.14 | 0.32 | 0.56 | 0.08 | 0.19 | 1.03 | 0.74 | 0.82 | 0.74 | 0.53 | 0.58 | 2.04 | 0.31 | 0.70 | 1.10 | 0.17 | 0.38 |
| | | High | 0.67 | 0.10 | 0.23 | 0.41 | 0.06 | 0.14 | 0.75 | 0.54 | 0.59 | 0.53 | 0.38 | 0.42 | 1.48 | 0.22 | 0.51 | 0.80 | 0.12 | 0.27 |
| | 90 Days | Low | 2.26 | 0.34 | 0.78 | 1.36 | 0.21 | 0.47 | 2.51 | 1.80 | 1.99 | 1.79 | 1.28 | 1.42 | 4.95 | 0.75 | 1.70 | 2.68 | 0.40 | 0.92 |
| | | Middle | 0.70 | 0.11 | 0.24 | 0.42 | 0.06 | 0.14 | 0.78 | 0.56 | 0.62 | 0.55 | 0.40 | 0.44 | 1.53 | 0.23 | 0.53 | 0.83 | 0.13 | 0.28 |
| | | High | 0.51 | 0.08 | 0.17 | 0.31 | 0.05 | 0.10 | 0.56 | 0.40 | 0.45 | 0.40 | 0.29 | 0.32 | 1.11 | 0.17 | 0.38 | 0.60 | 0.09 | 0.21 |
| | 180 Days | Low | 2.18 | 0.33 | 0.75 | 1.31 | 0.20 | 0.45 | 2.42 | 1.73 | 1.92 | 1.73 | 1.24 | 1.37 | 4.76 | 0.72 | 1.63 | 2.58 | 0.39 | 0.88 |
| | | Middle | 0.67 | 0.10 | 0.23 | 0.41 | 0.06 | 0.14 | 0.75 | 0.54 | 0.59 | 0.53 | 0.38 | 0.42 | 1.47 | 0.22 | 0.51 | 0.80 | 0.12 | 0.27 |
| | | High | 0.49 | 0.07 | 0.17 | 0.29 | 0.04 | 0.10 | 0.54 | 0.39 | 0.43 | 0.39 | 0.28 | 0.31 | 1.07 | 0.16 | 0.37 | 0.58 | 0.09 | 0.20 |
| Middle-level | 0 Days | Low | 10.9 | 1.65 | 3.74 | 9.50 | 1.43 | 3.26 | 6.48 | 4.64 | 5.13 | 4.83 | 3.46 | 3.83 | 10.6 | 1.60 | 3.64 | 6.49 | 0.98 | 2.23 |
| | | Middle | 3.38 | 0.51 | 1.16 | 2.94 | 0.44 | 1.01 | 2.00 | 1.44 | 1.59 | 1.50 | 1.07 | 1.19 | 3.29 | 0.50 | 1.13 | 2.01 | 0.30 | 0.69 |
| | | High | 2.45 | 0.37 | 0.84 | 2.13 | 0.32 | 0.73 | 1.45 | 1.04 | 1.15 | 1.08 | 0.78 | 0.86 | 2.38 | 0.36 | 0.82 | 1.46 | 0.22 | 0.50 |
| | 90 Days | Low | 8.21 | 1.24 | 2.81 | 7.14 | 1.08 | 2.45 | 4.87 | 3.49 | 3.86 | 3.64 | 2.61 | 2.88 | 7.98 | 1.21 | 2.74 | 4.88 | 0.74 | 1.67 |
| | | Middle | 2.54 | 0.38 | 0.87 | 2.21 | 0.33 | 0.76 | 1.51 | 1.08 | 1.19 | 1.13 | 0.81 | 0.89 | 2.47 | 0.37 | 1.85 | 1.51 | 0.23 | 0.52 |
| | | High | 1.84 | 0.28 | 0.63 | 1.60 | 0.24 | 0.55 | 1.09 | 0.78 | 0.87 | 0.82 | 0.58 | 0.65 | 1.79 | 0.27 | 0.61 | 1.09 | 0.17 | 0.38 |
| | 180 Days | Low | 7.90 | 1.19 | 2.71 | 6.88 | 1.04 | 2.36 | 4.69 | 3.36 | 3.72 | 3.50 | 2.51 | 2.77 | 7.69 | 1.16 | 2.64 | 4.70 | 0.71 | 1.61 |
| | | Middle | 2.45 | 0.37 | 0.84 | 2.13 | 0.32 | 0.73 | 1.45 | 1.04 | 1.15 | 1.08 | 0.78 | 0.86 | 2.38 | 0.36 | 0.82 | 1.45 | 0.22 | 0.50 |
| | | High | 1.77 | 0.27 | 0.61 | 1.54 | 0.23 | 0.53 | 1.05 | 0.75 | 0.83 | 0.79 | 0.56 | 0.62 | 1.72 | 0.26 | 0.59 | 1.05 | 0.16 | 0.36 |
| High | 0 Days | Low | 38.1 | 5.75 | 13.05 | 46.3 | 6.99 | 15.88 | 11.7 | 8.40 | 9.28 | 8.86 | 6.35 | 7.02 | 14.7 | 2.21 | 5.02 | 9.42 | 1.42 | 3.23 |
| | | Middle | 11.8 | 1.78 | 4.04 | 14.3 | 2.16 | 4.91 | 3.63 | 2.60 | 2.87 | 2.74 | 1.97 | 2.17 | 4.53 | 0.68 | 1.56 | 2.91 | 0.44 | 1.00 |
| | | High | 8.54 | 1.29 | 2.93 | 10.4 | 1.57 | 3.56 | 2.63 | 1.88 | 2.08 | 1.99 | 1.42 | 1.57 | 3.29 | 0.50 | 1.13 | 2.11 | 0.32 | 0.72 |
| | 90 Days | Low | 28.6 | 4.32 | 9.82 | 34.8 | 5.26 | 11.94 | 8.81 | 6.31 | 6.98 | 6.67 | 4.78 | 5.28 | 11.0 | 1.66 | 3.78 | 7.08 | 1.07 | 2.43 |
| | | Middle | 8.86 | 1.34 | 3.04 | 10.8 | 1.63 | 3.70 | 2.73 | 1.95 | 2.16 | 2.06 | 1.48 | 1.63 | 3.41 | 0.52 | 1.17 | 2.19 | 0.33 | 0.75 |
| | | High | 6.42 | 0.97 | 2.20 | 7.81 | 1.18 | 2.68 | 1.98 | 1.42 | 1.57 | 1.49 | 1.07 | 1.18 | 2.47 | 0.37 | 0.85 | 1.59 | 0.24 | 0.54 |
| | 180 Days | Low | 27.5 | 4.16 | 9.45 | 33.5 | 5.06 | 11.50 | 8.48 | 6.08 | 6.72 | 6.42 | 4.60 | 5.09 | 10.6 | 1.60 | 3.64 | 6.82 | 1.03 | 2.34 |
| | | Middle | 8.53 | 1.29 | 2.93 | 10.4 | 1.57 | 3.56 | 2.63 | 1.88 | 2.08 | 1.99 | 1.42 | 1.57 | 3.28 | 0.50 | 1.13 | 2.11 | 0.32 | 0.72 |
| | | High | 6.18 | 0.93 | 2.12 | 7.52 | 1.14 | 2.58 | 1.90 | 1.36 | 1.51 | 1.44 | 1.03 | 1.14 | 2.38 | 0.36 | 0.82 | 1.53 | 0.23 | 0.52 |

1. Low, middle and high malaria infection rates were based on the minimum tested range value, the value in the Parameter Values Tested in Time-Series Analyses section and the maximum tested range value, respectively for the average malaria infection/transmission rates for humans ($b_0$) and mosquitoes ($b_2$) from Appendix A and were related to each specific study that the values were tested.

2. Low, middle and high recovery rates were based on the minimum tested range value, the value in the Parameter Values Tested in Time-Series Analyses section and the maximum tested range value, respectively for the Infected to Susceptible Recovery Rate (h) and the Infected to Recovered/Immune Recovery Rate ($\alpha$) from Appendix A and were related to each specific study that the values were tested.

# APPENDIX C: MATLAB CODE

## C.1 - Ordinary Differential Equations

```
function yp=MFileforThesisODEs(t,y)

global t2 R0TOP R0BOTTOM R0 lambdaH S0 M0 N0 phi h delta rho alpha gamma b0
b1 b2 b3 muhum mumos lambdaQ psi BetHum BetMos

BetHum=b0.*(1+(b1.*(cos(2*pi*t+rho))));
BetMos=b2.*(1+(b3.*(cos(2*pi*t+rho))));

%Formulas for the Human Population
yp(1,:)=lambdaH-(1-phi)*BetHum.*( (y(1).*y(5))/(y(4)+y(5))  )
+h.*y(2)+delta.*y(3)-muhum.*y(1);
yp(2,:)=(1-phi)*BetHum.*(  (y(1).*y(5))/(y(4)+y(5))) -
(h+alpha+muhum+gamma)*y(2);
yp(3,:)=alpha.*y(2)-delta.*y(3)-muhum.*y(3);

%Formulas for the Mosquito Population
yp(4,:)=lambdaQ-(mumos.*y(4).*(1+psi))-((1-
phi)*BetMos.*((y(4).*y(2))/(y(1)+y(2)+y(3))));
yp(5,:)=-(mumos.*y(5).*(1+psi))+((1-
phi)*BetMos.*((y(4).*y(2))/(y(1)+y(2)+y(3))));
```

## C.2.A. - Tanzania Study Parameters Review – LLINs-Alone Group Values

```
%MFile to use the Malaria Math Model Program
clear all
global lambdaH phi nu h delta rho alpha gamma b0 b1 b2 b3 muhum mumos lambdaQ
psi BetHum BetMos r c x  q z S0 I0 Rt0 M0 N0

%%Human Birth Rate
lambdaH=((39.15/1000)/365.25)*10000;

%%Human Death Rate
muhum=(1/(61.7*365.25));

%%Human Additional Mortality Rate due to Malaria
gamma=0.000090137;

%%Transmission Rates - Humans
%%Infection Rate Parameters - BetaHuman, Susceptible to Infected Human Rate
%b0=0.008;
b0=0.0341;
%b0=0.1344;

b1=0.355;

rho=0;
%rho=90;
%rho=180;
```

```
%%Infected to Susceptible Human Rate
%h=0.00024;
h=0.00262;
%h=0.005;

%%Infected to Recovered Human Rate
%alpha=0.0024;
alpha=0.0262;
%alpha=0.05;

%%Recovered to Susceptible Human Rate
delta=1/(2*365.25);

%%Mosquito Birth Rate
lambdaQ=(3857/365.25);

%%Mosquito Death Rate
mumos=1/27;

%%Transmission Rate - Mosquitoes

%%Infection Rate Parameters - BetaMosquito, Susceptible to Infected Mosquito
Rate
%b2=0.102176;
b2=0.3157877;
%b2=0.9749568;

b3=0.065;

%%Additional Mosquito Death Rate due to Bed Nets
%psi=0; %test without nets
psi=0.42; % 0 washes
%psi=0.36; %20 washes

%%Proportion Reducing Effectiveness of Transmission - Bed Nets
%phi=0; %test without nets
phi=0.82; %0 washes
%phi=0.6; %20 washes

t0=0;
tf=1000;
y0=[8970,1030,0,9860,140];
tspan=[t0,tf];
[t,y]=ode45(@MFileforThesisODEs,tspan,y0);

S0=8970;
I0=1030;
Rt0=0;
M0=9860;
N0=140;

figure(1)
plot(t,y(:,1),'b--',t,y(:,2),'r--',t,y(:,3),'g--
',t,y(:,4),'m:',t,y(:,5),'k:')
```

```
xlabel('Time (Days)')
ylabel('Population')
legend('S - Susceptible Humans','I - Infected Humans','R - Recovered
Humans','M - Susceptible Mosquitoes','N - Infected Mosquitoes')

figure(2)
plot(t,y(:,1),'b--',t,y(:,2),'r--',t,y(:,3),'g--')
xlabel('Time (Days)')
ylabel('Population')
legend('S - Susceptible Humans','I - Infected Humans','R - Recovered Humans')

figure(3)
plot(t,y(:,4),'m--',t,y(:,5),'k--')
xlabel('Time (Days)')
ylabel('Population')
legend('M - Susceptible Mosquitoes','N - Infected Mosquitoes')

R0TOP2= ((1-phi)^2) *(b0.*(1+b1.*(cos(rho))))* (b2.*(1+b3.*(cos(rho)))) *S0.*
(M0.^2)*(S0+Rt0);
R0BOTTOM2= ((h+alpha+muhum+gamma)* mumos.* (1+psi)* ((M0+N0)^2)*
((S0+I0+Rt0)^2));
R0=sqrt(R0TOP2/R0BOTTOM2)
```

### C.2.B. - Tanzania Study Parameters Review – LLINs with IRS Group Values

```
%MFile to use the Malaria Math Model Program
clear all
global lambdaH phi nu h delta rho alpha gamma b0 b1 b2 b3 muhum mumos lambdaQ
psi BetHum BetMos r c S0 M0 N0 I0 Rt0

%%Human Birth Rate
lambdaH=((39.15/1000)/365.25)*10000;

%%Human Death Rate
muhum=(1/(61.7*365.25));

%%Human Additional Mortality Rate due to Malaria
gamma=0.000090137;

%%Transmission Rates - Humans
%%Infection Rate Parameters - BetaHuman, Susceptible to Infected Human Rate
%b0=0.007;
b0=0.044;
%b0=0.2548;

b1=0.355;

rho=0;
%rho=90;
%rho=180;

%%Infected to Susceptible Human Rate
%h=0.00024;
```

```
h=0.00262;
%h=0.005;

%%Infected to Recovered Human Rate
%alpha=0.0024;
alpha=0.0262;
%alpha=0.05;

%%Recovered to Susceptible Human Rate
delta=1/(2*365.25);

%%Mosquito Birth Rate
lambdaQ=(3857/365.25);

%%Mosquito Death Rate
mumos=1/27;

%%Transmission Rate - Mosquitoes
%%Infection Rate Parameters - BetaMosquito, Susceptible to Infected Mosquito
Rate
%b2=0.041412;
b2=0.181104;
%b2=0.7429968;

b3=0.065;

%%Additional Mosquito Death Rate due to Bed Nets
%psi=0;%test without nets
psi=0.42; % 0 washes
%psi=0.36; %20 washes

%%Proportion Reducing Effectiveness of Transmission - Bed Nets
%phi=0; %test without nets
phi=0.82; %0 washes
%phi=0.6; %20 washes



%%Proportion of Mosquitoes resistant to IRS Insecticide - IRS
c=0.257;

%%Proportion of Mosquitoes reduced to IRS insecticide - IRS
r=0.9322;

y0=[9160,840,0,9800,200];

%%%IDEs and ODEs code together to run below
t0=0;
tq=[];
yq=[];
yq=[];
mq=[];

%nu=7; %spraying at 1 week intervals
%nu=30.42; %spraying at 1 month intervals
```

```
%nu=60.83; %spraying at 2 month intervals
nu=91.25; %spraying at 3 month intervals

reps = (1000/nu);

for i=1:reps
 tspan=[t0 t0+nu];
 [t,y] = ode45(@MFileforThesisODEs,tspan,y0);
 n=length(y);
 y0=y(n,:);
 y0(4)=(1-r+(r.*c)).*y(n,4);
 y0(5)=(1-r+(r.*c)).*y(n,5);
 tf=t(n);
 tq=[tq;t(1:n)];
 yq=[yq;y((1:n),:)];
 mq=[mq;mean(y)];
 t0=tf;
end


figure(1)
plot(tq,yq(:,1),'b--',tq,yq(:,2),'r--',tq,yq(:,3),'g--', tq,yq(:,4),'m:',
tq,yq(:,5),'k:')
xlabel('Time (Days)')
ylabel('Population')
legend('S - Susceptible Humans','I - Infected Humans','R - Recovered
Humans','M - Susceptible Mosquitoes','N - Infected Mosquitoes')

figure(2)
plot(tq,yq(:,1),'b--',tq,yq(:,2),'r--',tq,yq(:,3),'g--')
xlabel('Time (Days)')
ylabel('Population')
legend('S - Susceptible Humans','I - Infected Humans','R - Recovered Humans')

figure(3)
plot(tq,yq(:,4),'m--',tq,yq(:,5),'k--')
xlabel('Time (Days)')
ylabel('Population')
legend('M - Susceptible Mosquitoes','N - Infected Mosquitoes')


%%%ODEs only
%t0=0;
%tf=1000;
%tspan=[t0,tf];
%[t,y]=ode45(@MFileforThesisODEs,tspan,y0);

%figure(1)
%plot(t,y(:,1),'b--',t,y(:,2),'r--',t,y(:,3),'g--
',t,y(:,4),'m:',t,y(:,5),'k:')
%xlabel('Time (Days)')
%ylabel('Population')
%legend('S - Susceptible Humans','I - Infected Humans','R - Recovered
Humans','M - Susceptible Mosquitoes','N - Infected Mosquitoes')
```

```
%figure(2)
%plot(t,y(:,1),'b--',t,y(:,2),'r--',t,y(:,3),'g--')
%xlabel('Time (Days)')
%ylabel('Population')
%legend('S - Susceptible Humans','I - Infected Humans','R - Recovered
Humans')

%figure(3)
%plot(t,y(:,4),'m--',t,y(:,5),'k--')
%xlabel('Time (Days)')
%ylabel('Population')
%legend('M - Susceptible Mosquitoes','N - Infected Mosquitoes')

S0=9160;
I0=840;
Rt0=0;
M0=9800;
N0=200;

R0TOP2= ((1-phi)^2)* (b0.*(1+b1.*(cos(rho))))* (b2.*(1+b3.*(cos(rho))))*
S0.*(M0.^2)*(S0+Rt0);
R0BOTTOM2=
((h+alpha+muhum+gamma)*mumos.*(1+psi)*((M0+N0)^2)*((S0+I0+Rt0)^2));
R0=sqrt(R0TOP2/R0BOTTOM2)
```

### C.3.A. - Benin Study Parameters Review – LLINs-Alone Group Values

```
%MFile to use the Malaria Math Model Program
clear all
global lambdaH phi nu h delta rho alpha gamma b0 b1 b2 b3 muhum mumos lambdaQ
psi BetHum BetMos r c S0 I0 Rt0 N0 M0

%%Human Birth Rate
lambdaH=((36.41/1000)/365.25)*10000;

%%Human Death Rate
muhum=(1/(63.4*365.25));

%%Human Additional Mortality Rate due to Malaria
gamma=0.000090137;

%%Transmission Rates - Humans
%%Infection Rate Parameters - BetaHuman, Susceptible to Infected Human Rate
%b0=0.010149;
b0=0.025396;
%b0=0.05524;

b1=0.355;

rho=0;
%rho=90;
%rho=180;

%%Infected to Susceptible Human Rate
```

```
%h=0.00024;
h=0.00262;
%h=0.005;

%%Infected to Recovered Human Rate
%alpha=0.0024;
alpha=0.0262;
%alpha=0.05;

%%Recovered to Susceptible Human Rate
delta=1/(2*365.25);

%%Mosquito Birth Rate
lambdaQ=(3857/365.25);

%%Mosquito Death Rate
mumos=1/27;

%%Transmission Rate - Mosquitoes
%%Infection Rate Parameters - BetaMosquito, Susceptible to Infected Mosquito
Rate
%b2=0.148473303;
b2=0.223045812;
%b2=0.33541728;

b3=0.065;

%%Additional Mosquito Death Rate due to Bed Nets
%psi=0;%test without nets
psi=0.44; %0 washes
%psi=0.29; %20 washes

%%Proportion Reducing Effectiveness of Transmission - Bed Nets
%phi=0; %test without nets
phi=0.14; %0 washes
%phi=0.1; %20 washes

t0=0;
tf=1000;
y0=[7470,2530,0,9720,280];

tspan=[t0,tf];
[t,y]=ode45(@MFileforThesisODEs,tspan,y0);

S0=7470;
I0=2530;
Rt0=0;
M0=9720;
N0=280;

figure(1)
plot(t,y(:,1),'b--',t,y(:,2),'r--',t,y(:,3),'g--
',t,y(:,4),'m:',t,y(:,5),'k:')
xlabel('Time (Days)')
ylabel('Population')
```

```
legend('S - Susceptible Humans','I - Infected Humans','R - Recovered
Humans','M - Susceptible Mosquitoes','N - Infected Mosquitoes')

figure(2)
plot(t,y(:,1),'b--',t,y(:,2),'r--',t,y(:,3),'g--')
xlabel('Time (Days)')
ylabel('Population')
legend('S - Susceptible Humans','I - Infected Humans','R - Recovered Humans')

figure(3)
plot(t,y(:,4),'m--',t,y(:,5),'k--')
xlabel('Time (Days)')
ylabel('Population')
legend('M - Susceptible Mosquitoes','N - Infected Mosquitoes')

R0TOP2= ((1-phi)^2)* (b0.*(1+b1.*(cos(rho))))*
(b2.*(1+b3.*(cos(rho))))*S0.*(M0.^2)*(S0+Rt0);
R0BOTTOM2= ((h+alpha+muhum+gamma)*
mumos.*(1+psi)*((M0+N0)^2)*((S0+I0+Rt0)^2));
R0=sqrt(R0TOP2/R0BOTTOM2)
```

### C.3.B. - Benin Study Parameters Review – LLINs with IRS Group Values

```
%MFile to use the Malaria Math Model Program
clear all
global lambdaH phi nu h delta rho alpha gamma b0 b1 b2 b3 muhum mumos lambdaQ
psi BetHum BetMos r c S0 I0 Rt0 M0 N0

%%Human Birth Rate
lambdaH=((36.41/1000)/365.25)*10000;

%%Human Death Rate
muhum=(1/(63.4*365.25));


%%Human Additional Mortality Rate due to Malaria
gamma=0.000090137;

%%Transmission Rates - Humans
%%Infection Rate Parameters - BetaHuman, Susceptible to Infected Human Rate
%b0=0.007344;
b0=0.02;
%b0=0.044791;

b1=0.355;

rho=0;
%rho=90;
%rho=180;

%%Infected to Susceptible Human Rate
%h=0.00024;
h=0.00262;
```

```
%h=0.005;

%%Infected to Recovered Human Rate
%alpha=0.0024;
alpha=0.0262;
%alpha=0.05;

%%Recovered to Susceptible Human Rate
delta=1/(2*365.25);

%%Mosquito Birth Rate
lambdaQ=(3857/365.25);

%%Mosquito Death Rate
mumos=1/27;

%%Transmission Rate - Mosquitoes
%%Infection Rate Parameters - BetaMosquito, Susceptible to Infected Mosquito
Rate
%b2=0.149444688;
b2=0.225665;
%b2=0.338761957;

b3=0.065;

%%Additional Mosquito Death Rate due to Bed Nets
%psi=0; %no nets
psi=0.44; %0 Washes
%psi=0.29; %20 Washes

%%Proportion Reducing Effectiveness of Transmission - Bed Nets
%phi=0; %no nets
phi=0.14; %0 Washes
%phi=0.1; %20 Washes

%%Proportion of Mosquitoes resistant to IRS Insecticide - IRS
c=0.257;

%%Proportion of Mosquitoes reduced to IRS insecticide - IRS
r=0.9322;

y0=[6270,3730,0,9680,320];

%%ODEs and IDEs run here
t0=0;
tq=[];
yq=[];
yq=[];
mq=[];

%nu=7; %spraying at 1 week intervals
%nu=30.42; %spraying at 1 month intervals
%nu=60.83; %spraying at 2 month intervals
nu=91.25; %spraying at 3 month intervals
```

```
reps = (1000/nu);

for i=1:reps
 tspan=[t0 t0+nu];
 [t,y] = ode45(@MFileforThesisODEs,tspan,y0);
 n=length(y);
 y0=y(n,:);
 y0(4)=(1-r+(r.*c)).*y(n,4);
 y0(5)=(1-r+(r.*c)).*y(n,5);
 tf=t(n);
 tq=[tq;t(1:n)];
 yq=[yq;y((1:n),:)];
 mq=[mq;mean(y)];
 t0=tf;
end

figure(1)
plot(tq,yq(:,1),'b--',tq,yq(:,2),'r--',tq,yq(:,3),'g--
',tq,yq(:,4),'m:',tq,yq(:,5),'k:')
xlabel('Time (Days)')
ylabel('Population')
legend('S - Susceptible Humans','I - Infected Humans','R - Recovered
Humans','M - Susceptible Mosquitoes','N - Infected Mosquitoes')

figure(2)
plot(tq,yq(:,1),'b--',tq,yq(:,2),'r--',tq,yq(:,3),'g--')
xlabel('Time (Days)')
ylabel('Population')
legend('S - Susceptible Humans','I - Infected Humans','R - Recovered Humans')

figure(3)
plot(tq,yq(:,4),'m--',tq,yq(:,5),'k--')
xlabel('Time (Days)')
ylabel('Population')
legend('M - Susceptible Mosquitoes','N - Infected Mosquitoes')


%%%ODEs only Run
%t0=0;
%tf=1000;
%tspan=[t0,tf];
%[t,y]=ode45(@MFileforThesisODEs,tspan,y0);

%figure(1)
%plot(t,y(:,1),'b--',t,y(:,2),'r--',t,y(:,3),'g--
',t,y(:,4),'m:',t,y(:,5),'k:')
%xlabel('Time (Days)')
%ylabel('Population')
%legend('S - Susceptible Humans','I - Infected Humans','R - Recovered
Humans','M - Susceptible Mosquitoes','N - Infected Mosquitoes')

%figure(2)
%plot(t,y(:,1),'b--',t,y(:,2),'r--',t,y(:,3),'g--')
%xlabel('Time (Days)')
%ylabel('Population')
```

```
%legend('S - Susceptible Humans','I - Infected Humans','R - Recovered
Humans')

%figure(3)
%plot(t,y(:,4),'m--',t,y(:,5),'k--')
%xlabel('Time (Days)')
%ylabel('Population')
%legend('M - Susceptible Mosquitoes','N - Infected Mosquitoes')

S0=6270;
I0=3730;
Rt0=0;
M0=9680;
N0=320;

R0TOP2= ((1-phi)^2)*(b0.*(1+b1.*(cos(rho))))*
(b2.*(1+b3.*(cos(rho))))*S0.*(M0.^2)*(S0+Rt0);
R0BOTTOM2= ((h+alpha+muhum+gamma)*mumos.*
(1+psi)*((M0+N0)^2)*((S0+I0+Rt0)^2));
R0=sqrt(R0TOP2/R0BOTTOM2)
```

### C.4.A. – The Gambia Study Parameters Review – LLINs-Alone Group Values

```
%MFile to use the Malaria Math Model Program
clear all
global lambdaH phi nu h delta rho alpha gamma b0 b1 b2 b3 muhum mumos lambdaQ
psi BetHum BetMos r c x S0 I0 M0 N0 Rt0

%%Human Birth Rate
lambdaH=((42.73/1000)/365.25)*10000;

%%Human Death Rate
muhum=(1/(62.2*365.25));

%%Human Additional Mortality Rate due to Malaria
gamma=0.000090137;

%%Transmission Rates - Humans
%%Infection Rate Parameters - BetaHuman, Susceptible to Infected Human Rate
%b0=0.00976;
b0=0.015744;
%b0=0.021728;

b1=0.355;

rho=0;
%rho=90;
%rho=180;

%%Infected to Susceptible Human Rate
%h=0.00024;
h=0.00262;
%h=0.005;
```

```
%%Infected to Recovered Human Rate
%alpha=0.0024;
alpha=0.0262;
%alpha=0.05;

%%Recovered to Susceptible Human Rate
delta=1/(2*365.25);

%%Mosquito Birth Rate
lambdaQ=(3857/365.25);

%%Mosquito Death Rate
mumos=1/27;

%%Transmission Rate - Mosquitoes
%%Infection Rate Parameters - BetaMosquito, Susceptible to Infected Mosquito
Rate
%b2=0.43171408;
b2=0.696404352;
%b2=0.961094624;

b3=0.065;

%%Additional Mosquito Death Rate due to Bed Nets
%psi=0;%test without nets
psi=0.42; % 0 washes
%psi=0.36; %20 washes

%%Proportion Reducing Effectiveness of Transmission - Bed Nets
%phi=0; %test without nets
phi=0.82; %0 washes
%phi=0.6; %20 washes

t0=0;
tf=1000;
y0=[8580,1420,0,9968,32];

%more susceptible as a test
tspan=[t0,tf];
[t,y]=ode45(@MFileforThesisODEs,tspan,y0);

figure(1)
plot(t,y(:,1),'b--',t,y(:,2),'r--',t,y(:,3),'g--
',t,y(:,4),'m:',t,y(:,5),'k:')
xlabel('Time (Days)')
ylabel('Population')
legend('S - Susceptible Humans','I - Infected Humans','R - Recovered
Humans','M - Susceptible Mosquitoes','N - Infected Mosquitoes')

figure(2)
plot(t,y(:,1),'b--',t,y(:,2),'r--',t,y(:,3),'g--')
xlabel('Time (Days)')
ylabel('Population')
```

```
legend('S - Susceptible Humans','I - Infected Humans','R - Recovered Humans')

figure(3)
plot(t,y(:,4),'m--',t,y(:,5),'k--')
xlabel('Time (Days)')
ylabel('Population')
legend('M - Susceptible Mosquitoes','N - Infected Mosquitoes')

S0=8580;
I0=1420;
Rt0=0;
M0=9968;
N0=32;

R0TOP2= ((1-phi)^2)*(b0.*(1+b1.*(cos(rho))))*(b2.*(1+b3.*
(cos(rho))))*S0.*(M0.^2)*(S0+Rt0);
R0BOTTOM2= ((h+alpha+muhum+gamma)*mumos.*
(1+psi)*((M0+N0)^2)*((S0+I0+Rt0)^2));
R0=sqrt(R0TOP2/R0BOTTOM2)
```

### C.4.B. – The Gambia Study Parameters Review – LLINs with IRS Group Values

```
%MFile to use the Malaria Math Model Program
clear all
global lambdaH phi nu h delta rho alpha gamma b0 b1 b2 b3 muhum mumos lambdaQ
psi BetHum BetMos r c S0 I0 N0 M0 Rt0

%%Human Birth Rate
lambdaH=((42.73/1000)/365.25)*10000;

%%Human Death Rate
muhum=(1/(62.2*365.25));


%%Human Additional Mortality Rate due to Malaria
gamma=0.000090137;

%%Transmission Rates - Humans
%%Infection Rate Parameters - BetaHuman, Susceptible to Infected Human Rate
%b0=0.003857;
b0=0.00703;
%b0=0.010203;

b1=0.355;

rho=0;
%rho=90;
%rho=180;

%%Infected to Susceptible Human Rate
%h=0.00024;
h=0.00262;
%h=0.005;
```

```
%%Infected to Recovered Human Rate
%alpha=0.0024;
alpha=0.0262;
%alpha=0.05;

%%Recovered to Susceptible Human Rate
delta=1/(2*365.25);


%%Mosquito Birth Rate
lambdaQ=(3857/365.25);

%%Mosquito Death Rate
mumos=1/27;

%%Transmission Rate - Mosquitoes
%%Infection Rate Parameters - BetaMosquito, Susceptible to Infected Mosquito
Rate
%b2=0.338365881;
b2=0.61672599;
%b2=0.895086099;

b3=0.065;

%%Additional Mosquito Death Rate due to Bed Nets
%psi=0;%test without nets
psi=0.42; % 0 washes
%psi=0.36; %20 washes

%%Proportion Reducing Effectiveness of Transmission - Bed Nets
%phi=0; %test without nets
phi=0.82; %0 washes
%phi=0.6; %20 washes

 %%Proportion of Mosquitoes resistant to IRS Insecticide - IRS
c=0.095367847;

%%Proportion of Mosquitoes reduced to IRS insecticide - IRS
r=0.94;

 y0=[8330,1670,0,9981,19];

%%%ODEs and IDEs code to run
t0=0;
tq=[];
yq=[];
yq=[];
mq=[];

%nu=7; %spraying at 1 week intervals
%nu=30.42; %spraying at 1 month intervals
%nu=60.83; %spraying at 2 month intervals
nu=91.25; %spraying at 3 month intervals
```

```
reps=(1000/nu);

for i=1:reps
 tspan=[t0 t0+nu];
 [t,y] = ode45(@MFileforThesisODEs,tspan,y0);
 n=length(y);
 y0=y(n,:);
 y0(4)=(1-r+(r.*c)).*y(n,4);
 y0(5)=(1-r+(r.*c)).*y(n,5);
tf=t(n);
 tq=[tq;t(1:n)];
 yq=[yq;y((1:n),:)];
 mq=[mq;mean(y)];
 t0=tf;
end

figure(1)
plot(tq,yq(:,1),'b--',tq,yq(:,2),'r--',tq,yq(:,3),'g--
',tq,yq(:,4),'m:',tq,yq(:,5),'k:')
xlabel('Time (Days)')
ylabel('Population')
legend('S - Susceptible Humans','I - Infected Humans','R - Recovered
Humans','M - Susceptible Mosquitoes','N - Infected Mosquitoes')

figure(2)
plot(tq,yq(:,1),'b--',tq,yq(:,2),'r--',tq,yq(:,3),'g--')
xlabel('Time (Days)')
ylabel('Population')
legend('S - Susceptible Humans','I - Infected Humans','R - Recovered Humans')

figure(3)
plot(tq,yq(:,4),'m--',tq,yq(:,5),'k--')
xlabel('Time (Days)')
ylabel('Population')
legend('M - Susceptible Mosquitoes','N - Infected Mosquitoes')

%%%ODEs only Run
%t0=0;
%tf=1000;
%tspan=[t0,tf];
%[t,y]=ode45(@MFileforThesisODEs,tspan,y0);

%figure(1)
%plot(t,y(:,1),'b--',t,y(:,2),'r--',t,y(:,3),'g--
',t,y(:,4),'m:',t,y(:,5),'k:')
%xlabel('Time (Days)')
%ylabel('Population')
%legend('S - Susceptible Humans','I - Infected Humans','R - Recovered
Humans','M - Susceptible Mosquitoes','N - Infected Mosquitoes')

%figure(2)
%plot(t,y(:,1),'b--',t,y(:,2),'r--',t,y(:,3),'g--')
%xlabel('Time (Days)')
%ylabel('Population')
%legend('S - Susceptible Humans','I - Infected Humans','R - Recovered
Humans')
```

```
%figure(3)
%plot(t,y(:,4),'m--',t,y(:,5),'k--')
%xlabel('Time (Days)')
%ylabel('Population')
%legend('M - Susceptible Mosquitoes','N - Infected Mosquitoes')

S0=8330;
I0=1670;
Rt0=0;
M0=9981;
N0=19;

R0TOP2= ((1-phi)^2)*(b0.*(1+b1.*(cos(rho))))*
(b2.*(1+b3.*(cos(rho))))*S0.*(M0.^2)*(S0+Rt0);
R0BOTTOM2= ((h+alpha+muhum+gamma)*mumos.*
(1+psi)*((M0+N0)^2)*((S0+I0+Rt0)^2));
R0=sqrt(R0TOP2/R0BOTTOM2)
```

## APPENDIX D. Efficacy of Only LLINs – New LLINs vs. Used LLINs

### Tanzania Study

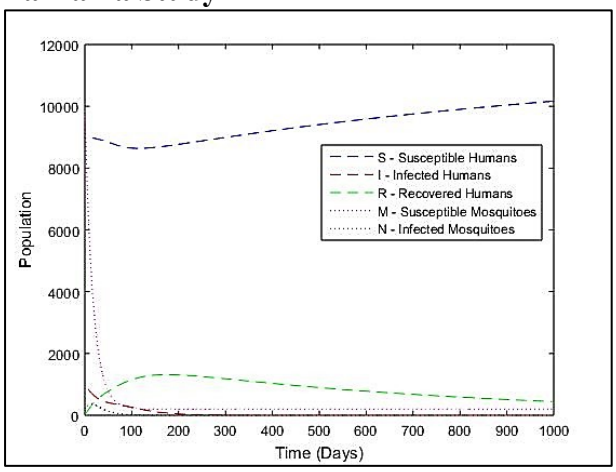



**Figure D.1A**: Tanzania Study, Group 1, New LLINs, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.51$

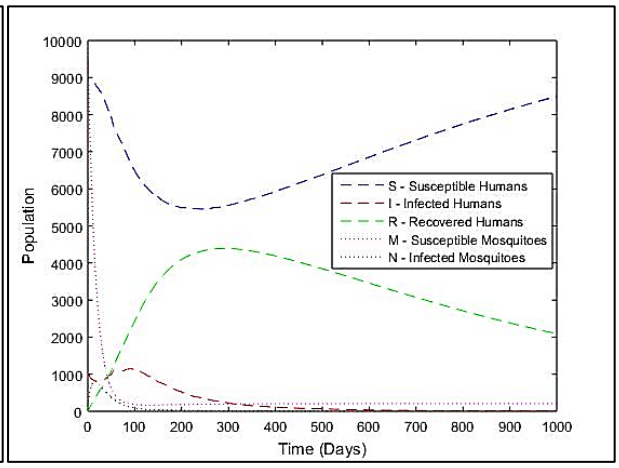



**Figure D.1B**: Tanzania Study, Group 1, Used LLINs, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.16$

### Benin Study

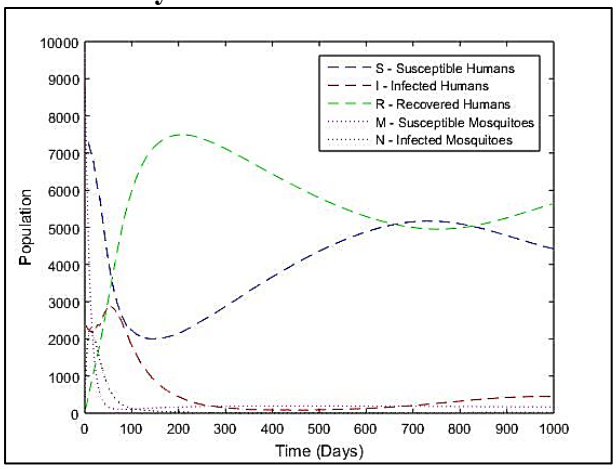



**Figure D.2A**: Benin Study, Group 1, New LLINs, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.44$

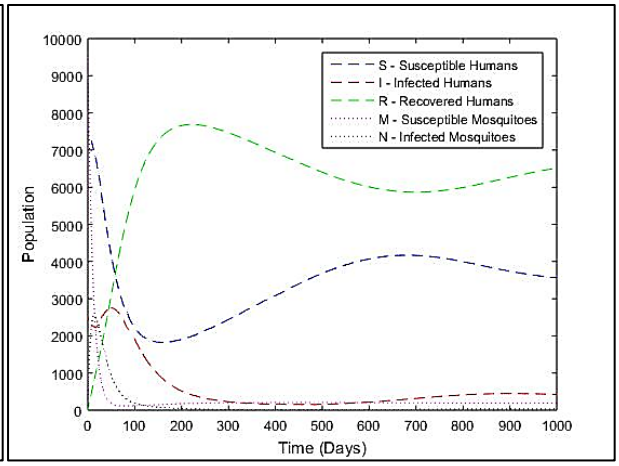



**Figure D.2B**: Benin Study, Group 1, Used LLINs, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.59$

## The Gambia Study

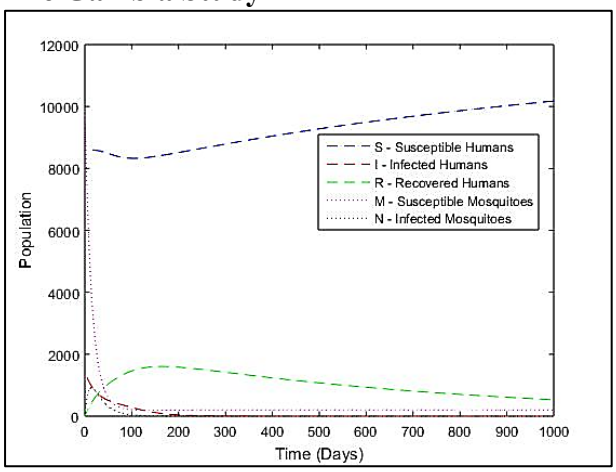



**Figure D.3A**: The Gambia Study, Group 1, New LLINs, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.50$

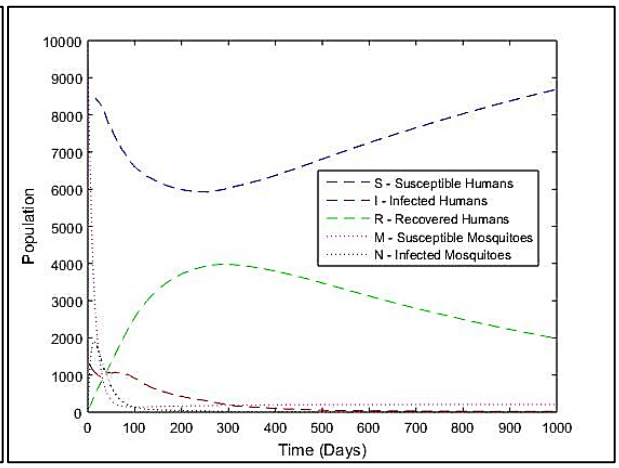



**Figure D.3B**: The Gambia Study, Group 1, Used LLINs, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.13$

## APPENDIX E. Efficacy of LLINs with IRS – New LLINs – Group 1 to Group 2 Comparisons

### Tanzania Study

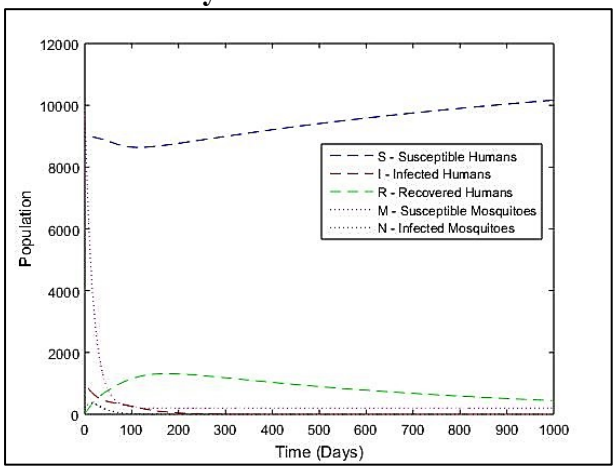



**Figure E.1A**: Tanzania Study, Group 1, New LLINs only, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.51$

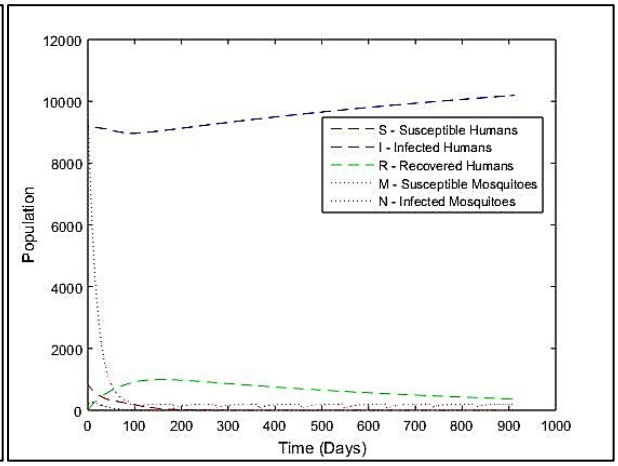



**Figure E.1B**: Tanzania Study, Group 2, New LLINs, IRS 3 month intervals, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.44$

### Benin Study

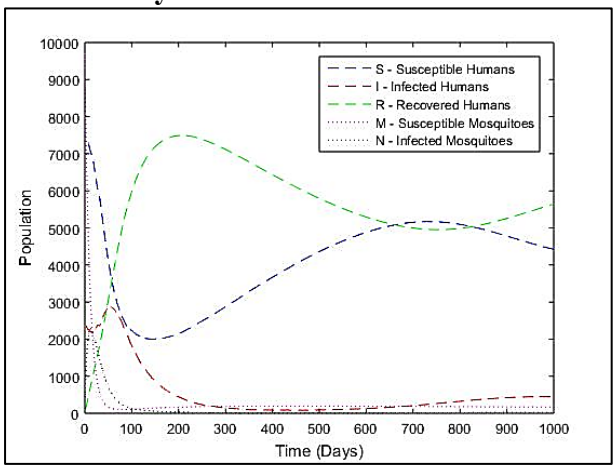



**Figure E.2A**: Benin Study, Group 1, New LLINs only, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.44$

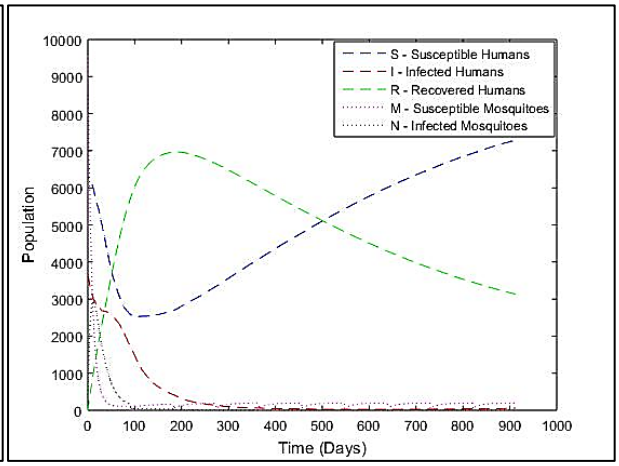



**Figure E.2B**: Benin Study, Group 2, New LLINs, IRS 3 month intervals, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.07$

## The Gambia Study

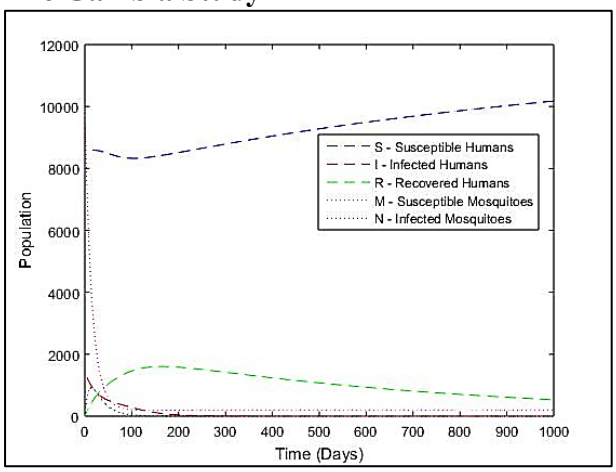



**Figure E.3A**: The Gambia Study, Group 1, New LLINs only, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.50$

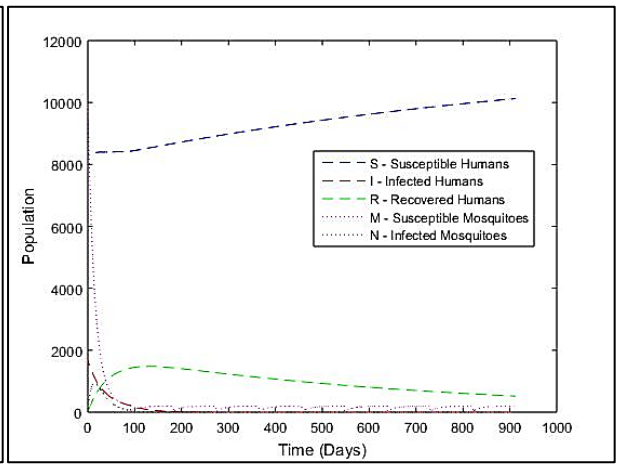



**Figure E.3B**: The Gambia Study, Group 2, New LLINs, IRS 3 month intervals, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.30$

## APPENDIX F. Efficacy of LLINs with IRS – Used LLINs

### Tanzania Study

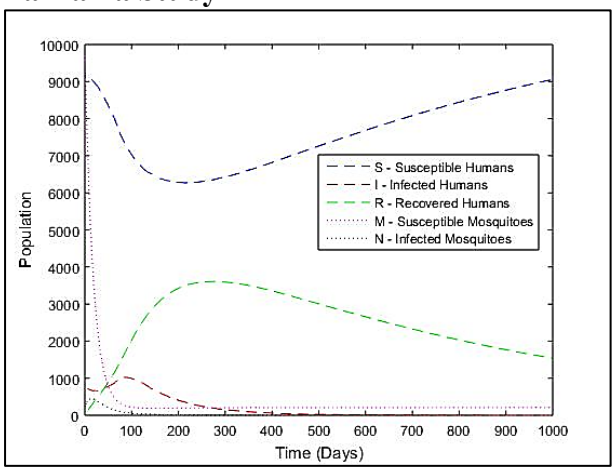



**Figure F.1A**: Tanzania Study, Group 2, Used LLINs only, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0$ = 1.01

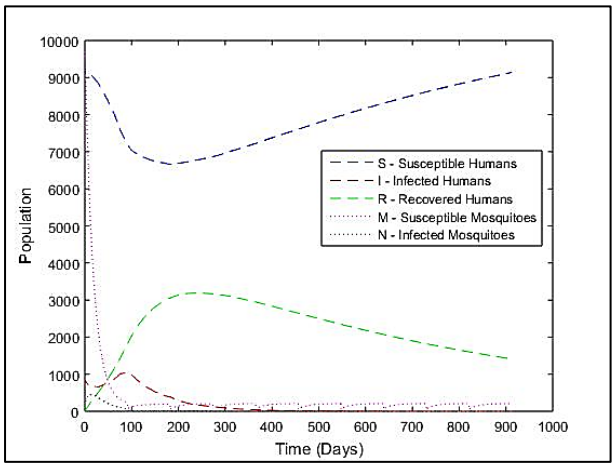



**Figure F.1B**: Tanzania Study, Group 2, Used LLINs, IRS 3 month intervals, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0$ =1.01

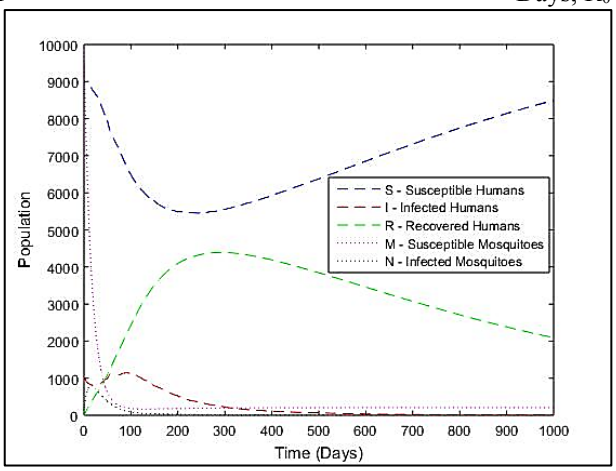



**Figure F.1C**: Tanzania Study, Group 1, Used LLINs only, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0$ = 1.16

## Benin Study

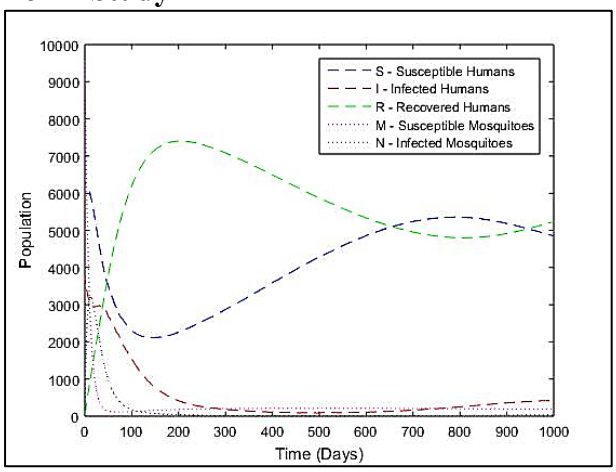



**Figure F.2A**: Benin Study, Group 2, Used LLINs only, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.19$

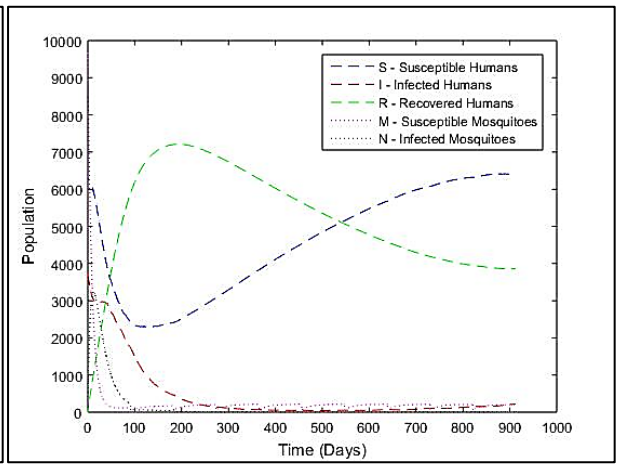



**Figure F.2B**: Benin Study, Group 2, Used LLINs, IRS 3 month intervals, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.19$

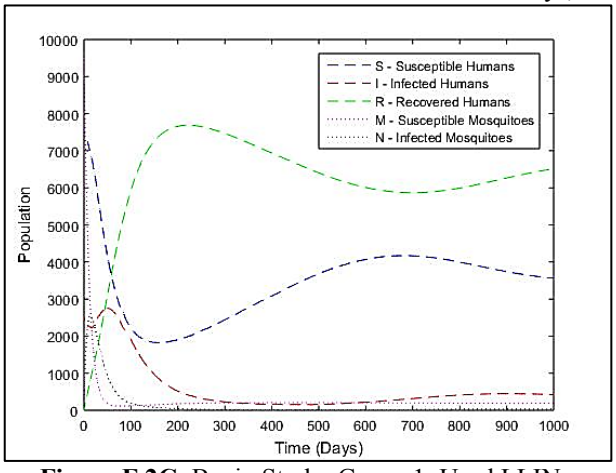



**Figure F.2C**: Benin Study, Group 1, Used LLINs only, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.59$

## The Gambia Study

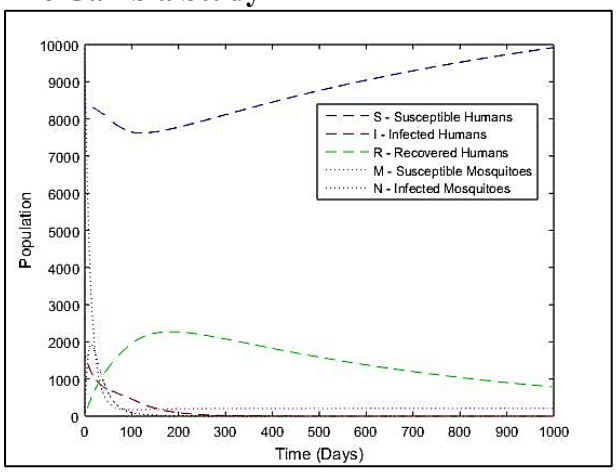



**Figure F.3A**: The Gambia Study, Group 2, Used LLINs only, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0$ = 0.69

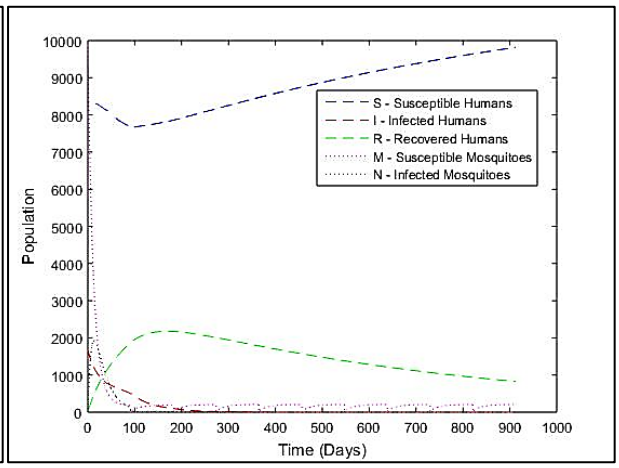



**Figure F.3B**: The Gambia Study, Group 2, Used LLINs, IRS 3 month intervals, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0$ = 0.69

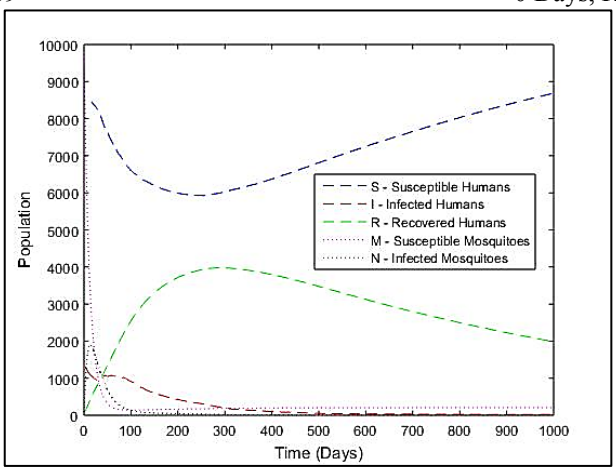



**Figure F.3C**: The Gambia Study, Group 1, Used LLINs only, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0$ = 1.13

## APPENDIX G. LLINs with IRS – Shorter IRS Intervals – New LLINs

### Tanzania Study

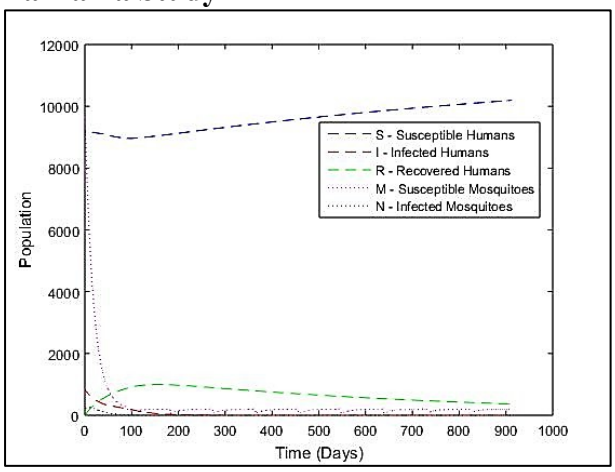



**Figure G.1A**: Tanzania Study, Group 2, New LLINs, IRS **3 Month Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.44$

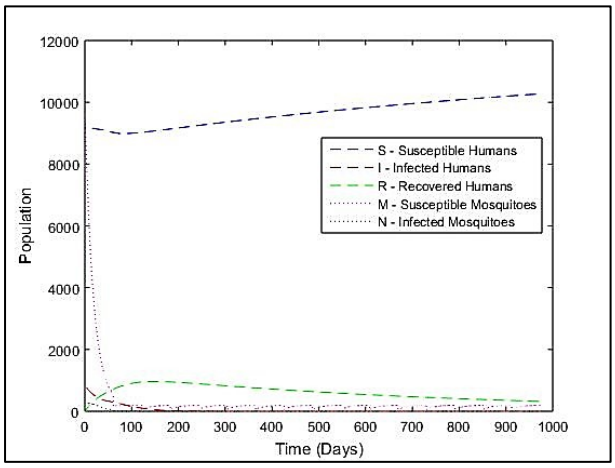



**Figure G.1B**: Tanzania Study, Group 2, New LLINs, IRS **2 Month Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.44$

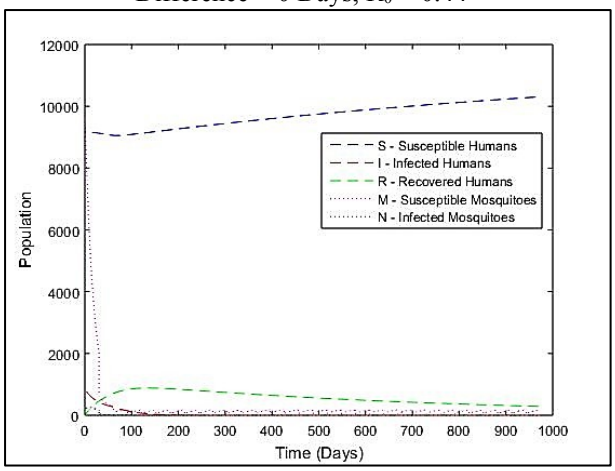



**Figure G.1C**: Tanzania Study, Group 2, New LLINs, IRS **1 Month Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.44$

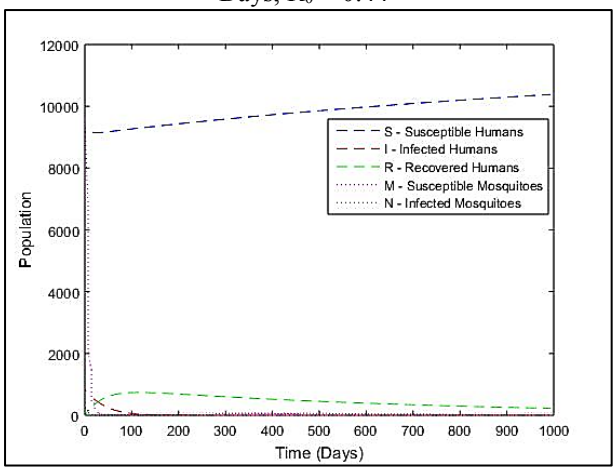



**Figure G.1D**: Tanzania Study, Group 2, New LLINs, IRS **1 Week Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.44$

## Benin Study

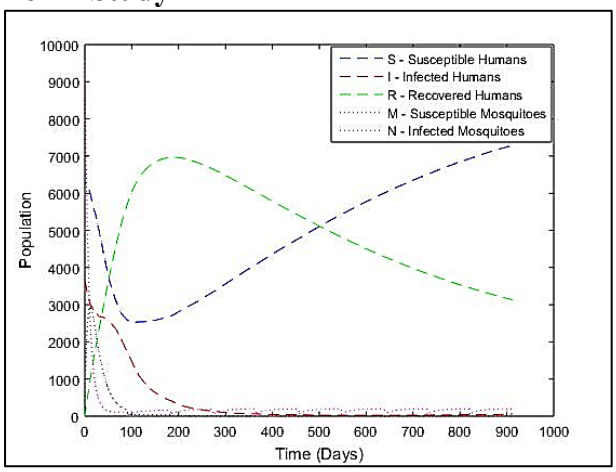



**Figure G.2A**: Benin Study, Group 2, New LLINs, IRS **3 Month Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.07$

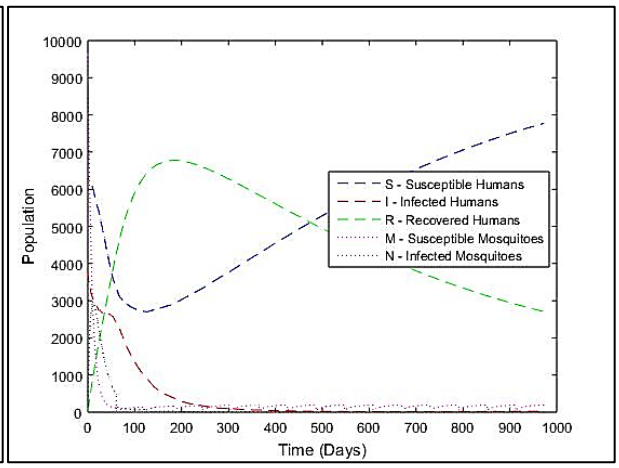



**Figure G.2B**: Benin Study, Group 2, New LLINs, IRS **2 Month Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.07$

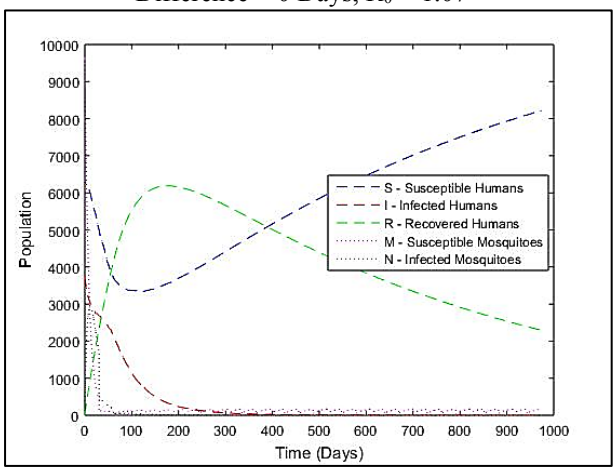



**Figure G.2C**: Benin Study, Group 2, New LLINs, IRS **1 Month Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.07$

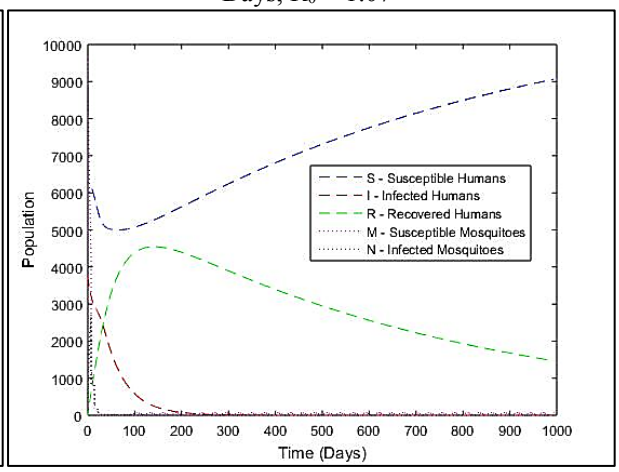



**Figure G.2D**: Benin Study, Group 2, New LLINs, IRS **1 Week Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.07$

## APPENDIX H. LLINs with IRS – Shorter IRS Intervals – Used LLINs

### Tanzania Study

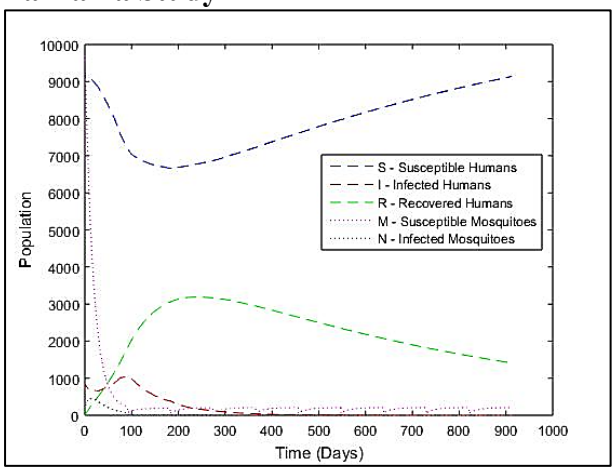



**Figure H.1A**: Tanzania Study, Group 2, Used LLINs, IRS **3 Month Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.01$

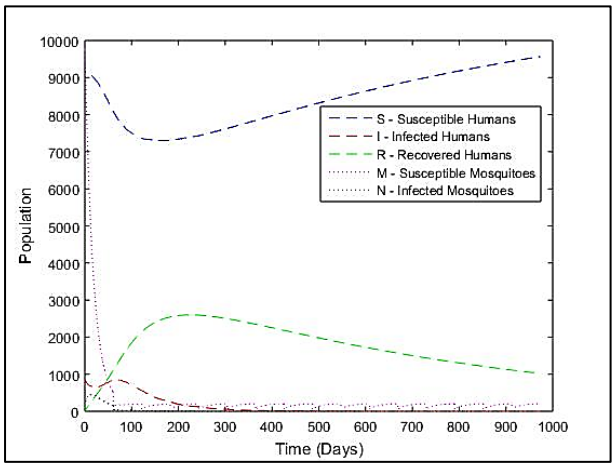



**Figure H.1B**: Tanzania Study, Group 2, Used LLINs, IRS **2 Month Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.01$

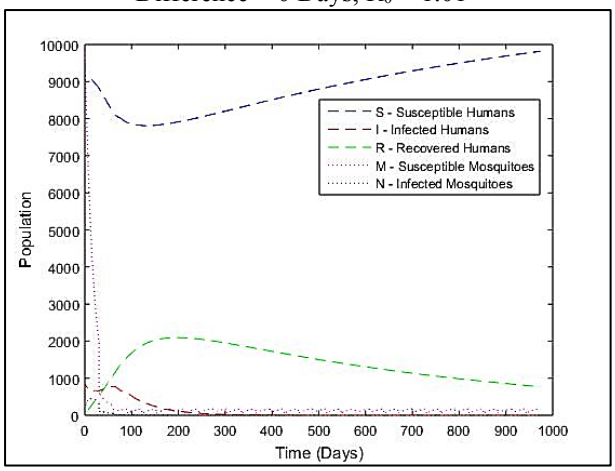



**Figure H.1C**: Tanzania Study, Group 2, Used LLINs, IRS **1 Month Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.01$

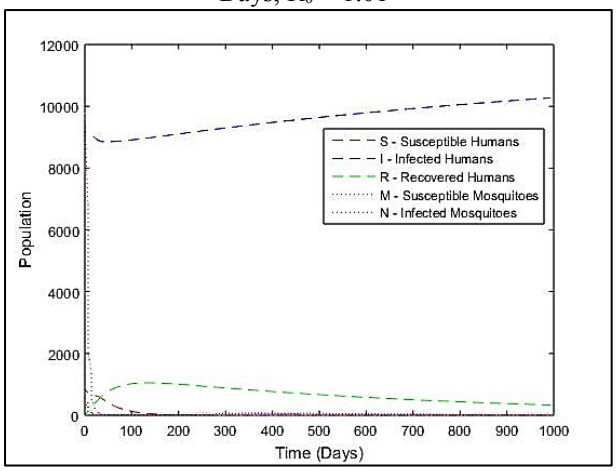



**Figure H.1D**: Tanzania Study, Group 2, Used LLINs, IRS **1 Week Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.01$

## Benin Study

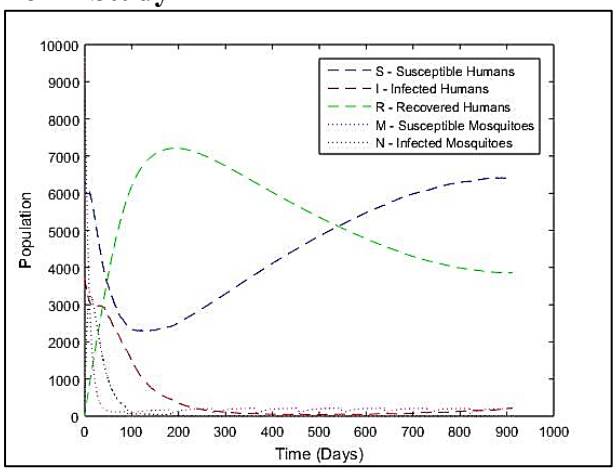



**Figure H.2A**: Benin Study, Group 2, Used LLINs, IRS **3 Month Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.19$

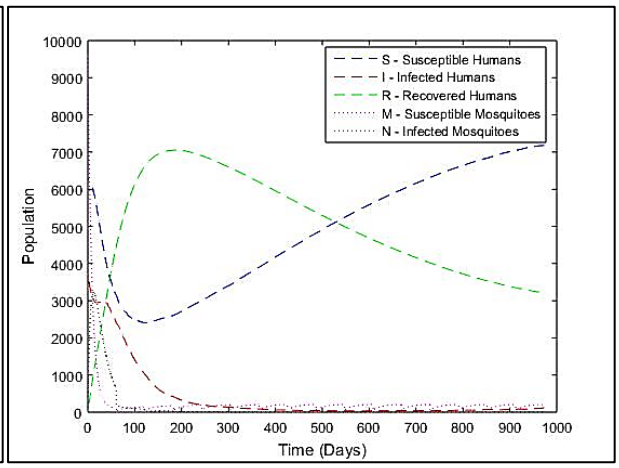



**Figure H.2B**: Benin Study, Group 2, Used LLINs, IRS **2 Month Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.19$

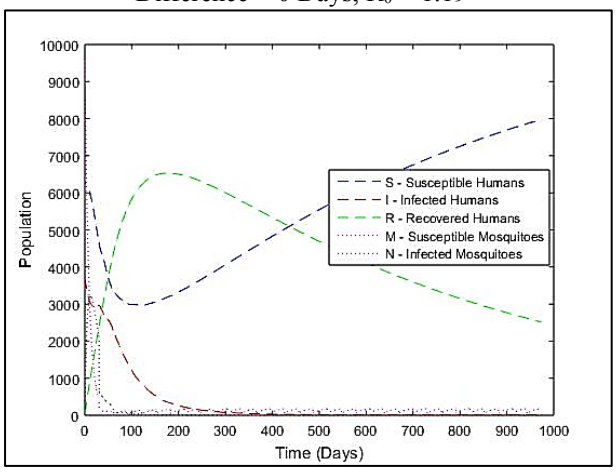



**Figure H.2C**: Benin Study, Group 2, Used LLINs, IRS **1 Month Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.19$

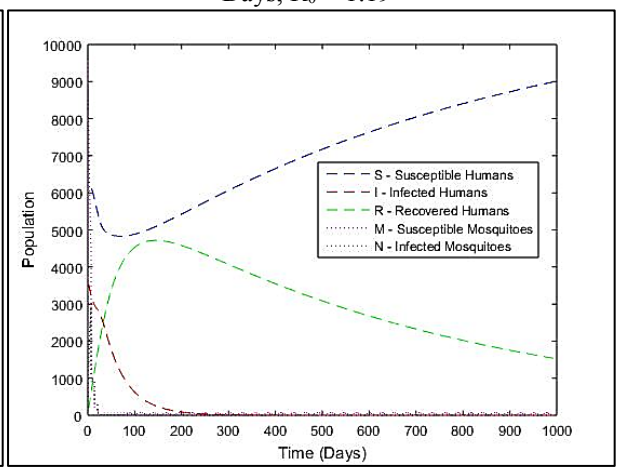



**Figure H.2D**: Benin Study, Group 2, Used LLINs, IRS **1 Week Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 1.19$

## The Gambia Study

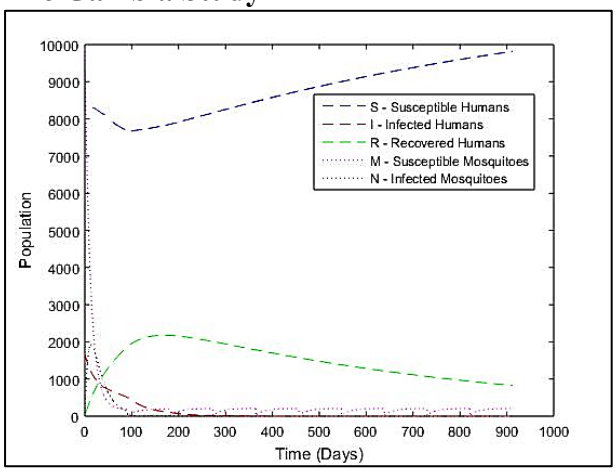



**Figure H.3A**: The Gambia Study, Group 2, Used LLINs, IRS **3 Month Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.69$

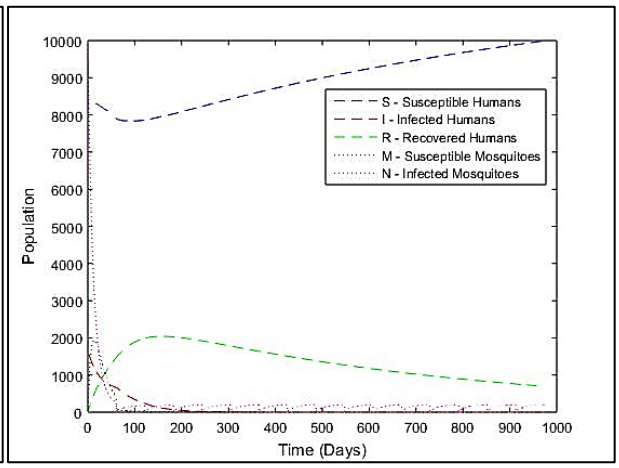



**Figure H.3B**: The Gambia Study, Group 2, Used LLINs, IRS **2 Month Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.69$

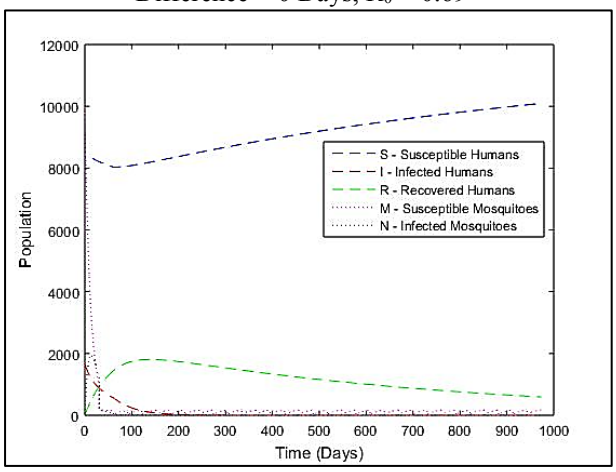



**Figure H.3C**: The Gambia Study, Group 2, Used LLINs, IRS **1 Month Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.69$

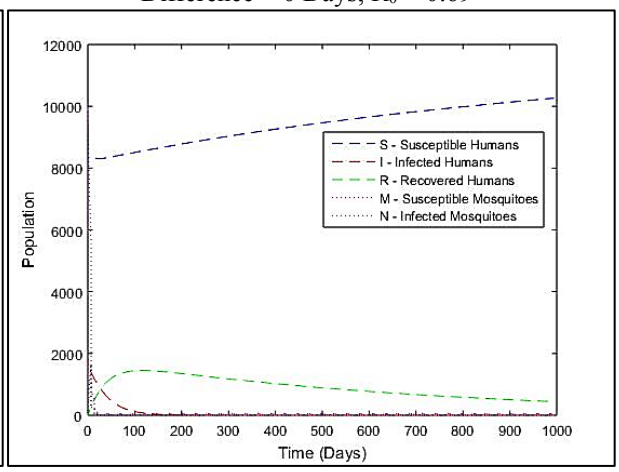



**Figure H.3D**: The Gambia Study, Group 2, Used LLINs, IRS **1 Week Intervals**, Middle-level Infection Rates, Middle-level Recovery Rates, Phase Difference = 0 Days, $R_0 = 0.69$

# APPENDIX I. Sensitivity and Uncertainty Analyses

## I.1 – Tanzania Study, Sensitivity and Uncertainty Analysis

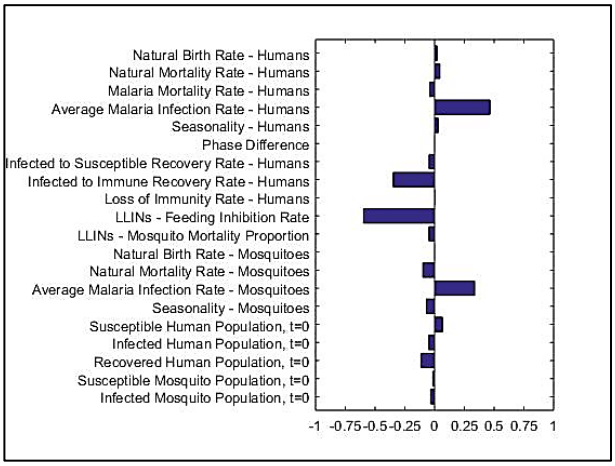



**Figure I.1A**: Tanzania Study, Group 1, Partial Rank Correlation Coefficients

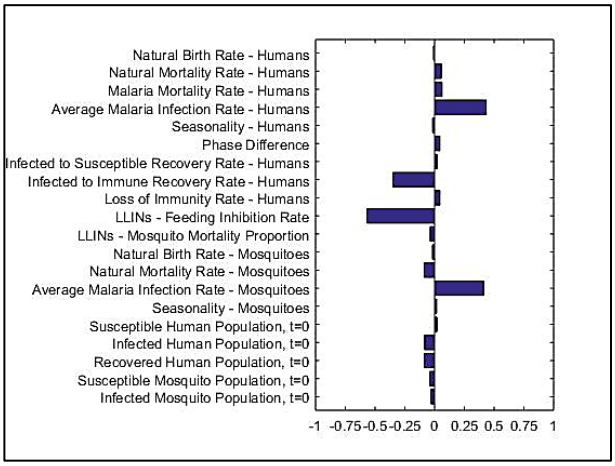



**Figure I.1B**: Tanzania Study, Group 2, Partial Rank Correlation Coefficients

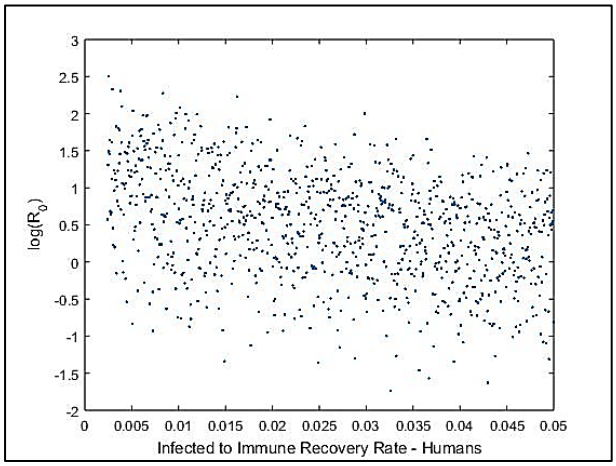



**Figure I.1C**: Tanzania Study, Group 1, Infected to Recovered/Immune Recovery Rate, Sensitivity Analysis

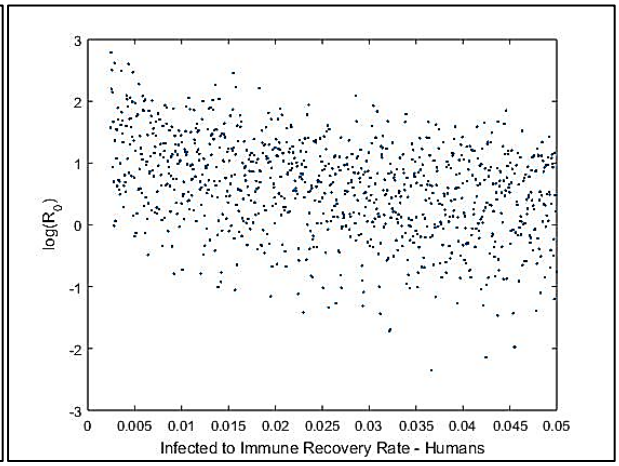



**Figure I.1D**: Tanzania Study, Group 2, Infected to Recovered/Immune Recovery Rate, Sensitivity Analysis

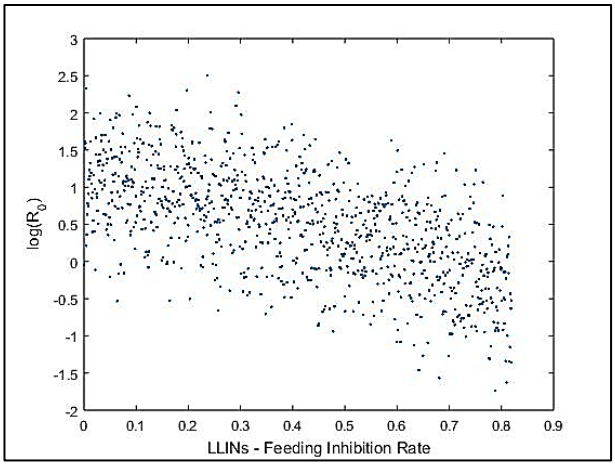



**Figure I.1E**: Tanzania Study, Group 1, LLIN – Feeding-Inhibition Rate, Sensitivity Analysis

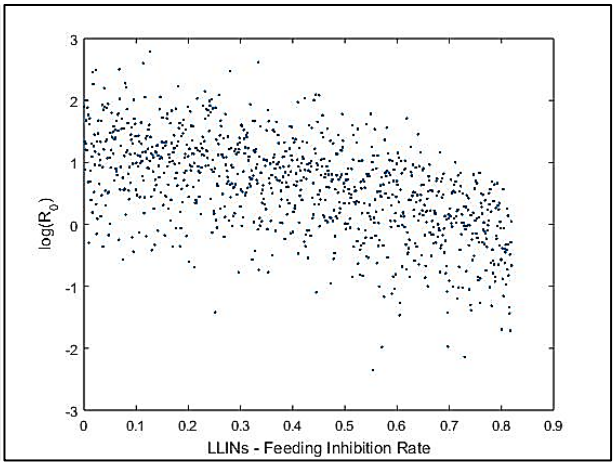



**Figure I.1F**: Tanzania Study, Group 2, LLIN – Feeding-Inhibition Rate, Sensitivity Analysis

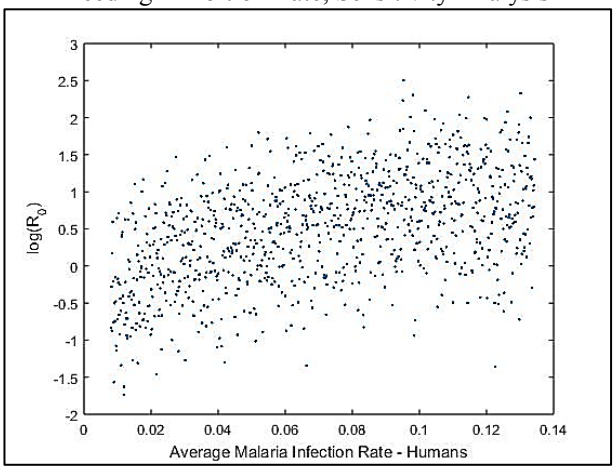



**Figure I.1G**: Tanzania Study, Group 1, Average Malaria Infection Rate – Humans, Sensitivity Analysis

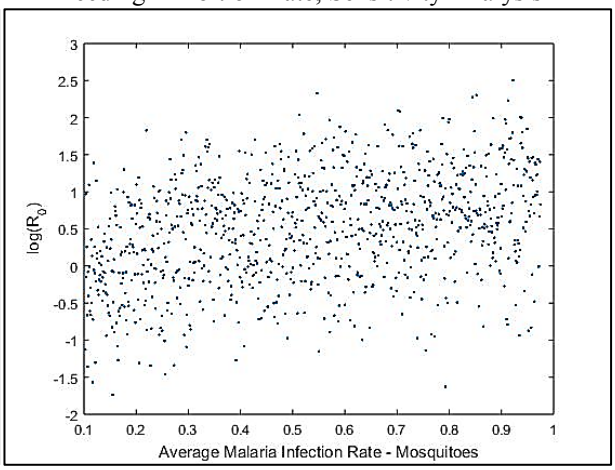



**Figure I.1H**: Tanzania Study, Group 1, Average Malaria Infection Rate – Mosquitoes, Sensitivity Analysis

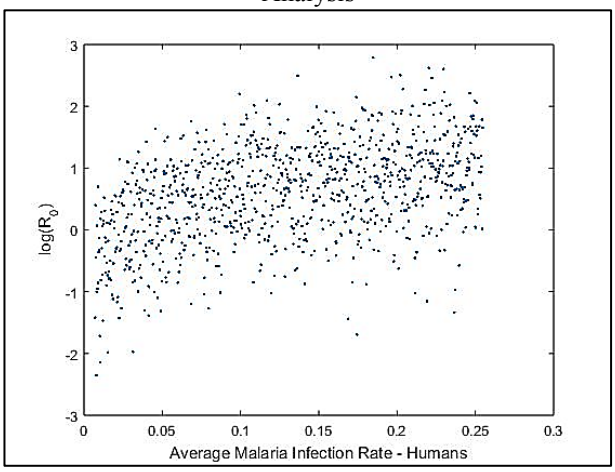



**Figure I.1I**: Tanzania Study, Group 2, Average Malaria Infection Rate – Humans, Sensitivity Analysis

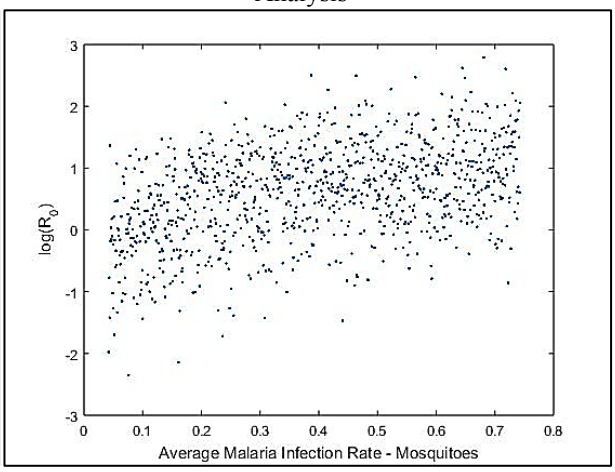



**Figure I.1J**: Tanzania Study, Group 2, Average Malaria Infection Rate – Mosquitoes, Sensitivity Analysis

## I.2 – Benin Study, Sensitivity and Uncertainty Analysis

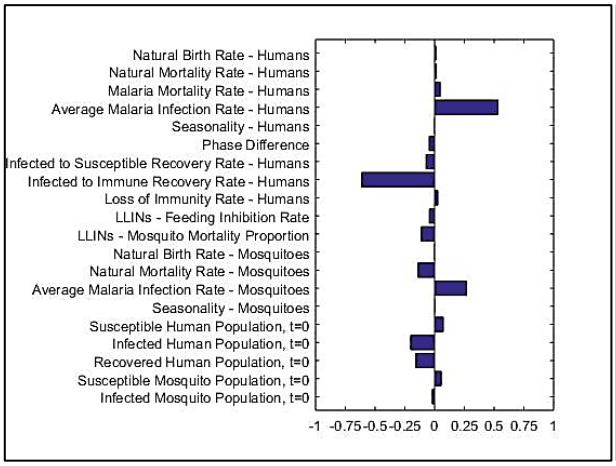



**Figure I.2A**: Benin Study, Group 1, Partial Rank Correlation Coefficients

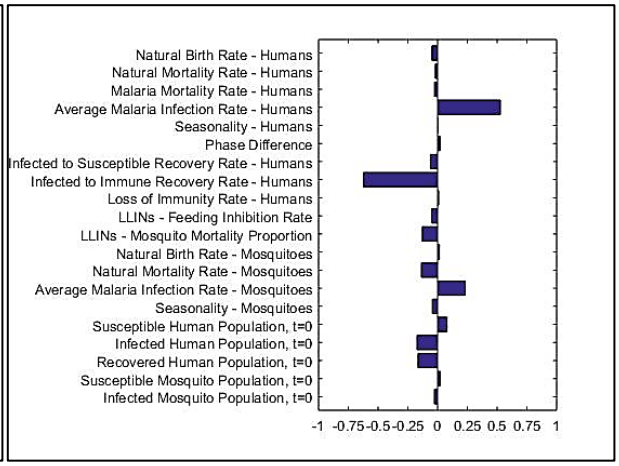



**Figure I.2B**: Benin Study, Group 2, Partial Rank Correlation Coefficients

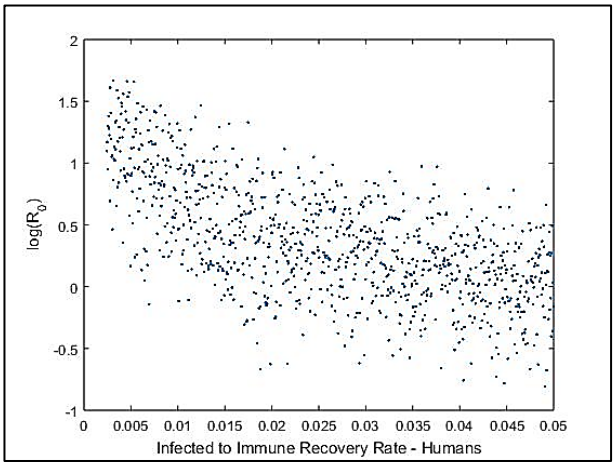



**Figure I.2C**: Benin Study, Group 1, Infected to Recovered/Immune Recovery Rate, Sensitivity Analysis

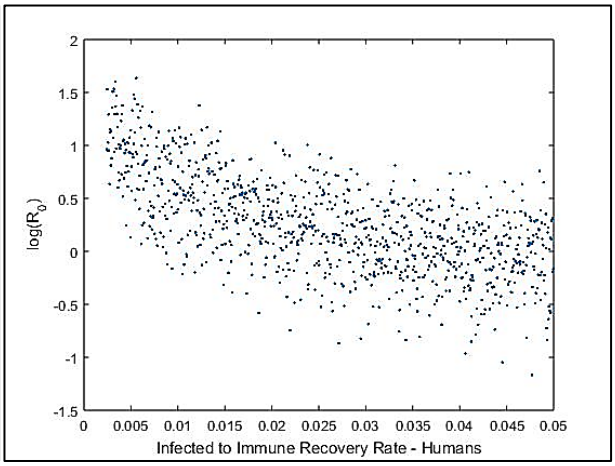



**Figure I.2D**: Benin Study, Group 2, Infected to Recovered/Immune Recovery Rate, Sensitivity Analysis

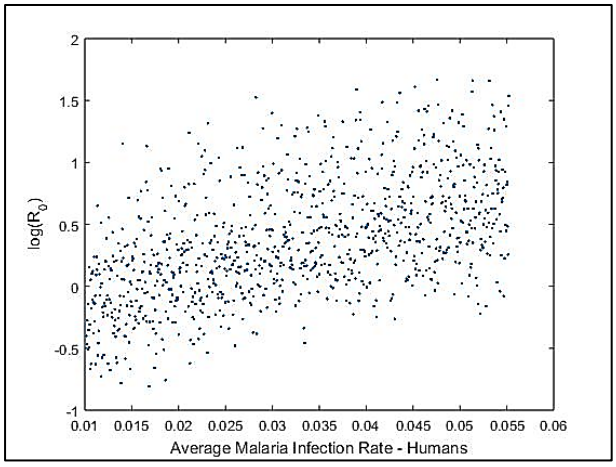



**Figure I.2E**: Benin Study, Group 1, Average Malaria Infection Rate – Humans, Sensitivity Analysis

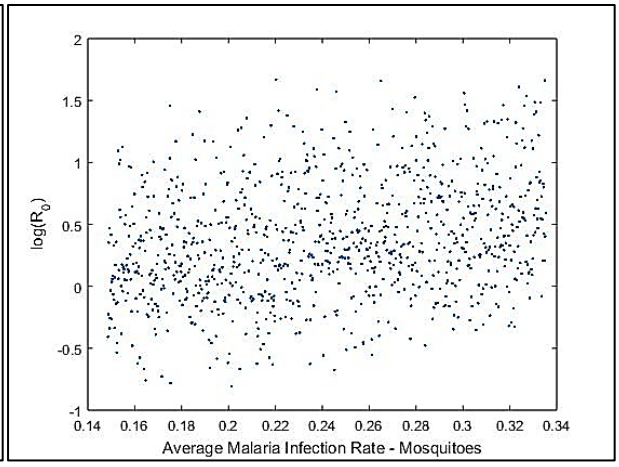



**Figure I.2F**: Benin Study, Group 1, Average Malaria Infection Rate – Mosquitoes, Sensitivity Analysis

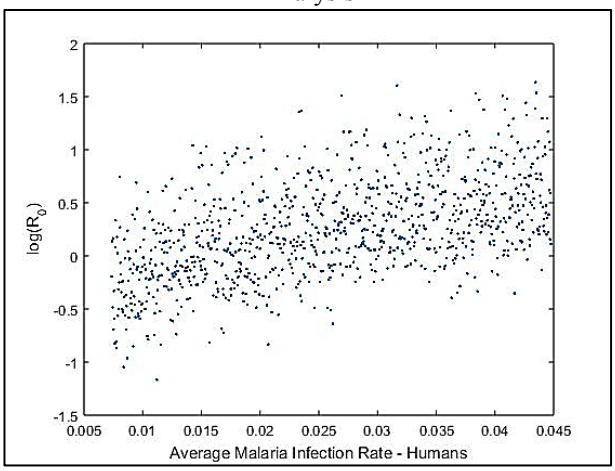



**Figure I.2G**: Benin Study, Group 2, Average Malaria Infection Rate – Humans, Sensitivity Analysis

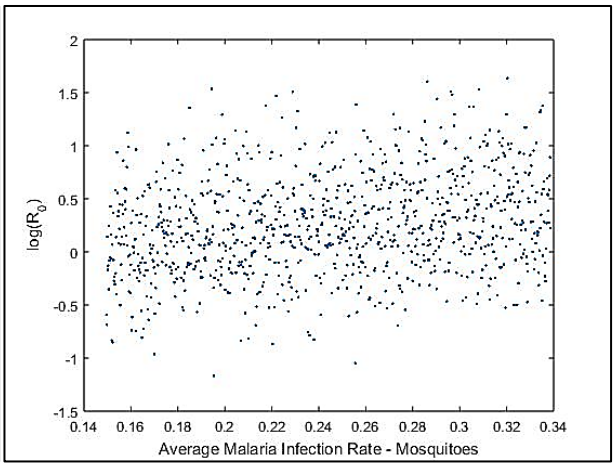



**Figure I.2H**: Benin Study, Group 2, Average Malaria Infection Rate – Mosquitoes, Sensitivity Analysis

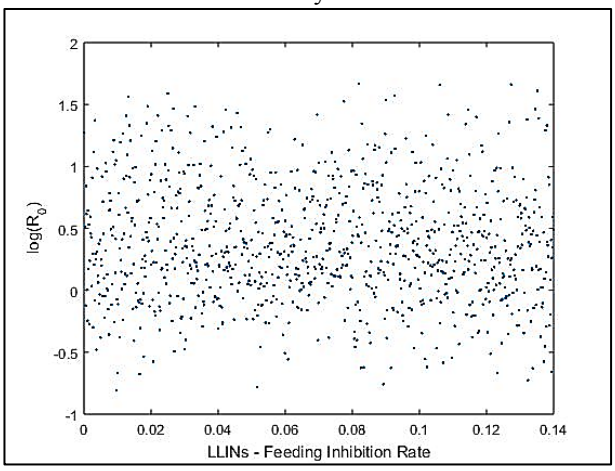



**Figure I.2I**: Benin Study, Group 1, LLIN – Feeding-Inhibition Rate, Sensitivity Analysis

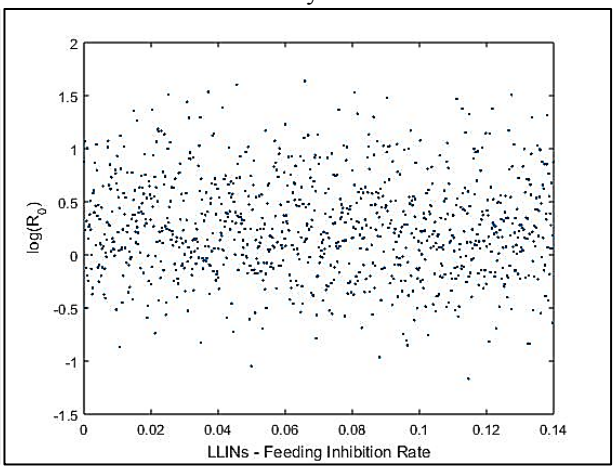



**Figure I.2J**: Benin Study, Group 2, LLIN – Feeding-Inhibition Rate, Sensitivity Analysis

## I.3 – The Gambia Study, Sensitivity and Uncertainty Analysis

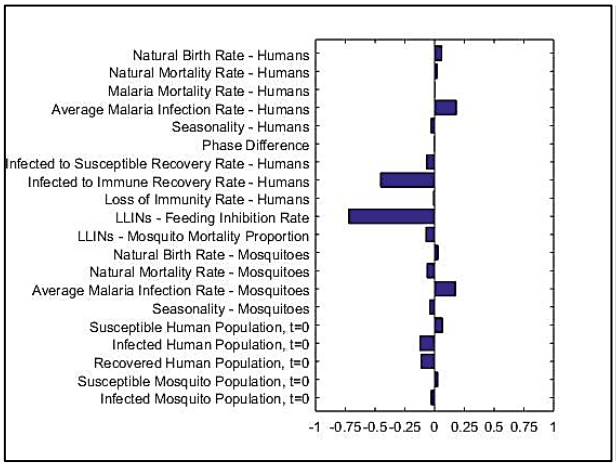



**Figure I.3A**: The Gambia Study, Group 1, Partial Rank Correlation Coefficients

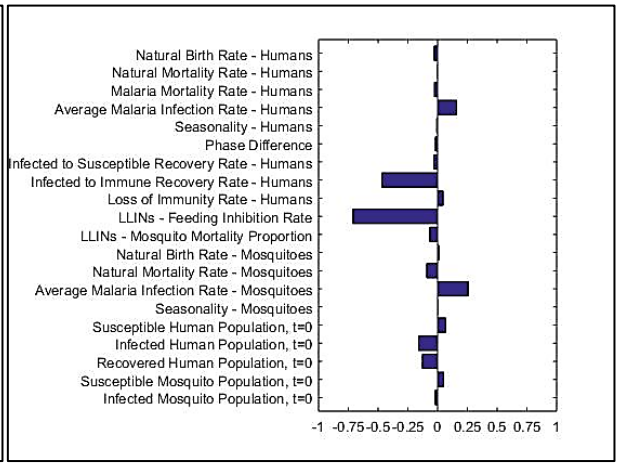



**Figure I.3B**: The Gambia Study, Group 2, Partial Rank Correlation Coefficients

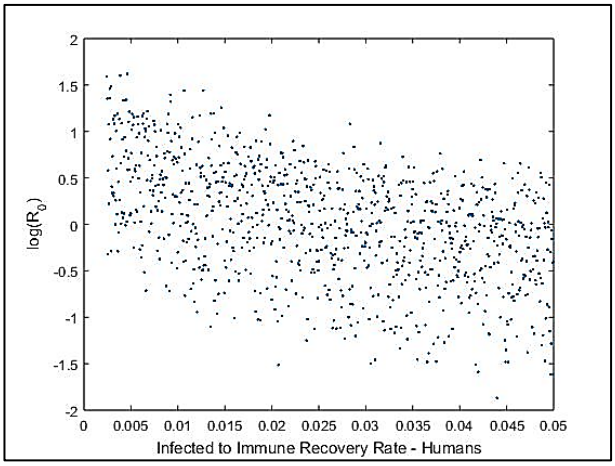



**Figure I.3C**: The Gambia Study, Group 1, Infected to Recovered/Immune Recovery Rate, Sensitivity Analysis

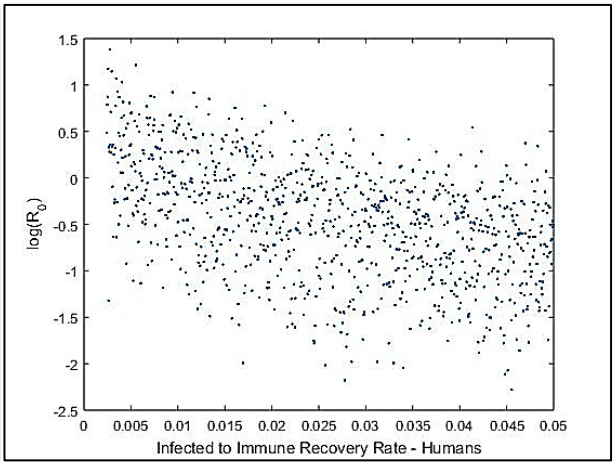



**Figure I.3D**: The Gambia Study, Group 2, Infected to Recovered/Immune Recovery Rate, Sensitivity Analysis

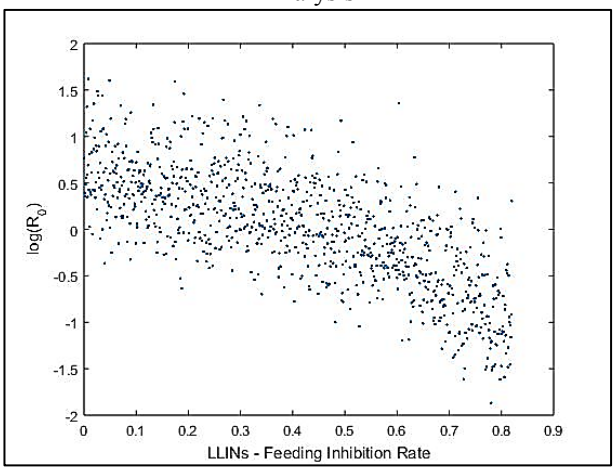



**Figure I.3E**: The Gambia Study, Group 1, LLIN – Feeding-Inhibition Rate, Sensitivity Analysis

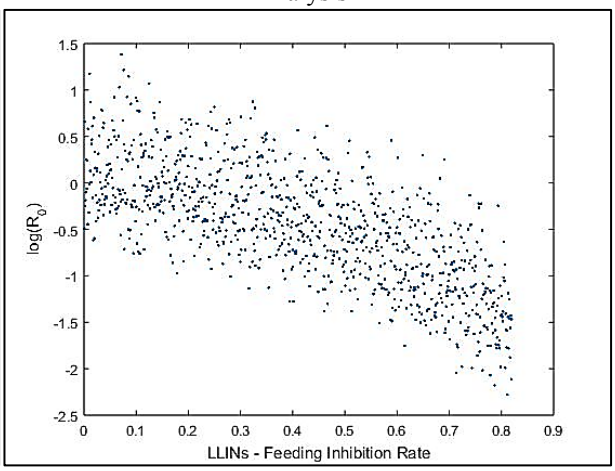



**Figure I.3F**: The Gambia Study, Group 2, LLIN – Feeding-Inhibition Rate, Sensitivity Analysis

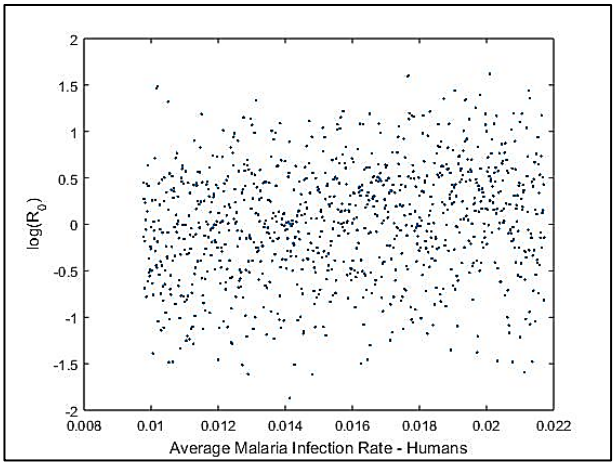



**Figure I.3G**: The Gambia Study, Group 1, Average Malaria Infection Rate – Humans, Sensitivity Analysis

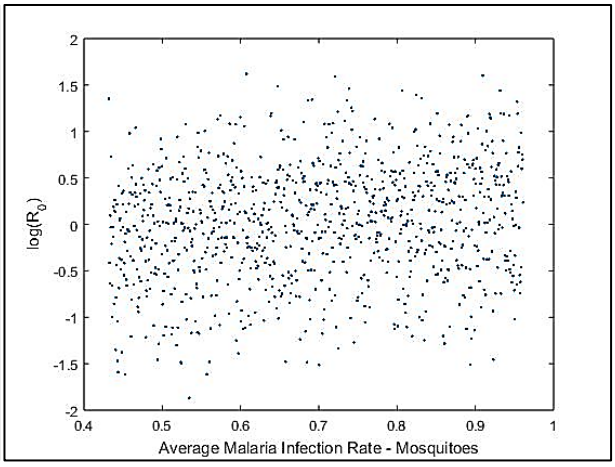



**Figure I.3H**: The Gambia Study, Group 1, Average Malaria Infection Rate – Mosquitoes, Sensitivity Analysis

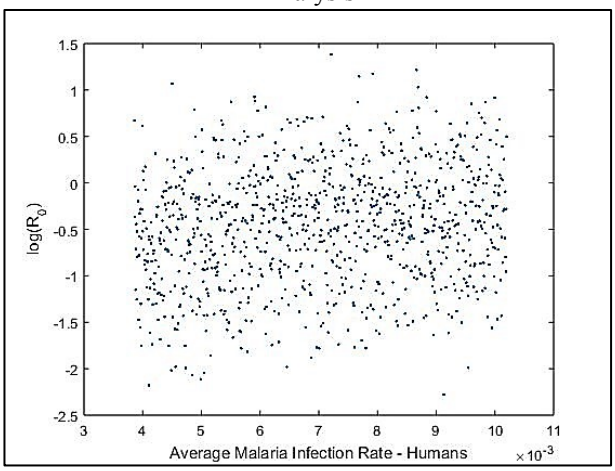



**Figure I.3I**: The Gambia Study, Group 2, Average Malaria Infection Rate – Humans, Sensitivity Analysis

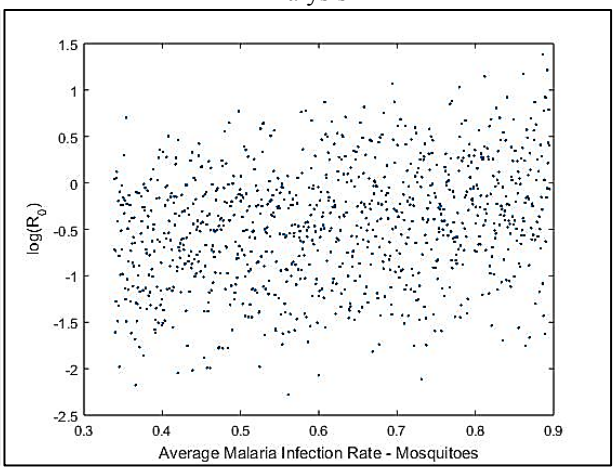



**Figure I.3J**: The Gambia Study, Group 2, Average Malaria Infection Rate – Mosquitoes, Sensitivity Analysis

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