When can malaria control and elimination programs safely reduce vector control efforts? a simulation study.

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Abstract

We use a simulation model of malaria epidemiology and immunology (OpenMalaria) to predict malaria transmission and disease outcomes after withdrawing vector control interventions under various settings. We analyze simulation results using logistic and linear regression in order to derive predicted probabilities of resurgence and predictions of severity of resurgence under scenarios defined by the baseline pre-intervention entomological inoculation rate (EIR), case management coverage, and vector control coverage, amongst other parameters. We also use Monte Carlo simulations to examine the precision and bias associated with metrics estimated by control programs to determine if a setting meets the criteria for the safe reduction in coverage of vector control interventions. Results indicate that, in the absence of secular changes in the underlying determinants of transmission (historically called receptivity), there are few scenarios under which vector control can be removed without a strong expectation of resurgence. These, potentially safe, scenarios are characterized by low historic EIR, successful control with vector control reaching elimination or near elimination, and effective surveillance systems with high coverage and effective treatment of malaria cases.

1 Background

The World Health Organization (WHO) Global Malaria Programme's (GMP) policy of universal coverage of long lasting insecticidal nets (LLINs) and/or indoor residual spraying (IRS) of people living in areas of malaria transmission, implemented as one of the fundamental components of malaria control and elimination strategies, and following the issuance of the Global Malaria Action Plan (GMAP) [1, 2], with funding from the Global Fund for HIV/AIDS, Tuberculosis and Malaria (GFATM), United States Agency for International Development (USAID) President's Malaria Initiative (PMI) and others, has led to large increases in global coverage of vector control for malaria and concomitant declines in malaria burden and transmission in many parts of the world [1]. This scale up, however, is not without cost and many national malaria control programs wonder if it is possible, after successful vector control has been achieved and burden reductions realized to scale down from universally applied vector control measures to more focal approaches, and if transmission and burden reductions could be maintained, even in the absence of vector control.

This document outlines the broad questions that need to be answered in order for the WHO to provide guidance on when or if such a reduction in vector control coverage might be possible for a specific place and time to transition from a target of universal coverage to either complete cessation of vector control activities or to lower or more focal coverage based on local data. We note here that the scale back of vector control interventions may be implemented at small sub-national scales and not only at the country level. The need for such guidance was further emphasized in country consultations during the development of the Global Technical Strategy.

Some points should be considered at the outset. Firstly, in historical examples, including many countries or areas which have achieved WHO certified malaria elimination, vector control may still be practiced and/or often remains a part of a response strategy to introduced malaria cases (often focally around the

cases). Secondly, even in countries with a long history of certified malaria elimination and an absence of demonstrated autochthonous transmission, malaria transmission potential may remain indefinitely [3] — as recent outbreaks of autochthonous transmission in Greece, the United States, the Bahamas, Singapore and other locations demonstrate [4, 5, 6, 7].

2 Questions

Four questions need to be answered to ensure that any guidance on scaling back from universal vector control coverage is accurate and safe. These are as follows:

1. In a place with historical malaria transmission and high coverage of vector control interventions, are there situations in which reduction in the level of effort or coverage of vector control activities will *not* result in resurgent transmission and accompanying increases in disease burden?
2. What set of indicators would be necessary to specifically identify locations and times in which the scaling back of vector control might be safely undertaken as per the conditions set above in Question 1?
3. What is the impact of the precision and bias associated with these measurements on estimates of the risk of resurgence following the scale back of vector control?
4. What sets of measurements of these indicators would indicate that vector control could be safely scaled back?

3 Methods

3.1 Outline

OpenMalaria is a simulation platform, consisting of an ensemble of models of malaria epidemiology and immunology, that allows the comparison of the effectiveness and cost-effectiveness of current and planned control interventions in various settings [8]. We run simulations of these models to determine the effects of scaling back from universal coverage of vector control interventions, specifically long lasting insecticidal nets (LLINs). We run simulations with multiple random seeds to include the effects of stochasticity; different model versions to include uncertainty in underlying model assumptions; and multiple parameterizations to allow for various assumptions of base (pre-intervention) transmission level, coverage of indoor vector control interventions, rate of imported infections, and coverage of case management and mass treatment interventions. The outputs of the simulations include the number of episodes of uncomplicated malaria, and the probability of resurgence following the scaling back of vector control.

3.2 Overview of Model

The OpenMalaria model platform combines an ensemble of stochastic individual-based model for malaria in humans with a periodically-forced deterministic model for malaria in mosquitoes, shown in a simple schematic in Figure 1. The model uses a discrete time step of five days and includes multiple aspects of the dynamics of malaria in humans, including demography; acquired immunity and superinfection; variations in parasite densities and infectiousness to mosquitoes; and the clinical effects of malaria and has been fit to multiple field data sets [9]. The model for malaria transmission in mosquitoes includes multiple mosquito species, nonhuman hosts, and a periodically varying emergence rate [10]. We show a schematic of the female mosquito's feeding cycle and the effects of vector control interventions in Figure 2. We have used this model platform to investigate the effects of vector control interventions, vaccines, chemoprophylaxis and case management in reducing malaria transmission and disease.

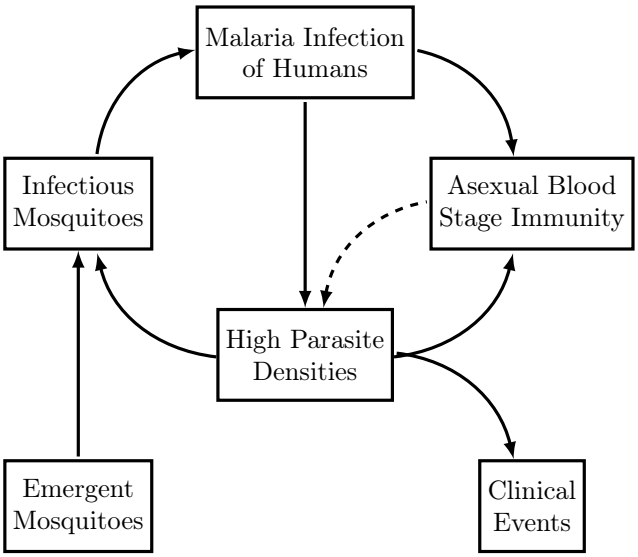

Figure 1: Schematic of the malaria transmission model with positive feedback shown by solid lines and negative feedback by dashed lines. Emergent mosquitoes biting on humans with high parasite densities are more likely to become infected and subsequently infectious if they live long enough. They, in turn, can infect humans, leading to high parasite densities and the build up of acquired immunity. Acquired immunity tends to moderate parasite densities, which can lead to clinical events, such as uncomplicated malaria, severe malaria, and death.

3.3 Model Simulations and Sensitivity Analysis

We create baseline parameterizations that describe pre-intervention transmission in western Kenya and the Solomon Islands(including the composition of mosquito vectors and the seasonal profile of transmission). We run numerical simulations for a population of 10,000 humans of this baseline scenario and of simulations with different coverage levels of vector control and active case detection interventions and varying levels of pre-intervention transmission, imported infections, and case management coverage.

We run the model for one human life span where humans are subjected to a periodically varying pre-intervention entomological inoculation rate (EIR) to induce malaria immunity population and to estimate the mosquito emergence rate that leads to this EIR. After this warm-up period and a short stabilizing period, we deploy LLINs to humans through four mass distribution campaigns repeated every three years. Coinciding with the last deployment of nets, we conduct quarterly mass screen and treat campaigns to simulate active case detection in the population for the remainder of the simulation. A schematic of the generic simulation scenario is shown in Figure 3.

We survey the population for a total of thirty-two years, measuring the annual EIR, the number of new infections, the number of patent infections, the number of uncomplicated clinical malaria cases per person per year, and the number of diagnostic tests used, amongst other parameters. We monitor the first three years as the baseline period in the absence of any interventions (but with ongoing case management of clinical cases). We monitor the following nine years as the vector control period (between the first and the fourth deployment of LLINs) and additionally determine the probability of elimination within this period. We monitor the final twenty years as the post-vector control period and additionally determine the probability of resurgence within this period. We note that the post-vector control period begins directly after the final distribution of LLINs so a proportion of the population will be initially protected by effective LLINs.

Since the simulations stochastically include imported infections, complete cessation of all transmission is

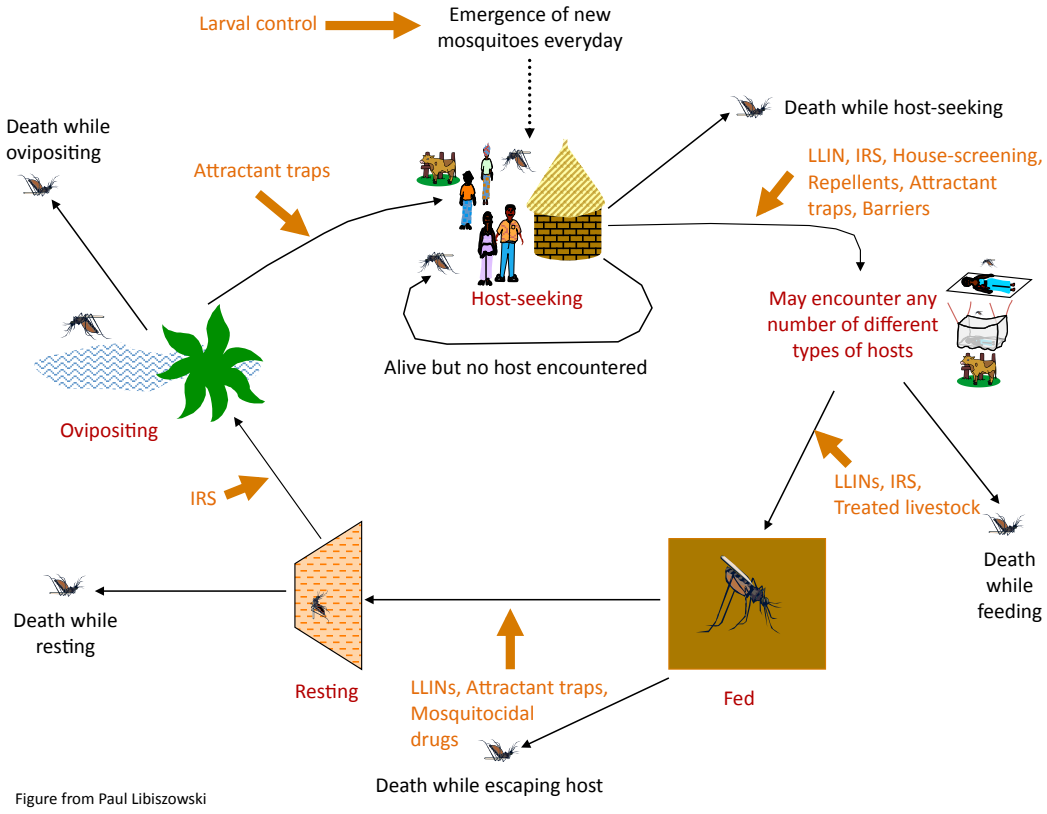

Figure 2: Schematic of mosquito feeding cycle dynamics including the effects of interventions.

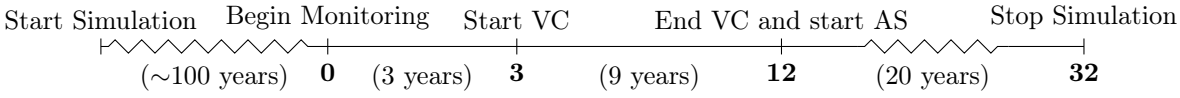

Figure 3: Schematic of generic scenario description for OpenMalaria simulations conducted for this study. "VC" stands for vector control and "AS" stands for active surveillance. Bold numbers indicate reference years for monitoring.

unlikely. Therefore, we define elimination during the vector control period as occurring when the number of new infections on one year is less than 3 times the 97.5 percentile of the Poisson distribution of the number of imported infections (in one year), as defined in a previous publication [11]. Similarly, we define resurgence in the post-vector control period as occurring when the number of new infections in one year is greater 3 times the 97.5 percentile of the Poisson distribution of the number of imported infections (in one year).

3.3.1 Baseline Western Kenya Parameterization

We use previously published work [12] to form the baseline transmission parameterization for western Kenya, and the parameterization of the initial effectiveness of nets and their rate of decay.

3.3.2 Baseline Solomon Islands Parameterization

For the baseline transmission in Solomon Islands, we use United Nations population data [13] to estimate the human demographic profile. The main vector species in the Solomon Islands is *Anopheles farauti*. We use a seasonality profile for the EIR calculated from climate data by the EMOD model [14]. We determine the extrinsic incubation period and the duration of the mosquito resting phase from average temperature data in Guadalcanal. We use data for *An. farauti* from Papua New Guinea for the human blood index [15] and for the probability of mosquitoes host seeking the same day as oviposition [16]. We use data from northern Guadalcanal for the parous proportion of mosquitoes and the proportion of mosquitoes that biting indoors at the time when humans are sleeping indoors [17]. Other parameters such as the treatment drugs, decay and effectiveness of LLINs and sensitivity of rapid diagnostic tests are assumed to be similar to Kenya.

3.3.3 Experiment Set-up

To conduct a more thorough sensitivity analysis, we vary:

Transmission level: we consider levels of baseline (pre-intervention) EIR of $\{0.1, 0.5, 1, 2, 5\}$ infectious bites per adult per year to represent historical transmission;

Coverage of vector control interventions: we vary coverage of LLINs of $\{0, 0.2, 0.5, 0.8\}$;

Importation rate: we model importation rates of $\{0.1, 1, 10\}$ infections per 1000 people per year;

Case management coverage: we assume case management coverage of $\{0.2, 0.5, 0.8\}$ of all uncomplicated cases that are treated effectively;

Active case detection: we simulate mass screen and treat interventions every 3 months at coverage levels of $\{0, 0.025, 0.1, 0.2\}$ to model increased active surveillance;

Stochasticity: we use 10 random seeds per model parameterization;

Model variants: we use 14 model variants as described in a previous publication [18] to explore the implications of various model assumptions such as possible decay of immunity and correlation of heterogeneities.

3.4 Precision and Bias

In order to examine the potential for real surveillance systems to mis-measure or misclassify important metrics suggested here as tools for determining the safety of vector control withdrawal we have conducted several additional simulation exercises using Monte Carlo Simulation algorithms developed using R software [19] to estimate the precision and bias inherent in measurements of the infection importation rate (IIR) and the annual blood examination rate (ABER).

3.4.1 Infection Importation Rate

In order to estimate the precision and bias associated with measurement of IIR we conducted simulations of importation and measurement assuming that the number of importations weekly was given by a Poisson distribution with a mean of the true IIR, we then assumed that there was a observation process given by a binomial distribution which determined whether each of the imported infections was actually detected. We simulated this process for a one year period (52 weeks) and repeated the simulations for 10,000 iterations assuming varied mean true IIRs (from 1 per 1,000 persons per annum to 5 per 1,000 persons per annum) and varied detection rates (from 20% to 80%). We then tested each result against a threshold of 2 per 1,000 per annum to determine if, for each simulation, a Poisson significance test would determine that the number of imported infections per year would be determined to be statistically significantly below the threshold with $\geqslant 90\%$ confidence. This sequence of results were then analyzed with logistic regression and the predicted probability of concluding that IIR (based on the measurement) was below the threshold was summarized by true IIR and the detection probability in the surveillance system.

3.4.2 Annual Blood Examination Rate

In order to estimate the potential bias associated with utilizing ABER as a metric for surveillance system coverage we conducted simulations designed to determine the divergence between ABER and the total proportion of a population tested during one year with multiple active case searches covering varying proportions of the population where individuals have varied probabilities to be covered: in other words, where the active searches are likely to repeatedly test or miss the same individuals. We simulated a cohort of individuals with either independent probabilities of being tested in each round, equal to the total proportion covered during said round, or by assuming that all individuals in the cohort had a constant predetermined probability of inclusion during all rounds. These probabilities were generated by simulating from a beta distribution with a known mean. The actual inclusion of an individual as tested in a round was drawn from a binomial distribution with probability determined in one of the two above methods. The annual blood examination rate was calculated as,

$$\text{ABER} = \frac{\text{Number of Tests Conducted}}{\text{Person-Years}}, \tag{1}$$

while the the proportion of the population actually tested was calculated as,

$$\text{PT} = \frac{\text{Number of Individuals Tested}}{\text{Person-Years}}. \tag{2}$$

4 Results

4.1 Precision and Bias

The predicted probabilities from the logistic model for decisions based on IIR are shown in Figure 4. These results indicate that as the surveillance system improves (increases the probability of detecting imported infections) that there is relatively little chance of incorrectly concluding that the importation rate is below a specified threshold in error. However, the results also show that when the surveillance system has a high probability of detecting imported infections, programs will often not be able to conclude that the IIR is low enough to withdraw vector control unless the true IIR is significantly below the acceptable threshold of risk.

The results of simulation of ABER are shown in Figure 5. They indicate that although ABER and the proportion of the population actually tested by a surveillance system are likely to greatly diverge at high values, at the lower levels of interest here, they are likely to be largely similar. Thus at least at lower levels of testing, ABER is likely to be a reliable metric for the monitoring surveillance system coverage.

Results of an analysis of OpenMalaria simulation outputs indicates a further complication in monitoring and determining whether an area meets the acceptability threshold for withdraw of vector control, which is that the annual parasite index (API) and ABER are both highly correlated in these individual simulation

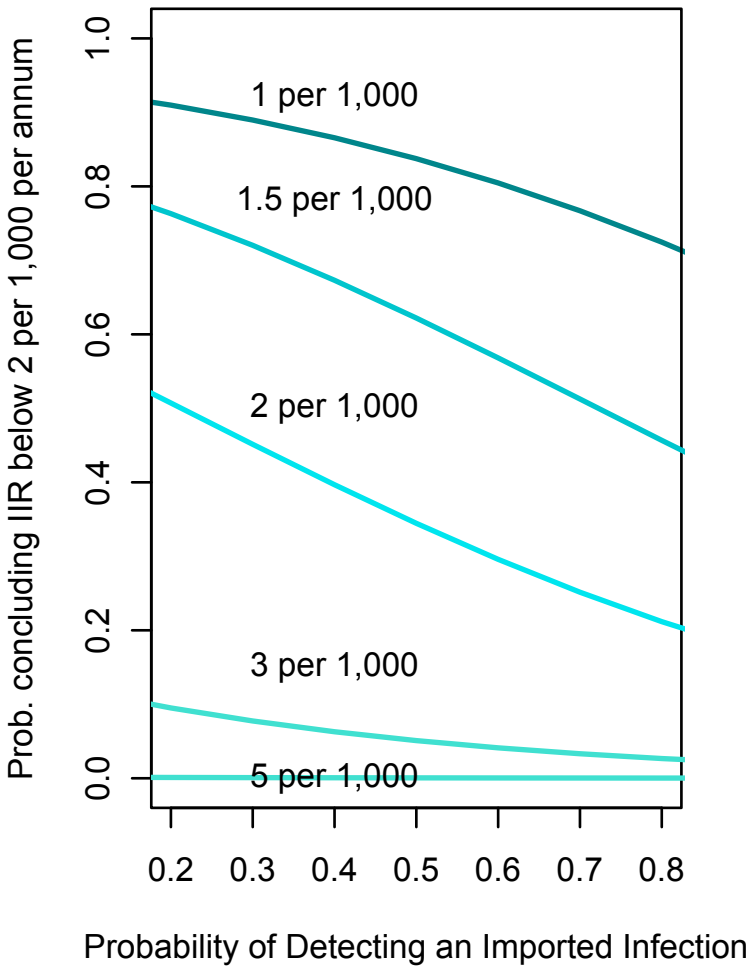

Figure 4: Simulation Results for Measurement of Infection Importation Rate

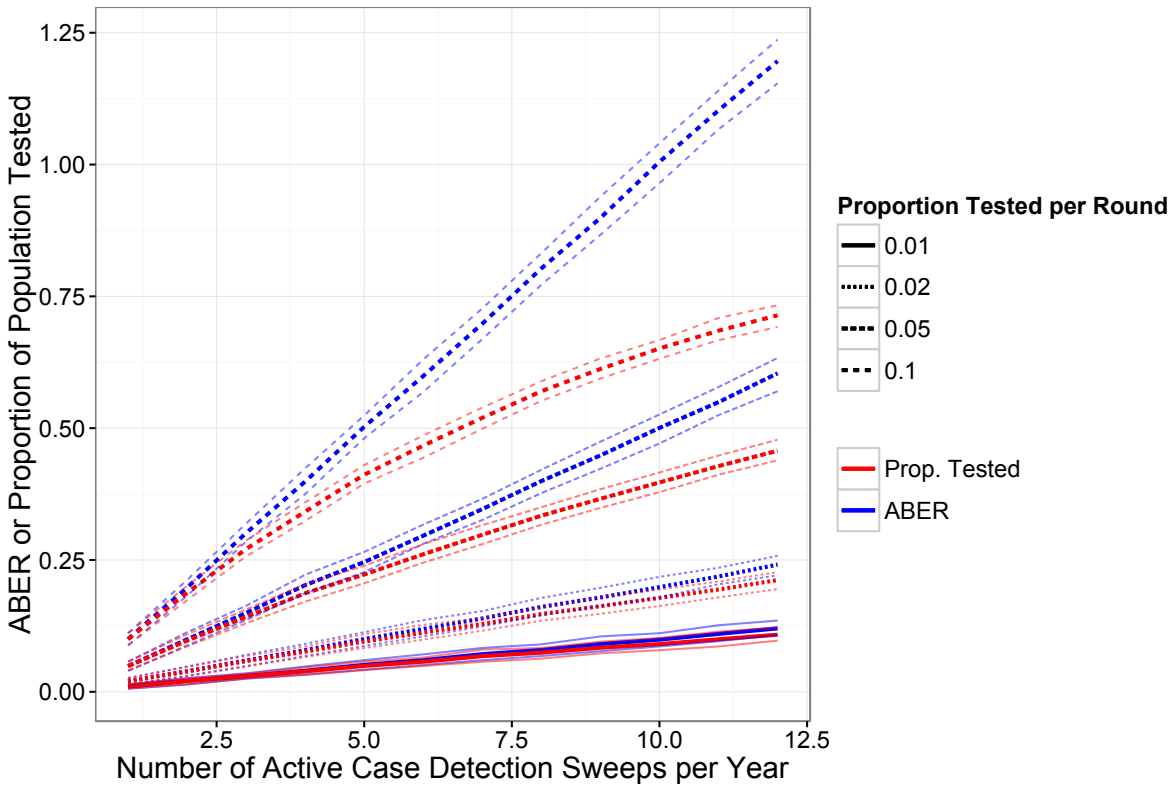

Figure 5: Simulation Results for Measurement of the Annual Blood Examination Rate.

outputs. This is likely because API is essentially a product of the positivity rate among those tested and ABER, therefore, API tends to increase with increases in ABER. We elaborate on this point further in the discussion.

4.2 Descriptive results of OpenMalaria simulation outputs: Kenyan Context

Simulation outputs allowed for the calculation of the time course of API, ABER and the incidence of new malaria infections (or force of infection (FOI)). The results of some sample simulations are shown in Figure 6. Results of a subset of simulations for ABER are shown in Figure 7. API provides a metric for estimation of true infection incidence, especially at high case management coverage and low EIR. However, because this metric can be biased by health system access (case management coverage) and active surveillance activities, we do not use it to define the occurrence of a resurgence of malaria or as a metric for determining that vector control has successfully interrupted transmission or reduced it to any significant extent. We instead use the number of new infections (including super infections) at each model time step. This metric is similar to a molecular force of infection (mFOI) measure, and also to standard FOI measures at low transmission where super-infection is expected to be rare. Figure 8 shows the results of simulations of this metric for a subset of relevant simulation outputs.

We determined for each simulation run, if transmission had effectively been interrupted by vector control and whether or not there was a resurgence of transmission following the withdrawal of vector control. Descriptive results are shown in Tables 1–6 for elimination and resurgence by various input parameters. Most simulations resulted in elimination during vector control roll-out. However, a similar fraction of simulations

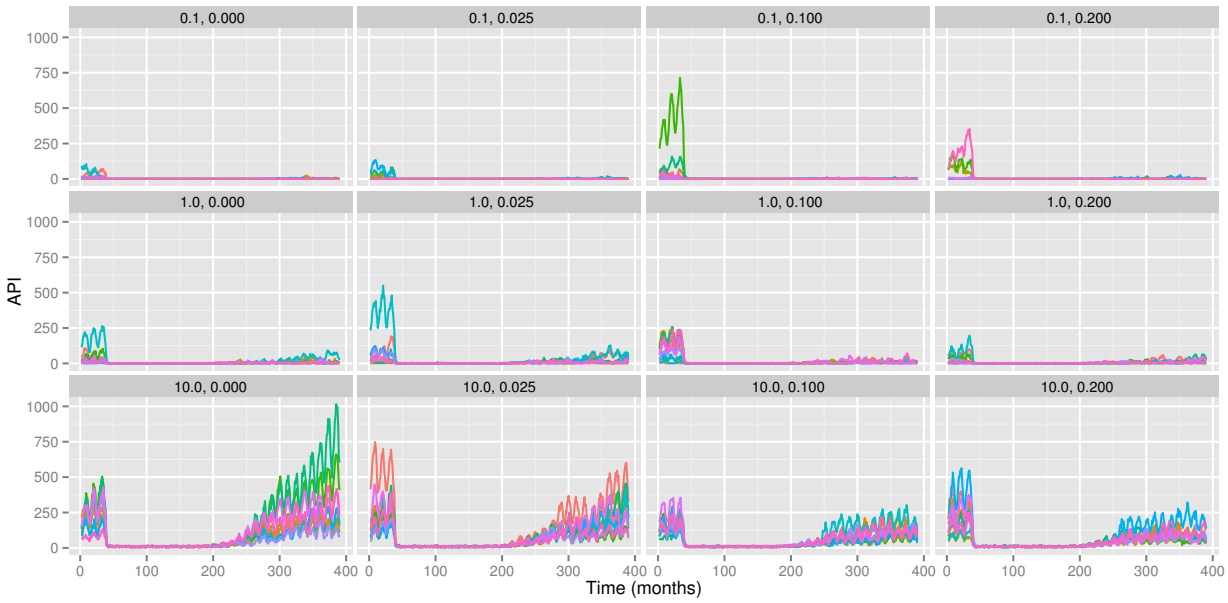

Figure 6: OpenMalaria simulation results for API per 1,000 per annum (Kenya scenario) with an annual pre-intervention EIR of 0.1, case management coverage of 80%, and LLIN coverage of 80% during the period of vector control implementation. Each chart shows simulations results for varied levels of the infection importations rate and active surveillance (through quarterly mass screening and treatment (MSAT) coverage). These values are shown just above each chart in the form (IIR per thousand per year, proportion of population tested per quarter). Colors of lines within the chart represent various simulation runs with differing random seeds (thus capturing stochastic uncertainty). API is the annual parasite incidence computed at each time step and the x-axis is in months. LLINs are distributed at months 36, 72, 108, 144. Increased active surveillance starts immediately coincident with the last distribution of vector control.

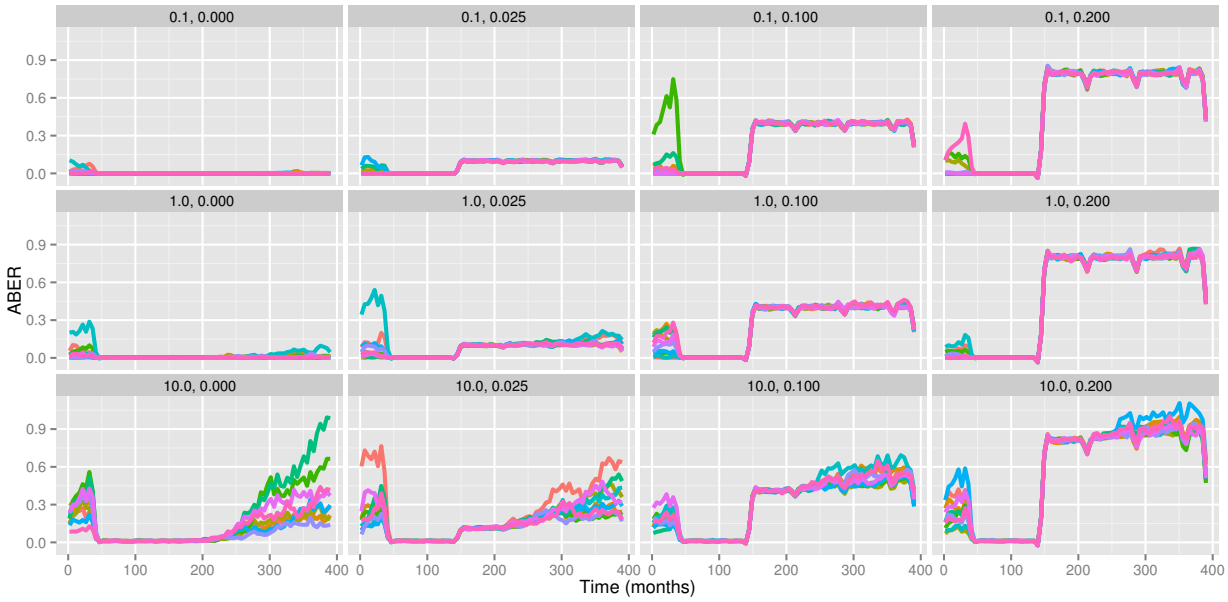

Figure 7: OpenMalaria simulation results for ABER (Kenya scenario) with an annual pre-intervention EIR of 0.1, case management coverage of 80%, and LLIN coverage of 80% during the period of vector control implementation. Each chart shows simulations results for varied levels of the infection importations rate and active surveillance (through quarterly mass screening and treatment (MSAT) coverage). These values are shown just above each chart in the form (IIR per thousand per year, proportion of population tested per quarter). Colors of lines within the chart represent various simulation runs with differing random seeds (thus capturing stochastic uncertainty). ABER is the annual blood examination rate (smoothed to remove the visual effects of widely varying ABER between time periods with quarterly MSAT surveys) and the x-axis is in months. LLINs are distributed at months 36, 72, 108, 144. Increased active surveillance starts immediately coincident with the last distribution of vector control.

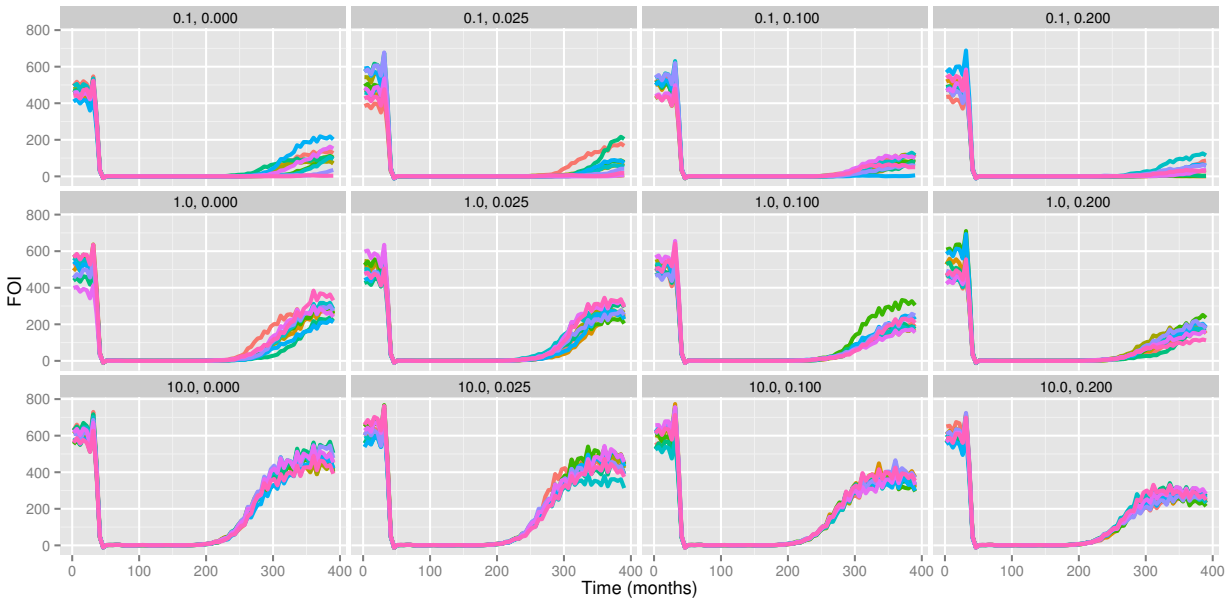

Figure 8: OpenMalaria simulation results for mFOI per 1,000 per annum (Kenya scenario) with an annual pre-intervention EIR of 1, case management coverage of 80%, and LLIN coverage of 80% during the period of vector control implementation. Each chart shows simulations results for varied levels of the infection importations rate and active surveillance (through quarterly mass screening and treatment (MSAT) coverage). These values are shown just above each chart in the form (IIR per thousand per year, proportion of population tested per quarter). Colors of lines within the chart represent various simulation runs with differing random seeds (thus capturing stochastic uncertainty). mFOI is the molecular force of infection per 1,000 people per year and the x-axis is in months. LLINs are distributed at months 36, 72, 108, 144. Increased active surveillance starts immediately coincident with the last distribution of vector control.

showed resurgence after vector control withdrawal (Table 1). When results for resurgence and elimination were examined in bivariate analysis for background characteristics of simulation, occurrence of a resurgence was statistically significantly associated with infection importation rate, case management coverage, active surveillance coverage, input EIR, model variant and the level of vector control coverage achieved (Tables 2–7). While elimination was associated with level of vector control coverage achieved, case management coverage, input EIR and model variant (Tables 2 and 7).

Overall, there were 99,977 successfully completed simulations (a small number of simulation runs (23) failed to complete). In the majority of simulations (69%) the level of malaria transmission during vector control deployment met the criteria for elimination during vector control deployment. The majority of simulations (55%) also resulted in a resurgence after vector control withdraw (Table 1). Table 1 shows the proportion of simulations which resulted in elimination and resurgence.

Variable	**Levels**	$\mathbf{n}_0$	$\%_0$	$\mathbf{n}_1$	$\%_1$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	30978	100.0	0	0.0	30978	31.0
	1	0	0.0	68999	100.0	68999	69.0
$p < 0.0001$	all	30978	100.0	68999	100.0	99977	100.0
Resurgence	0	1519	4.9	43923	63.7	45442	45.5
	1	29459	95.1	25076	36.3	54535	54.5
$p < 0.0001$	all	30978	100.0	68999	100.0	99977	100.0

Table 1: Simulation outputs for elimination and resurgence

Increasing coverage of ITNs during vector control deployment was associated with increased probabilities of elimination and as well as reduced probabilities of resurgence (Table 2).

Variable	**Levels**	$\mathbf{n}_0$	$\%_0$	$\mathbf{n}_{0.2}$	$\%_{0.2}$	$\mathbf{n}_{0.5}$	$\%_{0.5}$	$\mathbf{n}_{0.8}$	$\%_{0.8}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	23530	94.2	7342	29.4	106	0.4	0	0.0	30978	31.0
	1	1456	5.8	17642	70.6	24915	99.6	24986	100.0	68999	69.0
$p < 0.0001$	all	24986	100.0	24984	100.0	25021	100.0	24986	100.0	99977	100.0
Resurgence	0	1728	6.9	11683	46.8	15275	61.0	16756	67.1	45442	45.5
	1	23258	93.1	13301	53.2	9746	39.0	8230	32.9	54535	54.5
$p < 0.0001$	all	24986	100.0	24984	100.0	25021	100.0	24986	100.0	99977	100.0

Table 2: Simulation outputs for elimination and resurgence in terms of ITN coverage during vector control

Changes in active surveillance across the range tested was not statistically significantly related to the probability of elimination. Increasing active surveillance coverage was significantly associated with a downward trend in the probability of resurgence. Since active surveillance was not deployed during the period of vector control in these simulations the lack of any association with elimination during vector control is expected (Table 3).

Variable	**Levels**	$\mathbf{n}_0$	$\%_0$	$\mathbf{n}_{0.025}$	$\%_{0.025}$	$\mathbf{n}_{0.1}$	$\%_{0.1}$	$\mathbf{n}_{0.2}$	$\%_{0.2}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	7804	31.0	7558	31.0	7830	31.1	7786	30.9	30978	31.0
	1	17389	69.0	16837	69.0	17367	68.9	17406	69.1	68999	69.0
$p = 0.98$	all	25193	100.0	24395	100.0	25197	100.0	25192	100.0	99977	100.0
Resurgence	0	10499	41.7	10442	42.8	11672	46.3	12829	50.9	45442	45.5
	1	14694	58.3	13953	57.2	13525	53.7	12363	49.1	54535	54.5
$p < 0.0001$	all	25193	100.0	24395	100.0	25197	100.0	25192	100.0	99977	100.0

Table 3: Simulation outputs for elimination and resurgence in terms of active surveillance coverage

Changes in the level of case management coverage were associated with differences in the probability of elimination and resurgence (Table 4).

Variable	**Levels**	$\mathbf{n}_{0.2}$	$\%_{0.2}$	$\mathbf{n}_{0.5}$	$\%_{0.5}$	$\mathbf{n}_{0.8}$	$\%_{0.8}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	11439	34.0	10015	30.5	9524	28.4	30978	31.0
	1	22161	66.0	22781	69.5	24057	71.6	68999	69.0
$p < 0.0001$	all	33600	100.0	32796	100.0	33581	100.0	99977	100.0
Resurgence	0	11646	34.7	15419	47.0	18377	54.7	45442	45.5
	1	21954	65.3	17377	53.0	15204	45.3	54535	54.5
$p < 0.0001$	all	33600	100.0	32796	100.0	33581	100.0	99977	100.0

Table 4: Simulation outputs for elimination and resurgence in terms of case management coverage

Input entomological inoculation rate (EIR) was strongly associated with probabilities of both elimination and resurgence. These associations showed trends in the expected directions with elimination much less likely to occur at higher input EIRs and resurgence much more likely to occur at higher baseline EIRs (Table 5).

Variable	**Levels**	$\mathbf{n}_{0.1}$	$\%_{0.1}$	$\mathbf{n}_{0.5}$	$\%_{0.5}$	$\mathbf{n}_1$	$\%_1$	$\mathbf{n}_2$	$\%_2$	$\mathbf{n}_5$	$\%_5$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	3753	18.8	4845	24.2	5206	26.0	7151	35.8	10023	50.1	30978	31.0
	1	16224	81.2	15155	75.8	14794	74.0	12849	64.2	9977	49.9	68999	69.0
$p < 0.0001$	all	19977	100.0	20000	100.0	20000	100.0	20000	100.0	20000	100.0	99977	100.0
Resurgence	0	15531	77.7	12172	60.9	9313	46.6	6348	31.7	2078	10.4	45442	45.5
	1	4446	22.3	7828	39.1	10687	53.4	13652	68.3	17922	89.6	54535	54.5
$p < 0.0001$	all	19977	100.0	20000	100.0	20000	100.0	20000	100.0	20000	100.0	99977	100.0

Table 5: Simulation outputs for elimination and resurgence in terms of input entomological inocculation rate

Infection Importation Rate (IIR) was significantly associated with the probability of resurgence but not with elimination (Table 6).

Variable	**Levels**	$\mathbf{n}_{0.1}$	$\%_{0.1}$	$\mathbf{n}_{1}$	$\%_{1}$	$\mathbf{n}_{10}$	$\%_{10}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	10370	31.1	10428	31.3	10180	30.5	30978	31.0
	1	22939	68.9	22887	68.7	23173	69.5	68999	69.0
$p = 0.07$	all	33309	100.0	33315	100.0	33353	100.0	99977	100.0
Resurgence	0	20920	62.8	14157	42.5	10365	31.1	45442	45.5
	1	12389	37.2	19158	57.5	22988	68.9	54535	54.5
$p < 0.0001$	all	33309	100.0	33315	100.0	33353	100.0	99977	100.0

Table 6: Simulation outputs for elimination and resurgence in terms of infection importation rate per 1,000 per annum

Model variant was also significantly associated with the probability of resurgence and elimination (Table 7).

Variable	Levels	n_{R0063}	$\%_{R0063}$	n_{R0065}	$\%_{R0065}$	n_{R0068}	$\%_{R0068}$	n_{R0111}	$\%_{R0111}$	n_{R0115}	$\%_{R0115}$	n_{R0121}	$\%_{R0121}$	n_{R0125}	$\%_{R0125}$	n_{R0131}	$\%_{R0131}$	n_{R0132}	$\%_{R0132}$	n_{R0133}	$\%_{R0133}$	n_{R0670}	$\%_{R0670}$	n_{R0674}	$\%_{R0674}$	n_{R0678}	$\%_{R0678}$	n_{base}	$\%_{base}$	n_{all}	$\%_{all}$
Elimination	0	2421	34.0	2197	30.8	2202	30.8	2253	31.6	2088	29.2	2229	31.2	2064	28.9	2167	30.3	2131	29.9	2143	30.0	2191	30.7	2319	32.5	2323	32.5	2250	31.5	30978	31.0
	1	4707	66.0	4942	69.2	4941	69.2	4887	68.5	5057	70.8	4916	68.8	5076	71.1	4978	69.7	5009	70.2	4997	70.0	4954	69.3	4825	67.5	4817	67.5	4893	68.5	68999	69.0
$p < 0.0001$	all	7128	100.0	7139	100.0	7143	100.0	7140	100.0	7145	100.0	7145	100.0	7140	100.0	7145	100.0	7140	100.0	7140	100.0	7145	100.0	7144	100.0	7140	100.0	7143	100.0	99977	100.0
Resurgence	0	3373	47.3	3831	53.7	3504	49.1	3418	47.9	3687	51.6	3314	46.4	3147	44.1	3156	44.2	2915	40.8	3203	44.9	3300	46.2	2691	37.7	2552	35.7	3351	46.9	45442	45.5
	1	3755	52.7	3308	46.3	3639	50.9	3722	52.1	3458	48.4	3831	53.6	3993	55.9	3989	55.8	4225	59.2	3937	55.1	3845	53.8	4453	62.3	4588	64.3	3792	53.1	54535	54.5
$p < 0.0001$	all	7128	100.0	7139	100.0	7143	100.0	7140	100.0	7145	100.0	7145	100.0	7140	100.0	7145	100.0	7140	100.0	7140	100.0	7145	100.0	7144	100.0	7140	100.0	7143	100.0	99977	100.0

Table 7: Simulation outputs for elimination and resurgence in terms of Model Variant (Kenya Vector Parametrization). Details of the models variants are provided in [18].

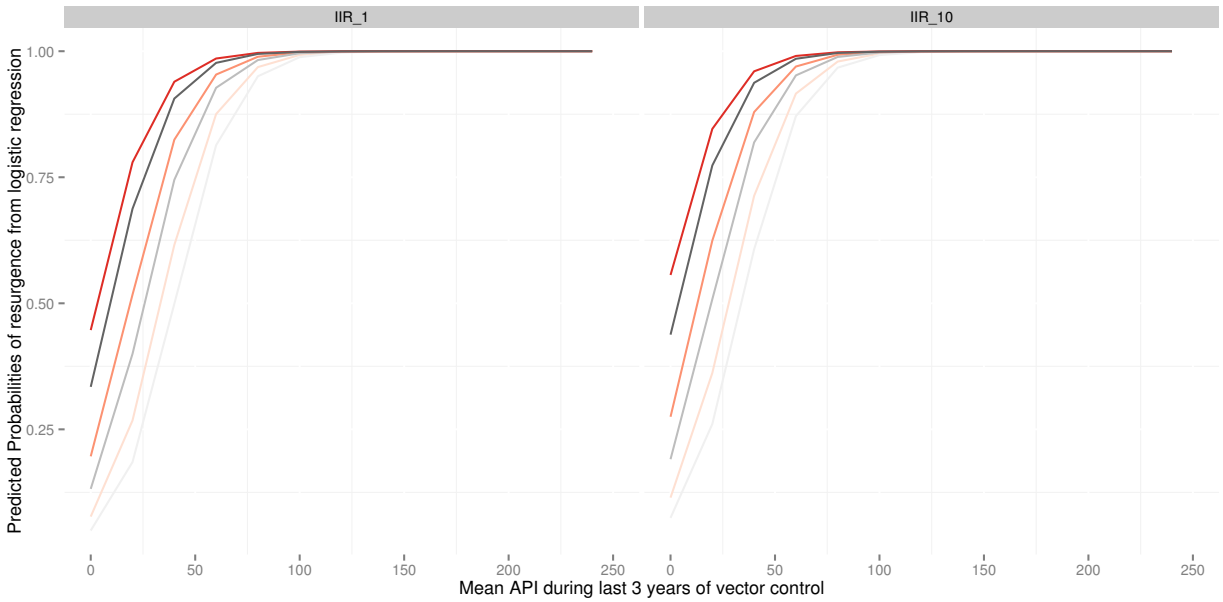

Figure 9: Predicted probabilities of resurgence based on regression results in Table 8. Darker lines represent increasing EIR (0.1, 1, 2), while grey lines represent Active surveillance coverage of 1% per quarter and red lines represent Active surveillance coverage of 10% per quarter. All slopes here are for ITN coverage of 80%, case management coverage of 50% and using the base model variant.

4.3 Regression results: Kenya

In order to estimate the impact of various predictors on the probability of resurgence and severity of resurgence following scale back of vector control in a multivariate framework, we applied logistic and linear regression using the input parameters, and malaria outcomes during vector control, of each simulation as predictors and the occurrence post-withdrawal as the outcome. The results are summarized in Table 8.

These results indicate that most parameters which were significant in bivariate analysis retained important predictive vale for the probability of a resurgence in multivariate analysis. Overall model results reinforce the importance of pre-intervention EIR, case management coverage, active surveillance coverage, infection importation and the level of control success during vector control deployment as major driving factors in predicting the probability of resurgence after withdrawal.

These logistic regression model results can be used to summarize the predicted probability of a resurgence occurring with varying levels of input parameters. Figure 9 shows the predicted probability of resurgence at varying levels of API, IIR, EIR and active surveillance coverage for the base model variant.

The predicted probability of resurgence is generally high for most parameter combinations and only falls below 0.25 for a set of simulations in which pre-intervention EIR was less than 1, IIR was 1 per 1,000 per year, mean API during vector control deployment was below 25 per 1,000 persons per year and there was some level of active surveillance. While the definition of a safe probability of resurgence would need to be defined for each particular setting, it is unlikely that a probability of resurgence greater than 0.25 would fall under this definition.

In order to estimate the effects of the various parameters on the severity of resurgence following vector control withdrawal we also used the proxy,

$$\text{Mean API}_{\text{After VC WD}} - \text{Mean API}_{\text{End VC}},$$

for the linear regression. Table 9 shows the results of this regression analysis.

Table 8: Logistic regression of input model parameters on resurgence

	Dependent variable:
	Resurgence
Mean API During VC (per 1000)	1.077***
	(1.072, 1.082)
Case Management Cov.	0.021***
	(0.019, 0.023)
EIR	3.304***
	(3.239, 3.371)
(10x) Active Surv. Cov.	0.590***
	(0.573, 0.606)
0.2 ITN	0.151***
	(0.135, 0.169)
0.5 ITN	0.066***
	(0.058, 0.074)
0.8 ITN	0.040***
	(0.035, 0.045)
IIR 1	10.492***
	(9.858, 11.171)
IIR 10	16.272***
	(15.093, 17.547)
R0063	0.839***
	(0.751, 0.938)
R0065	0.443***
	(0.395, 0.497)
R0068	0.798***
	(0.714, 0.891)
R0111	0.870**
	(0.778, 0.972)
R0115	0.620***
	(0.554, 0.693)
R0121	1.041
	(0.932, 1.162)
R0125	1.362***
	(1.221, 1.519)
R0131	1.349***
	(1.209, 1.505)
R0132	1.865***
	(1.672, 2.080)
R0133	1.242***
	(1.114, 1.386)
R0670	1.065
	(0.954, 1.189)
R0674	2.535***
	(2.273, 2.828)
R0678	3.175***
	(2.846, 3.542)
Constant	1.295***
	(1.127, 1.487)
Observations	99,977
Log Likelihood	−27,763.340
Akaike Inf. Crit.	55,572.680

Note: *p<0.1; **p<0.05; ***p<0.01

Table 9: Linear regression of input model parameters on severity of resurgence

	Dependent variable:
	Severity
Case Management Coverage	-22.556^{***}
	$(-24.297, -20.814)$
EIR	25.159^{***}
	(24.916, 25.403)
(10x) Active Surv. Cov.	-22.664^{***}
	$(-23.213, -22.115)$
0.2 ITN	114.327^{***}
	(113.115, 115.538)
0.5 ITN	92.436^{***}
	(91.225, 93.647)
0.8 ITN	82.356^{***}
	(81.145, 83.568)
IIR 1	13.891^{***}
	(12.841, 14.940)
IIR 10	42.480^{***}
	(41.431, 43.529)
R0063	-6.729^{***}
	$(-8.996, -4.462)$
R0065	-9.763^{***}
	$(-12.029, -7.497)$
R0068	-13.066^{***}
	$(-15.332, -10.801)$
R0111	-0.152
	$(-2.418, 2.114)$
R0115	-3.142^{***}
	$(-5.407, -0.876)$
R0121	1.162
	$(-1.103, 3.428)$
R0125	7.219^{***}
	(4.953, 9.485)
R0131	3.641^{***}
	(1.376, 5.907)
R0132	9.744^{***}
	(7.478, 12.010)
R0133	4.068^{***}
	(1.802, 6.334)
R0670	2.115^{*}
	$(-0.150, 4.381)$
R0674	18.523^{***}
	(16.258, 20.789)
R0678	19.057^{***}
	(16.791, 21.323)
Constant	-84.231^{***}
	$(-86.380, -82.082)$
Observations	99,977
R^2	0.489
Adjusted R^2	0.489
Residual Std. Error	69.086 (df = 99955)
F Statistic	$4{,}558.459^{***}$ (df = 21; 99955)
Note:	*p<0.1; **p<0.05; ***p<0.01

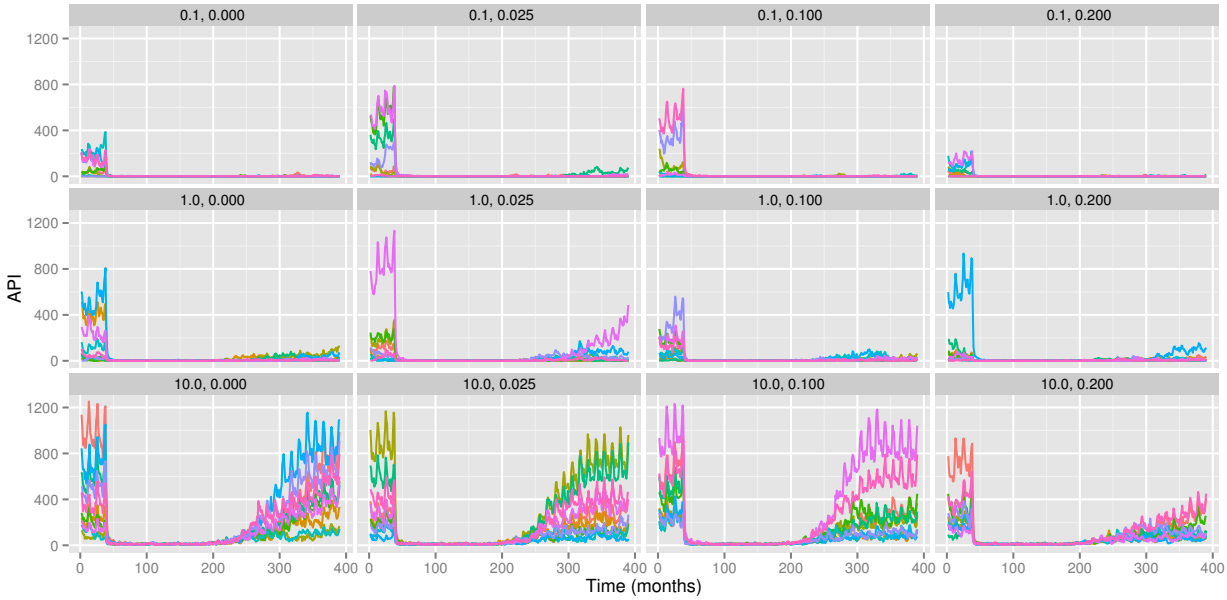

Figure 10: OpenMalaria simulation results for API per 1,000 per annum (Solomon Islands scenario) with an annual pre-intervention EIR of 0.1, case management coverage of 80%, and LLIN coverage of 80% during the period of vector control implementation. Each chart shows simulations results for varied levels of the infection importations rate and active surveillance (through quarterly mass screening and treatment (MSAT) coverage). These values are shown just above each chart in the form (IIR per thousand per year, proportion of population tested per quarter). Colors of lines within the chart represent various simulation runs with differing random seeds (thus capturing stochastic uncertainty). API is the annual parasite incidence computed at each time step and the x-axis is in months. LLINs are distributed at months 36, 72, 108, 144. Increased active surveillance starts immediately coincident with the last distribution of vector control.

4.4 Descriptive results of OpenMalaria simulation outputs: Solomon Islands Context

Simulation outputs allowed for the calculation of the time course of API, ABER and FOI in the Solomon Islands context. The results for API of some sample simulations are shown in Figure 10. Results of a subset of simulations for ABER are shown in Figure 11. Figure 12 shows the results of simulations of FOI for a subset of relevant simulation outputs.

Descriptive results are shown here in Tables 10–15 for elimination and resurgence by various input parameters. Most simulations (65%) resulted in "elimination" during vector control roll-out. However, a similar fraction (61%) of simulations showed resurgence after vector control withdrawal (Table 10). When results for resurgence and elimination were examined in bivariate analysis for background characteristics of simulation, occurrence of a resurgence was statistically significantly associated with infection importation rate, input EIR, active surveillance coverage, case management coverage, and the level of vector control coverage achieved and model variant (Tables 11–16). Elimination was associated with level of vector control coverage achieved, case management coverage, infection importation rate, input EIR and model variant (Tables 11–16).

Overall, there were 100,000 successfully completed simulations. In the majority of simulations (65%) the level of malaria transmission during vector control deployment met the criteria for elimination during vector control deployment. The majority of simulations (61%) also resulted in a resurgence after vector control withdraw (Table 10). Table 10 shows the proportion of simulations which resulted in elimination

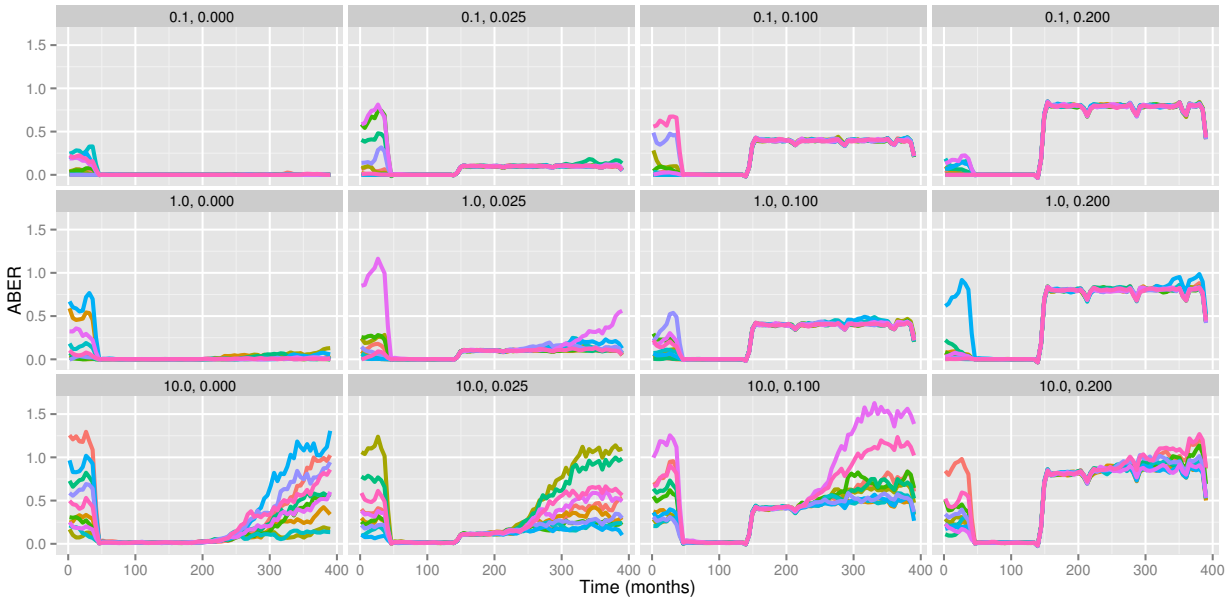

Figure 11: OpenMalaria simulation results for ABER (Solomon Islands scenario) with an annual pre-intervention EIR of 0.1, case management coverage of 80%, and LLIN coverage of 80% during the period of vector control implementation. Each chart shows simulations results for varied levels of the infection importations rate and active surveillance (through quarterly mass screening and treatment (MSAT) coverage). These values are shown just above each chart in the form (IIR per thousand per year, proportion of population tested per quarter). Colors of lines within the chart represent various simulation runs with differing random seeds (thus capturing stochastic uncertainty). ABER is the annual blood examination rate (smoothed to remove the visual effects of widely varying ABER between time periods with quarterly MSAT surveys) and the x-axis is in months. LLINs are distributed at months 36, 72, 108, 144. Increased active surveillance starts immediately coincident with the last distribution of vector control.

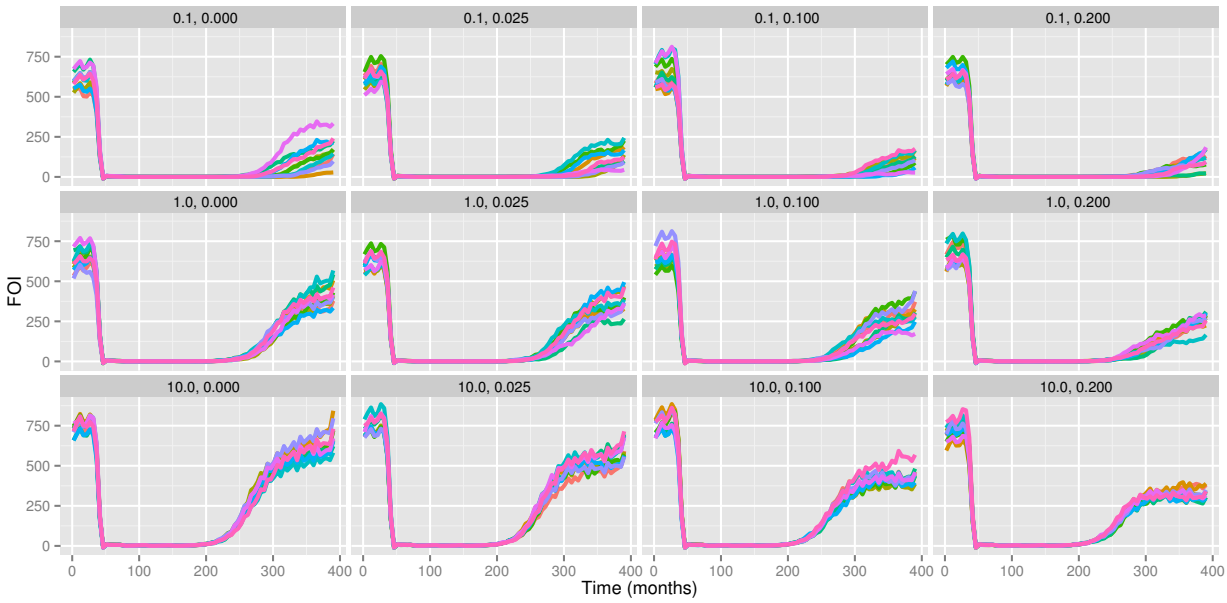

Figure 12: OpenMalaria simulation results for mFOI per 1,000 per annum (Solomon Islands scenario) with an annual pre-intervention EIR of 1, case management coverage of 80%, and LLIN coverage of 80% during the period of vector control implementation. Each chart shows simulations results for varied levels of the infection importations rate and active surveillance (through quarterly mass screening and treatment (MSAT) coverage). These values are shown just above each chart in the form (IIR per thousand per year, proportion of population tested per quarter). Colors of lines within the chart represent various simulation runs with differing random seeds (thus capturing stochastic uncertainty). mFOI is the molecular force of infection per 1,000 people per year and the x-axis is in months. LLINs are distributed at months 36, 72, 108, 144. Increased active surveillance starts immediately coincident with the last distribution of vector control.

and resurgence.

Variable	**Levels**	$\mathbf{n}_0$	$\%_0$	$\mathbf{n}_1$	$\%_1$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	35178	100.0	0	0.0	35178	35.2
	1	0	0.0	64822	100.0	64822	64.8
$p < 0.0001$	all	35178	100.0	64822	100.0	100000	100.0
Resurgence	0	1971	5.6	36664	56.6	38635	38.6
	1	33207	94.4	28158	43.4	61365	61.4
$p < 0.0001$	all	35178	100.0	64822	100.0	100000	100.0

Table 10: Simulation outputs for elimination and resurgence

Increasing coverage of ITNs during vector control deployment was associated with increased probabilities of elimination and as well as reduced probabilities of resurgence (Table 11).

Variable	**Levels**	$\mathbf{n}_0$	$\%_0$	$\mathbf{n}_{0.2}$	$\%_{0.2}$	$\mathbf{n}_{0.5}$	$\%_{0.5}$	$\mathbf{n}_{0.8}$	$\%_{0.8}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	23953	95.8	9523	38.1	1671	6.7	31	0.1	35178	35.2
	1	1037	4.2	15467	61.9	23359	93.3	24959	99.9	64822	64.8
$p < 0.0001$	all	24990	100.0	24990	100.0	25030	100.0	24990	100.0	100000	100.0
Resurgence	0	1226	4.9	9532	38.1	13155	52.6	14722	58.9	38635	38.6
	1	23764	95.1	15458	61.9	11875	47.4	10268	41.1	61365	61.4
$p < 0.0001$	all	24990	100.0	24990	100.0	25030	100.0	24990	100.0	100000	100.0

Table 11: Simulation outputs for elimination and resurgence in terms of ITN coverage during vector control (Solomon Islands)

Changes in active surveillance coverage across the range tested was not statistically significantly related to the probability of elimination or resurgence. Though increasing active surveillance coverage did show a downward trend. Since active surveillance was not deployed during the period of vector control in these simulations the lack of any association with elimination during vector control is expected (Table 12).

Variable	**Levels**	$\mathbf{n}_0$	$\%_0$	$\mathbf{n}_{0.025}$	$\%_{0.025}$	$\mathbf{n}_{0.1}$	$\%_{0.1}$	$\mathbf{n}_{0.2}$	$\%_{0.2}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	8873	35.2	8616	35.3	8839	35.1	8850	35.1	35178	35.2
	1	16327	64.8	15784	64.7	16361	64.9	16350	64.9	64822	64.8
$p = 0.95$	all	25200	100.0	24400	100.0	25200	100.0	25200	100.0	100000	100.0
Resurgence	0	8570	34.0	8639	35.4	10067	40.0	11359	45.1	38635	38.6
	1	16630	66.0	15761	64.6	15133	60.0	13841	54.9	61365	61.4
$p < 0.0001$	all	25200	100.0	24400	100.0	25200	100.0	25200	100.0	100000	100.0

Table 12: Simulation outputs for elimination and resurgence in terms of active surveillance coverage (Solomon Islands)

Changes in the level of case management coverage were associated with differences in both the probability of elimination and resurgence (Table 13).

Variable	**Levels**	$\mathbf{n}_{0.2}$	$\%_{0.2}$	$\mathbf{n}_{0.5}$	$\%_{0.5}$	$\mathbf{n}_{0.8}$	$\%_{0.8}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	13358	39.8	11292	34.4	10528	31.3	35178	35.2
	1	20242	60.2	21508	65.6	23072	68.7	64822	64.8
$p < 0.0001$	all	33600	100.0	32800	100.0	33600	100.0	100000	100.0
Resurgence	0	9818	29.2	13051	39.8	15766	46.9	38635	38.6
	1	23782	70.8	19749	60.2	17834	53.1	61365	61.4
$p < 0.0001$	all	33600	100.0	32800	100.0	33600	100.0	100000	100.0

Table 13: Simulation outputs for elimination and resurgence in terms of case management coverage (Solomon Islands)

Pre-intervention EIR was strongly associated with probabilities of both elimination and resurgence. These associations showed trends in the expected directions with elimination much less likely to occur at higher input EIRs and resurgence much more likely to occur at higher baseline EIRs (Table 14).

Variable	**Levels**	$\mathbf{n}_{0.1}$	$\%_{0.1}$	$\mathbf{n}_{0.5}$	$\%_{0.5}$	$\mathbf{n}_{1}$	$\%_{1}$	$\mathbf{n}_{2}$	$\%_{2}$	$\mathbf{n}_{5}$	$\%_{5}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	4125	20.6	5031	25.2	5916	29.6	8432	42.2	11674	58.4	35178	35.2
	1	15875	79.4	14969	74.8	14084	70.4	11568	57.8	8326	41.6	64822	64.8
$p < 0.0001$	all	20000	100.0	20000	100.0	20000	100.0	20000	100.0	20000	100.0	100000	100.0
Resurgence	0	13779	68.9	10079	50.4	7809	39.0	5292	26.5	1676	8.4	38635	38.6
	1	6221	31.1	9921	49.6	12191	61.0	14708	73.5	18324	91.6	61365	61.4
$p < 0.0001$	all	20000	100.0	20000	100.0	20000	100.0	20000	100.0	20000	100.0	100000	100.0

Table 14: Simulation outputs for elimination and resurgence in terms of input entomological inoculation rate (Solomon Islands)

Infection Importation Rate (IIR) was significantly associated with the probability of resurgence and elimination (Table 15).

Variable	**Levels**	$\mathbf{n}_{0.1}$	$\%_{0.1}$	$\mathbf{n}_{1}$	$\%_{1}$	$\mathbf{n}_{10}$	$\%_{10}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	12319	37.0	11866	35.6	10993	33.0	35178	35.2
	1	21001	63.0	21454	64.4	22367	67.0	64822	64.8
$p < 0.0001$	all	33320	100.0	33320	100.0	33360	100.0	100000	100.0
Resurgence	0	19522	58.6	11849	35.6	7264	21.8	38635	38.6
	1	13798	41.4	21471	64.4	26096	78.2	61365	61.4
$p < 0.0001$	all	33320	100.0	33320	100.0	33360	100.0	100000	100.0

Table 15: Simulation outputs for elimination and resurgence in terms of infection importation rate per 1,000 per annum (Solomon Islands)

Model variant was also significantly associated with the probability of resurgence and elimination (Table 16).

Variable	Levels	n_{base}	$\%_{base}$	n_{R0063}	$\%_{R0063}$	n_{R0065}	$\%_{R0065}$	n_{R0068}	$\%_{R0068}$	n_{R0111}	$\%_{R0111}$	n_{R0115}	$\%_{R0115}$	n_{R0121}	$\%_{R0121}$	n_{R0125}	$\%_{R0125}$	n_{R0131}	$\%_{R0131}$	n_{R0132}	$\%_{R0132}$	n_{R0133}	$\%_{R0133}$	n_{R0670}	$\%_{R0670}$	n_{R0674}	$\%_{R0674}$	n_{R0678}	$\%_{R0678}$	n_{all}	$\%_{all}$
Elimination	0	2604	36.5	2866	40.1	2495	34.9	2474	34.6	2594	36.3	2341	32.8	2557	35.8	2340	32.8	2423	33.9	2355	33.0	2316	32.4	2480	34.7	2659	37.2	2674	37.5	35178	35.2
	1	4541	63.5	4279	59.9	4645	65.1	4671	65.4	4546	63.7	4804	67.2	4588	64.2	4800	67.2	4722	66.1	4785	67.0	4824	67.6	4665	65.3	4486	62.8	4466	62.5	64822	64.8
$p < 0.0001$	all	7145	100.0	7145	100.0	7140	100.0	7145	100.0	7140	100.0	7145	100.0	7145	100.0	7140	100.0	7145	100.0	7140	100.0	7140	100.0	7145	100.0	7145	100.0	7140	100.0	100000	100.0
Resurgence	0	2920	40.9	3059	42.8	3409	47.8	3117	43.6	2937	41.1	3050	42.7	2865	40.1	2532	35.5	2586	36.2	2364	33.1	2563	35.9	2785	39.0	2271	31.8	2177	30.5	38635	38.6
	1	4225	59.1	4086	57.2	3731	52.2	4028	56.4	4203	58.9	4095	57.3	4280	59.9	4608	64.5	4559	63.8	4776	66.9	4577	64.1	4360	61.0	4874	68.2	4963	69.5	61365	61.4
$p < 0.0001$	all	7145	100.0	7145	100.0	7140	100.0	7145	100.0	7140	100.0	7145	100.0	7145	100.0	7140	100.0	7145	100.0	7140	100.0	7140	100.0	7145	100.0	7145	100.0	7140	100.0	100000	100.0

Table 16: Simulation outputs for elimination and resurgence in terms of Model Variant (Solomon Islands Vector Parametrization). Details of the models variants are provided in [18].

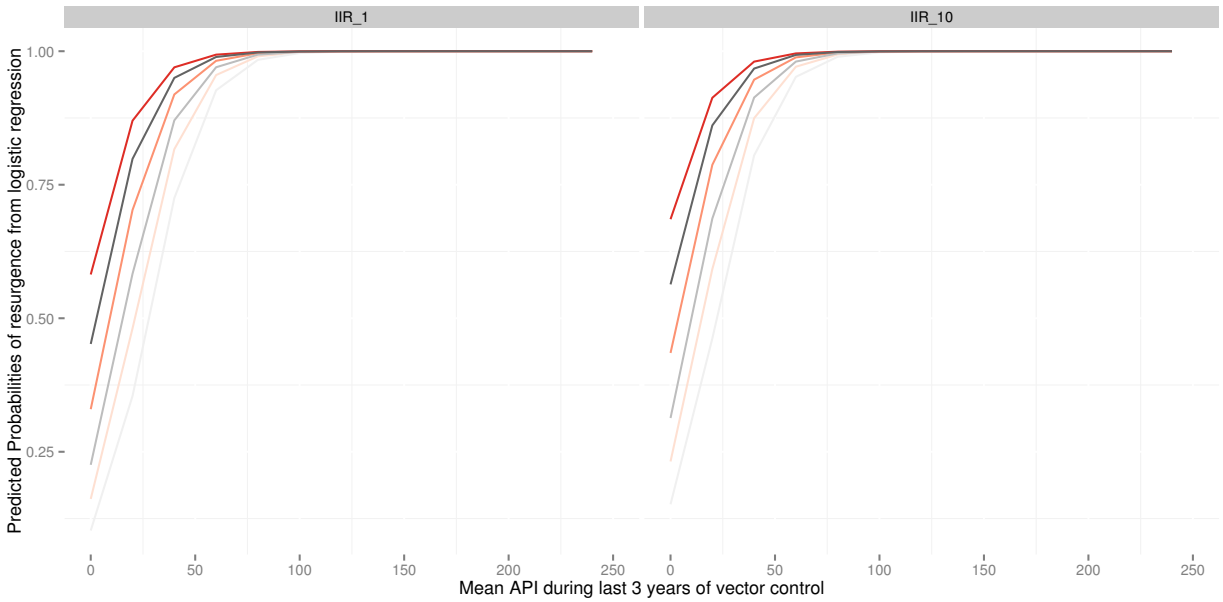

Figure 13: Predicted probabilities of resurgence based on regression results in Table 17 (Solomon Islands Scenario). Darker lines represent increasing EIR (0.1, 1, 2), while grey lines represent Active surveillance coverage of 1% per quarter and red lines represent Active surveillance coverage of 10% per quarter. All slopes here are for ITN coverage of 80%, Case management coverage of 50% and the base model variant.

4.5 Regression results: Solomon Islands

We applied logistic and linear regression using input parameters, and malaria outcomes during vector control interventions, of each simulation as predictors and the probability of resurgence post withdrawal of vector control as the outcome for logistic regression. Similarly we used the severity of resurgence for the outcome in the linear regression as previously defined for the analysis of the Kenya simulations. The results are summarized in Tables 17 & 18.

These results indicate that most parameters which were significant in bivariate analysis retained important predictive vale for the probability of a resurgence in multivariate analysis. Overall model results reinforce the importance of pre-intervention EIR, case management coverage, active surveillance coverage, infection importation and the level of control success during vector control deployment as major driving factors in predicting the probability of resurgence after withdrawal.

These logistic regression model results can be used to summarize the predicted probability of a resurgence occurring with varying levels of input parameters. Figure 13 shows the predicted probability of resurgence at varying levels of API, IIR, EIR and Active Surveillance coverage for the base model variant.

The predicted probability of resurgence is generally high for most parameter combinations and only falls below 0.25 for a set of simulations in which input EIR was less than 1, IIR was 1 per 1,000 per year, mean API during vector control deployment was below 25 per person per year and there was some level of active surveillance. While the definition of a safe probability of resurgence should be defined by local tolerance to risk and expected severity, it is unlikely that a probability of resurgence greater than 0.25 would fall under this definition.

Table 17: Logistic regression of input model parameters on resurgence (Solomon Islands)

	Dependent variable:	
	Resurgence	
Mean API During VC (per 1000)	1.082***	
	(1.077, 1.086)	
Case Management Cov.	0.038***	
	(0.035, 0.042)	
EIR	2.830***	
	(2.776, 2.885)	
(10x) Active Surv. Cov.	0.559***	
	(0.544, 0.574)	
0.2 ITN	0.262***	
	(0.232, 0.296)	
0.5 ITN	0.140***	
	(0.123, 0.159)	
0.8 ITN	0.093***	
	(0.081, 0.106)	
IIR 1	9.840***	
	(9.292, 10.425)	
IIR 10	15.403***	
	(14.305, 16.587)	
R0063	0.363***	
	(0.326, 0.403)	
R0065	0.256***	
	(0.229, 0.285)	
R0068	0.181***	
	(0.162, 0.202)	
R0111	0.284***	
	(0.255, 0.316)	
R0115	0.343***	
	(0.308, 0.382)	
R0121	0.310***	
	(0.279, 0.345)	
R0125	0.387***	
	(0.348, 0.430)	
R0131	0.626***	
	(0.562, 0.696)	
R0132	0.585***	
	(0.526, 0.650)	
R0133	0.783***	
	(0.704, 0.871)	
R0670	0.603***	
	(0.542, 0.671)	
R0674	0.430***	
	(0.386, 0.478)	
R0678	0.865***	
	(0.778, 0.963)	
Constant	2.843***	
	(2.455, 3.292)	
Observations		100,000
Log Likelihood	26	−29,467.250
Akaike Inf. Crit.		58,980.500
Note:		*p<0.1; **p<0.05; ***p<0.01

Table 18: Linear regression of input model parameters on severity of resurgence (Solomon Islands)

	Dependent variable:
	Severity
Case Management Coverage	-20.783^{***}
	$(-22.703, -18.864)$
EIR	28.872^{***}
	$(28.603, 29.140)$
(10x) Active Surv. Cov.	-27.918^{***}
	$(-28.524, -27.313)$
0.2 ITN	125.793^{***}
	$(124.457, 127.128)$
0.5 ITN	114.914^{***}
	$(113.579, 116.249)$
0.8 ITN	104.205^{***}
	$(102.869, 105.540)$
IIR 1	17.617^{***}
	$(16.461, 18.774)$
IIR 10	49.822^{***}
	$(48.666, 50.978)$
R0063	-23.737^{***}
	$(-26.235, -21.239)$
R0065	-30.010^{***}
	$(-32.509, -27.512)$
R0068	-32.958^{***}
	$(-35.456, -30.459)$
R0111	-36.839^{***}
	$(-39.337, -34.341)$
R0115	-24.585^{***}
	$(-27.084, -22.087)$
R0121	-29.339^{***}
	$(-31.837, -26.841)$
R0125	-22.064^{***}
	$(-24.562, -19.566)$
R0131	-16.834^{***}
	$(-19.332, -14.335)$
R0132	-18.154^{***}
	$(-20.652, -15.655)$
R0133	-10.975^{***}
	$(-13.473, -8.476)$
R0670	-17.170^{***}
	$(-19.669, -14.672)$
R0674	-21.107^{***}
	$(-23.605, -18.609)$
R0678	-0.092
	$(-2.590, 2.406)$
Constant	-77.644^{***}
	$(-80.013, -75.274)$
Observations	100,000
R^2	0.515
Adjusted R^2	0.515
Residual Std. Error	27 76.167 (df = 99978)
F Statistic	$5{,}051.379^{***}$ (df = 21; 99978)
Note:	*p<0.1; **p<0.05; ***p<0.01

5 Discussion and Limitations

We conducted Monte Carlo simulations to examine precision and bias associated with IIR measurement and ABER measurement; and a full factorial simulation experiment using the OpenMalaria simulation platform to identify determinants of potentially safe withdrawal of vector control. Overall the results indicate that only in a small minority of situations could withdrawal of vector control be expected to be safe (with a low probability of resurgence). These situations are characterized by low historic EIRs, low importation rates, highly successful vector control activities and high case management and surveillance coverage. In addition, we find that ABER and the infection importation rate may be useful indicators for measuring importation risk (or vulnerability) and surveillance coverage. While both have significant potential for bias in general the largest biases and the most important effects of their limited precision are likely to either result in conservative decisions, such as maintaining vector control, or to be of a small magnitude at relevant levels of the indicators. However, care should be taken to ensure that these indicators are measured in spatially (geographically) and temporally (seasonally) representative manners.

This study relies on Monte Carlo simulation and a stochastic agent-based simulation model of malaria epidemiology and immunology. While mathematical modelling techniques have been highly useful in malaria epidemiology and control, as well as program planing, they contain inherent simplifications of the real world. Model structures and assumptions can result in biases inherent in the models and limit their use for predicting real world outcomes. In particular, OpenMalaria does not explicitly model spatial dynamics and thus cannot simulate targeting interventions around index cases (such as focal vector control or screening and treatment) or control based on other local circumstantial knowledge. Such focal strategies are likely to be an important part of scaling back from universal coverage of vector control interventions in some situations and the results in this document do not explicitly capture this possibility.

We have chosen a particular definition of resurgence for the analysis of the simulation results in this experiment. We used this definition, both to be consistent with previous work [11], but also because it is strict and consistent with re-establishment of endemic transmission. Other definitions may produce different conclusions. One consequence of using a definition based on IIR is that higher IIR scenarios can experience significantly more cases without them being defined as resurgent. Another aspect of the definition is that it is limited to a defined temporal period. It is possible that the simulations we conducted that did not show resurgence would have shown resurgence in the months or years following the end of our simulation, although this is likely mitigated by the long length of monitoring (20 years) after the withdrawal of vector control in these simulations.

Finally these simulations assume that the receptivity of an area is stable. As such they do not include the potential effects of secular changes such as improved housing, general economic development, etc. on the likelihood of resurgence. Such changes might occur despite, or possibly as a consequence of changes in malaria transmission during vector control deployment [20].

While these simulation results suggest that there are a set of scenarios in which it is possible to withdraw vector control without a significant probability of resurgence, they suggest that these situations are limited. Furthermore, there is no guarantee that resurgence will not occur even when probability is low. Therefore, it is crucial that programs maintain surveillance coverage (both clinical as well as entomological) not only for the benefits related to preventing resurgence, but also so that malaria control and elimination programs which choose to scale back vector control are aware and prepared to make rapid responses should resurgence occur.

6 Conclusion

In areas with ongoing local malaria transmission the scale-back of vector control is likely to lead to resurgence and a return to pre-intervention levels of malaria parasite transmission and disease. The speed and severity of such a resurgence might be exacerbated by high pre-intervention malaria transmission, poor vector control coverage during interventions, and low case management coverage.

In areas in which local malaria transmission has been substantially reduced or interrupted, the scale-back of vector control is also associated with a high probability of resurgence for the vast majority of situations. The conditions which hold a low probability of resurgence include having a low pre-intervention EIR, high case management coverage, low importation and very successful control of transmission during intervention. The degree to which programs can safely plan to withdraw or scale back vector control must be determined by the tolerance of a program for risk of resurgence and its expected severity. When tolerance for the risk of resurgence is low, few situations would be a priori suitable for vector control withdrawal. If a 20% probability of resurgence is considered to be a threshold for safety, only scenarios with a pre-intervention EIR below 1 and moderate case management coverage (>50%) with successful achievement of universal vector control coverage (>80%) during the intervention phase were considered safe for withdrawal. This held for both Solomon Islands and Kenyan scenarios.

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