involve
a journal of mathematics

A simple agent-based model of malaria transmission investigating intervention methods and acquired immunity

Karen A. Yokley, J. Todd Lee, Amanda K. Brown,
Mary C. Minor and Gregory C. Mader

msp

2014 vol. 7, no. 1

INVOLVE 7:1 (2014)
dx.doi.org/10.2140/involve.2014.7.15

A simple agent-based model of malaria transmission investigating intervention methods and acquired immunity

Karen A. Yokley, J. Todd Lee, Amanda K. Brown,
Mary C. Minor and Gregory C. Mader

(Communicated by Suzanne Lenhart)

Malaria, an infectious disease prevalent in sub-Saharan Africa, is transmitted to humans through mosquito bites, and ordinary differential equation models have often been used to describe the spread of the disease. A basic agent-based model (ABM) of malaria transmission is established and compared to an ODE model of the disease in order to ascertain the similarity of the ABM to typical modeling approaches. Additionally, the ABM is described using protocol from current literature. In order to illustrate the flexibility of the ABM, the basic ABM is modified to incorporate the use of insecticide-treated bed nets (ITNs) and the effect of acquired immunity. The simulations incorporating acquired immunity and the use of ITNs show a decrease in the prevalence of the disease due to these factors. Additionally, the ABM can easily be modified to account for other complicated issues affecting malaria spread.

1. Introduction

Malaria, a blood-borne infectious disease widespread in sub-Saharan Africa, is characterized by cases of high fever, chills, nausea, sweating, and fatigue. According to the Center for Disease Control in Atlanta (CDC), each year there are 350 to 500 million reported cases of malaria, and around 1 million people die worldwide from this disease with 90% of these occurring in areas south of the Sahara [CDC 2012a]. Although malaria has not been eradicated, the spread of malaria can be controlled through both infection and disease prevention. Current and potential intervention methods for malaria that are used throughout the world include vaccination, insecticide-treated bed nets (ITNs) and insecticides such as indoor residual spray. Disease prevention efforts include antimalarial drugs that

MSC2010: 92-08, 92D25.
Keywords: malaria, agent-based modeling, population modeling.

are administered before infection and hinder the development of malaria parasites [CDC 2011].

Female *Anopheles* mosquitoes bite humans in order to obtain a blood meal for reproduction [Aron and May 1982]; the malaria parasite is transferred to humans through mosquito saliva and to mosquitoes via human blood taken in the blood meal. An infected mosquito will bite a susceptible (uninfected) human and transfer malaria sporozoites from the saliva into the human's blood, and the sporozoites then develop in a cycle in the human liver before causing symptoms. After a period of time (latency), the parasite is then prevalent in the human bloodstream and able to be passed to a mosquito drawing blood for reproduction. The parasite follows a cycle in the mosquito's gut and after some time is ready for transmission to a susceptible human [CDC 2012c].

Mathematical models of malaria have examined immunity [Aron 1988; 1983; De Zoysa et al. 1991; Gu et al. 2003; Gurarie and McKenzie 2007; Maire et al. 2006; Tumwiine et al. 2007], control methods [Chiyaka et al. 2008], climate [Dembele et al. 2009], drug resistance [Aneke 2002; Chiyaka et al. 2009; Koella and Antia 2003], vaccinations [Smith et al. 2006] and transmission parameters related to malaria spread [Chitnis et al. 2008]. Environmental, social and economic factors that contribute to the spread of malaria have also been modeled [Yang and Ferreira 2000], and several reviews and summaries have been written on existing mathematical models of malaria [Anderson and May 1991; Koella 1991; Nedelman 1985]. Ronald Ross generated one of the earliest mathematical models [Ross 1910; Spielman and D'Antonio 2001].

The basis for many of the deterministic models of malaria transmission is the Ross–MacDonald differential equation model [MacDonald 1957], but MacDonald himself also investigated more stochastic approaches [MacDonald et al. 1968] which modeled malaria through simulations based on four key epidemiologic parameters: the biting rate of the mosquito, the mosquito survival rate, the human recovery rate, and the reproduction number. These simulations incorporated seasonal changes but no incubation period of the infection. MacDonald et al. [1968] pursued computational approaches to malaria modeling "in order to adapt the model better to the detailed study of various preventive measures and to the process of eradication which cannot be handled by a deterministic model that deals only in numbers which never reach very low finite levels." However, the predictions from [MacDonald et al. 1968] were shown to have discrepancies with field research [Nájera 1974].

The current study is intended to investigate malaria transmission through an agent-based approach. Although many sophisticated malaria differential equation models have been developed, this investigation seeks to consider a simplistic agent-based approach and how that approach compares to ordinary differential equation modeling.

Agent-based approaches have been used previously for biological modeling of processes that are discrete [Castiglione et al. 2007; Eubank et al. 2004; Hinkelmann et al. 2011; Pogson et al. 2006; Wang et al. 2009]. This study uses an agent-based model (ABM) not only because actual infections in small populations may be more reasonably predicted by low finite numbers [MacDonald et al. 1968], but also because of the great potential for modeling complex aspects involved in malaria transmission.

The major objectives of the study include directing the focus of malaria modeling to agent-based approaches as in [MacDonald et al. 1968] in light of continuing computational advances and describing this approach in the language of current literature as in [Grimm et al. 2006]. The ABM presented in this study is very simplistic in order to establish a basic framework but still allow for easy incorporation of the many complex factors that affect the spread of malaria. A simple ODE system of malaria transmission based on the Ross–MacDonald model is used for comparison since ODE models are often used to model malaria. Because a simplistic ABM approach is considered, the ABM results are compared to output from the very basic and well established Ross–MacDonald ODE model. Two examples of how the ABM can be adapted to incorporate complexity are presented. These examples will investigate the effect of ITNs and acquired immunity on the spread of malaria.

2. Modeling malaria transmission

Most mathematical models representing the spread of malaria involve systems of differential equations [Aneke 2002; Chiyaka et al. 2009; 2007; 2008; Dembele et al. 2009; Koella 1991; Koella and Antia 2003; MacDonald 1957; Ngwa 2006; Tumwiine et al. 2007], and some have involved stochastic processes [Gu et al. 2003; Gurarie and McKenzie 2007; MacDonald et al. 1968; Maire et al. 2006; Smith et al. 2006]. The equations used in differential equation models describe the rates of change of the mosquito and human populations, most using standard SIR or related models. Because most malaria modeling involves deterministic differential equations, a basic ODE model is used for comparison purposes.

In addition to establishing a basic ODE model of malaria transmission, an ABM is created to describe the spread of the disease through simulated random interactions of population agents. The deterministic ODE and the ABM are compared in order to investigate how similar the modeling approaches are at a basic level. While models can be created involving both differential equations and stochastic processes, the current study investigates simplistic models that do not combine the two. Additionally, the ABM is modified for investigations related to preventative

methods and immunity. All ABM simulations and ODE solutions in this study were computed using Mathematica (versions 6.0, 7.0, and 8.0).

2.1. ***Differential equation model.*** The ODE model used in this study is based on the deterministic Ross–MacDonald model [MacDonald 1957] and other quantitative models of malaria transmission [Daley and Gani 1999] with the addition of latency. This ODE model describes the population flow between three subgroups of humans and mosquitoes: those that are susceptible (without malaria), those that are latent (harboring the parasite but not yet able to transmit) and those that are infectious (infected and able to transmit).

In order to more accurately model the spread of malaria, a latency state for both humans and mosquitoes is added to the ODE system as in [Aneke 2002; Aron and May 1982]. Latency can be interpreted as the time between when a mosquito obtains a blood meal from a human and when the newly infected host can transmit the parasite. The incorporation of latency assists in accounting for hosts that carry the disease but cannot yet transmit the parasite. The time that it takes for a host to leave the latent state is referred to as the incubation time.

The population subgroups will be considered as percentages or proportions rather than in absolute numbers. The notation of lowercase h indicates a proportion of the human population with a subscript denoting which population (infected or latent) the proportion represents. The same notation with m in place of h will be used for the mosquito populations. Since the overall populations will be assumed to be constant, the susceptible population can be represented as the remainder of the total population ($h_s = 1 - h_l - h_i$, $m_s = 1 - m_l - m_i$). Hence, four differential equations are needed to describe the total population of humans and mosquitoes when latency is incorporated. The following equations (based on the system presented in [Daley and Gani 1999] with the addition of latency) represent the rates of change of the percentages of each population:

$$\frac{dh_l}{dt} = \gamma_{mh}\beta N m_i(1 - h_l - h_i) - \frac{1}{\lambda_h}h_l, \tag{1}$$

$$\frac{dh_i}{dt} = \frac{1}{\lambda_h}h_l - \frac{1}{\mu_h}h_i, \tag{2}$$

$$\frac{dm_l}{dt} = \gamma_{hm}\beta h_i(1 - m_l - m_i) - \frac{1}{\lambda_m}m_l - \frac{1}{\mu_m}m_l, \tag{3}$$

$$\frac{dm_i}{dt} = \frac{1}{\lambda_m}m_l - \frac{1}{\mu_m}m_i. \tag{4}$$

Each of the terms in the equations describes how individuals (proportionally) are entering into or exiting out of the particular population subgroup. The first term in (1) involves the interaction of infectious mosquitoes and susceptible humans. Susceptible humans become infected and enter the latent state based upon the ratio

of mosquitoes to humans ($N = M_n/H_n$, where M_n is the total number of mosquitoes and H_n is the total number of humans), the rate mosquitoes bite humans β, and the transmission probability from mosquito to human γ_{mh}. These parameters are multiplied by the proportion of susceptible humans $1 - h_l - h_i$ and the proportion of infectious mosquitoes m_i. The second term in (1) represents the loss of latent humans to the infectious state based upon the human incubation time λ_h and also represents the same proportion as those moving into infectivity in (2). The human incubation time λ_h is the number of days in the latency period. The second term in (2) describes humans' recovering from malaria and returning to the susceptible population, and μ_h is the average number of days for human recovery. Equations (3) and (4) describe changes in the mosquito population using the same notation and structure as (1) and (2).

The following assumptions are used with both the ODE model and the ABM discussed in Section 2.2:

- Constant population sizes are assumed for both human and mosquito populations.
- Constant parameters are used and assumed to be sufficient for this modeling investigation.
- No individual experiences superinfection (the contraction of more than one strain of the parasite at a time).
- Climate and geography have no effect on the interactions of the populations.
- Only human and mosquito populations are considered, although mosquitoes do bite other mammals.

The parameters used in both the ODE model and ABM simulation (as described in Section 2.2) are presented in Table 1. The transmission rate from human to mosquito γ_{hm} is based on a probability-of-transfer parameter used in the original Ross–MacDonald model [MacDonald 1957]. The mosquito bite rate is based upon an assumption that mosquitoes breed on average once a week. The associated parameter β can be thought of as the overall bite rate times the proportion of human bites as in [Smith et al. 2007]. All simulations in this study used initial conditions reflecting the idea that 10% of infected humans encountered a currently uninfected mosquito population (initial proportion infected humans $h_0 = 0.1$; initial proportion infected mosquitoes $m_0 = 0$). The simulations produced for the ODE model are presented as a comparison for the ABM simulation output in Figures 1, 3, and 5.

A stability analysis was conducted on the model in (1)–(4) in order to further understand model behavior around equilibria. When evaluating the subpopulations using the parameters in Table 1, two equilibrium solutions are obtained. One of these equilibrium solutions is when all the populations are zero (the disease-free

Parameter	Definition	Value	Source
β	mosquito bite rate	$\frac{1}{7}$ bite/day	assumption
γ_{mh}	transmission probability $m \to h$	0.6	Spielman and D'Antonio 2001
γ_{hm}	transmission probability $h \to m$	1.0	MacDonald 1957
μ_m	mosquito life span	21 days	World Book 2008
μ_h	recovery time for humans	14 days	CDC 2012a
N	mosquito/human ratio	5	Shililu et al. 1998
λ_m	mosquito incubation time	7 days	CDC 2012b
λ_h	human incubation time	10 days	CDC 2012a

Table 1. Parameter values used in the ODE model and the ABM.

equilibrium, or DFE) and the other is $h_i = 0.478142$, $m_i = 0.441919$, $h_l = 0.34153$, $m_l = 0.147306$, $h_s = 0.180328$, and $m_s = 0.410774$ (the endemic equilibrium). The Jacobian matrix J for the ODE system is shown below:

$$J = \begin{pmatrix} \frac{\partial}{\partial h_l}\left[\frac{dh_l}{dt}\right] & \frac{\partial}{\partial h_i}\left[\frac{dh_l}{dt}\right] & \frac{\partial}{\partial m_l}\left[\frac{dh_l}{dt}\right] & \frac{\partial}{\partial m_i}\left[\frac{dh_l}{dt}\right] \\ \frac{\partial}{\partial h_l}\left[\frac{dh_i}{dt}\right] & \frac{\partial}{\partial h_i}\left[\frac{dh_i}{dt}\right] & \frac{\partial}{\partial m_l}\left[\frac{dh_i}{dt}\right] & \frac{\partial}{\partial m_i}\left[\frac{dh_i}{dt}\right] \\ \frac{\partial}{\partial h_l}\left[\frac{dm_l}{dt}\right] & \frac{\partial}{\partial h_i}\left[\frac{dm_l}{dt}\right] & \frac{\partial}{\partial m_l}\left[\frac{dm_l}{dt}\right] & \frac{\partial}{\partial m_i}\left[\frac{dm_l}{dt}\right] \\ \frac{\partial}{\partial h_l}\left[\frac{dm_1}{dt}\right] & \frac{\partial}{\partial h_i}\left[\frac{dm_i}{dt}\right] & \frac{\partial}{\partial m_l}\left[\frac{dm_i}{dt}\right] & \frac{\partial}{\partial m_i}\left[\frac{dm_i}{dt}\right] \end{pmatrix}$$

$$= \begin{pmatrix} -N\beta\gamma_{mh}m_i - \lambda_h & -N\beta\gamma_{mh}m_i & 0 & N\beta\gamma_{mh}(1-h_i-h_l) \\ \lambda_h & -\gamma_h & 0 & 0 \\ 0 & \beta\gamma_{hm}(1-m_i-m_l) & -\beta\gamma_{hm}h_i - \lambda_m - \gamma_m & -\beta\gamma_{hm}h_i \\ 0 & 0 & \lambda_m & -\gamma_m \end{pmatrix}.$$

When evaluating the matrix J at the DFE, the eigenvalues consist of two real roots of opposite sign and two complex roots with negative real parts; hence, the DFE is a saddle point (hyperbolic fixed point). At the endemic equilibrium, the eigenvalues consist of two negative real roots and two complex roots with negative real parts, indicating stability and attraction. If the dynamics of malaria can be controlled in such a way that the nonzero equilibrium point is closer to the origin, then the total number of overall cases of infection will most likely decrease.

2.2. ***Agent-based model (ABM).*** Although an ODE model of malaria spread may reasonably model the spread of infection, the incorporation of some specific biological and environmental features of the disease (such as immunity) may result in very complex, nonlinear models. ABMs allow research to be performed by looking at the interaction of individuals in the simulated populations to model large-scale occurrences. The idea behind the ABM is that the simulation stores information about each individual mosquito and human and randomly simulates the interactions of these agents. Unless otherwise stated, the parameters used in the ABM will

be denoted as they were in the ODE model discussed in Section 2.1 with values from Table 1. The ABM is conceptually similar to the work in [MacDonald et al. 1968], which uses a decision-based computer simulation to model the transmission of malaria. The study in [MacDonald et al. 1968] does use random numbers to simulate transmission of malaria in a finite population, but latency is not incorporated. The current ABM differs from [MacDonald et al. 1968] by incorporating latency, defining mosquitoes as individual agents, and not modeling seasonal effects.

An array of mosquitoes and an array of humans were created in the computer simulations and are referred to as *agents*. These agents have attributes regarding malarial infection and each are stored through advancements in the simulation representing the passage of time. Much of the ABM simulation involves random selection of two agents (one mosquito and one human) to interact and produce an infected mosquito, infected human, both, or neither (if neither is infected). Each agent has qualities stored in the code. The infective status and latent status of the agent is stored within the array (infectious, latent) with a 1 indicating yes and 0 indicating no. Hence, $(1, 0)$ describes an agent that is infectious, $(0, 1)$ describes an agent that is in the latent stage, and $(0, 0)$ describes an agent with no infection.

The simulation begins by tracking the mosquitoes that take a blood meal. A human is then randomly selected as the target of the mosquito taking the blood meal. The simulation checks if either or both the selected agents are infectious and if transmission of the parasite occurs based on model probabilities. Whether an agent moves from the susceptible state to the latent stage through infection, moves to the infectious state from the latent state, or returns to the susceptible state from the infectious state is determined stochastically. The probabilities used in the ABM are based on the parameters from the ODE model, and how they are used is more specifically outlined in the Appendix.

Various methods have been used with ABMs and protocol to standardize descriptions has been suggested [Grimm et al. 2006]. A description following the overview, design concepts, and details (ODD) protocol [Grimm et al. 2006] of the basic ABM for malaria transmission is presented in the Appendix. The description in the Appendix includes flow charts and details for the basic simulation (Figures 6 and 7) and for the simulations involving preventative measures and immunity as presented in Section 3 (Figures 8 and 9). The primary method of investigation of the models in this study was through simulation, although alternate methods of analysis exist using other frameworks [Hinkelmann et al. 2011].

The ABM was simulated over a 6 month interval and the output proportions for the infectious mosquitoes are plotted versus the proportions of infectious humans in Figure 1. The corresponding output of the ODE model is also presented in Figure 1 for comparison. Noise and variation are apparent in the ABM simulation as is expected because of the stochastic nature of the model. The ODE solution

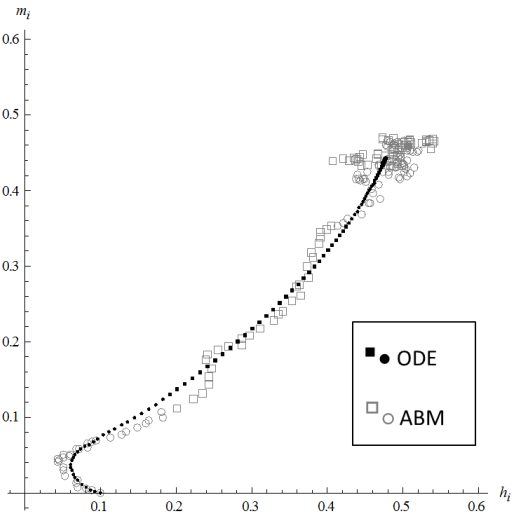


Figure 1. Plot of output from the ABM simulation, shown by the open gray shapes. The solid black shapes represent output from the ODE model with latency as described in Section 2.1. The simulations were generated over approximately six months (180 days). The horizontal axis represents proportions of infectious humans in the simulated population, and the vertical axis represents proportions of infectious mosquitoes in the simulated population. The symbols change from one shape to another at the end of each 30 day period.

moves toward an equilibrium point (which we know is stable based on analysis presented in Section 2.1). The ABM output also settles around a relatively similar point. Figure 1 illustrates that although the ABM and the ODE model do not have identical output, the two models make very similar predictions in value of output, shape of the output curve, and a nonzero settling point. Figure 1 presents the ABM output of one simulation in order to show the randomness of the approach. MacDonald et al. [1968] presented graphical representations of single simulations of their results but stated that several replicates were needed to describe the overall picture. Overall trends of the ABM using the parameters in Table 1 are presented in the black graphs in Figure 2.

3. ABM model investigations

3.1. ***ABM model sensitivity.*** The local sensitivity of the ABM was investigated visually by varying all the parameters in Table 1. Graphs were generated with ellipses surrounding each point representing potential deviation from equilibrium

due to randomness of the simulation for three values of each parameter: 25% below the value in Table 1, the value in Table 1, and 25% above the value in Table 1. The two exceptions to this are for γ_{hm} and N. The transmission probability from humans to mosquitoes γ_{hm} is already at a maximum reasonable value of 1, and therefore the visual sensitivity analysis was performed with only the value from Table 1 and a value 25% below. Since the ABM uses virtual mosquitoes and humans, the value of N was kept as a whole number and sensitivity simulations were performed for two different sets of values of N (4,5,6 and 3,5,7). For each individual parameter investigation, all other parameter values were set to the values listed in Table 1.

Some parameters showed little change in the resulting ABM simulations. Neither set of simulations for varying N produced significant changes in model output. Only small changes in model output were seen when varying γ_{mh}. Slightly greater model output changes were seen with variation in γ_{hm}. The model output followed the same basic path when the values of β and λ_m were varied, but the settling points varied somewhat. The greatest sensitivity was observed when varying μ_m, μ_h, and λ_h, and graphs with these results are presented in Figure 2. Multiple simulations were run and averaged in order to obtain a more accurate representation of the trend of the simulations, and Figure 2 contains average model output over 500 simulations that were run for a six month time period. Each ellipse in Figure 2 is centered on the average value found for that point after 500 runs of the simulation plus one standard deviation in the direction of the major and minor axes.

3.2. ***Insecticide-treated bed nets.*** The ABM was modified to investigate the effects of the use of ITNs. In the ABM, the major assumptions made regarding the use of bed nets are as follows:

- A strict proportion of humans will receive bed nets in the initialization of the simulation and will continue use of bed nets until the model is run completely.
- Once a bed net is hung, it is assumed to stay intact and be used every night.
- A six month time frame (one season) is used unless otherwise indicated.
- ITNs are assumed to be 96% effective, meaning a mosquito has a 4% chance of continued interaction with the human when attempting to take a blood meal from an individual using an ITN. The level of effectiveness of ITNs is expected to be somewhere from 95% to 99%, taking into account efficacy as well as potential wear [Curtis et al. 1992; N'Guessan et al. 2001].

A more formal description of the ABM process incorporating the use of bed nets is presented in Appendix A.3.2.

Trends of infection were compared between populations with proportions of humans using bed nets ranging from 10% to 70%. The plots in Figure 3 show examples of simulations using a six month period where the given proportion of

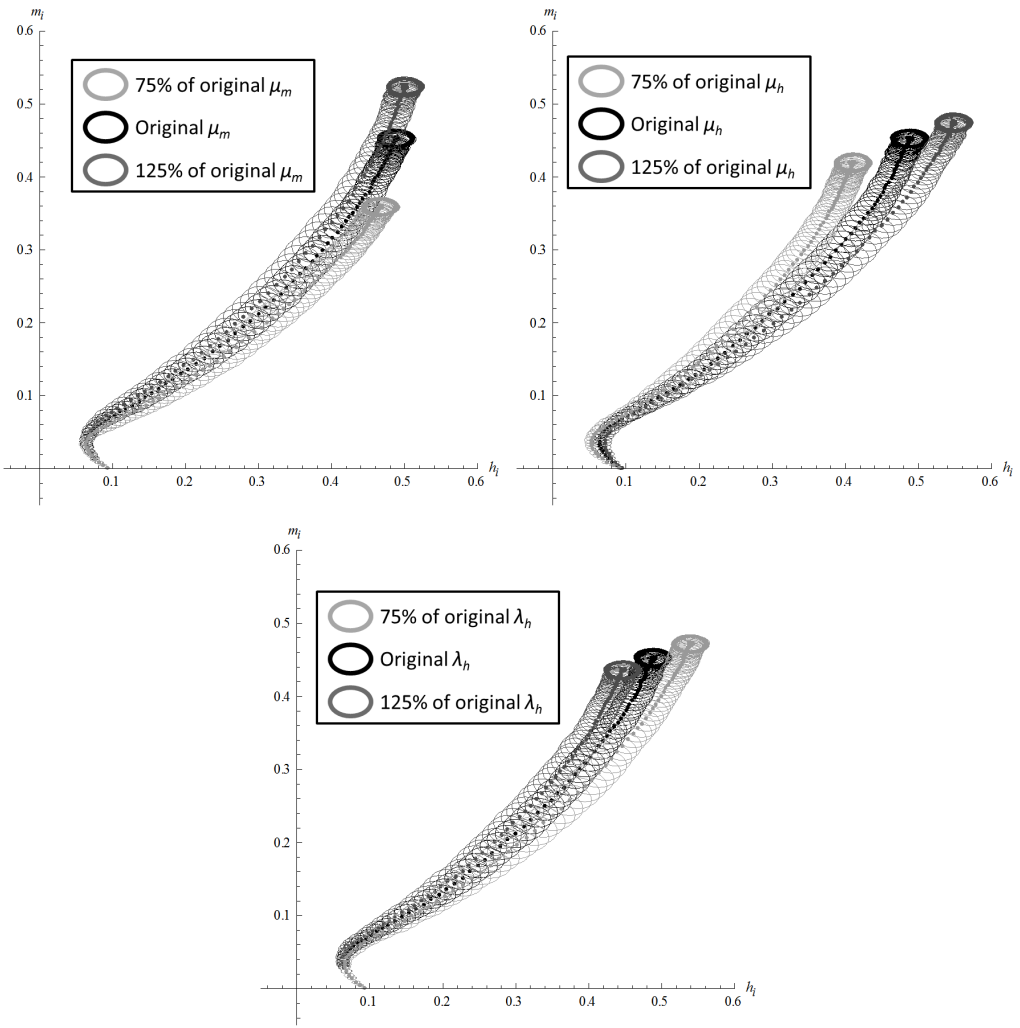


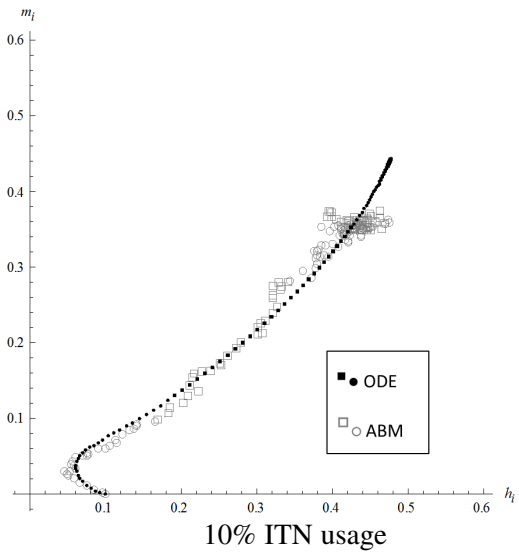
Figure 2. Plots of output from the ABM simulation for varying values of μ_m (top left), μ_h (top right), and λ_h (bottom). The simulations are based on a time span of six months and used averages from 500 runs of the simulation. The ellipses surrounding each point represent potential deviation from equilibrium due to randomness of the simulation. The black graph uses the value of the investigated parameter from Table 1, the light gray graph uses 75% of this value, and the dark gray graph uses 125% of this value. Parameters other than the investigated parameter were defined as in Table 1. The horizontal axis represents proportions of infectious humans in the simulated population, and the vertical axis represents proportions of infectious mosquitoes in the simulated population.

humans had bed nets. The corresponding output for the ODE model is also presented in the plots in Figure 3 to show the decreasing proportion of infected individuals with increasing ITN usage. The ABM predictions in Figure 3 are for individual runs of the simulation and have not been averaged since they are intended as examples of simulation output.

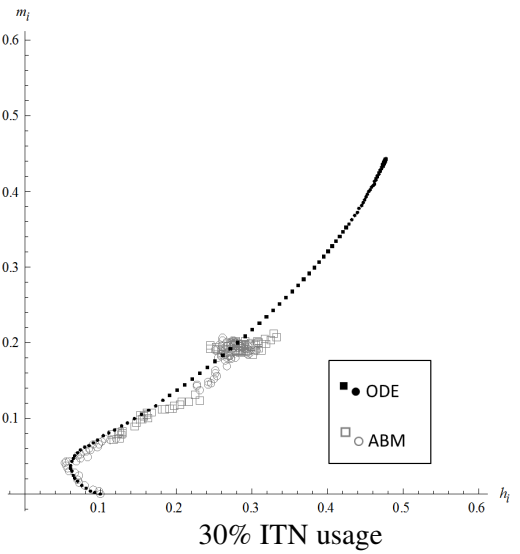
In order to demonstrate the overall trend of infection with increasing ITN usage in the current study, the average equilibrium points (h_i, m_i) for the ABM simulation were calculated for each proportion of bed net use by humans, from 1 to 100 percent. Again, several replicates should be simulated in order to describe the overall system [MacDonald et al. 1968]. The ABM was run 500 times to allow for variation with random numbers used in the simulation. A time period of two years was used in order to allow for more settling to the equilibrium points. The average equilibrium points were calculated using the ABM output for h_i and m_i in the last 500 days of each two-year simulation run, and the equilibrium points were averaged across various simulations. The simulation appears to settle after six months; hence, the output in the last 500 days of the two-year run represents output after the simulation has localized. Successive equilibrium points from 1 percent to 100 percent bed net usage are displayed in Figure 4 along with ellipses representing the error due to variability. The rightmost point on the plot represents the average equilibrium point with 1 percent of humans using bed nets, and this percentage increases moving right to left on the plot. The ellipses are centered around the mean equilibrium coordinates for humans and mosquitoes using major and minor axes with lengths of two standard deviations. The ellipses are presented to illustrate the variability in the individual simulation runs.

3.3. ***Acquired immunity.*** Acquired immunity is gained through repeated exposure to the malaria parasite, and the effects of acquired immunity have been previously modeled [Aron 1983; Chiyaka et al. 2007; Gu et al. 2003; Gurarie and McKenzie 2007; Milligan and Downham 1996; Tumwiine et al. 2007]. Previous models have considered acquired immunity as leading to milder forms of the disease [Tumwiine et al. 2007] and have defined acquired immunity in a host as protection against severe illness [Chiyaka et al. 2007]. Chiyaka et al. [2007] also asserted that while this immunity may be beneficial to the individual, these immune individuals disrupt the control strategies for the disease. When infection is mild the infected person may not seek medical attention which allows susceptible mosquitoes to become infected and spread the disease to other susceptible human hosts.

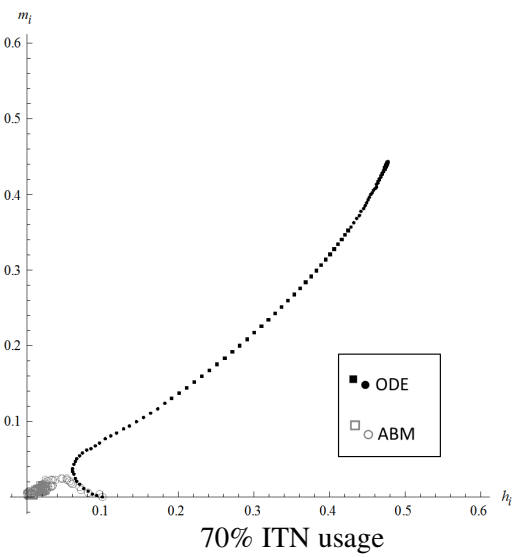
In modeling the spread of acquired immunity in the current ABM, human agents were assumed to gain immunity after a certain number of infections as in [Milligan and Downham 1996]. Once a host has reached a certain level of infections, the host was assumed to lose immunity at a particular rate (if not reinfected) [Aron



10% ITN usage



30% ITN usage



70% ITN usage

Figure 3. Plot of output from the ABM simulation incorporating ITN usage, shown by the open gray shapes. The solid black shapes represent output from the ODE model with latency as described in Section 2.1, shown for comparison. The simulations were generated over approximately 6 months (180 days). The horizontal axis represents proportions of infectious humans in the simulated population, and the vertical axis represents proportions of infectious mosquitoes in the simulated population. The symbols change from one shape to another at the end of each 30 day period.

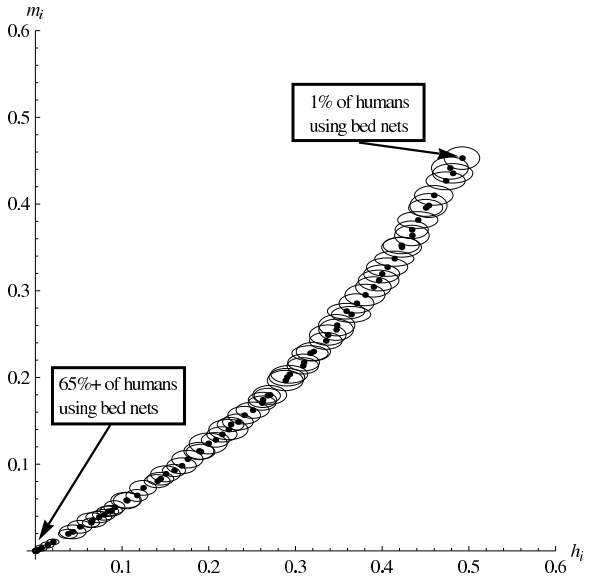


Figure 4. For each proportion of humans using ITNs, a settling point of the ABM was calculated based on an average of 500 simulation runs over a 2 year period. The equilibrium point for 1% ITN use is found on the top right with nearly 50% infectivity. As ITN usage increases, the equilibrium points trend toward (0, 0) or no infection. The ellipses surrounding each point represent potential deviation from equilibrium due to randomness of the simulation. The ellipses surrounding each point represent potential deviation from equilibrium due to randomness of the simulation.

1983; Milligan and Downham 1996]. Gu et al. [2003] investigated an ABM with acquired immunity, but their model did not incorporate latency and did allow for superinfection. Although acquired immunity could be described using only the number of infections a person has experienced as in [Gu et al. 2003], the ABM in the current study was constructed to model immunity as time-dependent.

A third characteristic is added to the array for humans in the ABM that represents a quantitative measure of acquired immunity. Each exposure to the disease is expected to add to this quantitative measure; once a certain level of exposure to malaria is reached, acquired immunity begins. In the ABM for acquired immunity a person is assumed to resist infection to malaria after roughly three infections. Each time the characteristic array of the human is changing from susceptible to latent, I_{ex} (which was set to 30) arbitrary units are added to the immunity characteristic. The quantity of this characteristic at which a person is expected to be immune I_c

is set to 70. Hence, the simulations allow for a person to be immune after three infections in a short time period.

Once a person has acquired immunity, the immunity is assumed to decrease with time. Once the human has returned to the susceptible state, one unit of immunity is lost as each iterate (or day) passes without another infection. Resistance to the disease is treated discretely; a person will not become latent if immunity is 70 or above and a person is equally susceptible to infection if immunity is anything between 0 and 69. Although acquired immunity may lead to milder forms of disease, the ABM was designed (in this initial investigation) to model immunity very simply. Individuals are also assumed to have a limit to the amount of immunity they can acquire, and the maximum quantity of immunity, $I_{\max}$ is set to 100. A more detailed description of the process of the ABM with acquired immunity is presented in Appendix A.3.2.

ABM simulation results incorporating acquired immunity are presented in Figure 5, and the numerical solution to the ODE model described in Section 2.1 is plotted for comparison. The ABM simulation does not appear to settle into an equilibrium point in the first six months, and ABM simulations were produced over two-year time periods to allow for more settling to potentially identify an equilibrium. As with the sensitivity analysis and the investigation into ITN usage, an overall trend was desired in line with suggestions from [MacDonald et al. 1968]. Figure 5 contains average model output over 500 simulations that were run for a two-year time period. Each ellipse in Figure 5 represents the average value found for that point after 500 runs of the simulation plus one standard deviation in the direction of the major and minor axes.

4. Discussion

The ABM of malaria transmission makes very similar predictions to the ODE model based on the work of Ross and MacDonald [1957] altered to account for latency. The ABM in the current study is similar in concept to the computational framework described in [MacDonald et al. 1968] with the addition of latency and without seasonal effects. The ABM is intended to be simple and straightforward and provides a convenient way to add complexity in modeling malaria transmission, such as incorporating the effects of bed nets and immunity. Since the output of the ODE model and the ABM are similar, the ABM simulations likely also have asymptotic behavior around the nonzero equilibrium point or endemic equilibrium. Strategies of reducing the spread of malaria could be determined by investigating changes that move the settling point of the ABM closer to the origin. The basic ODE model had an asymptotically stable endemic equilibrium, and all simulations of the ABM became localized after some length of time. By describing the populations in

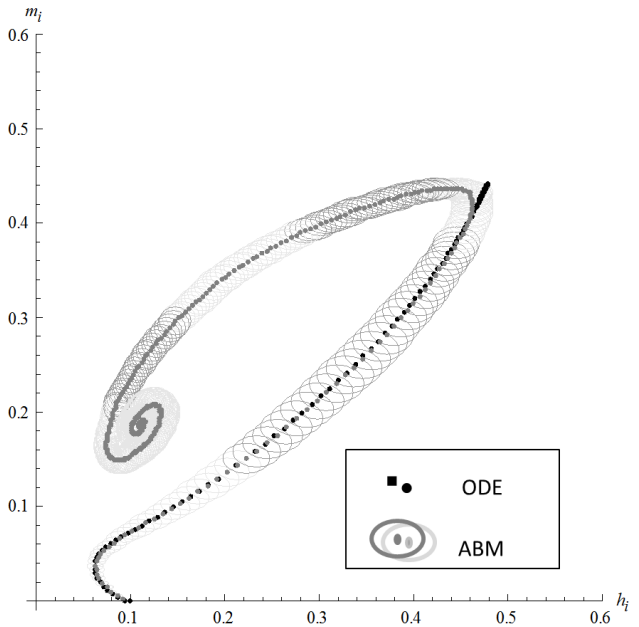


Figure 5. Plot of output from the ABM simulation incorporating acquired immunity based on a time span of 2 years and using averages from 500 runs of the simulation. The averages of model output of the two year period are shown by the gray dots and surrounding lighter gray ellipses. The ellipses change from one gray shade to another at the end of each 30 day period. The black dots represent output from the ODE model with latency as described in Section 2.1, shown for reference. The ellipses surrounding each point represent potential deviation from equilibrium due to randomness of the simulation. The horizontal axis represents proportions of infectious humans in the simulated population, and the vertical axis represents proportions of infectious mosquitoes in the simulated population.

terms of individual agents, the ABM may be better constructed to deal with disease eradication [MacDonald et al. 1968].

The addition of bed nets into the ABM demonstrated a clear decrease in infection compared with the base model. More specifically, increasing the amount of bed net usage resulted in a reduction in infection prevalence in both human and mosquito populations. Furthermore, infection is nearly eliminated from both human and mosquito populations if only 70% of the human population is protected with bed nets. This leads to the conclusion that bed nets, when used among the majority of a

population, have the power of protecting more than just the individuals sleeping directly under them. Hence, the results suggest that protecting a given threshold of individuals within a population extends disease protection to everyone in that population. The ABM simulation did assume that once an ITN was put in place, the individual using it would continue to use the bed net, which may need to be more fully considered.

Additionally, the ABM is intended as a base framework for miscellaneous investigations; and through modification of the ABM, one could easily study the effects of bed nets combined with other considerations (seasonality, etc.). As described in Appendix A.3.2, the ABM simulation was modified by the addition of an element to the individual's characteristic array which indicates the presence of a bed net and a step to check if the ITN prevents a mosquito from biting a human. The use of ITNs can be incorporated into an ODE model, but the purpose of this investigation is not only to find specific results but also to illustrate an example of how the ABM can be easily adapted.

As also discussed in Appendix A.3.2, acquired immunity was modeled in the ABM through an element in the agent's characteristic array, and this element was affected only by infection history and time. Hence, the ABM did not require computational solving of a nonlinear system. A reduction in the proportion of infectious individuals was expected due to acquired immunity, and the ABM of malaria transmission was relatively easy to alter to incorporate this complicated issue of malaria transmission. As with the ABM investigation involving ITNs, the investigation incorporating acquired immunity is intended as an example of how the ABM can be easily modified for issues surrounding malaria or other diseases.

The ABM simulations incorporating acquired immunity show spiraling behavior as time increases as shown in Figure 5, and this model behavior may be worth investigating further. The description of acquired immunity may require additional sophistication in the ABM as the results presented in this study were based on the idea that an individual was either completely immune or completely susceptible, which is oversimplified and was warned against in [Gurarie and McKenzie 2007]. A probabilistic approach could be used to describe an agent as less likely (but not completely immune) to contract the disease after repeated exposures. The structure of the ABM is not currently constructed to investigate questions such as how mildly affected individuals' not seeking treatment would change transmission dynamics (as mentioned in [Chiyaka et al. 2007]), but the ABM could be modified to do so through larger arrays describing the agents. Additionally, combining the dynamics of ITN usage and acquired immunity in the ABM may provide even greater insight into the effect of preventative measures in the population. The results of a model combining these issues may suggest an even lower percentage of ITN usage is needed for a significant reduction in infection.

The ABM for malaria transmission does not currently incorporate spatial considerations. The interactions are all treated randomly, and the agents are assumed to be distributed in such a way that random interaction is reasonable. However, where humans and mosquitoes are located in an area likely does affect which humans are selected as blood-meal targets if the distributions of either group are not uniform. The ABM could be adapted to describe smaller populations within the larger community in order to account for this in some way. An additional characteristic could easily be added to represent a finite number of locations that have different parameters and interaction details associated with them.

Although the predictions from the ABM and the ODE model are similar in shape, they do differ somewhat with time. The predictions are not equal at each time point with the ABM simulations moving toward the settling point more quickly than the numerical solution of the ODE system. The reason for the time difference has not yet been identified and may be a focus for future work. This is an important issue since the time difference could have implications on what public health professionals should expect from real-world dynamics.

Many aspects of malaria transmission have not been incorporated into the ODE model or the ABM. Seasonality, climate, emigration, and other environmental factors are assumed to not have an impact on the model, but these factors do all affect the spread of the disease. Some of the simulations are computed over two years, which does involve seasonal changes; therefore, assuming climate has no affect is an oversimplification. However, the ABM uses a structure that is easily adaptable to different situations, and many of these aspects should be relatively straightforward to include in the ABM. In order to establish the ABM as a reasonable vehicle to describe malaria transmission, a basic ABM was created to compare to a fairly simple ODE model. The similarity of the two models has been established, and future work will incorporate greater complexity. Additional studies may also consider the comparison between more complicated models of both structures.

Appendix: ODD protocol

Various techniques and methods have been used in simulation models involving ABMs, and [Grimm et al. 2006] presents the overview, design concepts, and details (ODD) protocol for describing ABMs. The following is a description of the malaria transmission ABM used in this study based on the ODD protocol.

A.1. *ODD protocol: overview.*

A.1.1. *Purpose.* The purpose of the ABM malaria model in this study is to describe malaria infection on a population level in order to better understand transmission of the disease. Additionally, the framework of this ABM allows for fairly easy additions of very complicated factors of malaria spread.

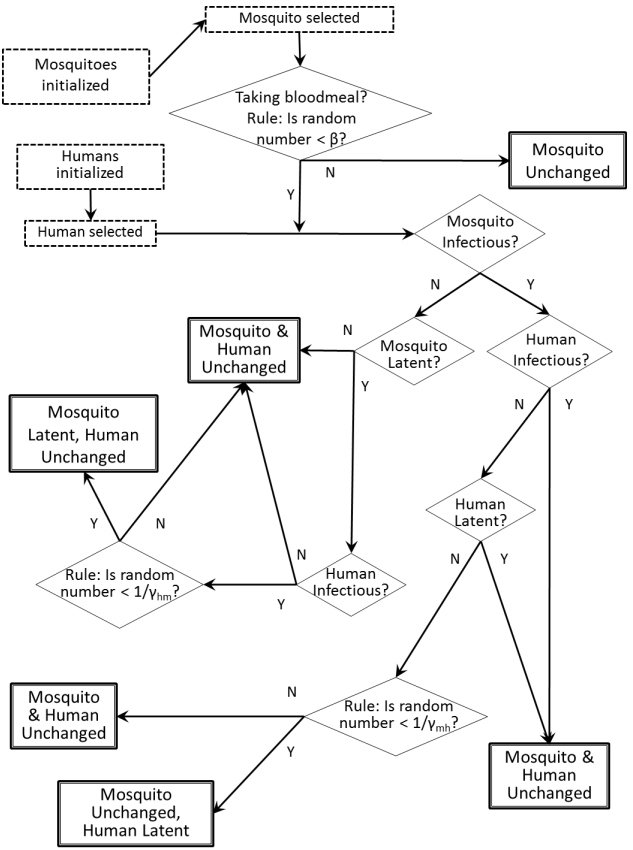


Figure 6. Flow chart showing the ABM rules of malaria transmission during a blood meal. This chart describes how agents move from the susceptible stage to the latent stage, but does not account for the modeling of an agent's move from the latent stage to the infectious stage. The continued process of the ABM is shown in Figure 7. The notation used for parameters is the same as in Section 2.1 and the parameter values used are presented in Table 1.

A.1.2. *State variables.* The agents in the basic ABM are mosquitoes and humans in closed populations. Each agent has two characteristics, whether the individual is latent and whether the individual is infectious. The characteristics are indicated using 0 and 1; 0 indicates the individual does not have the particular characteristic (latent or infectious), and 1 indicates the individual does have the characteristic.

When modeling ITN usage, a third characteristic is added to the human individuals indicating whether or not the individual was given a bed net at the beginning of the simulation. The third number in the individual's characteristic array would

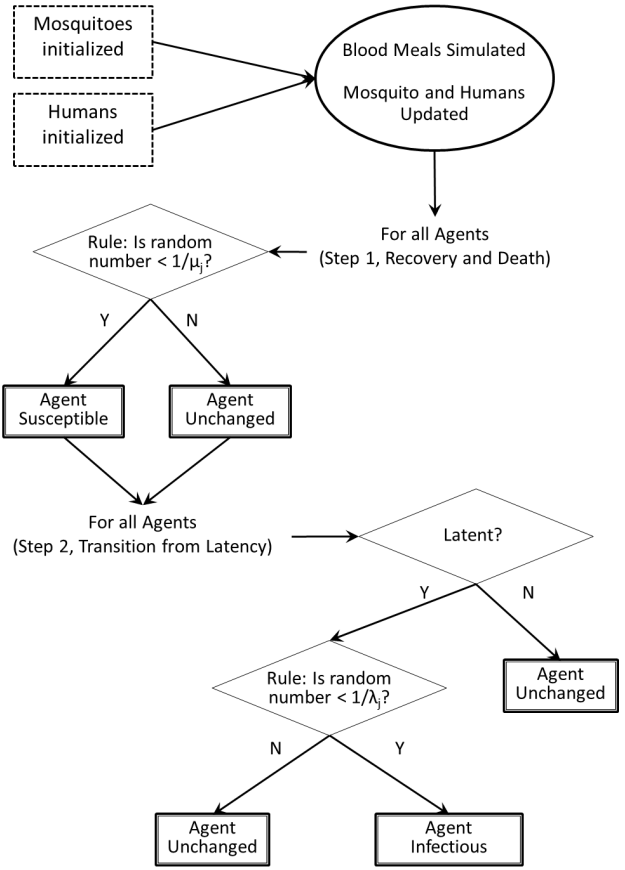


Figure 7. Flow chart showing the ABM rules defining transitions from latency to the infectious state and returning from the infectious state to the susceptible state. The details involved in the oval for blood meals is expanded in Figure 6. The subscript j is either m or h depending on whether the agent is a mosquito or a human. The notation used for parameters is the same as in Section 2.1 and the parameter values used are presented in Table 1.

then be 1 if the individual was using an ITN and 0 if not. In investigations with immunity, an third characteristic is also added to the human individuals indicating a level of acquired immunity which will be described more fully in Appendix A.3.2.

A.1.3. *Process overview.* The primary interaction modeled in the ABM for malaria transmission is the contact between a mosquito taking a blood meal and the individual human being bitten. Time is treated discretely, using steps of days. The beginning process of the ABM is outlined in Figure 6 showing how the individual biting events are modeled. The process of agents' moving to latency is presented in

Figure 7. The process in Figure 7 applies to both mosquito and human populations, with the rules based on appropriate parameters. The subscript j in the diagram indicates m or h depending on whether the agent is a mosquito or a human. Although the process is the same for both types of agents, the left side of the diagram (step 1) has different meaning depending on the type of agent. Since the population of mosquitoes is assumed to remain constant, if a mosquito is selected to "die" (the selected random number is less than $1/\mu_m$), then a new mosquito essentially takes its place by changing the characteristic array to describe a susceptible mosquito. The parameter μ_h indicates the recovery time of humans, so the change of the characteristic array to indicate susceptibility is assumed to (most likely) be describing the same human individual who has now recovered from the disease. The notation used for parameters is the same as in Section 2.1 and the parameter values used are presented in Table 1. All random numbers are selected from a uniform distribution between 0 and 1.

A.2. ***ODD protocol: design concepts.*** The interaction between mosquitoes and humans is modeled explicitly, and all rules of the ABM are based on probabilities. Mosquitoes and humans from the list or array of agents were chosen randomly and proximity or location was not incorporated.

A.3. ***ODD protocol: details.***

A.3.1. *Initialization.* The parameters in Table 1 were initialized and kept fixed throughout the simulations of the ABM. The total number of humans simulated was 500 except in a few simulations investigating sensitivity as described in Section 3.1. (Note that since the ratio of mosquitoes to humans is a fixed parameter in the model, defining the number of humans also defines the total number of mosquitoes.) The initial proportion of infectious humans was set to be 10%, and the initial proportion of infectious mosquitoes was set to be 0%. No agents were initialized in the latent stage. All simulations used the same initial proportions.

The individual simulations involving ITNs and acquired immunity did involve more initialized values. The details of those simulations are presented in Appendix A.3.2.

A.3.2. *Submodels.*

Insecticide-treated bed nets. The ABM for malaria transmission was adapted to predict the spread of the disease when insecticide-treated bed nets are used. The process of simulated malaria transmission when bed nets are used is shown in Figure 8. In the initialization of the simulations with ITN usage, the percentage of how many humans would be using bed nets was set and fixed for the rest of that simulation. To ascertain the effect of ITNs on the spread of malaria, different simulations were varied using percentages of ITN usage. The parameter δ was not

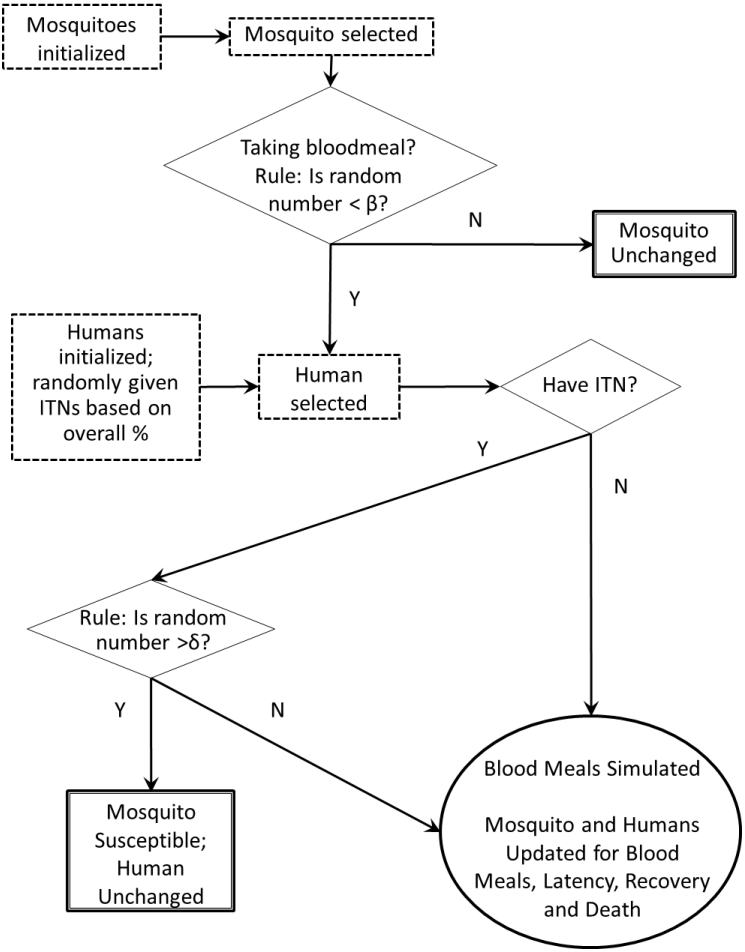


Figure 8. Flow chart showing the ABM rules defining malaria transmission when bed nets are used by the human population. The notation used for parameters is the same as in Section 2.1 and the parameter values used are presented in Table 1 except for the parameter δ indicating the probability that a mosquito will survive once it tries to bite a human using a bed net.

in either original model and represents the probability that a mosquito will survive once it tries to take a blood meal from a human using a bed net. Since bed net usage was expected to be 96% effective (see Section 3.2), δ was set to be 0.04 for all simulations. After the simulation checks if the mosquito dies while trying to take a blood meal, the simulation proceeds as described in Section A.1.3. As in the basic simulation, if an agent "dies," its characteristic array is changed to represent

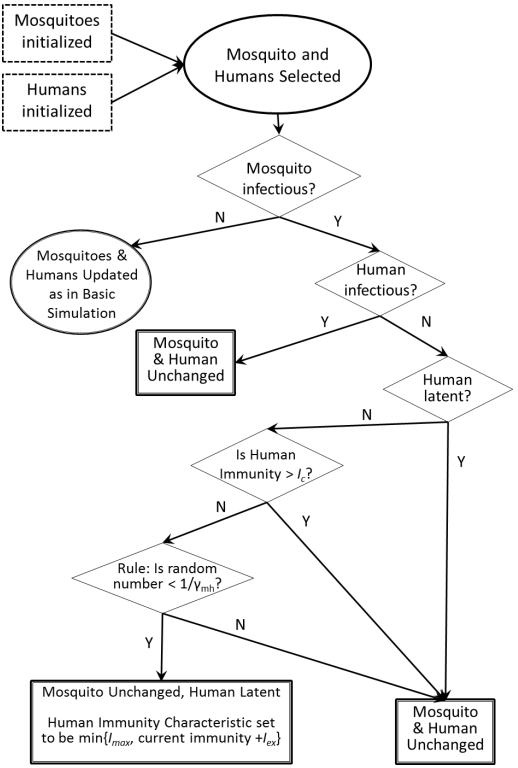


Figure 9. Flow chart showing the ABM rules defining malaria transmission when human agents may be able to acquire immunity to the disease. The parameter I_c indicates the numerical immunity that is necessary to avoid infection, I_{ex} indicates the addition to the immunity characteristic when the human is successfully infected, and I_{max} is the largest allowable value for the immunity characteristic. Otherwise, the notation used for parameters is the same as in Section 2.1 and the parameter values used are presented in Table 1. This flow chart does not include the entire ABM simulation for malaria transmission with acquired immunity as it does not show steps modeling the move from latency to being infectious, modeling recovery or death, or modeling how individual immunity decreases.

a newly born, susceptible agent. The oval in Figure 8 contains all steps shown in Figure 6 and Figure 7.

Acquired immunity. In order to model malaria transmission, a third element was added to the agent characteristic array. This third characteristic quantifies the immunity of the individual human agent. A flow chart describing the ABM with malaria

transmission when acquired immunity is incorporated is presented in Figure 9. Each time a human is successfully infected (which means that the human moves to the latent stage) an immunity exposure value I_{ex} is added to the immunity characteristic of that human. Human agents are expected to have a maximum to the immunity they can obtain; therefore, the human immunity characteristic is limited by a maximum value I_{max}. Once a human has immunity above a critical value I_c, that individual will be protected from transmission from an infectious mosquito. The flow chart in Figure 9 only shows the portion of the simulation through the blood-meal process, similar to the basic simulation flow shown in Figure 6. The simulations for the ABM with acquired immunity also proceed through the steps outlined in Figure 7. Additionally, each iteration of the simulation represents one day, and the immunity characteristic (if nonzero) of susceptible humans decreases by 1 with each iteration. In all simulations, we use $I_c = 70$, $I_{ex} = 30$, and $I_{max} = 90$ as is described more fully in Section 3.3.

Acknowledgements

The authors would like to thank Dr. Crista Arangala for helpful comments and discussions throughout the investigation.

References

[Anderson and May 1991] R. Anderson and R. May, *Infectious diseases of humans: dynamics and control*, Oxford University Press, 1991.

[Aneke 2002] S. J. Aneke, "Mathematical modelling of drug resistant malaria parasites and vector populations", *Math. Methods Appl. Sci.* **25**:4 (2002), 335–346. MR 2002m:92031 Zbl 0994.92025

[Aron 1983] J. L. Aron, "The dynamics of immunity boosted by exposure to infection", *Math. Biosci.* **64**:2 (1983), 249–259. Zbl 0515.92026

[Aron 1988] J. L. Aron, "Mathematical modelling of immunity to malaria", *Math. Biosci.* **90**:1-2 (1988), 385–396. MR 89f:92032 Zbl 0651.92018

[Aron and May 1982] J. L. Aron and R. May, "The population dynamics of malaria", pp. 139–179 in *The population dynamics of infectious disease: theory and applications*, edited by R. Anderson, Chapman and Hall, London, 1982.

[Castiglione et al. 2007] F. Castiglione, K. Duca, A. Jarrah, R. Laubenbacher, D. Hochberg, and D. Thorley-Lawson, "Simulating Epstein–Barr virus infection with C-ImmSim", *Bioinformatics* **23**:11 (2007), 1371–1377.

[CDC 2011] Centers for Disease Control and Prevention, "Drugs used in the prophylaxis of malaria", 2011. See http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/malaria#1939.

[CDC 2012a] Centers for Disease Control and Prevention, "Malaria", 2012, http://www.cdc.gov/malaria.

[CDC 2012b] Centers for Disease Control and Prevention, "Malaria: biology", 2012, http://www.cdc.gov/malaria/about/biology.

[CDC 2012c] Centers for Disease Control and Prevention, "Malaria: frequently asked questions", 2012, http://www.cdc.gov/malaria/about/faqs.html.

[Chitnis et al. 2008] N. Chitnis, J. M. Hyman, and J. M. Cushing, "Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model", *Bull. Math. Biol.* **70**:5 (2008), 1272–1296. MR 2009g:92111 Zbl 1142.92025

[Chiyaka et al. 2007] C. Chiyaka, W. Garira, and S. Dube, "Transmission model of endemic human malaria in a partially immune population", *Math. Comput. Model.* **46**:5-6 (2007), 806–822. MR 2008b:92131 Zbl 1126.92043

[Chiyaka et al. 2008] C. Chiyaka, J. M. Tchuenche, W. Garira, and S. Dube, "A mathematical analysis of the effects of control strategies on the transmission dynamics of malaria", *Appl. Math. Comput.* **195**:2 (2008), 641–662. MR 2008m:92052 Zbl 1128.92022

[Chiyaka et al. 2009] C. Chiyaka, W. Garira, and S. Dube, "Effects of treatment and drug resistance on the transmission dynamics of malaria in endemic areas", *Theor. Popul. Biol.* **75** (2009), 14–29. Zbl 1210.92005

[Curtis et al. 1992] C. F. Curtis, J. Myamba, and T. J. Wilkes, "Various pyrethroids on bednets and curtains", *Mem. Inst. Oswaldo Cruz* **87**:Supplement 3 (1992), 363–370.

[Daley and Gani 1999] D. J. Daley and J. Gani, *Epidemic modelling: an introduction*, Cambridge Studies in Mathematical Biology **15**, Cambridge University Press, 1999. MR 2000e:92042 Zbl 0922.92022

[De Zoysa et al. 1991] A. P. K. De Zoysa, C. Mendis, A. C. Gamage-Mendis, S. Weerasinghe, P. R. J. Herath, and K. N. Mendis, "A mathematical model for *Plasmodium vivax* malaria transmission: estimation of the impact of transmission-blocking immunity in an endemic area", *B. World Health Organ.* **69**:6 (1991), 725–734.

[Dembele et al. 2009] B. Dembele, A. Friedman, and A.-A. Yakubu, "Malaria model with periodic mosquito birth and death rates", *J. Biol. Dyn.* **3**:4 (2009), 430–445. MR 2011g:34094

[Eubank et al. 2004] S. Eubank, H. Guclu, V. S. Anil Kumar, M. V. Marathe, A. Srinivasan, Z. Toroczkai, and N. Wang, "Modelling disease outbreaks in realistic urban social networks", *Nature* **429**:6988 (2004), 180–184.

[Grimm et al. 2006] V. Grimm, U. Berger, F. Bastiansen, S. Eliassen, V. Ginot, J. Giske, J. Goss-Custard, T. Grand, S. K. Heinz, G. Huse, A. Huth, J. U. Jepsen, C. Jørgensen, W. M. Mooij, B. Müller, G. Pe'er, C. Piou, S. F. Railsback, A. M. Robbins, M. M. Robbins, E. Rossmanith, N. Rüger, E. Strand, S. Souissi, R. A. Stillman, R. Vabø, U. Visser, and D. L. DeAngelis, "A standard protocol for describing individual-based and agent-based models", *Ecol. Model.* **198**:1–2 (2006), 115–126.

[Gu et al. 2003] W. Gu, G. F. Killeen, C. M. Mbogo, J. L. Regens, J. I. Githure, and J. C. Beier, "An individual-based model of *Plasmodium falciparum* malaria transmission on the coast of Kenya", *Trans. R. Soc. Trop. Med. Hyg.* **97**:1 (2003), 43–50.

[Gurarie and McKenzie 2007] D. Gurarie and F. E. McKenzie, "A stochastic model of immune-modulated malaria infection and disease in children", *Math. Biosci.* **210**:2 (2007), 576–597. MR 2008k:92056 Zbl 1134.92024

[Hinkelmann et al. 2011] F. Hinkelmann, D. Murrugarra, A. S. Jarrah, and R. Laubenbacher, "A mathematical framework for agent based models of complex biological networks", *Bull. Math. Biol.* **73**:7 (2011), 1583–1602. MR 2012f:92003 Zbl 1225.92001

[Koella 1991] J. C. Koella, "On the use of mathematical models of malaria transmission", *Acta Tropica* **49**:1 (1991), 1–25.

[Koella and Antia 2003] J. C. Koella and R. Antia, "Epidemiological models for the spread of anti-malarial resistance", *Malaria J.* **2**:3 (2003).

[MacDonald 1957] G. MacDonald, *The epidemiology and control of malaria*, Oxford University Press, London, 1957.

[MacDonald et al. 1968] G. MacDonald, C. B. Cuellar, and C. V. Foll, "The dynamics of malaria", *B. World Health Organ.* **38**:5 (1968), 743–755.

[Maire et al. 2006] N. Maire, T. Smith, A. Ross, S. Owusu-Agyei, K. Dietz, and L. Molineaux, "A model for natural immunity to asexual blood stages of *Plasmodium falciparum* malaria in endemic areas", *Amer. J. Trop. Med. Hyg.* **75**:Supplement 2 (2006), 19–31.

[Milligan and Downham 1996] P. J. M. Milligan and D. Y. Downham, "Models of superinfection and acquired immunity to multiple parasite strains", *J. Appl. Probab.* **33**:4 (1996), 915–932. MR 97g:92021 Zbl 0871.92025

[Nájera 1974] J. A. Nájera, "A critical review of the field application of a mathematical model of malaria eradication", *B. World Health Organ.* **50**:5 (1974), 449–457.

[Nedelman 1985] J. Nedelman, "Introductory review: some new thoughts about some old malaria models", *Math. Biosci.* **73**:2 (1985), 159–182. MR 86d:92022 Zbl 0567.92020

[N'Guessan et al. 2001] R. N'Guessan, F. Darriet, J. M. C. Doannio, F. Chandre, and P. Carnevale, "Olyset Net® efficacy against pyrethroid-resistant *Anopheles gambiae* and *Culex quinquefasciatus* after 3 years' field use in Côte d'Ivoire", *Med. Vet. Entomol.* **15**:1 (2001), 97–104.

[Ngwa 2006] G. A. Ngwa, "On the population dynamics of the malaria vector", *Bull. Math. Biol.* **68**:8 (2006), 2161–2189. MR 2007k:92119

[Pogson et al. 2006] M. Pogson, R. Smallwood, E. Qwarnstrom, and M. Holcombe, "Formal agent-based modelling of intracellular chemical interactions", *BioSystems* **85**:1 (2006), 37–45.

[Ross 1910] R. Ross, *The prevention of malaria*, Dutton, New York, 1910.

[Shililu et al. 1998] J. I. Shililu, W. A. Maier, H. M. Seitz, and A. S. Orago, "Seasonal density, sporozoite rates, and entomological inoculation rates of *Anopheles gambiae* and *Anopheles funestus* in a high-altitude sugarcane growing zone in Western Kenya", *Trop. Med. Int. Health* **3**:9 (1998), 706–710.

[Smith et al. 2006] T. Smith, G. F. Killeen, N. Maire, A. Ross, L. Molineaux, F. Tediosi, G. Hutton, J. Utzinger, K. Dietz, and M. Tanner, "Mathematical modeling of the impact of malaria vaccines on the clinical epidemiology and natural history of *Plasmodium falciparum* malaria: overview", *Amer. J. Trop. Med. Hyg.* **75**:Supplement 2 (2006), 1–10.

[Smith et al. 2007] D. L. Smith, F. E. McKenzie, R. W. Snow, and S. I. Hay, "Revisiting the basic reproductive number for malaria and its implications for malaria control", *PLoS Biol.* **5**:3 (2007), 531–542.

[Spielman and D'Antonio 2001] A. Spielman and M. D'Antonio, *Mosquito: a natural history of our most persistent and deadly foe*, Hyperion, New York, 2001.

[Tumwiine et al. 2007] J. Tumwiine, J. Y. T. Mugisha, and L. S. Luboobi, "A mathematical model for the dynamics of malaria in a human host and mosquito vector with temporary immunity", *Appl. Math. Comput.* **189**:2 (2007), 1953–1965. MR 2332148 Zbl 1117.92039

[Wang et al. 2009] Z. Wang, C. M. Birch, J. Sagotsky, and T. S. Deisboeck, "Cross-scale, cross-pathway evaluation using an agent-based non-small cell lung cancer model", *Bioinformatics* **25**:18 (2009), 2389–2396.

[World Book 2008] World Book, "Mosquito", in *The World Book Encyclopedia*, World Book, Chicago, 2008.

[Yang and Ferreira 2000] H. Yang and M. Ferreira, "Assessing the effects of global warming and local social and economic conditions on malaria transmission", *Rev. Saúde Públ.* **34**:3 (2000), 214–222.

Received: 2012-05-04 Revised: 2013-02-08 Accepted: 2013-05-23

kyokley@elon.edu *Department of Mathematics and Statistics, Elon University, Elon, NC 27244, United States*

tlee@elon.edu *Department of Mathematics and Statistics, Elon University, CB 2320, Elon, NC 27244, United States*

akbrown19@gmail.com *University of Texas Health Science Center at Houston, Houston, TX 77030, United States*

mchristina.minor@gmail.com *Fitts Department of Industrial and Systems Engineering, North Carolina State University, Raleigh, NC 27695, United States*

gmader16@gmail.com *Department of Mathematics, North Carolina State University, Raleigh, NC 27695, United States*

involve

msp.org/involve

See inside back cover or msp.org/involve for submission instructions. The subscription price for 2014 is US $120/year for the electronic version, and $165/year (+$35, if shipping outside the US) for print and electronic. Subscriptions, requests for back issues from the last three years and changes of subscribers address should be sent to MSP.

Involve (ISSN 1944-4184 electronic, 1944-4176 printed) at Mathematical Sciences Publishers, 798 Evans Hall #3840, c/o University of California, Berkeley, CA 94720-3840, is published continuously online. Periodical rate postage paid at Berkeley, CA 94704, and additional mailing offices.

Involve peer review and production are managed by EditFLOW® from Mathematical Sciences Publishers.

PUBLISHED BY

mathematical sciences publishers

nonprofit scientific publishing

http://msp.org/

involve
2014 vol. 7 no. 1