

Reduction of Mosquito Abundance Via Indoor Wall Treatments: A Mathematical Model

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Abstract

Insecticidal indoor residual wall treatment is a major tool for the control of malaria, with the goals of reducing indoor vector density and vector life span, in addition to reducing transmission rates of disease. Dynamics of the malaria vector, *Anopheles gambiae*, in the Emutete region in the Western Kenya highlands are based on an already existing model in the literature. In this paper, the framework is used to predict vector reduction due to four types of indoor wall treatments: two cases of indoor residual spraying of DDT and two types of pyrethrin-based INESFLY insecticidal paint. These treatments differ primarily in the duration of their persistence on walls. The model shows the extent of suppression of vector abundance over time due to each of the four treatments. It predicts that indoor residual spraying may have no noticeable effect at all if the percent coverage is not high enough or the persistence of the mortality effect is low, but will have a substantial effect at higher coverage rates and/or higher persistence. For treatments with longer persistence of mortality, the model predicts a coverage threshold above which extra treatment has little to no effect. For treatments of short persistence of mortality, the seasonal timing of treatment has a noticeable effect on the duration of vector suppression. Overall, the model supports claims in the literature that wall treatments have the capacity to reduce the vector burden.

Key words: *Anopheles gambiae*, mosquito population model, mosquito control insecticide treatment, indoor residual spray

Some deadly infectious diseases such as malaria require a vector as part of the disease cycle; thus controlling the vector is one approach to controlling spread of disease. Vector control is a key component in the effort to eradicate malaria from any region. Spraying the walls of houses, where mosquitoes rest after a bloodmeal, is a widespread practice known as Indoor Residual Spraying, with known positive effects on disease transmission (Fullman *et al.* 2013). The World Health Organization (WHO) used to recommend that DDT should be re-sprayed every 6–12 mo when thus used (WHO 1992). Now, a range of other insecticides are used (WHO 2013b). Alternatively, insecticidal paint may be used on interior household walls for the same purpose (Mosqueira *et al.* 2010). Although the ultimate goal is to reduce malaria transmission, the direct effect of these interventions is to kill vectors. Reduction of mosquito populations via these methods is likely to be accompanied by a reduced entomological inoculation rate, which is the number of infectious bites per individual per day. This rate (called the EIR) has a strong relationship with malaria infection rates (Beier *et al.* 1999). Understanding the extent to which mosquito populations are reduced, both in magnitude and duration, is a key to predicting malaria prevalence outcomes and determining best practices.

Thus, there is a need for mosquito population models to prove their utility by offering guidance on the likely effects of interventions

currently in use on overall vector abundance. This guidance would include an understanding of the effect of timing of application, coverage rates, and choice of insecticide on the expected reduction in indoor resting density (IRD) of local mosquito populations. Here we present a model that distinguishes interventions based on choice of insecticide, timing of application, and household coverage rates.

Prior Models Exist That Study the Impact of Insecticide Treatments on Malaria prevalence

Many malaria models of varying complexity exist (Reiner *et al.* 2013). However, when offered comparable assumptions and pressed to predict the resulting incidence of malaria or the better of two potential interventions, these models disagree (Wallace *et al.* 2014). We describe below three studies that model the problem of indoor residual spray and its effect on either vector or disease prevalence. Each of these studies has useful features and also limitations. Therefore, this study predicts the impact of a range of interventions on the vector population itself, which is measurable via the IRD in a region. The IRD will have a relationship with the entomological inoculation rate, which can then be an input to a suite of malaria models if desired.

Smith? *et al.* (2008) propose a mosquito population model independent of temperature and rainfall. They then use impulsive

Ordinary Differential Equations to represent spraying events that kill a fixed number of mosquitoes at recurring times. Although suggestive, the results cannot be applied outright because mosquito populations rise and fall with availability of aquatic habitat and in response to temperature. The mortality associated with IRS decays over time, unlike the mortality used in the [Smith \(2008\)](#) study.

[Yakob et al. \(2010\)](#) use a Gaussian to represent the decaying efficacy of indoor residual spraying of Dichloro Diphenyl Trichloroethane (DDT) and pyrethrin, as we do here. Their study assumes that, in the absence of intervention, the basic reproduction rate (R_0) remains constant. This unchanging R_0 represents unchanging mosquito populations, similar to the study described previously ([Smith et al. 2008](#)). Infected populations are not tracked dynamically, rather R_0 itself is tracked directly using a calculation from [Smith and McKenzie \(2004\)](#). For practical purposes, neither mosquito populations nor R_0 are likely to remain constant in the absence of treatment.

Unlike Yakob and Smith, [Worrall et al. \(2007\)](#) does present a mosquito population that is correlated with rainfall, and which has a gonotrophic cycle that depends on temperature ([Worrall et al. 2007](#)). Both rainfall and temperature were based on a region in the Western Highlands of Kenya. The insect model coupled with disease transmission is used to investigate the impact of timing of spray events. However, spray efficacy is modeled as a linear decrease over a 6-mo period and is not based on bioassays of efficacy of a particular chemical.

To incorporate factors missing in these earlier studies, we developed a model for time varying mosquito populations and the decay properties of four specific treatments. As in [Worrall et al. \(2007\)](#), the model used here has a mosquito population that changes with rainfall and temperature, although the model is developed as a dynamical system as in ([Wallace et al. 2016](#)), and is extended to include experimentally determined decay properties for four treatments. Like [Yakob et al. \(2010\)](#), this study uses Gaussian functions to match experimental data for these treatments. As in several of the studies, we are concerned with the impact of timing of interventions and percent coverage of households.

To be useful, a model of the mosquito life cycle must be tuned to a particular geographic context and species and adapted to the question of interest.

The mosquito population model introduced here is based on one in [Wallace et al. \(2016\)](#). Although similar in form to earlier in models, it was adapted and tuned to describe a generic year in Emutete, a town in the Western Kenya Highlands. Field data on larval counts, laboratory data on temperature dependence of larval stages, IRD collected by the Kenya Medical Research Institute, and counts of dwellings from remotely sensed images, were all combined in that model to produce mosquito populations that give reasonably good IRD of *Anopheles gambiae* throughout an annual cycle.

Indoor Residual Spraying Is Thought to Reduce Overall Vector Abundance

Insecticides are applied to the interior walls of dwellings with the goal of interrupting the transmission of malaria. The insecticide acts directly by killing the vector, with the potential for an accompanying reduction in vector abundance.

[Okumu et al. \(2013b\)](#) offer a detailed analysis of mosquito behavior in a hut, concluding that minimal personal protection is given by adding indoor residual spraying to the use of treated bednets and concludes that it offers “limited community protection”. However, in this study we look at the use of wall treatments in the absence of treated bednets.

[Gunasekaran et al. \(2005\)](#) note a reduction in IRD of *Anopheles fluviatilis* in villages in Orissa, India that were treated with indoor residual spraying of DDT ([Gunasekaran et al. 2005](#)). The authors hypothesized that the reduction in IRD was due to the increased mortality of the resting females. Similar claims have been made for insecticide-treated bed nets ([Lindblade et al. 2006](#), [Bayoh et al. 2010](#)). Here this hypothesis is tested on a mosquito population model for the mortality rates described for DDT indoor residual spraying and pyrethrin-based insecticidal paint. Both of these interventions increase the mortality of only female mosquitoes resting on walls of houses after a bloodmeal.

Four Interventions Are Modeled

As with the pharmacokinetics of drugs in the body, the efficacy of indoor residual spray or insecticidal paint declines over time. Two studies of indoor spraying of DDT ([Gunasekaran et al. 2005](#), [Okumu et al. 2013a](#)) and one study of two variations of insecticidal paint ([Mosqueira et al. 2010](#)) provide the data for mortality of resting females over time. The action of each insecticide is coupled with the mosquito population model developed for the Emutete region in Kenya to give a comparison of the predicted effects of these interventions on mosquito populations over time. To compare the existing models with our model, we assume that the mortality rates of *A. gambiae* in the Highlands of the Kenya are comparable to the species considered in the literature.

[Gunasekaran et al. \(2005\)](#) used cone bioassays to measure mortality rates of *A. fluviatilis* over a period of 17 wk when subjected to walls sprayed with 1 g/m² DDT. Cone bioassays to determine mosquito mortality were conducted in randomly selected sprayed and unsprayed houses to determine mosquito mortality. As part of the same study, an accompanying field experiment conducted in several villages of the Malkangiri and Koraput Districts of Orissa, India reported IRD data over a period of 7 mo. Coverage of houses in villages in Malkangiri ranged from 44.6 to 100% (overall: 74.2%) and coverage of individual rooms ranged from 30.6 to 84.6% (overall: 48.6%). Coverage of houses in villages in the Koraput District was 68.6–100% (overall: 86.2%) and coverage of walls ranged from 36.2 to 92% (overall: 56.6%). Coverage rates of 10, 25, 50, and 70% were used as benchmarks for comparisons among treatments in our model.

[Mosqueira et al. \(2010\)](#) studied the efficacy of the commercial insecticidal paint Inesfly, which contains active compounds, one of which is a pyrethrin. Experimental huts in Benin, West Africa were treated with either one or two coats of this paint, and bioassays of *A. gambiae* and *Culex quinquefasciatus* mortality rates were conducted over a course of 9 mo. In our study, we model mortality for both the one and two coat experiments.

[Okumu et al. \(2013a\)](#) used a setting of experimental mud-walled huts sprayed with DDT to test mortality rates of *Anopheles arabiensis* mosquitoes collected from a study area in southeast Tanzania, measuring the residual activity of the spray over 6 mo ([Okumu et al. 2013a](#)). Test walls were sprayed with 2 g/m² DDT and monthly bioassays of insect mortality were taken. The study also investigated three other insecticides, finding that, of the four, DDT had the highest sustained mortality rates over this period. In our study, we only look at the mortality data of DDT derived from this data.

Materials and Methods

Overview

We have adapted a prior model of larval population dynamics ([Wallace et al. 2016](#)) that is based on two studies, a field study in the town of Emutete in the Western Kenya highlands and a laboratory study ([Munga](#)

et al. 2007, Bayoh and Lindsay 2003). That model reproduces the ratios of *A. gambiae* instar types in the field study, and the emergence rate of adults per square meter (Munga et al. 2007), and predicts number of adult mosquitoes at equilibrium in a given region in terms of available aquatic habitat. Precipitation is used as a proxy for aquatic habitat by comparing monthly rainfall pattern to observed IRDs. Rainfall and temperature data as well as IRD samples were provided by the Kenya Medical Research Institute, and human dwellings were estimated from remotely sensed images. Smooth dependence of linear mortality rates and maturation rates of larvae on temperature are given by curves fitted to experimental data (Bayoh and Lindsay 2003), which are coupled with the dynamical model including eggs, four larval instars, pupae, and adults to predict fluctuating mosquito populations.

Here we extend the model by Wallace et al. (2016) to include five stages of the adult *A. gambiae* gonotrophic cycle. Minor adjustments of parameters for the adult portion of the life cycle gives the same pattern of mosquito abundance as in the prior paper, but now only one of the five adult stages lays eggs and only two of the stages represent mosquitoes resting on interior walls of houses. A compartment diagram for the model used here is shown in Fig. 1.

Equations

Several habitat-based models for larval development are in the literature (Depinay et al. 2004, Gu and Novak 2005, Ermert et al. 2011). In Wallace et al. a model similar to that of Depinay et al. is tuned to a particular region in the Western Kenya highlands using a combination of laboratory experiment (Bayoh et al. 2003), field study (Munga et al. 2007), remotely sensed images and data on IRDs from the Kenya Medical Research Institute. This model is modified for the application needed here.

The model of insect dynamics used here has 11 equations, as shown below. Equations 2.2–2.6 are exactly as in Wallace et al., with the same parameters and functions describing temperature-dependent death and maturation, and varying habitat (Wallace et al. 2016).

From Wallace et al. (2016), we have a larval population model for C m² of aquatic habitat that includes eggs, four larval instars, and pupae. Death rates are given by a linear rate that depends on temperature (Bayoh et al. 2003) and a density-dependent rate derived from field measurement (Munga et al. 2007).

To summarize that model, change in eggs (E) is given by birth (bA) less maturation (n_eE) and death (q_eE). Four larval instar stages

are represented: L₁, L₂, L₃, L₄. For each of these, the rate of change (L_i') is given by maturation (n_{i-1}L_{i-1}) less maturation into the next stage (n_iL_i), a linear death rate (f_iL_i), and a density-dependent death rate (q_iL_i²/C). Both the relative rates for linear maturation and death (n_i and f_i) are taken to be temperature dependent. The rate of change in pupae is given by maturation (n₄L₄), emergence as adults (n_pP), and death (f_pP). The relative maturation and death rates (n_p and f_p) are taken to be temperature dependent but no density-dependent death is included for pupae. Temperature and precipitation were derived from weather station records for the region and habitat (C) was modeled as a translated and scaled version of rainfall, giving an approximate match to IRD data for the region.

Equations 1 and 7–11 were altered and added as necessary to split a single compartment for adults into five compartments corresponding to a 5-d gonotrophic cycle.

The movement of females through the gonotrophic cycle is given by the terms of form mA_i. These may be described as searching for bloodmeals (A₁ and A₃), resting after bloodmeals (A₂ and A₄), and searching for an oviposition site (A₅).

Additional death due to treatment with insecticide is described by d_{tr} for compartments A₂ and A₄.

The following equations are used for all simulations in this study:

$$E' = bA_5 - n_e E - q_e E \tag{1}$$

$$L_1' = n_1 E - n_2 L_1 - f_1 L_1 - q_1 L_1^2 / C \tag{2}$$

$$L_2' = n_2 L_1 - n_3 L_2 - f_2 L_2 - q_2 L_2^2 / C \tag{3}$$

$$L_3' = n_3 L_2 - n_4 L_3 - f_3 L_3 - q_3 L_3^2 / C \tag{4}$$

$$L_4' = n_4 L_3 - n_5 L_4 - f_4 L_4 - q_4 L_4^2 / C \tag{5}$$

$$P' = n_5 L_4 - n_p P - f_p P \tag{6}$$

$$A_1' = n_p P / 2 + m A_5 - m A_1 - d A_1 \tag{7}$$

$$A_2' = m A_1 - m A_2 - d A_2 - d_{tr} A_2 \tag{8}$$

$$A_3' = m A_2 - m A_3 - d A_3 \tag{9}$$

$$A_4' = m A_3 - m A_4 - d A_4 - d_{tr} A_4 \tag{10}$$

$$A_5' = m A_4 - m A_5 - d A_5 \tag{11}$$

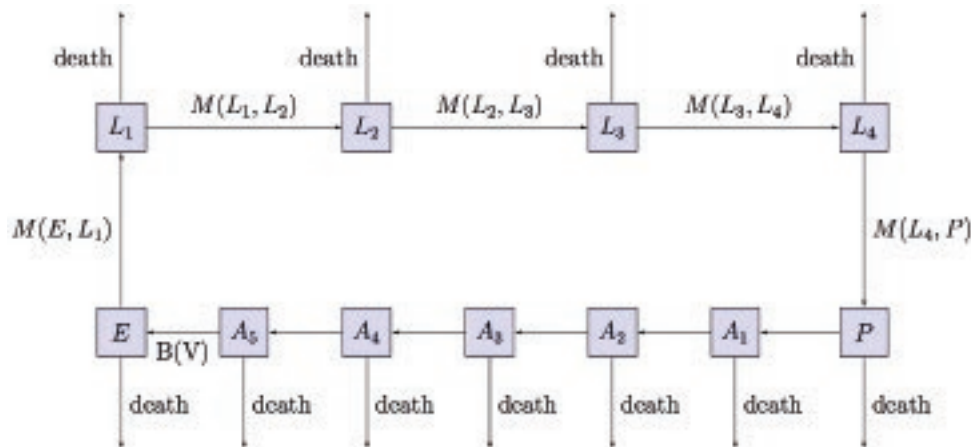


Fig. 1. Compartment model for the system of ordinary differential equations. E = eggs, L₁ = first instars, L₂ = second instars, L₃ = third instars, L₄ = fourth instars, P = pupae, A₁ to A₅ various stages of gonotrophic cycle: A₁, A₃ = adult females searching for bloodmeals, A₂, A₄ = adult females resting after bloodmeals and, A₅ = adult females searching for an oviposition site.

Here $n_1, n_2, n_3, n_4, f_1, f_2, f_3, f_4$ are all temperature dependent. The carrying capacity, C is dependent on precipitation. The maturation parameters n_i are given by $n_i(T) = \ln(2)/D_i(T)$, where the $D_i(T)$ are fit to data from Bayoh and Lindsay (2003) with functional form $D_i(T) = a_i + b_i/(1 + (T/c_i)^d)$. These dependencies, as well as all parameter values except d_r and m , are taken directly from prior work (Wallace et al. 2016). The intent to track only females is reflected by the factor of 1/2 in Equation 7. This factor serves to model solely the female adults, which then trickles down through the entire model to solely look at all female mosquitoes at every stage. Projected IRD values in this study are given by dividing the projected number of resting female *Anopheles* by the number of houses in the region.

Modeling Treatments

Increased death rates due to wall treatments are given by $d_r A_2$ and $d_r A_4$. The second and fourth day of the gonotrophic cycle *Anopheles* females are assumed to require rest and would, therefore, potentially come in contact with a treated wall. We note that this is an underestimate of the time that mosquitoes spent resting on treated walls and thus the model would underestimate the mortality of resting mosquitoes. The relative rate d_r is a function of time, as all wall treatments eventually degrade and lose their efficacy.

Four treatments were considered. All of them were applied to interior walls of houses. Two were sprayed with DDT, referred to as “indoor residual spraying” the other two treatments were insecticidal paint. This treatment method is designed to kill resting females (A_2 and A_4 in the model) and thus prevent transmission of malaria parasites picked up during the bloodmeal. Each of the four insecticide treatments was modeled separately based on published experiments. In no case did the efficacy drop to zero in 6 mo. Even the most quickly declining treatment (treatment 4) was at 50% efficiency ~6 mo after application.

Treatment 1 is taken from a paper by Gunasekaran et al. (2005) in which was a field study of vector mortality on walls in India sprayed with DDT over the course of several months. Treatments 2 and 3 are from another field study by Mosqueira et al. (2010) of walls in West Africa painted with one or two coats of a pyrethrum-based insecticidal paint. The fourth treatment is a study of mortality of DDT spray by Okumu et al. (2013a).

One expects the efficacy of insecticide-treated surfaces to diminish over time. All of these sources report death rates for resting mosquitoes of various species on treated walls over the course of many months. Gaussian functions proved to be a good fit for these data in all four cases, as seen in Fig. 2a. The data used from these sources

and the functional form of the fitted curve are given in Table 1. A Heaviside function was used to adjust the timing of application.

One cannot assume that all houses are treated, nor that all walls in houses are treated. Gunasekaran et al. (2005) report coverage of about 70% of houses and about 50% of rooms. We adjust death rates proportionally to account for varying coverage. Fig. 2b shows the average IRD, over the course of a year, produced by the model for each of the four treatments at 50% coverage. Parameter values and functional forms are given in Table 1.

These models were implemented in a variety of experiments on the simulated Emutete vector populations in an attempt to determine the effects of timing of application, percentage of households treated, and type of treatment on the duration of time for which the IRD of mosquitoes is significantly lowered.

Numerical Simulations

The timing of application of interior residual insecticide could be a factor in how long insect populations are suppressed. Insecticide application was tested at 12 points in the annual population cycle corresponding to every 30 d. January 1 corresponds to day 365 in all figures. The model uses a contracted 360-d year as the basis for its population cycles, and 30-d months for graphing purposes.

Coverage rates are also likely to have an effect on insect populations. Coverage rates were tested at 10% point intervals. All combinations of date of application and coverage rates were tested for all four types of insecticide application described in the literature (Gunasekaran et al. 2005, Mosqueira et al. 2010, Okumu et al. 2013a). For each of the numerical experiments, the number of days that the IRD fell below a given threshold was recorded. IRD thresholds of 1 and 2 insects were used for the purposes of comparing the insect suppression of the four treatments.

Fig. 3 shows typical population dynamics of treated and untreated populations at four specific coverage rates. Note that the computation of the total number of days that a population is below a given threshold does not require that the days be consecutive. As the rainy and dry seasons alternate, the population dips and rises accordingly. Even for the most effective treatment (treatment 3), the average IRD rises above the lower threshold of 1 at times and then falls back below.

Fig. 3a–d shows the pattern of insect reduction over the course of 2 yr when the treatment is applied on January 1. Horizontal lines depict IRD thresholds of 1 and 2. Note that the control, or untreated, population never produces an IRD below 1, although it gets close at one point during the year. This is the reason for the choice of 1 as a threshold for comparison, and 2 as an alternative threshold.

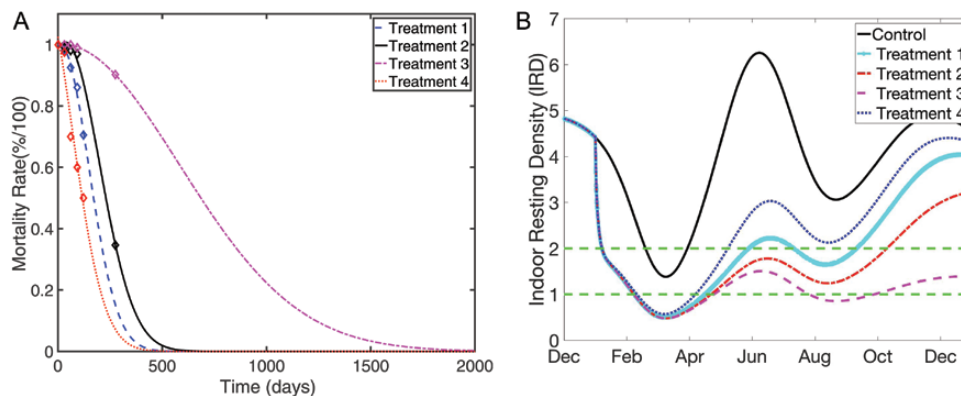


Fig. 2. (a) Gaussian fit. (b) Effect of time of the treatment application on the IRD on January 1; percent household is chosen to be 50%.

Table 1. Default parameters and functional forms derived for this model

Parameter description	Symbol	Value		
Egg production rate per adult mosquito per day	b	21.5		
Egg death rate per day	q_e	0.054		
Adult death rate (per day) d_a	d_a	0.167		
Adult stage transitions	m	1		
Density dependent parameters: egg	q_e	0.0542		
First instar L_1	q_1	0.000 257		
Second instar L_2	q_2	0.0008		
Third instar L_3	q_3	0.0128		
Fourth instar L_4	q_4	0.0229		
Functional forms				
Larval death rate (per day) as a function of temperature T,		0.666733		
All stages, f_1-f_p		$-0.056977 * T$		
Temperature-dependent development time for jth instar		$+0.00125224 * T^2$		
Development rate for jth instar	$D_j(T) = a_j + b_j / (1 + (T/c_j)^d)$			
Parameters temperature dependent development time	a	b	c	d
Egg	1.10316852	12.552629	15.218947	6.4686913
First instar L_1	2.711278535	18.3520244	15.619128	5.84551382
Second instar L_2	4.244561306	136.345723	10.359964	4.78352380
Third instar L_3	6.470424176	664586953	0.6330792	5.32923550
Fourth instar L_4	8.141977001	12.7923999	22.283373	10.2777593
Pupa	8.583819474	18.155935	21.553376	7.85246264
Temperature as a function of time, t	$T_{av} + 0.6346 * \cos(t * 0.0172) + 0.7731 * \sin(t * 0.0172)$			
Habitat, C, as a function of time, t	$C = (135000) + 35000 * (-1.446 * \cos(t * 0.0172) +$ $-0.7109 * \sin(t * 0.0172) + -1.347 * \cos(2 * t * 0.0172) +$ $-1.408 * \sin(2 * t * 0.0172) + 0.9942 * \cos(3 * t * 0.0172) +$ $0.2396 * \sin(3 * t * 0.0172));$			
Gunasekaran	$a_1 e^{-(t-b)_1/c_1}$	$a_1 = 0.9981$	$b_1 = 11.17$	$c_1 = 192.3$
IRD spray DDT: d_{tr1}				
Mosqueira Inesfly 1 coat: d_{tr2}	$a_2 e^{-(t-b)_2/c_2}$	$a_2 = 1.008$	$b_2 = 34.73$	$c_2 = 233$
Mosqueira Inesfly 2 coats: d_{tr3}	$a_3 e^{-(t-b)_3/c_3}$	$a_3 = 1.001$	$b_3 = 15.12$	$c_3 = 804.3$
Okumu	$a_4 e^{-(t-b)_4/c_4}$	$a_4 = 1.188$	$b_4 = -81.49$	$c_4 = 212.8$
IRD spray DDT: d_{tr4}				

The percent coverage of the treatment has an effect on the number of days that the IRD is suppressed below a given threshold, as shown in Fig. 4 (threshold IRD = 1) and Fig. 5 (threshold IRD = 2). Curves in these figures correspond to different dates of application, from day 365 forward in 30-d intervals. The vertical spread of the curves shows how the date of application will affect the mosquito reduction for a given percent coverage.

The effect of timing of treatments is shown in Fig. 6 (threshold IRD = 1) and Fig. 7 (threshold IRD = 2). In these figures, each curve represents a different percent coverage rate. For these figures, the vertical spread of the curves illustrates the effect of percent coverage for any given date of application.

In Fig. 8, the four treatments are compared with each other at 50% coverage on four different dates of application, for threshold IRD = 2.

In Fig. 9, the control and treated mosquito population (for all four treatments) was compared against the rainfall pattern obtained from the Kakamega weather station by the Kenya Medical Research Institute, as described in Wallace et al. (2016). The experiment was run for percent household of 50% and the treatment was applied on January 1.

In Fig. 10, we compare best treatment and worst times for spray treatments with annual rainfall patterns. For a particular threshold

(IRD = 1 or 2) and ph (0.25 or 0.5 or 0.75) and treatments (1, 2, 3, or 4), the number of days below said threshold are calculated for every date of application from 365 to 724 (year 2). The code examines the amount of days under threshold for a year following the chosen date of application. Then 365–724 is split up into 12 mo of 30 d, and the average number of days under threshold for a given month is found. All the months for a particular threshold, ph, and treatment were compared to find the best month(s) and worst month(s) to spray (looking at the max and min averages among all months). Sometimes, there are ties and hence on the final graph, the red and blue lines can be longer than a month.

All simulations were carried out using MATLAB software (Mathworks 2016a).

Results

All four treatments have some effect in reducing insect populations, as seen in Fig. 3. Treatment 3 is clearly the most effective. At peak mosquito densities, the simulation of untreated household produces a maximum IRD of about 7. Treatments applied on January 1 (Fig. 2b) show a reduction of IRD at this peak to slightly above 3 (treatment 4), below 3 (treatment 1), approximately 2 (treatment 2), and below 2 (treatment 3). This represents a 50–70% reduction

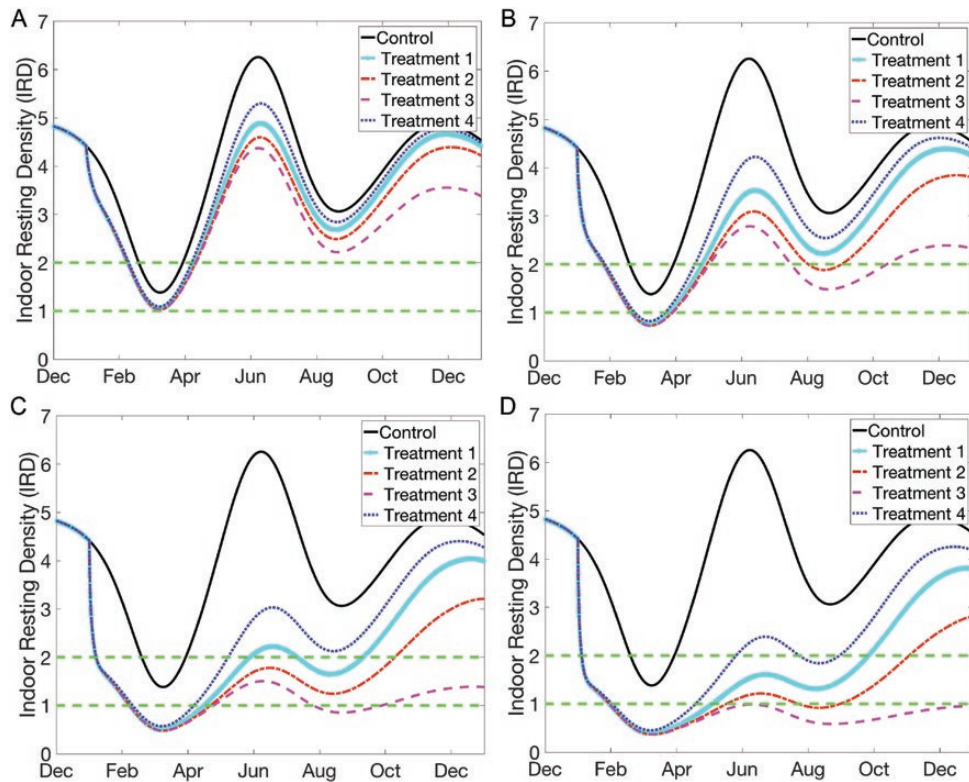


Fig. 3. Effect of various percent households on the IRD of control and treated population. Treatment is applied on January 1 of every year. (a) Percent household coverage = 10%. (b) Percent household coverage = 25%. (c) Percent household coverage = 50%. (d) Percent household coverage = 70%.

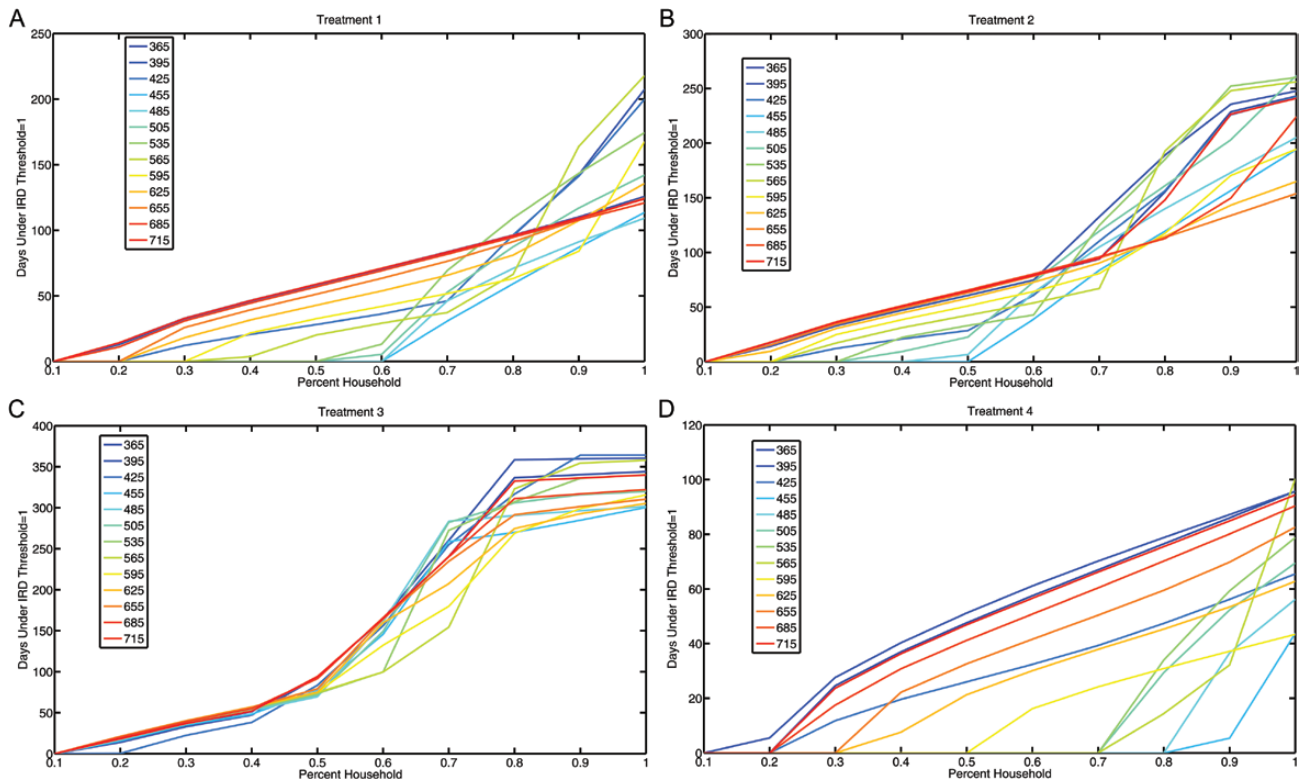


Fig. 4. Effect of percentage household coverage on the number of days under IRD threshold = 1. Each line represents a different date of application of treatment. (a) Treatment 1 (DDT indoor residual spray [9]). (b) Treatment 2 (one coat of Inesfly [8]). (c) Treatment 3 (two coats of Inesfly [8]). (d) Treatment 4 (DDT indoor residual spray [7]).

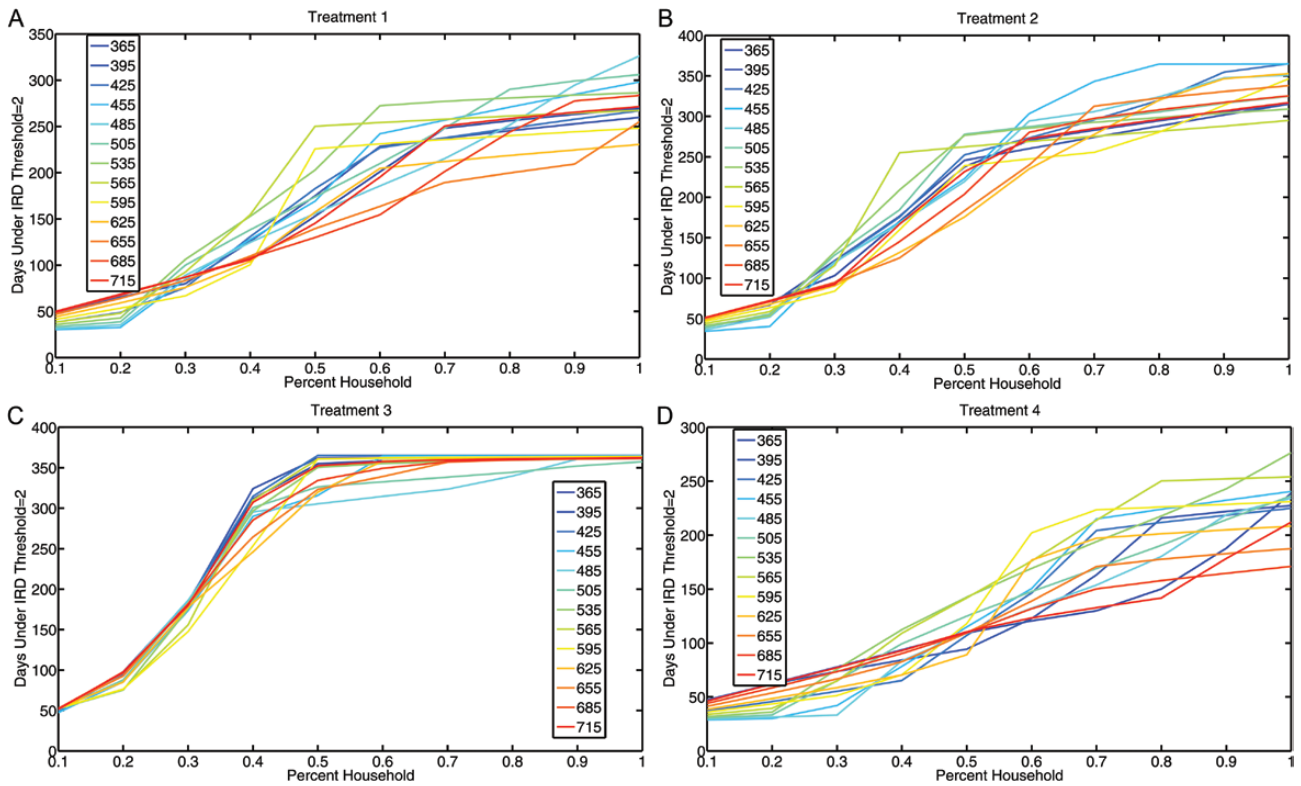


Fig. 5. Effect of percentage household coverage on the number of days under IRD threshold = 2. Each line represents a different date of application of treatment. (a) Treatment 1 (DDT indoor residual spray [9]). (b) Treatment 2 (one coat of Inesfly [8]). (c) Treatment 3 (two coats of Inesfly [8]). (d) Treatment 4 (DDT indoor residual spray [7]).

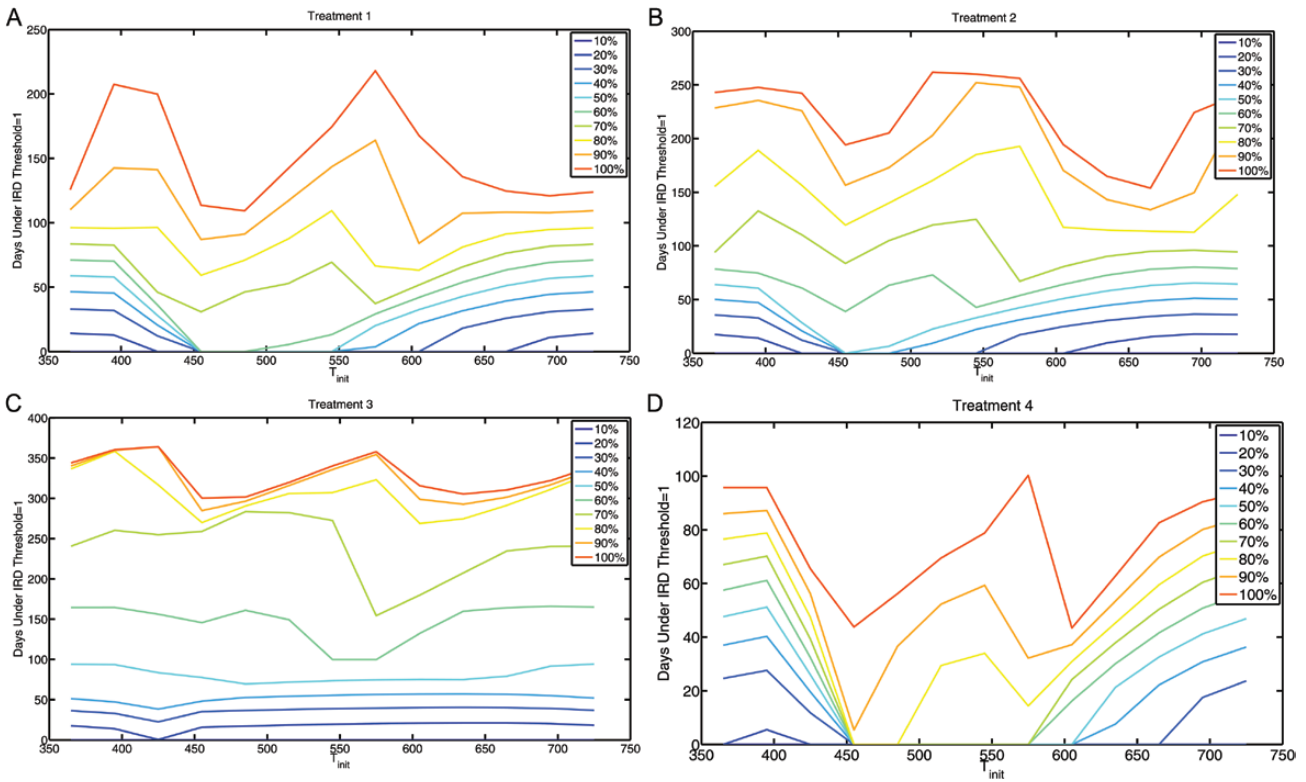


Fig. 6. Effect of date of treatment application on the number of days under IRD threshold = 1. Each line represents percentage household coverage. (a) Treatment 1 (DDT indoor residual spray [9]). (b) Treatment 2 (one coat of Inesfly [8]). (c) Treatment 3 (two coats of Inesfly [8]). (d) Treatment 4 (DDT indoor residual spray [7]).

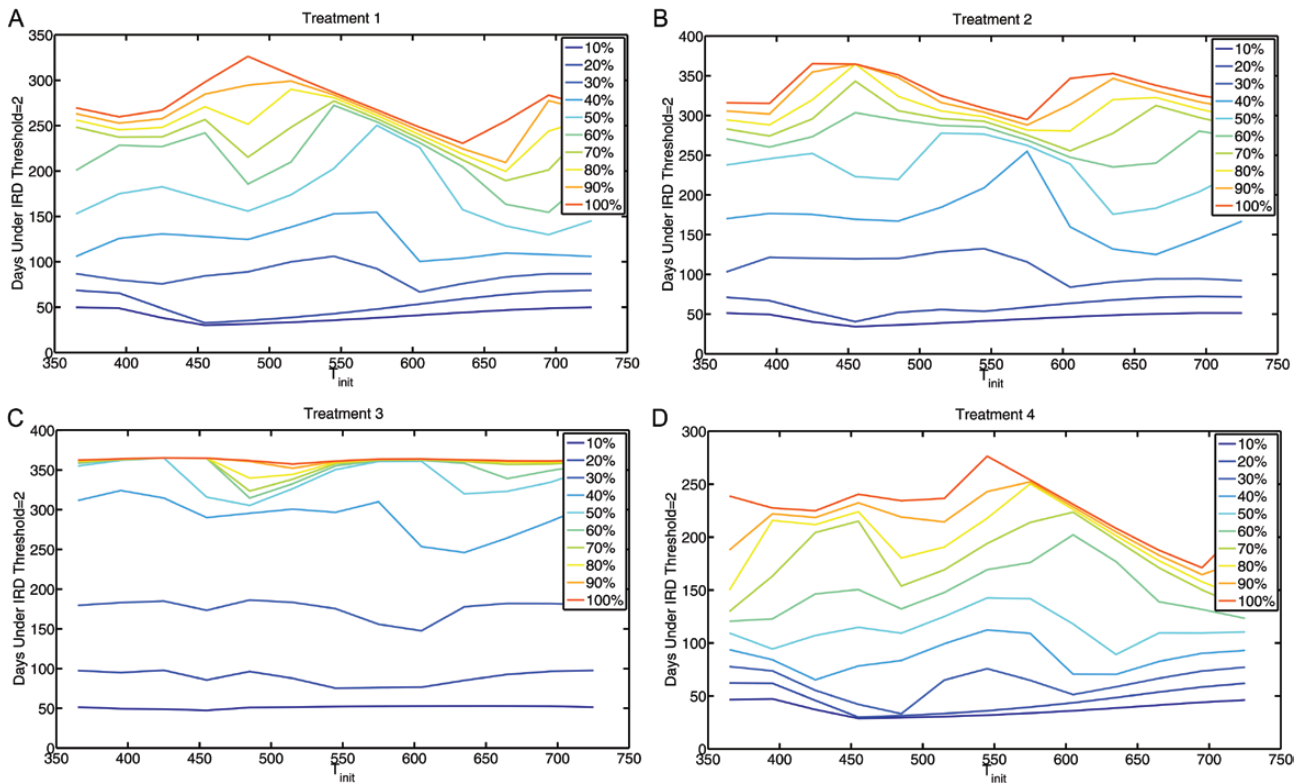


Fig. 7. Effect of date of treatment application on the number of days under IRD threshold = 2. Each line represents percentage household coverage. (a) Treatment 1 (DDT indoor residual spray [9]). (b) Treatment 2 (one coat of Inesfly [8]). (c) Treatment 3 (two coats of Inesfly [8]). (d) Treatment 4 (DDT indoor residual spray [7]).

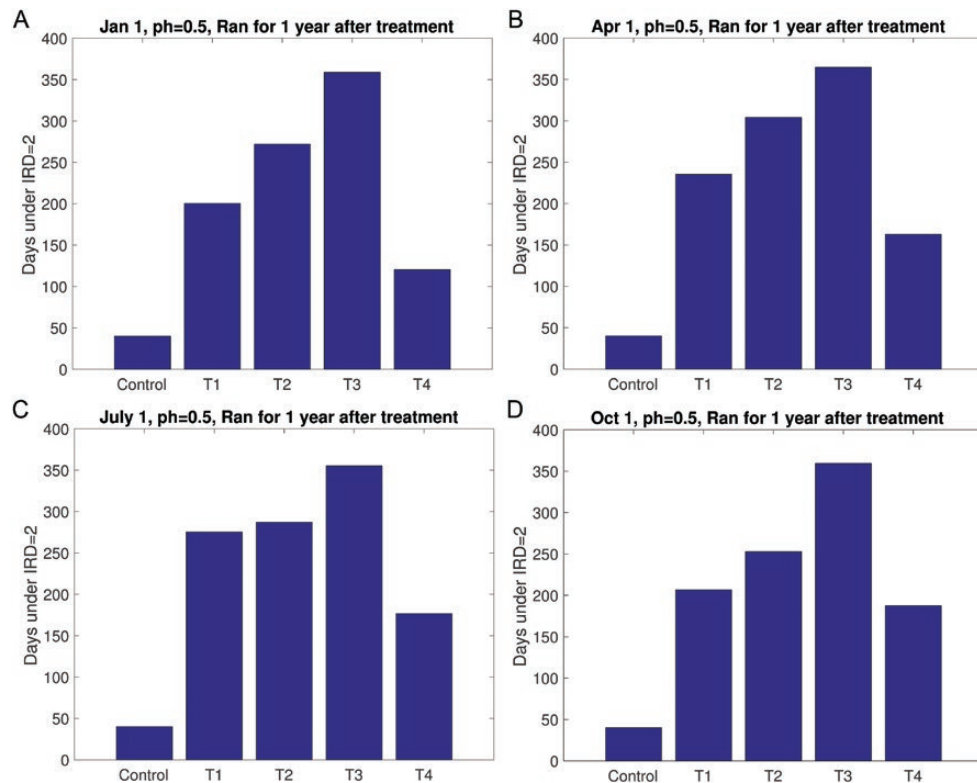


Fig. 8. Comparison of the effect of different dates of applications of different treatments on the days under IRD 2: (a) January 1, (b) April 1, (c) July 1, and (d) October 1. The percentage household coverage was fixed to be 50% for this experiment.

in mosquito populations during peak. The resulting IRD at peak for treatments 2 and 3 are comparable to the minimal IRD for the control run.

It is expected that the treatments that have longer duration also suppress insect populations the longest. What is surprising is the extent to which they do so. Fig. 2a shows smooth functions fit to the

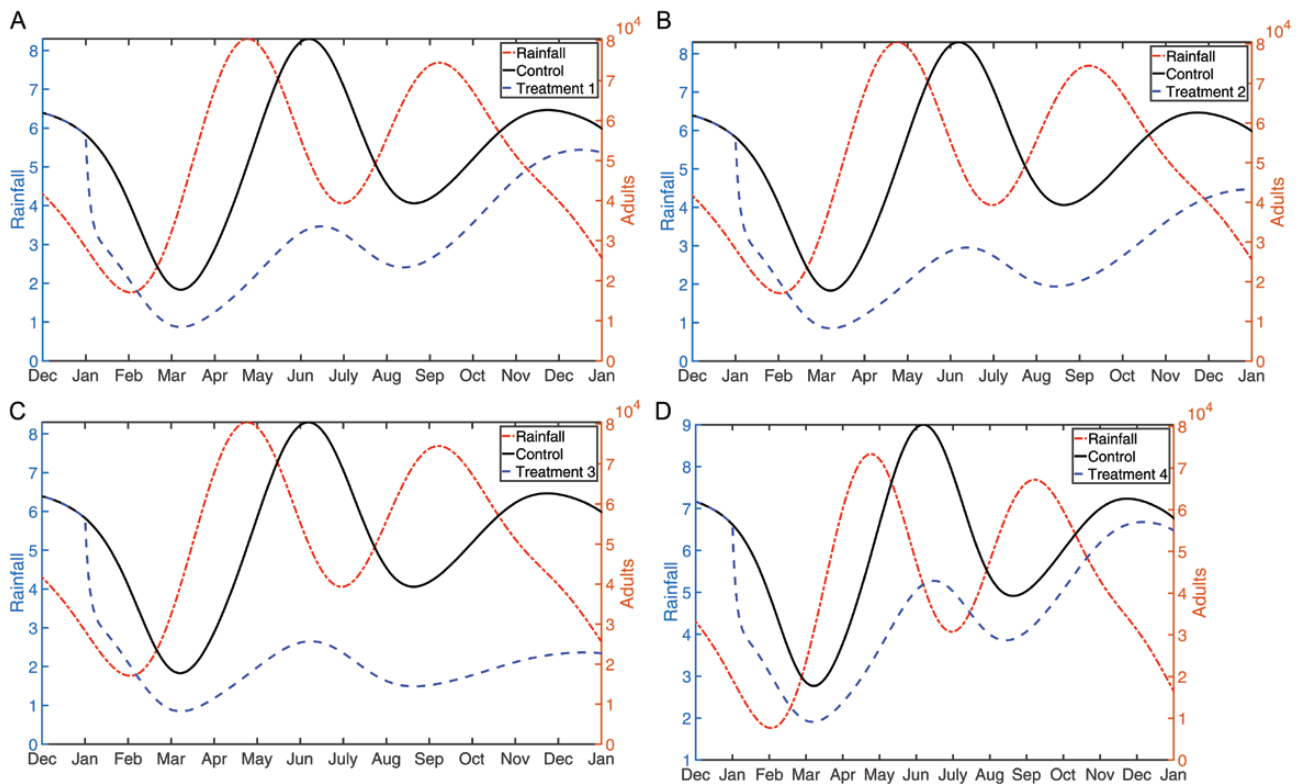


Fig. 9. Temporal dynamics of rainfall, control population, and treated population: (a) Treatment 1 (DDT indoor residual spray [9]). (b) Treatment 2 (one coat of Inesfly [8]). (c) Treatment 3 (two coats of Inesfly [8]). (d) Treatment 4 (DDT indoor residual spray [7]). The percentage household coverage was fixed to be 50% and the treatment is applied on January 1.

mortality rates reported for each of the four treatments. Treatment 3 clearly has the longest duration of action. At only 50% coverage, treatment 3 (two coats of Inesfly) applied on January 1 keeps the IRD below 2 for an entire year, according to the simulation pictured in Fig. 3c. This treatment appears to have significantly longer duration of action than any of the other three, as seen in Fig. 2a and b.

The untreated control IRD rises to 7 at its peak and only drops below 2 for a short period during the dry season, as is visible in Figs. 2b and 3a–d. At 70% coverage, treatment 3 keeps the IRD below 2 for more than 1 yr, and close to 1 for most of the first year of application (Fig. 3d).

The Importance of Percent Households Covered

It is rare that an intervention that involves entering private homes would reach every single household. Gunasekaran *et al.* (2005) used treatment 1 on villages in India and were able to reach 50–70% coverage, depending on whether they measured number of households or actual interior wall coverage. They mentioned various reasons why householders were reluctant to allow treatment, some of which were religious prohibitions. In any case, as with vaccinations, it is unreasonable to expect complete coverage, but it is safe to say that maximum coverage is the most effective.

Figs. 4 and 5 show the number of days that mosquito populations are suppressed below IRD thresholds of 1 and 2, respectively, for various dates of application and with increasing percent coverage. For example, suppose it were determined that suppressing the IRD for 150 d could make a measurable impact on disease transmission. Treatment 1 can keep the IRD below 2 for this time period at 60% coverage no matter what date of application is used (Fig. 5a) but it cannot keep the IRD below 1 for 150 d at 60% coverage no matter what date the treatment is applied (Fig. 4a).

A similar statement holds for treatment 2 (Figs. 4b and 5b). Treatment 4 is not able to reduce IRD below 1 for 150 d no matter how good the coverage is (Fig. 4d) but it can keep the IRD below 2 for that period no matter what date of application if coverage is 90% or more (Fig. 5d). Treatment 3 can keep the IRD below 1 for 150 d at 60% coverage for some dates of application but not all (Fig. 4c), and it can suppress the IRD below 2 for about a year at 60% coverage.

For all treatments, an increase in coverage leads to longer periods of sub-threshold IRD at low levels of coverage. The effect is particularly visible in Fig. 5. For treatment 4, the effect is more or less linear, as seen in Fig. 5d, but for the other treatments, there is a noticeable inflection in the response of mosquito populations to further coverage. Treatment 1 sees longer durations when IRD is <2, up to about 75% coverage, as in Fig. 5a. Further coverage does not improve the effects much. Similarly, treatment 2 improves considerably up to about 60% coverage and then levels off, as in Fig. 5b. The strongest effect is from treatment 3, with no further improvement in duration of suppression after 50% coverage is reached, as in Fig. 5c. Treatment 3 also shows this phenomenon clearly for an IRD threshold of 1, where no further gains are made beyond the 80% coverage rate, as seen in Fig. 4c.

The Importance of Timing of Application

Figs. 6 and 7 show the effect of varying the date of application of each treatment for a variety of percent coverage. To take the example of 60% coverage, the number of days below IRD threshold 1 can vary from 0 to 75 for treatment 1 (Fig. 6a), <50 to 75 for treatment 2 (Fig. 6b), 100–160 for treatment 3 (Fig. 6c), and 0–60 for treatment 4 (Fig. 6d). For IRD threshold equal to 2, the variation is less pronounced but still fairly large for treatments 1 and 4.

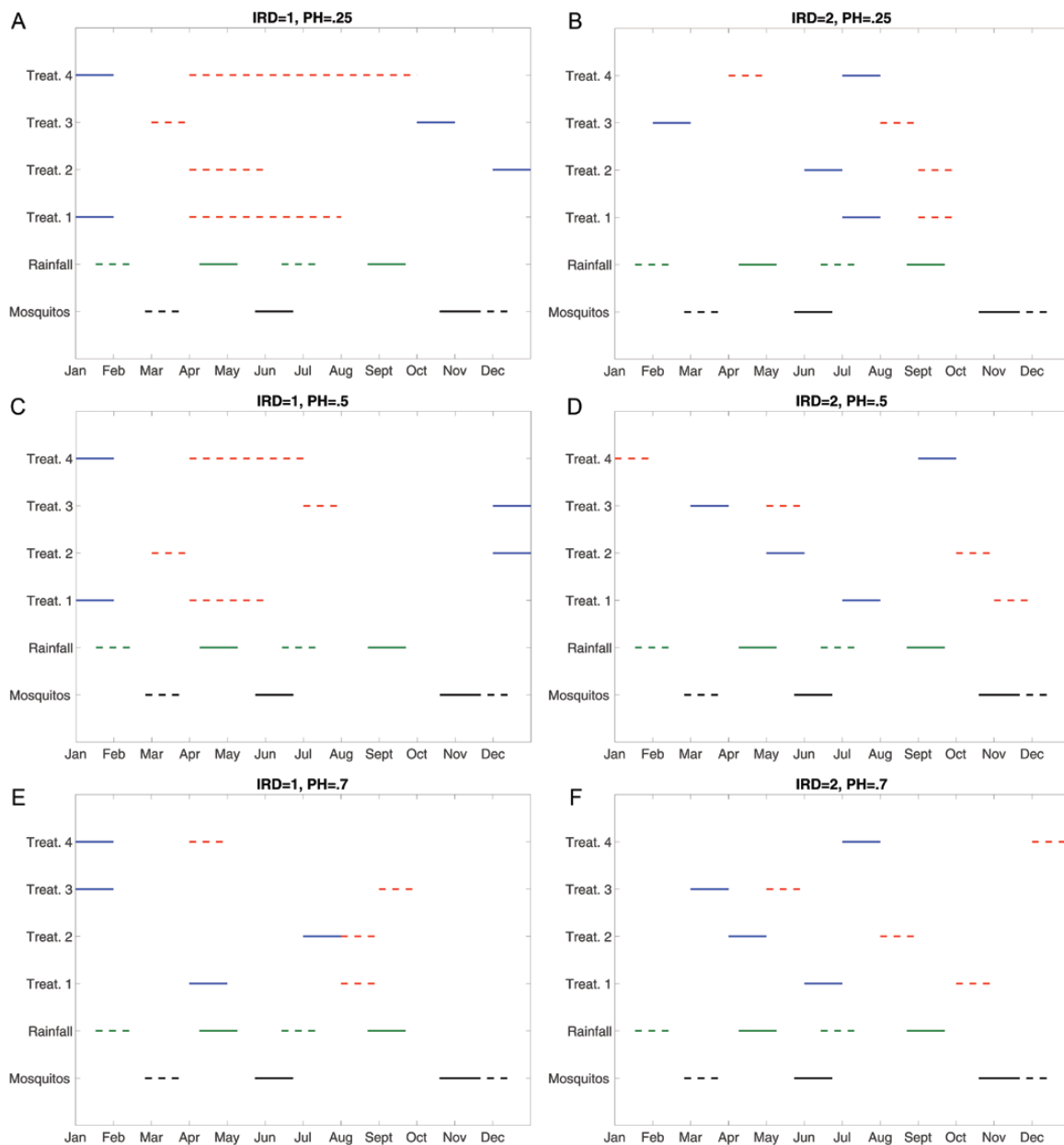


Fig. 10. The combined qualitative picture of the dry and rainy seasons and control and treated populations. Solid green lines correspond to rainy season and dashed green lines correspond to dry season. Solid black lines correspond to maximum control population and dashed black lines correspond to minimum control population. Blue lines correspond to the best time to apply the treatment and red lines correspond to the worst time to apply the treatment. (a) IRD = 1, percent household = 25%, (b) IRD = 2, percent household = 25%, (c) IRD = 1, percent household = 50%, (d) IRD = 2, percent household = 50%, (e) IRD = 1, percent household = 75%, (f) IRD = 2, percent household = 75%.

For the low thresholds used in this study, we see that at low percent coverage of 10–30%, the timing appears to matter very little (Figs. 6 and 7). Also, the longer the effectiveness of the treatment, the less timing matters. This is evident both from the minor variation of all of the curves in Figs. 6c and 7c for treatment 3, and the corresponding narrowness of spread of the curves in Figs. 4c and 5c.

The variation of periods of mosquito suppression below IRD 1 shown in Fig. 6 indicate that there are optimal times to treat houses during the annual cycle in order to keep insect populations low for the most time. This phenomenon is most visible in Fig. 6a and 6c. In this figure, we see that, at 50% coverage, both examples of indoor residual DDT spray are able to suppress IRD below 1 for about 50 d when applied on some dates, and not at all if applied on other

dates. Fig. 7 shows that the effect of timing of application is less pronounced when a less stringent threshold is set.

Fig. 8 summarizes the relative impacts of these four treatments at 50% coverage for four different dates of application. For the experiment, percentage household coverage is chosen to be 50% and the IRD = 2. It is observed that the best scenario is when treatment is applied on July 1 (Fig. 8c) because in this case even treatment 1 is as efficient as treatment 2, which is never the case for the other dates of application (Fig. 8a, b, and d). This result indicates that under these conditions, DDT spray and one coat of insecticidal paint has the same effect.

Fig. 9 shows the comparison of the mosquito abundance for the control and all the four treatments in reference to the rainy season.

For this simulation experiment, the percent household coverage fixed is to be 50% and the treatment is applied on January 1. It is observed that there is a time lag of almost a month between the peak of the rainfall and the control population. In case of treatments 1, 2, and 4, the adult population decreases when the treatment is applied, but it increases slowly and comes to almost the same level as the control population in a year. In case of treatment 3, the treatment population is not able to recover back to the level of control population during one annual cycle.

It is known that temperature determines maturation rates and overall mosquito populations, and this effect is built into the model. However, in the Emutete region described by this model, the annual temperature variation is quite small and population sizes are driven largely by available larval habitat produced (and assumed to correlate with) rainfall. Fig. 10 shows the efficacy of spray timing changes with respect to rainy and dry periods and adult mosquito populations. The answer to the question ‘when is the best time to spray?’ depends not only on which treatment is considered but also on the percent of households covered and on the objective of the treatment.

For example, comparing treatment 4 with an objective of keeping the IRD below 1, we see from Fig. 10a, c, and e that it is best to spray in January no matter what percent coverage is achieved. However, if the objective is to keep the IRD below 2 for as long as possible, the best time to spray will vary from August (Fig. 10b) to September (Fig. 10d).

From Figs. 4 to 7, we know that at very low or very high percent, household coverages timing makes less of a difference. Fig. 10c and d shows best times to spray at an intermediate 50% coverage, where timing will make a big difference. Sometimes the best time to spray is consistent across treatments. Fig. 10c shows that, if the goal is to reduce IRD below 1 for as long as possible, it is always better to apply any of these four wall treatments during the drier months of December and January. However, Fig. 10d shows that if the goal is just to reduce IRD below 2 for as long as possible, those months are not optimal. As reduction below IRD 2 will be for a longer period, it becomes a question of strategy as to whether it is better to have more intense vector suppression for a short period or less suppression for a longer period.

Discussion

Comparison With Field Observations

Although the treatments described in this paper have never been used in the town of Emutete, Kenya the source for treatment 1 describes resulting reduction of IRDs of *Anopheles fluviialis* in two districts of India (Gunasekaran *et al.* 2005). In that study, treatment in October reduced average IRD from about 10 to negligible in the district of Malkangiri and from over 40 to well under 5 in the district of Koraput for a period of 3 mo following application. There is no data past that time period (see Fig. 2a in Gunasekaran *et al.* 2005). The paper estimated coverage of 74.2% of households and 48.6% of rooms in different villages of Malkangiri District and coverage of 86.2% of households and 56.6% of rooms in Koraput district.

IRD patterns in our model are a bit different, with maximum IRD at about 7 (as in Fig. 3). Weather patterns in India are obviously different from those in Kenya, so there is no point in matching dates of application of treatment 1. Even the insect is different, although the mortality rates used in treatment 1 are derived from that study.

Nonetheless, we find that in simulations, treatment 1 can reduce IRD to below 2 for 90 d or more no matter what date of application if coverage is around 40% or more, as in Figs. 5a and 7a. This result is consistent with the observations of Gunasekaran *et al.* and

supports the authors’ conclusion that indoor residual spraying was the cause of significant reduction of indoor resting mosquitoes in that study.

Timing of Intervention

A study similar to this one was done by Worrall *et al.* (2007), which modeled monthly application of indoor residual spray and the consequential malaria burden. That study was also built initially from data in the Western Kenya highlands, and then tested against data from a region in Zimbabwe. The Worrall *et al.* model made the fundamental assumption that the abundance of female *Anopheles* vectors was proportional to cumulative monthly rainfall, and tuned the resulting epidemiological model to malaria data from a region in Kenya where malaria is unstable and prone to epidemics. The insecticide treatment was modeled as a linear decline from 100% efficacy to 0 at 6 mo. The study assumed 24% coverage of households.

However, the model of insect abundance developed by Wallace *et al.* (2016) for a similar region in Kenya shows a distinct short delay between peak rainfall (rather than cumulative rainfall) and peak adult mosquito abundance. This delay is likely to affect the conclusions about timing somewhat. As the model is tuned to a region where malaria is endemic and the IRD nonzero for most of the year, aquatic habitat never drops to zero in simulations. So, in contrast with Worrall *et al.*, even if cumulative monthly rainfall was near zero there would still be habitat, and therefore adult mosquitoes, present. This is also shown in our study (see Fig. 9). In addition, the same general region of Kenya has towns where malaria is unstable, seasonal and prone to epidemics, and other regions where it is endemic and stable. These regions exist in proximity to each other and differ in mosquito abundance even though the same general weather pattern holds for both (Wanjala *et al.* 2011). In the model, we base this application on, habitat is estimated directly from IRDs and published fieldwork, allowing it to be retuned to other regions without the need for malaria data as required in the Worrall *et al.*’s study.

We also note that the timing of application did not matter much for the longer lasting treatments 2 and 3. Nonetheless, both the Worrall model and this model show that timing matters in the application of less persistent indoor wall treatments.

The treatment examined here, that is closest to Worrall *et al.*, is treatment 4 with 20–30% coverage. Fig. 4d shows that at 25% coverage, the number of days under IRD 1 can vary from 0 to over 20 d. For this case, Fig. 10a shows January as the optimal month to spray. Fig. 5d shows that at 25% coverage, the number of days under IRD 2 can vary from 30 to about 75 d. For this case, Fig. 10b shows July/August to be the optimal time to spray. From their model, Worrall *et al.* conclude that spraying in February is not as effective as spraying in October. Worrall *et al.* point out that this amounts to spraying before peak vector abundance. In our model, the results do not point to quite such a simple interpretation, although we can say that their answer is closer to what our model gives for IRD threshold 2. We remind the reader that Worrall *et al.* assumed that mortality is given as a linear function of time with zero effectiveness after 6 mo. Measured mortality of DDT neither declines linearly nor reaches zero at 6 mo, so perhaps this accounts some of the discrepancy.

Threshold Behavior for Coverage

Gunasekaran *et al.* (2005) describe the difficulty in achieving good coverage in villages in India, which they attribute largely to a religious reluctance to allow outsiders into prayer rooms. It is a matter of great practical importance what fraction of houses or walls must be treated in order to see any reduction of IRD.

Fig. 6 shows evidence of a threshold for some treatments above which further spraying has little impact. For treatment 1, Fig. 6a suggests that increasing coverage would increase the length of time that the IRD is suppressed. For the least effective treatment (treatment 4, DDT, Okumu *et al.* 2013a, Fig. 6d) there is no pronounced threshold, but for treatments 2 and 3 (Inesfly paint, one and two layers, Mosqueira *et al.* 2010, Fig. 6b and c) there is a distinct threshold at ~45 and 80%, respectively, above which there is little gain in mosquito mortality. Our models suggest that using two coats of Inesfly on 50% of walls in a village (Fig. 6c) is as good as using one coat of Inesfly on 70% of walls (Fig. 6d), if the goal is to reduce IRD below 1 for as long as possible.

Sources of Error

The shape of the mortality data sets reported (Gunasekaran *et al.* 2005, Mosqueira *et al.* 2010, Okumu *et al.* 2013a) suggested the use of Gaussian functions to model decay properties of wall treatments. It is possible that with a longer time frame for the data, a better choice of function would be apparent and this could alter the very long-term dynamics, in particular, of treatment 3. The model for *A. gambiae* lifecycle dynamics, and in particular the carrying capacity for larvae, was derived from data collected in 2004–2005 in Emutete, Kenya and the model derived gives only a rough approximation of the sparsely collected IRD data during that period. A better data set could improve the parameters in that model. Finally, spatial heterogeneity is not taken into account, nor is the weather-related flushing of larvae during downpours.

Comparison With WHO and the President's Malaria Initiative Recommendations

For all types of indoor residual spray, the WHO recommends 'high coverage,' defined as >85% of all structures that are potential resting places (WHO 2013a). Our results indicate that little gain in mosquito reduction is achieved beyond 70% coverage. While our results are consistent with the idea that 85% coverage will suffice, they also indicate that a slightly lower coverage rate of 70% may also suffice. At high levels of coverage, simulation results shown in Figs. 5 and 6 suggest that timing of spray is less important.

On the whole, our results strongly confirm the WHO recommendation that, 'In areas where malaria transmission occurs throughout the year, at least two spray rounds may be needed to cover the whole transmission period' (WHO 2013a). Malaria transmission occurs throughout the year in Emutete, and except for treatment 3 (two coats of INESFLY), the effect on mosquito mortality wanes before the year ends, as seen in Fig. 3.

The authors in Chandonait 2015 point out that timing recommendations may differ depending on the pesticide, saying that, 'The effectiveness of residual spraying depends on the timing of the spraying relative to the peak of transmission, taking into consideration the residual effect of the pesticide that is applied. Some pesticides stay effective longer than others and decision makers should account for these differences when determining how many times a year to spray.' The model developed here indicates that these differences do matter.

For lower coverage rates, timing of spray becomes quite important. In the case of a single rainy season of 4–5 mo, the WHO recommends that the IRS cycle should be completed in the 1 mo prior to the first rains (WHO 2013a). It does not offer specific advice about annual spraying when there are multiple rainy seasons. The region modeled in this study has two distinct rainy periods per year, April–May and August–September. Our results, on timing of spray, suggest

a far more complex picture than is captured by the WHO recommendation. Fig. 10 shows optimal timings of IRS application in terms of vector reduction (not disease reduction). If the public health official wishes to maximize the number of days that the IRD drops below 1, and has 50% coverage, Fig. 10c indicates an optimal application time of December–January, for all four types of treatment considered. This is not 1 mo prior to either rainy season, but rather during one of the drier periods. However, if the goal is to maximize the number of days that the IRD drops below 2 and assumes 50% coverage, Fig. 10d suggests that the optimal timing depends on the treatment used. For treatments 1 and 3, the optimal timing is indeed just before one of the two rainy seasons—but not the same one. For treatments 2 and 4, the optimal time overlaps with the rainy season but again, not the same one. The type of insecticide used does indeed matter, as pointed out by the President's Malaria Initiative. Whether it is better to suppress the IRD to a lower level for a shorter time or to suppress it less effectively longer is a question that must be addressed by a full epidemiological model.

Potential Challenges and Future Directions for Research

Vector reduction may not necessarily result in disease reduction, so a necessary further step is to couple the lifecycle model derived from Wallace *et al.* (2016) with a malaria transmission model, of which there are many (Reiner *et al.* 2013). It would be worth the trouble to extend the model in Wallace *et al.* (2016) to a full disease transmission model. As comparisons of optimal timing of application differ depending on the threshold IRD that is set, a full disease model will shed light on whether it is better to radically suppress the vector population for a short time or suppress the population somewhat less effectively for a longer duration. In addition, perhaps the threshold coverage for disease propagation is quite different from the threshold for suppressed IRD.

It is one thing to say that 45% of walls in houses must be treated to achieve a certain end, and it is another thing to say which houses it will be most useful to treat. It is well known that mosquito abundance and malaria incidence in the Western highlands of Kenya (and inevitably elsewhere) are heterogeneous, depending on topography (Wanjala *et al.* 2011) and types of larval habitat (Ndenga *et al.* 2006, 2011, 2012). Topography probably interacts with daily weather to influence the extent to which larvae are flushed from their habitats and die, a known phenomenon (Paaijmans *et al.* 2007). In addition, it is known that mosquitoes travel in search of oviposition sites as well (Menach *et al.* 2005). The model used here could yield useful insights about treatment when reworked as a patch model incorporating these heterogeneities.

Insecticide resistance can reduce the effectiveness of any treatment. To address this potential problem, one recommendation from the WHO (2013a) is 'judicious use and through rotation among the four classes of insecticide.' A modeling approach similar to the one used in this paper could be implemented to test this recommended strategy by including multiple strains of mosquitoes resistant to the various treatments, and simulating a rotating 4-yr cycle of treatments.

Another challenge is to take into account outdoor transmission. Although *A. gambiae* prefers to feed on humans and rest indoors, there could be communities where people spend a lot of time outside during the feeding peak hours. In such cases, feeding mosquitoes may rest on surfaces that are not treated. In these situations, the model would have to be modified to take these untreated resting surfaces into account by adjusting the level of coverage accordingly.

The presence of a threshold for the more effective treatments begs an economic question. It is likely to be more time consuming and expensive to apply insecticidal paint such as Inesfly as in treatments 2 and 3 than to spray walls with insecticide as in treatments 1 and 4. However, for the insecticidal paint, much lower coverage is necessary to achieve the same reduction in IRD counts. An economic analysis of these methods could shed light on whether one is more cost effective than the other.

Summary

We have presented a model of the likely vector suppression due to four types of indoor wall treatments, based on previously modeled vector dynamics of the Emutete region in the Western Kenya highlands. The model supports claims in the literature that wall treatments have the capacity to reduce the vector burden (Gunasekaran et al.). In particular, it shows that 50% coverage of walls is enough to make a noticeable reduction in vector burden, and the duration of that reduction depends on the specific treatment and its persistence. The model also supports claims that indoor residual spraying may have no noticeable effect at all (Okumu 2013b), if the percent coverage is not high enough. For each treatment of longer persistence, there appears to be a threshold coverage above which further coverage adds little to no value. For treatments of shorter persistence, the timing of treatment has a noticeable effect on vector suppression.

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