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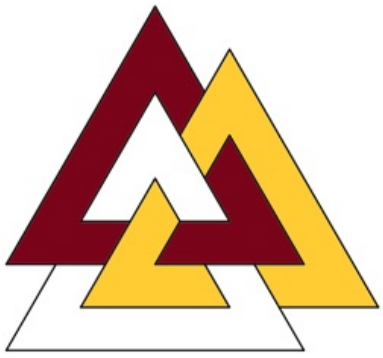

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Abstract. Dengue fever is primarily an urban disease of the tropics and is caused by one of four virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). Symptoms of the virus include high fever, muscle and joint pain, and rash. Since dengue fever is a mosquito-borne virus transmitted by the *Aedes aegypti* mosquito, the spread of the disease can be modeled by both agent-based models and equation-based models. The purpose of this study is to compare a simple agent-based model built in Netlogo against a more traditional equation-based model. In addition, the emerging preventative measure of injecting mosquitoes with the *Wolbachia* bacterium is incorporated into each model and further explored. Multiple *Wolbachia* release strategies are presented.

1. Introduction

The global prevalence of dengue fever has increased dramatically in recent decades. With an estimated 390 million cases of the disease each year and about half of the world's population now at risk, dengue fever poses a large threat to human health as well as global economies [10]. Dengue fever is primarily an urban disease of the tropics and is caused by one of four virus serotypes. Symptoms of the virus include high fever, muscle and joint pain, and rash. While each person is affected differently based on age and health, dengue fever is not usually fatal unless dengue hemorrhagic fever develops, which is a rare consequence with symptoms including severe pain, shock, and bleeding [4]. While contracting one serotype provides immunity to that specific serotype, there is no cross-protective immunity to the disease. Thus, a person could contract all four serotypes in a lifetime, and is in fact more likely to contract dengue hemorrhagic fever once they have been infected with an initial serotype [9]. So far, there is no cure and no tetravalent dengue fever vaccine is available. While dengue fever remained only a small threat for a long period of time, due to lack of transportation, modern travel patterns now pose a risk to the spread of dengue fever across the globe [8]. The threat of the distribution of this disease has led to the recent development and encouragement of new prevention methods, which can affect the output of mathematical models for dengue transmission.

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Dengue fever is transmitted through human interaction with the *Aedes aegypti* mosquito, or vector. The day-biting nature of the *Aedes aegypti* mosquito creates an atmosphere that is less conducive to traditional preventative measures used with other mosquito born illnesses, such as bed nets. Scientists are currently studying the possibility of infecting mosquitoes with the bacterium *Wolbachia*, which has the potential to block the transmission of dengue fever to said mosquitoes [7]. *Wolbachia* is a bacterium common among insects but does not infect the *Aedes aegypti* mosquito, the main carrier of dengue fever. Since mosquitoes infected with *Wolbachia* do not transmit dengue to humans, this bacterium has the potential to slow the spread of dengue fever among populations or eradicate dengue fever all together in the long run. This paper compares an equation-based model with an agent-based model of a single serotype system with *Wolbachia* introduced. In addition, different strategies for the release of *Wolbachia* are simulated in order to argue the best strategy for eradicating the disease.

2. Dengue Fever Simulation

Only female mosquitoes take a blood meal. Hence upon contact with a human, the mosquito, also called the vector, is assumed to take a blood meal half of the time [8]. Once the vector takes a blood meal, it takes 3-5 days for eggs to develop and it will take between 8 and 10 days for the eggs to develop into adult mosquitoes [6]. In this model, we assume that the time from blood meal to hatched adult offspring takes 12 days. We also assume that the vector does not take another blood meal during this 12 day period and hatches only one additional vector during reproduction. This reproduction assumption is to control the number of vectors in a small simulation region, this assumption could be easily altered.

When an infected mosquito bites a human, there is about a 75% chance that the human will contract dengue fever from the vector [2]. We will assume that if a susceptible mosquito bites an infected human, the mosquito will contract the disease. This is a common assumption in literature. Although it is most common for a human to show systems of dengue fever for between 2 and 10 days [4], the human can be infectious prior to showing systems and after symptoms have subsided. In this simulation, it is assumed that a human can be infectious for up to 20 days, incorporating both the period of the systems and extended infectious period. Similar behaviors can be seen with a slightly decreased human infectious period in both the agent-based and equation based models. Once the human recovers from a serotype of dengue fever, they remain immune to that serotype indefinitely and, in fact, have a short period of immunity, to the remaining serotypes [9]. Table 1 displays a list of assumed parameters in the presented agent-based simulation.

Parameter	Value
Vector daily bite rate	0.50
Transmission probability from vector to human	0.75
Transmission probability from human to vector	1.00
Vector lifespan (temperature dependent)	40-60 days
Human infectious period	20 days

Table 1. Parameters used in presented agent-based model [3, 5, 6, 9].

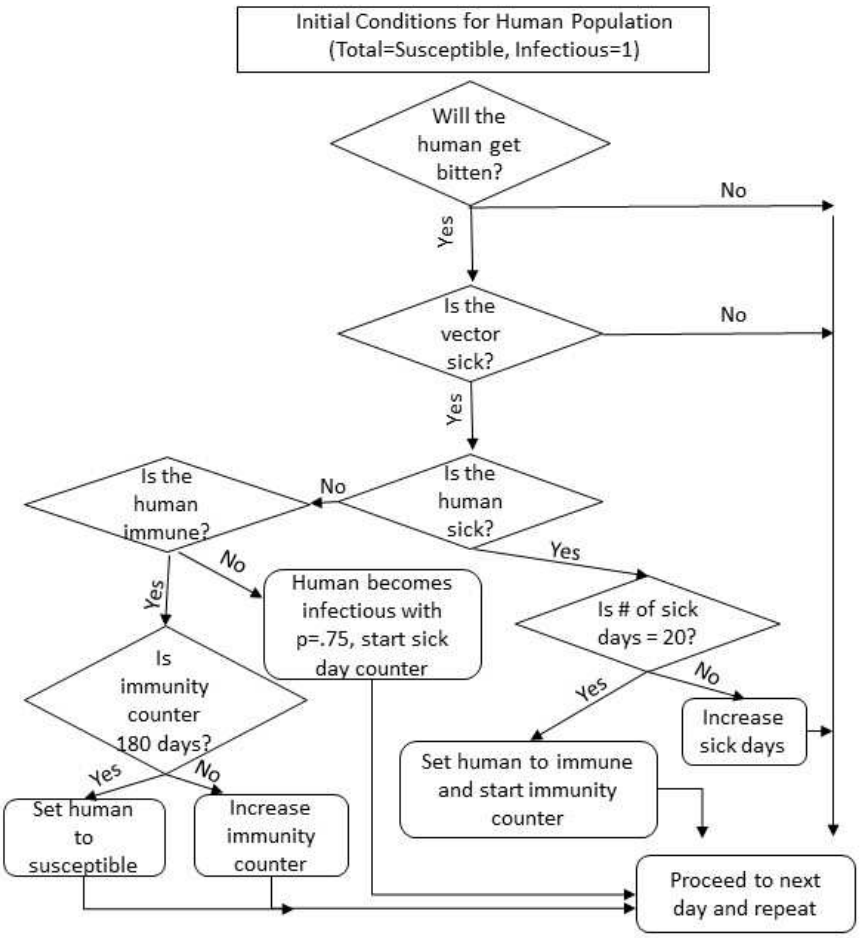

FIGURE 1. Flowchart description of human agent decisions\behavior.

The presented agent-based simulation was developed in Netlogo Version 6.0.4 using the framework of the flowcharts presented in Figures 1 and 2. Netlogo is a two-dimensional world which is partitioned by a square grid. Each square in the grid is called a patch and both humans and vectors are placed on the grid based on a random x-y coordinate assignment. In Netlogo, one must set the size of the investigation region, which is typically rectangular and defined by the number of patches in each direction. Basic behaviors, such as biting and reproducing of vector offspring, happen within a patch and movement only happens to adjacent patches in subsequent time steps, called ticks. The results of this simulation are somewhat sensitive to the size of the investigated region (in patches). The front end of the Netlogo simulation can be seen in Figure 3 and, in Figure 4, the reader can see the results of a simulation of a single serotype outbreak with several different region sizes. In each of these simulations, the total number of humans and the initial number of vectors remains constant. We will also assume that initially there is 1 infected human and no infected vectors.

These results are similar to those produced by the differential equations model developed from Derouich and Boutayeb [2]. Whereas the Derouich and Boutayeb model assume

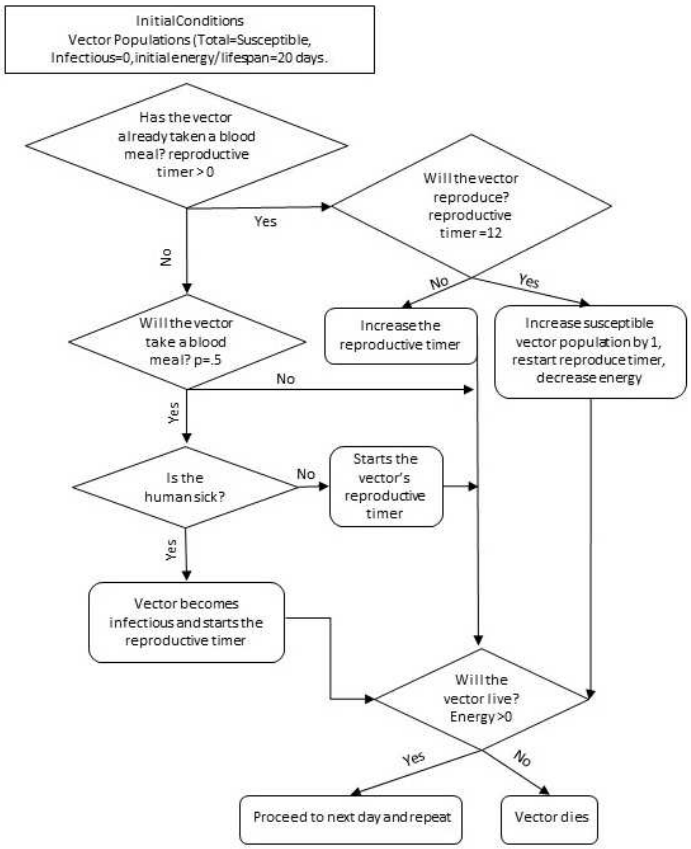

FIGURE 2. Flowchart description of vector agent decisions\behavior.

exponential growth of mosquitoes, represented by the term $b_v T_v$, Equations (1)-(6) integrate logistic growth of mosquitoes into the model with the term $\frac{T_v(K-T_v)}{K}$. Let S_h, I_h, and R_h represent the susceptible, infected, and recovered human populations, and S_v, I_v, and T_v represent the susceptible, infected, and total vector populations.

$$S_h' = -\tau_{vh}\frac{I_v S_h}{N_h}, \tag{1}$$

$$I_h' = \tau_{vh}\frac{I_v S_h}{N_h} - \rho I_h \tag{2}$$

$$R_h' = \rho I_h \tag{3}$$

$$S_v' = b_v\frac{T_v(K-T_v)}{K} - \tau_{hv} I_h S_v - d_v S_v \tag{4}$$

$$I_v' = \tau_{hv} I_h S_v - d_v I_v \tag{5}$$

$$T_v' = b_v\frac{T_v(K-T_v)}{K} - d_v S_v - d_v I_v, \tag{6}$$

where τ_{vh} represents the contact rate of vector to human, which is a product of bites per infectious vector per day and transmission probability of humans to vectors, and ρ represents the recovery rate of humans. Additional vector parameters b_v represents the recruitment rate of vectors, d_v represents the death rate, and τ_{hv} represents the contact

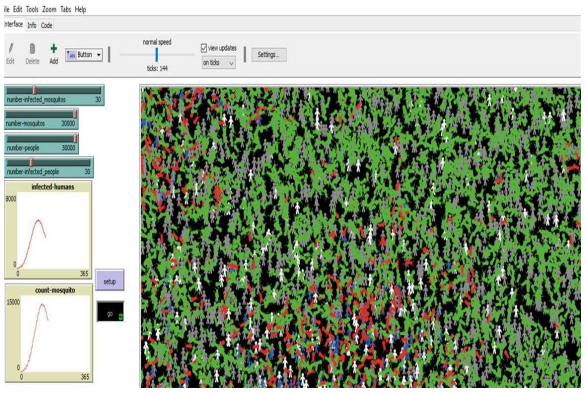

FIGURE 3. Visual of Netlogo agent-based simulation model.

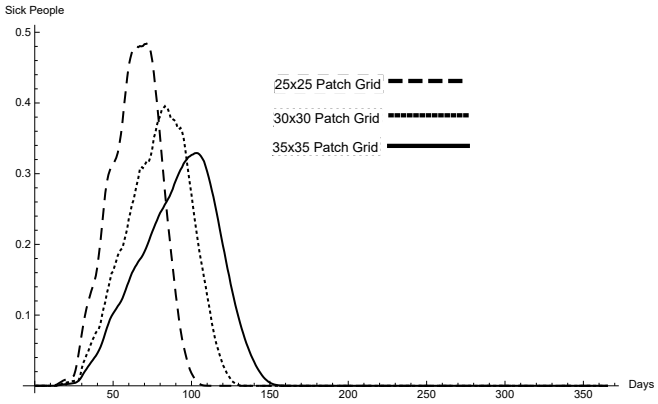

FIGURE 4. Single serotype model results of infected humans for 3 different region sizes.

rate of human to vector, a product of bites per susceptible vector per day and transmission probability of vectors to humans. In this equation based model, we assume that the human population remains constant. Figure 5 shows a comparison of the results from a single serotype dengue simulation described in this section and the results of the differential equations model in Equations (1)-(6). It is interesting to note, that although the initial rate of growth and shape of these two models are slightly different, the number of total human infections remains the same.

3. INTRODUCING *Wolbachia*

Wolbachia is a bacterium that is naturally found in many types of insects. *Aedes aegypti*, the main vector that spreads dengue fever is not one of these, but scientists have been able to infect these mosquitoes with *Wolbachia* in labs. *Wolbachia* has two effects that help prevent the spread of dengue fever. First, mosquitoes infected with *Wolbachia* have a shortened lifespan, approximately 25 days [5], and a greatly reduced ability to transmit dengue fever. In fact, *Wolbachia* in *Aedes aegypti* inhibits replication, dissemination, and transmission of the dengue fever virus [1]. Additionally, *Wolbachia* reduces the overall

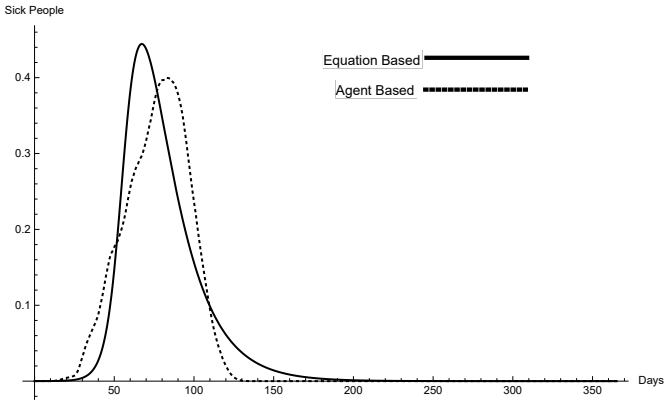

FIGURE 5. Single serotype dengue simulation results with $\tau_{vh} = \frac{1}{32}, \tau_{hv} = \frac{1}{2}$, $b_v = \frac{1}{12}, d_v = \frac{1}{40}$, $r = \frac{1}{20}, K = 80,000, N_h = 15999, I_h(0) = 1, T_v(0) = 30000$, and $I_v(0) = 0$. Simulation was done with 30×30 patches. Comparison of agent-based versus equation based single serotype models.

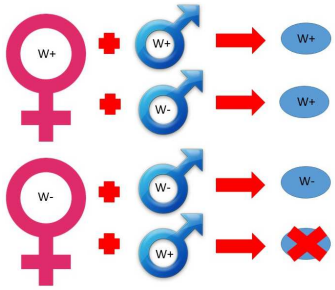

FIGURE 6. Patterns of crosses and inheritance related to *Wolbachia*.

mosquito population while propagating itself by being passed on to offspring. This occurs due to an unusual pattern of breeding and inheritance.

Female mosquitoes with *Wolbachia* will always have offspring with *Wolbachia*, no matter who they mate with. Females without *Wolbachia* and males without *Wolbachia* will produce normal offspring that also do not have *Wolbachia*. Finally, males with *Wolbachia* and females without *Wolbachia* produce eggs that do not hatch. This is due to cytoplasmic incompatibility, a reproductive abnormality that leads to infertile embryos [1]. These patterns of crosses and inheritance can be seen in Figure 6.

Given that it may be difficult to simultaneously infect a large number of mosquitoes with *Wolbachia* prior to release, in this section we explore several different release options. We begin by exploring results from agent-based and equation based single serotype dengue fever models incorporating *Wolbachia* with a large single initial release. In the Netlogo agent-based model, like dengue fever infected and susceptible mosquitoes, *Wolbachia* infected mosquitoes are initially placed at random throughout the investigation region. Primary effects of *Wolbachia* on the vectors in the model are related to a slightly shortened lifespan and reproduction, where there is an equal chance that a female will mate with a *Wolbachia* male versus a male without *Wolbachia*. A female vector's *Wolbachia* status

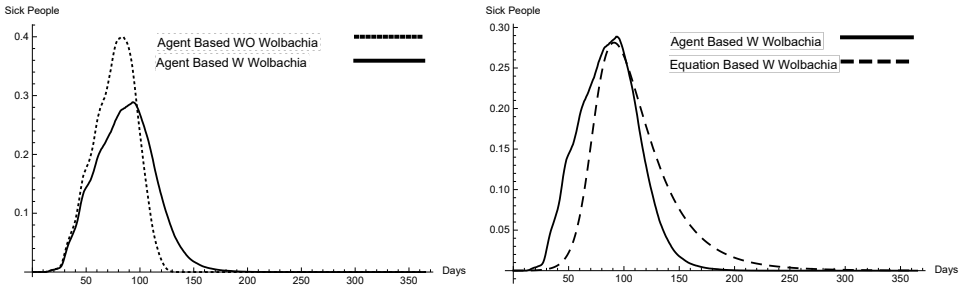

FIGURE 7. Single serotype dengue fever simulation with an initial large release of *Wolbachia* results with $\tau_{vh} = \frac{1}{16}, \tau_{hv} = 1$, $b_v = \frac{1}{15}, d_v = \frac{1}{25}$, $d_w = \frac{1}{20}$, $r = \frac{1}{20}, K_1 = 30,000, K_2 = 1500, N_h = 15999, I_h(0) = 1, W_v(0) = 1460, S_v(0) = 28540$ and $I_v(0) = 0$. Simulation was done with 30×30 patches.

along with that of her mate designate what will happen to their offspring based on Figure 6. Agent-based models with alternative release strategies for incorporating *Wolbachia* into the population are explored as well.

The agent-based model seen in Figure 7 produces similar results to those that can be seen from the equation based model in Equations (7)-(12), a similar model to that in Equations (1)-(6) with *Wolbachia* incorporated.

$$S_h' = -\tau_{vh}\frac{I_v S_h}{N_h}, \tag{7}$$

$$I_h' = \tau_{vh}\frac{I_v S_h}{N_h} - \rho I_h \tag{8}$$

$$R_h' = \rho I_h \tag{9}$$

$$S_v' = \frac{1}{2}b_v\frac{(S_v+I_v)^2(K_1-(S_v+I_v))}{K_1(S_v+I_v+W_v)} - \tau_{hv}I_h S_v - d_v S_v \tag{10}$$

$$I_v' = \tau_{hv}I_h S_v - d_v I_v \tag{11}$$

$$W_v' = b_v\left(\frac{W_v(S_v+I_v)(K_1-(S_v+I_v))}{K_1(S_v+I_v+W_v)} + \frac{W_v(K_2-W_v)}{K_2}\right) - d_w W_v, \tag{12}$$

where W_v represents the population of *Wolbachia* vectors and K_1 and K_2 represent capacity constants for the total vector and *Wolbachia* vector populations respectively. Notice, in particular, the differential equation for S_v and W_v, Equations (10) and (12), that integrate the change in offspring type based on the interactions described in Figure 6. For example, Equation (12) includes interactions between *Wolbachia* males and non-*Wolbachia* infected females as well as *Wolbachia* females with *Wolbachia* males. With each of these terms, the assumption that mosquito growth is logistic remains similar to what is seen in Equation (6); however, in Equation (12), each sub-population could have a unique capacity constant. Also note that the parameters, assigned in Figure 7, reflect the biological assumptions articulated earlier. The transmission from human to vector, τ_{hv}, is 100%, the transmission from vector to human, τ_{vh}, determined to be the probability that the interacting mosquito has not taken a blood meal (1/12) times the probability of transmission (3/4). It is also important to note that although vector death rate is assumed to be $d_v = 1/25$, vectors with *Wolbachia* have been proven to live slightly shorter lives.

Thus, both the death rate and birth rates were slightly reduced in this model, $b_v = 1/15$, $d_w = 1/20$. The initial number of *Wolbachia* mosquitoes released in this simulation was $4 \cdot 365$ for comparison with later discussion.

4. Strategies for *Wolbachia* Release

In this section, we will explore how the incorporation of *Wolbachia* infected vectors could affect the number of human infections. Results of three particular strategies will be presented here: (1) an initial release of a large number of *Wolbachia* vectors, (2) a small release of *Wolbachia* vectors each day, and (3) a small release of *Wolbachia* vectors when an outbreak is detected. Even though this paper focuses on a single serotype of dengue fever, the percent of *Wolbachia* mosquitoes in the vector population would affect future outbreaks of dengue, which could be dependent on the multiserotype model. In order to infect a vector with *Wolbachia* in the lab, the vector must be injected with the bacteria. We acknowledge that this may be a difficult procedure and that it may be more practical to infect a few vectors per day for release rather that a large group of vectors initially. One can see that the results of an initial release of $1460 = 4 \cdot 365$, roughly 4% of vectors produces roughly the same results as a daily release of vectors in Figure 8. Figure 9 is of particular interest in this regard as this will show the reader the percent of non-*Wolbachia* vectors remaining in the population at the tale end of the single dengue fever outbreak.

Since little difference is seen in infection rates with the single serotype model, agent-based models with all four serotypes were further explored. First, the agent-based model was created in Netlogo without the presence of *Wolbachia*. Recall that once a human is infected with a dengue fever serotype, they have full immunity to that particular serotype, but only temporary immunity to the other serotypes. Secondary infections with dengue fever are more severe than primary infections. In this Netlogo simulation, vectors can carry only one of the four serotypes at a time, and thus the four serotype agent-based model, in this case, is similar to the vectors contracting a single serotype four separate

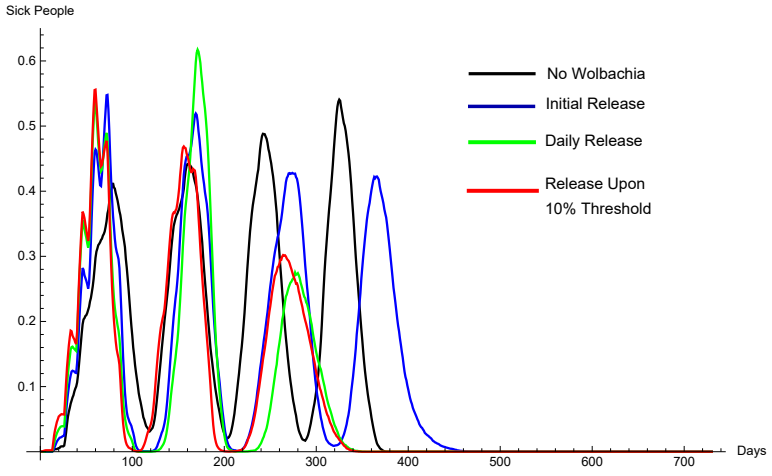

Figure 8. Human outbreaks with four serotype agent-based model with varying release methods of *Wolbachia*.

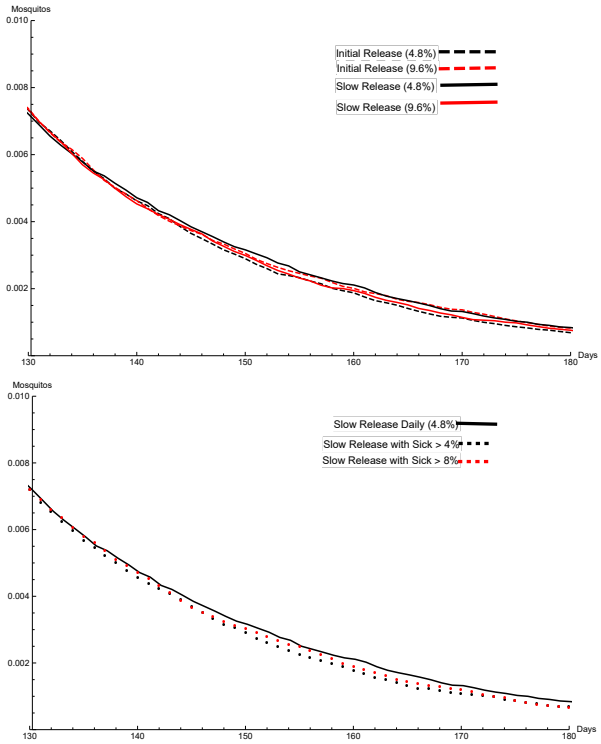

FIGURE 9. Non-*Wolbachia* population toward the end of the outbreak using different release strategies.

times. Biologically it is possible for vectors to carry more than one serotype simultaneously.

Once the four-serotype agent-based model was created, several different release strategies for *Wolbachia*-infected mosquitoes were explored. First, a strategy of releasing 12 mosquitoes every day for the full two years was tested. Although the strategy generates a significant drop in overall infection rates, this strategy may not be feasible due to the difficult nature of producing this number of *Wolbachia*-infected mosquitoes. Next, models were generated to take an illness threshold into consideration for the release of *Wolbachia*-infected mosquitoes. For example, the first threshold model simulated only released the 12 *Wolbachia* mosquitoes per day when the rate of infected humans reaches 4% or above. The next two threshold models were created following a similar pattern and only released 12 *Wolbachia* mosquitoes per day when the rate of infected humans reaches 8% or above and 10% or above. The most significant advantage to these models is the decrease in need for *Wolbachia* mosquitoes since the infection process has proved difficult so far. Figure 8 shows the human infection results for this four-serotype model with a variety of release methods of *Wolbachia*.

Since *Wolbachia* has yet to be implemented on a large scale, it is important to consider the long-term impacts of *Wolbachia* on the mosquito population. Figure 10 shows the simulation results of the four-serotype agent-based model with varying release methods of *Wolbachia*. While the decrease in number of mosquitoes as seen in Figure 10 assists in the prevention of dengue fever, it is important that the number of mosquitoes does not reach zero and instead levels out after about a year in most models. This simulation

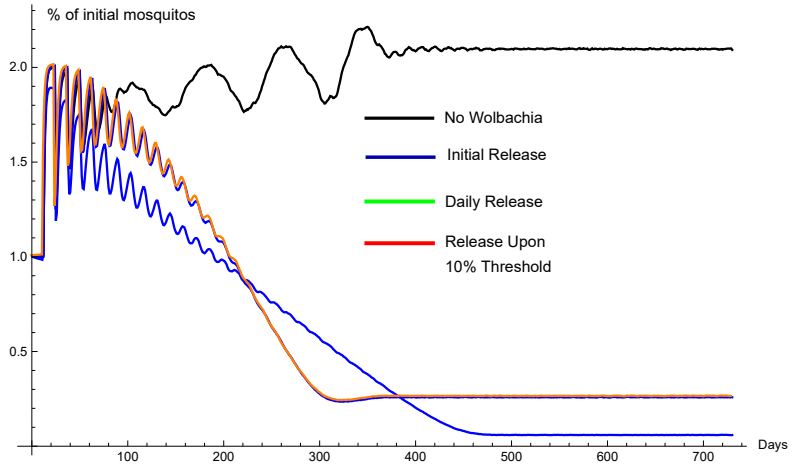

FIGURE 10. Mosquito count with four serotype agent-based model with varying release methods of *Wolbachia*.

Release type	Number of infections per person	% of *Wolbachia* vectors released relative to the initial vector pop
No *Wolbachia*	4.00	0.0%
Full initial release	3.96	14.6%
Daily release	2.65	14.6%
4% threshold	2.88	8.4%
8% threshold	2.82	7.8%

TABLE 2. Infections with *Wolbachia* strategies.

is important in assuring that the ecosystem is not too disturbed by a massive drop in number or the eradication of mosquitoes in a region with dengue fever.

In conclusion, the use of the *Wolbachia* bacterium appears to reduce the total number of human outbreaks in a four-serotype agent-based model. As seen in Table 2, the model incorporating a daily release of *Wolbachia* mosquitoes reduces infection rate quite a bit when compared to the original model without the presence of *Wolbachia*. The daily release model reduces infection by almost 1 whole infection per person. However, this model requires the release of almost 30% of vectors present in the population. This percentage leads to a lot of *Wolbachia* mosquitoes which are difficult to produce with today's technology. In addition, it can be difficult to know population number of mosquitoes. Thus, perhaps the most viable strategy is to set an illness threshold, such as 10% infected humans, that reduces infection by roughly half an infection by person and only requires the introduction about 7.7% of the mosquito population.

Further research on this subject includes allowing for vectors to transmit more than one dengue fever serotype simultaneously or increasing the illness threshold to determine the possibility of creating an even better infection rate while reducing the number of required mosquitoes. Another topic for further research includes creating a model to incorporate the concentration of the release of *Wolbachia* in areas where there is a larger infection rate. A deeper exploration of parameter identification could also be explored.

5. Acknowledgments

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