Application of mathematical modeling for malaria control decision-making in settings of varying transmission intensity

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It is not just about deciding yes or no… but about deciding on one of many possible strategies based on an admittedly incomplete understanding of an extremely complex system. Accordingly, providing a clear recommendation for a way forward is far from trivial.

Reto Knutti

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Summary

Background

Planning for the control of Plasmodium falciparum malaria at the population level demands models of malaria epidemiology that provide realistic quantitative prediction of likely epidemiological outcomes of a wide range of control strategies. This project applies mathematical modeling parameterized both generally and with site-specific field data to better understand transmission dynamics of malaria across sites with varying transmission intensity and seasonality, primarily the highlands of western Kenya and in the lowlands of Zambia's Southern Province. Simulation results explore possible epidemiological scenarios for malaria in the presence and absence of a mix of control interventions, and for different amounts and patterns of seasonality of transmission. Together with a cost effectiveness analysis, results form the basis of recommendations for control programs.

Methods

Individual-based stochastic models of malaria epidemiology were developed by the Swiss Tropical and Public Health Institute (Swiss TPH). To provide the site-specific parameters needed to fit the models to the study areas data on existing entomological, demographic, intervention deployment and health systems was gathered from field studies conducted by collaborating institutes and a literature review. Model simulations were run on an ensemble of models with multiple random seeds on the OpenMalaria simulator. Simulation outputs were compared to the observed data from the study areas in order to assess the validity of the model and a sensitivity analysis was conducted to address uncertainty. The model was then used to predict the impact of different combinations of malaria control interventions, and the impact of different seasonal transmission patterns, on impact measures.

Results and Significance

The models were able to simulate the transmission patterns of malaria in the study areas of western Kenyan highlands and Zambia lowlands and gain insight into the potential impact of malaria control interventions currently being un- or under- utilized in these areas. Despite the ability of mathematical modeling to be used to translate between measures of malaria

transmission and indicators of disease burden in areas where sparse data renders evidence-based programmatic decision-making challenging, these models remain largely inaccessible to program managers. Results from such models can provide public health officials with accurate estimates of transmission, by seasonal pattern, that are necessary for assessing and tailoring malaria control and elimination programs to specific settings.

1. Introduction

1.1 Current status of malaria control and elimination and burden of disease

Morbidity and mortality due to malaria has decreased significantly over the past decade. In fact, half of malaria endemic countries are on track to meet their target of a 75% reduction in malaria cases by 2015 compared to 2000 [1]. This progress can be attributed in large part due to the scale-up of commodities-based interventions such as vector control with long-lasting insecticide-treated bednets (LLINs), and highly effective malaria treatment in the form of Artimisinin combination therapies (ACTs), facilitated by a steep increase in global funding for malaria control over the same period [1]. As a result of the achievement of high LLIN coverage levels, many malaria endemic countries are focusing on the question of what is the next step in order to further drive down transmission and prevalence.

Successful malaria control remains challenging due to the complex dynamics between the human stages of the *Plasmodium falciparum* parasite, the interaction of the *Anopheles* mosquito with the natural environment, and inequities in access to malaria prevention and treatment. These factors, coupled with lessons learned from the Global Malaria Eradication Program in the mid-20th century, make it clear that malaria control requires a holistic, context-specific response with a strong surveillance component in order to be successful. While the threats of drug and insecticide resistance are important and identifying mitigation strategies critical, of greater short term concern is the gap between available financial resources and what is required for effective global malaria control. The Roll Back Malaria Partnership (RBM) estimates a gap of US$3.8 billion between 2013 and 2015 alone in order to ensure sufficient commodities to achieve universal coverage [2]. Without the certainty of sustaining the recently made gains in malaria control achieved by availability of vector control interventions, and with the goal of elimination in many minds, it is increasingly important to identify the most cost effective combination of malaria control intervention strategies for a given location.

1.2 Modeling approach: history and methodology

Mathematical modeling was first applied to malaria at the turn of the 20th century with Sir Ronald Ross' attempts to explain the dynamics of malaria prevalence [3]. This was accomplished with a model that focused on the changing densities of susceptible versus infected mosquitoes and susceptible versus infected human hosts and identified population thresholds for eliminating malaria rather than the need to eliminate the entire mosquito population in a given area [3]. By the 1950's the concept of the basic reproduction number (R_0) in terms of malaria (the average number of secondary cases produced by an infectious index case) was defined and applied by Macdonald [4], showing that an intervention to reduce the mosquito population (e.g. larviciding) has less of an impact on R_0 compared to an intervention targeting a reduction in the biting rate (e.g. use of bed nets) and the mortality rate of adults.

By the end of the 20th century the goal of modeling of malaria evolved into bridging the gap between theoretical simulations and decision-making by giving malaria control program managers the tools they need to decide on the right mix of control interventions in their particular transmission context. Epidemiological, statistical, spatial, and mathematical models have not only attempted to predict areas at risk of malaria, but to describe morbidity, mortality, cost–effectiveness, and effectiveness of programs following the large-scale roll out of malaria control programs in sub-Saharan Africa[5] [6] [7] [8] [9] [10] [11] [12]. Improvements on the Ross and Macdonald models beginning with the Garki project in the 1970's incorporate a latent period in the mosquito portion of the model as well as super-infection and acquired partial immunity in the human portion of the model improving the estimates of prevalence of infectious mosquitoes and age-specific patterns of infection [13] [5]. These models are population-based and deterministic where non-linear relationships between factors determine whether individuals and mosquitoes are susceptible, infected or infectious resulting in approximations of disease dynamics in large populations. While they continue to be useful in simulating malaria prevalence in endemic areas, these types of models are less useful for modeling heterogeneity of infection, super- infection, immunity, and rare events such as death [14].

More recently, the Swiss Tropical and Public Health Institute (Swiss TPH) developed stochastic individual-based models of malaria transmission that focus on simulation of infection in individuals and are able to simulate the impact (cost-effectiveness, clinical and epidemiological) of a range of intervention options for malaria control [15]. These models are part of the larger OpenMalaria project by a team from the Swiss TPH and the Liverpool School of Tropical Medicine (LSTM) with financial support from the Bill & Melinda Gates Foundation which makes the considerable code base written in C++ accessible to the end user through an online wiki. Users are able to carry out predictive simulations either via a downloadable stand-alone program, via the BOINC volunteer computing platform and semi-automated experiment design and analysis, or via a GUI-driven job submission system capable of deploying simulations on different computer resources.

The OpenMalaria project makes use of a general platform for comparing, fitting, and evaluating different models of malaria epidemiology, health systems, economics, and malaria interventions, as well as analyzes the uncertainty associated with sets of model predictions. These individual-based models are able to combine the elements of simulations of acquired partial immunity in individuals based on their age, super-infection, and mortality, which proves difficult in deterministic models. They are also able to simulate seasonality of malaria in a way not done previously.

There remain a few disadvantages to this approach including the numerous simulations that need to be run in order to obtain useful predictions, the requirement of many more inputs than other models, the difficulty in checking the code and slow running speeds for simulations of large populations requiring the use of a volunteer network of computers, and fewer available tools to analyze the simulation outputs. Despite the drawbacks, the stochastic approach results in the incorporation of chance into predictions and more realistic predictions than deterministic models are able to provide. As areas on the fringes of the malaria map approach elimination these models can adequately simulate how and when interruption of transmission can be expected to occur.

1.3 Application of OpenMalaria model

Rationale and strategy for approach

Evidence from a number of field trials has demonstrated the protective efficacy of malaria control interventions (i.e., LLINs, IRS, intermittent preventive treatment of pregnant women (IPTp) and infants (IPTi), use of timely diagnosis and correct treatment), providing the rationale for support of malaria control programs by the Global Fund for AIDS, TB and Malaria (GFATM), the President's Malaria Initiative and other major funding partners. Often overlooked, however, is the limited range of epidemiological environments in which these trials were conducted and the paucity of information on the impact of combinations of these interventions in areas of differing intensities of transmission. Moreover, the ability of malaria control program managers to make decisions about program design is limited by the difficulty of accurately measuring rates of malaria transmission and of monitoring the impact that interventions have on transmission. Such information is critical to enable malaria control professionals to decide on the optimal and most cost-effective malaria control strategies to use across the full range of transmission conditions.

There currently exists a gap in quantifying transmission in areas without data on transmission as measured by the entomological inoculation rate (EIR). By understanding the relationships between malaria indices it becomes possible for models to simulate the likely range of values in areas of differing transmission intensity without data sources all of the key malaria indices. Several study areas are able to provide site-specific malaria transmission rates in low/unstable and moderate transmission settings as well as data on the impact of multiple years of malaria control interventions representing ideal settings for applying models of malaria transmission to translate results into evidence-based decision making for malaria control program managers.

This project addresses the identified gaps by (i) calibrating different malaria indicators broadly across different patterns of seasonality to identify the best way of quantifying transmission for the purposes of specifying the seasonal patterns to drive the existing models, (ii) applying the Swiss TPH-developed individual-based stochastic models of malaria to malaria

transmission consortium (MTC) sites with transmission data to simulate the epidemiologic and economic impact of a range of malaria control strategies, and (iii) providing this information to the community of professionals who help make malaria control decisions both in the study areas and beyond.

1.4 Collaborating partners and study areas

Overview of the Malaria Transmission Consortium (MTC)

The MTC was founded in 2007 in partnership with the University of Notre Dame, the Swiss TPH, the London School of Hygiene and Tropical Medicine (LSHTM), the Liverpool School of Tropical Medicine (LSTM), the Center for Disease Control and Prevention (CDC), the Ifakara Health Institute (IHI), and the Indonesia Malaria Control Program (IMCP) with funding from the Bill and Melinda Gates Foundation in response to calls for innovative and validated methods for monitoring and evaluating large-scale vector control interventions. The overall goal of MTC was to enable operational program managers to achieve optimal implementation of transmission-reducing malaria control techniques by (i) developing meaningful measures of malaria transmission, (ii) assessing the effectiveness of various combinations of specific malaria control techniques under different epidemiological conditions, and (iii) assessing the actual effects on malaria control of some of the more widely observed biological phenomena like vector resistance to insecticides or different patterns of vector behavior.

The MTC strategy was to understand the dynamics of transmission across a range of epidemiological zones in order to (i) determine the value of simple field measures as predictors of this underlying dynamic system, (ii) assess the impact of specific interventions alone or in combination in these zones, and (iii) provide this information publicly to inform the development and implementation of malaria control programs. MTC worked in six nations on two continents with a wide range of epidemiologically distinct patterns of malaria transmission. MTC partner countries include Kenya, Tanzania, Zambia, and Indonesia, in addition to the Solomon Islands and Mali which joined the consortium in 2011.

The role of the Swiss TPH within the consortium was to twofold. Firstly, to produce site-specific stochastic simulation models of the dynamics of malaria, to validate these models by comparing predictions with observed data on impact (epidemiological and entomological), and to use them to predict the likely impact of intervention programs on entomological and epidemiological measures. Secondly, to use these same models to develop a system for predicting patterns and intensity of *P. falciparum* transmission in terms of the seasonal pattern of the EIR and its degree of heterogeneity.

Much of the work contained in this thesis builds on the MTC objectives described above, focusing on Rachuoyno South, a District in the former Nyanza Province in the highlands of western Kenya. This district lies on a "fringe" transmission area between Lake Victoria and the western highlands with altitudes from 1,400-1,600 meters above sea level. Due to the altitude and its associated temperature and rainfall the area supports low endemicity with marked seasonal variations in transmission and seasonal inter-annual variability [16] [17]. Recent evidence suggests the vector composition and biting behavior in the area has changed following sustained coverage of LLINs [18] shifting away from *Anopheles gambiae* and towards vectors biting outdoors and earlier in the evening [19]. The main control methods used today in the epidemic highland areas include mass-distribution of long-lasting insecticide-treated nets (LLINs), annual deployment of IRS using pyrethroids, and prompt and effective treatment of malaria using artemether-lumefantrine (AL) [20] [21].

Faced with potential change in vector population in this area of reduced transmission, and paired with recent entomological and epidemiological studies, a micro-simulation approach was useful at examining the effects of different intervention combinations. Experiment design and parameterization of the OpenMalaria model based on the context of Rachuonyo South District was conducted through collaboration with LSHTM and CDC/Kenya Medical Research Institute (KEMRI), which involved face to face meetings in London and a visit to Kenya which included a presentation to the MTC staff on how the modeling component fit in to the project goals, a workshop on parameterization and experiment design, and observation of the implementation of the 2011 entomological study and general operations of the study area.

Overview of MACEPA & Zambia

The Malaria Control and Evaluation Partnership in Africa (MACEPA), a program at PATH, has partnered with national governments and ministries of health in sub-Saharan Africa to control malaria since 2005. In partnership with the Zambia National Malaria Control Centre (NMCC), the goal in Southern Province, Zambia is to reduce transmission through increased access to diagnostics and treatment, maintenance of high levels of coverage with LLINs and IRS, and a range of surveillance methods [22]. This lowland province borders Lake Kariba and with a population of approximately 250,000 individuals and features a wide range of transmission intensities up to 18.6 infectious bites per person per year [23]. Beginning in 2011 the NMCC is currently piloting a three year test and treat campaign to aid local communities in identifying the levels of malaria and to determine if rigorous community testing and treatment of individuals with positive tests results in marked reduction of community level malaria [24].

Because AL is the first line treatment for malaria in Zambia in addition to being used as the drug of choice for this program, and because the trial design is unable to test all the possible options for roll out of this campaign, MACEPA staff in Atlanta, Washington, DC and Lusaka worked with the Swiss TPH and other modeling groups to assess the effectiveness of different operational strategies of the test and treat campaign. Simulation results and implications for the program were presented at the Zambia National Health Research Conference in Lusaka, Zambia in October 2013 and discussed with MACEPA program staff at a corresponding protocol development meeting for subsequent phases of the test and treat study design.

1.5 Objectives and outline

The goal of this project is to apply individual-based stochastic models of malaria to field sites so as to better understand transmission dynamics of malaria in different settings and to explore possible scenarios with different control interventions and strategies. This is accomplished through the following objectives:

- Investigate to what extent individual-based stochastic models can simulate the dynamics of malaria by applying OpenMalaria to the context discrete geographical areas, in each case adjusted to the measured patterns of transmission, and comparing predictions with data on impact collected from the different sites
- Investigate the likely impact of the current and future potential intervention programs on entomological and epidemiological measures in the study areas by applying simulation results of different intervention combinations to a costing model in order to put the epidemiological impact in the context of longer-term implications for malaria control programs
- Develop an alternative method of quantifying malaria transmission in areas with scarce data by simulating the relationships of malaria indicators across different levels of transmission and patterns of seasonality

Chapter 2 is an opinion piece setting the stage for basing the thesis on transmission estimation. It outlines the argument for why estimating transmission is important in the current state of global malaria control and elimination, demonstrates the role mathematical modeling can play in estimating transmission and the contexts in which it can be most useful, and presents a research agenda to move this approach forward. Parameterization, validation and a sensitivity analysis of the OpenMalaria transmission model based on the context in Rachuonyo South District, an area of low, unstable malaria transmission in the highlands of western Kenya, forms the basis for the content of Chapter 3.

Chapter 4 takes the validated site-specific parameterization described in Chapter 3 and applies the model to an experiment investigating different combinations and implementation strategies of malaria control interventions to determine which could have biggest impact on reducing malaria burden in the study area. An economic model is attached to simulation results providing a cost effectiveness analysis to make results more useful to malaria control program managers in western Kenya. The OpenMalaria transmission model is also applied to an additional site, the Zambia lowlands bordering Lake Kariba. To inform the ongoing development of a field trial, Chapter 5 describes a simulation experiment aimed at determining the

effectiveness of different operational strategies at delivering a test and treat campaign. Adding novel interventions including single low-dose Primaquine and Ivermectin are compared with the current ACT regimen, expanding the available options for human-based interventions in areas with high coverage of vector control interventions.

Because of the challenges with traditional methods of estimating malaria transmission in areas where transmission is low presented in Chapter 3, the methods proposed in Chapter 2 are then applied to an experiment examining the simulated relationships between malaria indicators and across different patterns of seasonality. Chapter 6 proposes a method of estimating transmission based on these simulation results and discusses the impact of seasonality of transmission on findings.

The final chapter places the experiments outlined in the previous thesis chapters in context, and summarizes limitations of and future research opportunities for OpenMalaria. It then discusses the current and potential future role of applied mathematical modeling for informing policy decisions, and the ways through which this role can be achieved by the malaria modeling community.

References

1. WHO: **World Malaria Report 2012.** Geneva: World Health Organization; 2013.

2. RBM: **Roll Back Malaria Annual Report 2012.** Roll Back Malaria Partnership; 2013.

3. Ross R: *The Prevention of Malaria.* London: Murray; 1911.

4. Macdonald G: *Malariology: A comprehensive survey of all aspects of this group of diseases from a global standpoint.* Philadelphia: W.B. Saunders Company; 1957.

5. Molineaux L, Gramiccia G: *The Garki project. Research on the epidemiology and control of malaria in the Sudan savanna of West Africa.* Geneva: World Health Organization; 1980.

6. Dietz K, Molineaux L, Thomas A: **A malaria model tested in the African savannah.** *Bull World Health Organ* 1974, **50:**347-357.

7. Koella JC, Antia R: **Epidemiological models for the spread of anti-malarial resistance.** *Malar J* 2003, **2:**3.

8. Labadin J, C. Kon ML, Juan SFS: **Deterministic Malaria Transmission Model with Acquired Immunity.** In *Proceedings of the World Congress on Engineering and Computer Science 2009; San Francisco, USA*WCECS 2009

9. Craig MH, Sharp BL, Mabaso ML, Kleinschmidt I: **Developing a spatial-statistical model and map of historical malaria prevalence in Botswana using a staged variable selection procedure.** *Int J Health Geogr* 2007, **6:**44.

10. McKenzie FE: **Why model malaria?** *Parasitol Today* 2000, **16:**511-516.

11. Gosoniu L, Vounatsou P, Sogoba N, Smith T: **Bayesian modelling of geostatistical malaria risk data.** *Geospat Health* 2006, **1:**127-139.

12. Brooker S, Clarke S, Njagi JK, Polack S, Mugo B, Estambale B, Muchiri E, Magnussen P, Cox J: **Spatial clustering of malaria and associated risk factors during an epidemic in a highland area of western Kenya.** *Trop Med Int Health* 2004, **9:**757-766.

13. Anderson RM, May RM: *Infectious Diseases of Humans: Dynamics and Control.* Oxford: Oxford university Press; 1991.

14. Macdonald G: *The Epidemiology and Control of Malaria.* London: Oxford University Press; 1957.

15. Smith T, Maire N, Ross A, Penny M, Chitnis N, Schapira A, Studer A, Genton B, Lengeler C, Tediosi F, et al: **Towards a comprehensive simulation model of malaria epidemiology and control.** *Parasitology* 2008, **135:**1507-1516.

16. Kristan M, Abeku TA, Beard J, Okia M, Rapuoda B, Sang J, Cox J: **Variations in entomological indices in relation to weather patterns and malaria incidence in East African highlands: implications for epidemic prevention and control.** *Malar J* 2008, **7:**231.

17. Mabaso ML, Craig M, Ross A, Smith T: **Environmental predictors of the seasonality of malaria transmission in Africa: the challenge.** *Am J Trop Med Hyg* 2007, **76:**33-38.

18. Bayoh MN, Mathias DK, Odiere MR, Mutuku FM, Kamau L, Gimnig JE, Vulule JM, Hawley WA, Hamel MJ, Walker ED: **Anopheles gambiae: historical population decline associated with regional distribution of insecticide-treated bed nets in western Nyanza Province, Kenya.** *Malar J* 2010, **9:**62.

19. Stevenson J, St. Lauernt B, Lobo N, Cooke M, Kahindi S, Oriango R, Harbach R, Cox J, Drakeley C: **Novel vectors of malaria parasite in the western highlands of Kenya [letter].** *Emerg Infect Dis* 2012 Sept, **[serial on the Internet]**.

20. DOMC: **National Guidelines for Diagnosis, Treatment and Prevention of Malaria in Kenya.** (Management DoMCC ed.2006.

21. Fillinger U, Ndenga B, Githeko A, Lindsay SW: **Integrated malaria vector control with microbial larvicides and insecticide-treated nets in western Kenya: a controlled trial.** *Bull World Health Organ* 2009, **87:**655-665.

22. PATH/MACEPA: **Fighting Malaria Today and Tomorrow.** 2013.

23. Kent RJ, Thuma PE, Mharakurwa S, Norris DE: **Seasonality, blood feeding behavior, and transmission of Plasmodium falciparum by Anopheles arabiensis after an extended drought in southern Zambia.** *Am J Trop Med Hyg* 2007, **76:**267-274.

24. PATH/MACEPA: **Malaria Test and Treat Campaign Summary - NMCC Briefing document.** Lusaka, Zambia: PATH/MACEPA; 2013.

2. Estimating malaria transmission through mathematical models

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2.1 Abstract

Evaluating the effectiveness of malaria control interventions on the basis of their impact on transmission is increasingly important as countries move from malaria control to pre-elimination programs. Mathematical modeling can examine relationships between malaria indicators, allowing translation of easily measured data into measures of transmission, and addressing key concerns with traditional methods for quantifying transmission. Simulations show these indicators are statistically correlated, allowing direct comparison of malaria transmission using data collected using different methods across a range of transmission intensities and seasonal patterns. Results from such models can provide public health officials with accurate estimates of transmission, by seasonal pattern, that are necessary for assessing and tailoring malaria control and elimination programs to specific settings.

2.2 From control to elimination: impact on measurement of malaria transmission

Substantial scale up in intervention coverage over the past decade has resulted in large reductions in malaria burden [2], and many malaria programs are considering reorientation towards long-term goals of malaria elimination [3]. Such reorientation requires quantitative measures of malaria transmission, which becomes more difficult as an area approaches malaria elimination. At a time when resources for malaria prevention and research are becoming increasingly scarce on both global and local scales, mathematical modeling can assist malaria control decision-makers by examining the relationship between transmission and more routinely measured indicators for burden of disease, without time- and resource-intense entomological surveys. In addition, models can efficiently explore the drivers behind observed relationships between malaria indicators, such as seasonality and heterogeneities in exposure. This method of estimating transmission can help malaria control decision-makers identify when to change strategy for malaria control interventions.

Overview of the use of models to estimate malaria transmission

Although areas where malaria is endemic are typically divided into categories of transmission such as holo-, hyper-, meso-, and hypoendemic, there is no approach for quantifying transmission, either from mosquitoes to humans or vice versa, that is applicable everywhere [4-6]. Transmission of *Plasmodium falciparum* across years or locations often cannot be compared because of differing indicators or measurement methods.

Mathematical models of malaria have been implemented since the early 20th century [7, 8]. Continuing advances in computing power now enable individual-based stochastic models to describe seasonality of transmission and capture elements of malaria biology, such as acquired partial immunity, superinfection, and impact on mortality, which are challenging to include in deterministic models [9-12]. Both statistical and mathematical models help to explain and make predictions about the dynamics of malaria epidemiology and control. Several reviews examining the range of existing models of malaria transmission have been published in recent years [13-16], and fitting such models statistically to field data is essential if they are to be useful for large-scale prediction.

However, there are always limitations to this approach. Models cannot fit perfectly to the multitude of observed field data owing to the small proportion of parasites, vectors, interventions, and types of acquired immunity in humans that models can cover out of the diversity that exists in the malaria-endemic world [17].In addition, it is unethical to explore directly the within-host and host-vector dynamics that influence prevalence of clinical disease and mortality. Nevertheless, with proper validation, models still provide a rational means of understanding the effects of control interventions on malaria transmission and converting between different measures of transmission.

Challenges of entomological measurement of malaria transmission

Where annual parasite index data are unreliable, entomological measures of transmission collected through mosquito capture, such as the entomological inoculation rate (EIR), are the most common measures of transmission. Despite being widely used, measurement of EIR is practicable only in areas of high transmission [4].

In areas of low transmission, measuring EIR through entomological studies is not feasible because of the difficulty in identifying a sufficient number of sporozoite-positive mosquitoes during months without substantial transmission and in catching sufficient adult mosquitoes in areas where mosquito abundance is non-uniform [4]. In addition, mosquito collection is often implemented only during the rainy seasons that usher in peaks of malaria transmission, creating gaps in seasonal transmission data [6, 18].

However, this does not mean data on mosquito bionomics are not needed. In fact they are essential for planning which vector control interventions are applicable in particular

settings. For example, studies conducted in the Kilombero valley of rural Tanzania [19] show that, following increased use of insecticide-treated nets (ITNs), vector biting behavior shifted outdoors and earlier in the evening. With detailed entomological surveys malaria control professionals are able to use this information to tailor vector control interventions to the changing context of an area.

Alternative measures of malaria transmission

It is possible to measure malaria disease burden in a location through indicators such as case incidence, hospitalization, or mortality rate [17]. Nevertheless, these depend on the performance of the health system and on the immune status of the population, both of which are likely to change over the course of an intervention program, making them unsuitable for directly monitoring changes over a wide range of transmission intensities. These indicators are only indirectly related to transmission; therefore, more direct indicators must be employed for transmission measurement, or more elaborate methods are needed to translate these into measures of transmission.

Alternative methods such as estimating EIR equivalents via seroconversion rates [20, 21] or calculating force of infection (FOI) by combining information from prevalence and treatment rates [6] are suitable in low-transmission settings. Serological measurements have been employed as an alternative method of measuring transmission [20-23]. This method has been shown to be preferable to entomological methods in areas of low transmission [24]; indeed, serological measurements are mainly useful for monitoring exposure when transmission is very low [25, 26]. However, serology is unable to provide an indication of seasonality of exposure unless estimates are calculated based on samples taken on a monthly basis.

Frequently, the simplest measurable indicator is parasite prevalence derived from population-based household surveys. The rate of acquisition of new infections in a homogenous human population without superinfection is equal to the prevalence divided by the average duration of the infections; this provides a means of estimating FOI, a direct measure of transmission [27, 28]. For malaria, however, the same prevalence value can result from a wide range of FOI values [29], depending mainly on levels of heterogeneity in exposure and on treatment rates when transmission is low. In this situation a simple

approximation can be used to estimate FOI from data on prevalence and treatment rates [6, 12, 28, 30]. This approach may be the best currently-available way to estimate transmission from routine data in moderately low-transmission settings.

Despite the value of these non-entomological methods in areas of low transmission, they are not suitable in areas of high transmission. In areas of high transmission, individuals are more likely to be concurrently infected with more than one strain of *P. falciparum* [31], making it difficult to identify which infection results in a clinical episode or to measure FOI.

Using modeling to determine transmission through other malaria indicators

Most efforts towards a better understanding of the relationships between malaria indicators have focused on EIR. Many data compilations, statistical models, and some mathematical models have been created to estimate the relationship between EIR and prevalence [32-34], FOI [35, 36], seroconversion rate [20-23], uncomplicated disease [18, 37], severe disease [18, 37, 38], and mortality [18, 39] with a reasonable degree of success. In addition, data have been collected to determine the relationship between prevalence and severe disease [38], prevalence and mortality [40], and severe disease and mortality [39], but there has been limited validation of current mathematical models to these observed relationships.

Models capturing relationships between indicators can in principle be used to address many concerns with available methods of quantifying transmission [5]. Measures can be superimposed onto each other to allow comparisons between transmission indicators estimated from one measure (e.g., age-prevalence) in one site to values estimated from another measure (e.g., EIR) elsewhere. Such models can thus be used to simulate the likely range of values in areas of differing transmission intensity without access to data for key measures. Accordingly, in addition to the previously established malaria eradication research agenda for modeling (i.e., to understand the dynamics of control interventions) [13], mathematical modeling can also contribute towards understanding how various indicators of malaria transmission relate to each other, and help fill the gap between what can be measured from field studies and what is necessary for adequate planning of malaria control and elimination.

2.3 The importance of seasonality: an example of application of the OpenMalaria

transmission model

It is well known that malaria burden differs between age groups [29, 41, 42], yet there are numerous potential sources of heterogeneity in disease burden [43]; chief among them is seasonality in transmission. Seasonality of malaria can be broadly defined as the concentration of transmission within certain seasons. A commonly used definition for seasonality is a threshold of the proportion of transmission that occurs within a certain number of consecutive months [44]. This is suitable for areas of high transmission, but a more precise definition is lacking.

Many malaria studies have investigated the relationship between rainfall and one or more malaria indicators [42]. Similarly, many transmission models of *P. falciparum* that include seasonality have focused on the association between climatic factors, vector abundance, and transmission intensity [45-47]. Although the relationships between the indicators themselves in the presence of varying levels of seasonality have been shown to be important [18], they are less well understood.

Simulations of a range of transmission intensities and seasonal patterns using the OpenMalaria modeling platform for a periodically forced difference equation model for malaria in mosquitoes [48], integrated with an ensemble of individual-based stochastic simulation models for malaria in humans [1], suggest that with equal levels of average

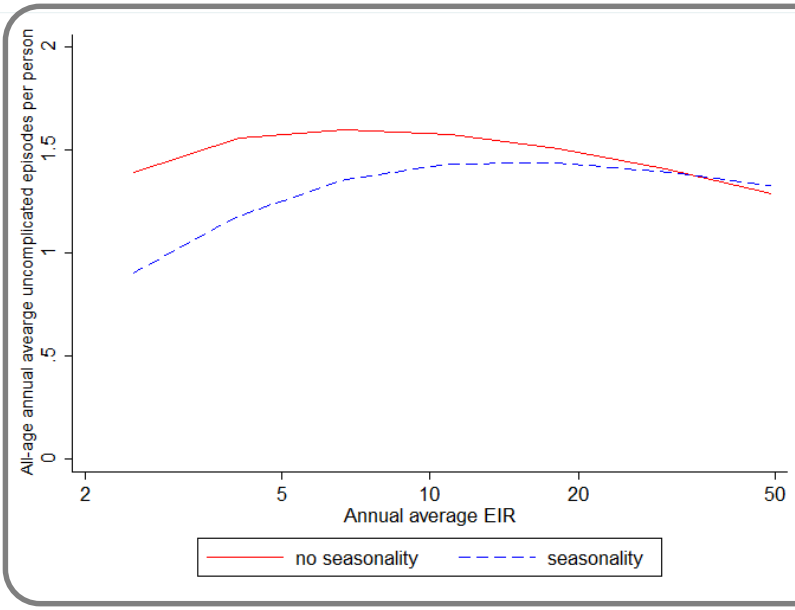

Figure 1. Relationship between uncomplicated episodes and entomological inoculation rate (EIR). The estimated relationship between annual average EIR and annual average uncomplicated episodes per person (all ages) for hypothetical areas with constant transmission (unbroken line) and with a high level of seasonality (dashed line), fitted to simulation results using fractional polynomial regression. Details of the models, seasonality profiles, and simulation methodology behind the fitted relationships can be found in **Box 1**.

Box 1. OpenMalaria simulations. Simulations referenced in this article employed stochastic simulation models of malaria as part of the OpenMalaria platform (see http://code.google.com/p/openmalaria/wiki/Start) based on the simulation of infections in humans linked to a deterministic model of malaria transmission between in mosquitoes and humans and to models of interventions that are able to simulate the dynamics of malaria in a given population [1]. Scenarios were run for one human lifespan to induce an 'equilibrium' level of immunity in a population of 100,000 individuals without exposure to malaria control interventions apart from an existing system of case management through the public sector, and repeated with multiple random seeds and an ensemble of 14 model variants [17] to address stochasticity and model uncertainty. Results represent simulated outputs for all ages averaged over 3 years for levels of annual average EIR ranging from 2.5 to 49.4 infective bites per person per year, with (**Figure IA**) and without (**Figure IB**) seasonal variation. These and other mathematical models of malaria can be used to quantify relationships between transmission and other indicators of disease burden such as parasite prevalence, as demonstrated in **Figure II**.

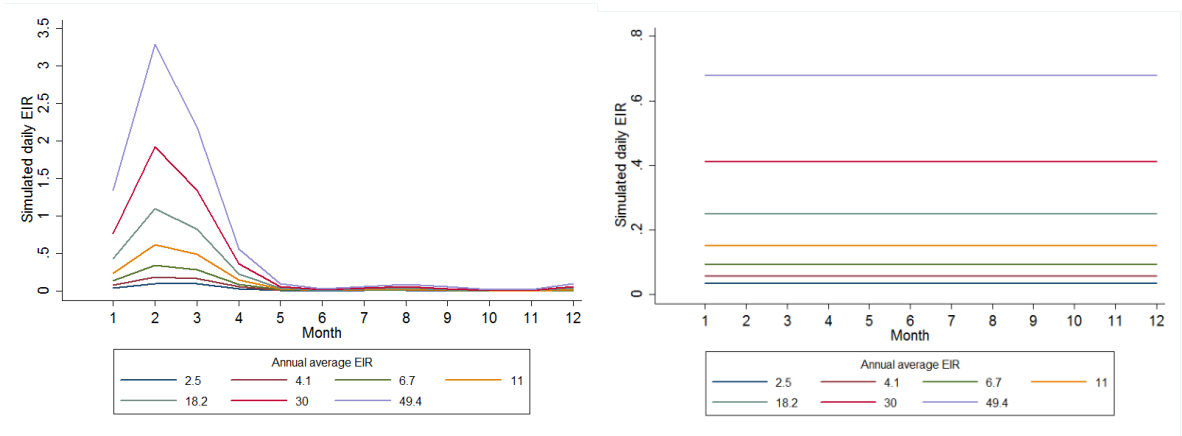

Figure I. (A) Annual patterns of transmission with seasonality. Lines represent the annual patterns of transmission with a high degree of seasonality over a period of 12 months. Colors represent the range of values for annual average entomological inoculation rate (EIR) (2.5–49.4) used for these patterns. **(B) Annual patterns of transmission without seasonality.** Lines represent the annual patterns of transmission without seasonality (constant transmission) over a period of 12 months. Colors represent the range of values for annual average EIR (2.5–49.4) used for these patterns.

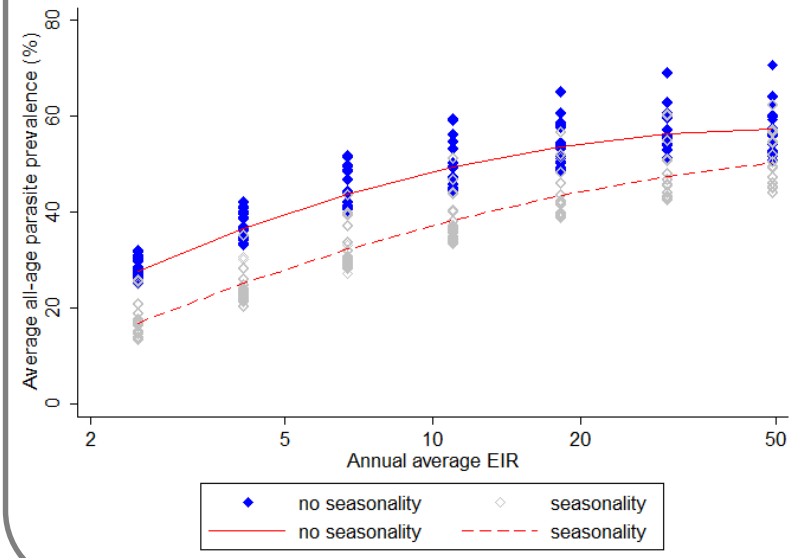

Figure II. Simulated effect of seasonality on the relationship between EIR and parasite prevalence. Dots represent simulated results for annual average EIR by all-age parasite prevalence averaged over a 3 year period, with (blue) and without (grey) seasonality. Lines show the estimated relationships with (red dashed) and without (red unbroken) seasonality as described in Figure IA,B, fitted using fractional polynomial regression.

annual transmission the level of seasonality in a locality affects the relationship between transmission and other indicators (Figure 1). As seasonality increases, the effect of EIR on other indices increases (Figure 1; Box 1). There is greater stochasticity in simulation results for scenarios with a high level of seasonality compared to scenarios with a constant level of transmission (Box 1).

These simulation results need further validation with field data, but they highlight the need for transmission data for multiple malaria indicators across areas with diverse seasonal patterns of transmission - such as the work done by Cairns *et al.* [42] - as opposed to the traditional strategy for survey site selection only based on annual average levels of transmission [18]. In addition to estimating overall malaria burden, understanding the seasonal pattern of malaria transmission is important for planning control interventions, including timing the deployment of indoor residual spraying, intermittent preventive treatment, and vaccines.

2.4 Limitations of model-based estimates of transmission

One clear limitation to a model-based approach is that most parameters measuring malaria in humans, such as prevalence, show saturation at moderate to high EIRs. Levels of heterogeneity in exposure can then be as important as the absolute value of the EIR in determining levels of infection or disease [29].

Analysis of data from the Kenyan highlands makes it clear that patterns of heterogeneity in transmission dominate in low-transmission settings [49]. In addition, age-patterns of malaria are also affected by spatiotemporal differences in exposure [50-52], acquisition of immunity [53], and other within-host dynamics [54] that become more important in high-transmission settings [29]. All these factors complicate relationships between different measures, but the sensitivity of prevalence estimates to exposure heterogeneity is greatest in low-transmission settings because at high levels of average exposure most of the population is likely to be infected.

Models parameterized by fitting to field data can show non-monotonic patterns with modeled indicators, such as morbidity rates, rates of severe disease, or malaria-specific mortality, peaking at intermediate levels of transmission as a secondary consequence of

rapid acquisition of immunity in the highest-transmission areas [43]. This phenomenon was widely discussed in the 1990s when there was a concern because of the implication that ITNs should therefore not be used in high-transmission settings [55, 56]. No direct evidence from the field supported this concern [55, 57]. Recent experience suggests ITN programs will substantially reduce transmission in a wide range of settings [2], rendering reconsideration of control programs unnecessary; however, this phenomenon presents a serious barrier to estimating transmission levels from morbidity rates because the estimated transmission for a given level of clinical disease may not be unique.

2.5 Future perspectives: a proposed research agenda for the application of mathematical models of malaria transmission

Obtaining accurate estimates of transmission, including seasonal patterns in addition to average transmission intensities, is critical for tailoring malaria control and elimination programs to specific country contexts. There is a need to validate simulation results with field data across a range of seasonal patterns in areas with data from a full year. Comparing relationships between indicators for levels of seasonality will allow for a wider application of model results for decision-making.

Another application of mathematical modeling is to examine countries approaching 'near-zero deaths', one of the main objectives of Roll Back Malaria's Global Malaria Action Plan (see http://www.rbm.who.int/gmap/index.html). Without an improvement of case-management systems, the case-fatality rate per infection increases as transmission decreases (Figure 2) as a result of the increased probability of a clinical episode becoming severe due to reduced immunity at lower levels of transmission. This makes prompt and effective treatment the key to achieving near-zero deaths and further emphasizes the need for quality surveillance response as transmission is reduced. More empirical and theoretical analyses focused on optimizing surveillance-response systems will aid in accomplishing this goal [58].

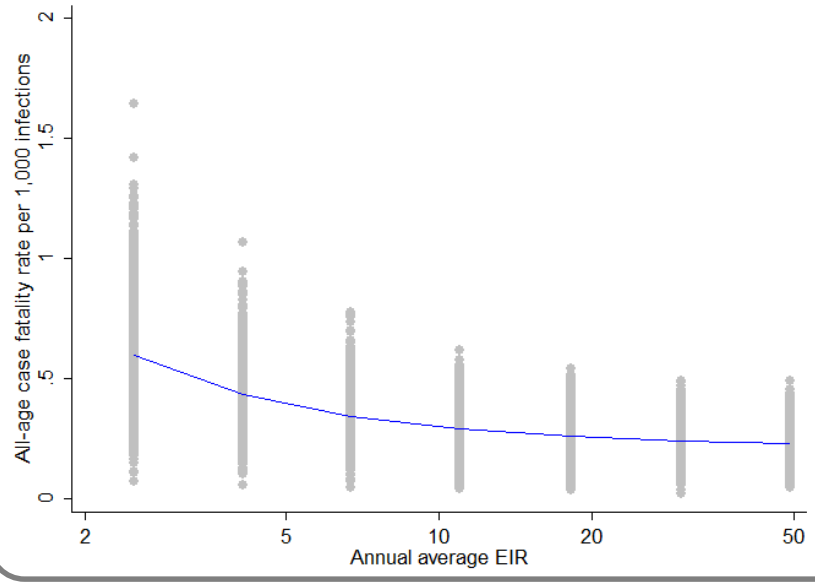

Figure 2. Case fatality-rate increases as transmission decreases. Dots represent the simulated all-age number of direct malaria deaths per 1000 infections by annual average entomological inoculation rate (EIR). The line shows the estimated relationship between the variables fitted using fractional polynomial regression. Details of the models, seasonality profiles, and simulation methodology behind the fitted relationships can be found in Box 1.

Further investigation of transmission heterogeneity existing in areas of low transmission will provide insight, enabling modelers to simulate elimination scenarios with greater accuracy [59]. In addition, models describing the dynamics of *Plasmodium vivax* malaria need to be developed and added to the existing simulation models of *P. falciparum* malaria [1, 10, 11, 60-62] for areas where both parasites are prevalent [63].

Properly-validated results from mathematical models can be compiled into a user-friendly interactive tool that would allow malaria control professionals to enter available data on an indicator and obtain the range of likely results for others. This will help detect changes of disease dynamics in a population and assist in the planning and assessment of the impact of malaria control interventions. With the call for more targeted and efficient use of increasingly scarce resources funding these life-saving interventions, such a tool would be useful.

2.6 Concluding remarks

Accurate measures of transmission are necessary for malaria elimination, yet at the same more difficult to collect as transmission is reduced. Measures of transmission cannot be standardized across all settings. In addition to statistical models, mathematical models provide a means of translating between measures of transmission and other indicators of disease burden, with the addition of exploring the impact of heterogeneities in exposure on

these relationships. The effect of seasonality on the relationships between malaria indicators is crucial and must be considered when designing surveys and analyzing data compilations. Mathematical modeling can contribute to evidence-based decision-making in the malaria control community by filling in knowledge gaps without substantial observational studies.

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2.8 References

1. Smith T, Ross A, Maire N, Chitnis N, Studer A, Hardy D, Brooks A, Penny M, Tanner M: **Ensemble modeling of the likely public health impact of a pre-erythrocytic malaria vaccine.** *PLoS medicine* 2012, **9:**e1001157.
2. WHO: **World Malaria Report 2012.** Geneva: World Health Organization; 2013.
3. Feachem RG, Phillips AA, Targett GA, Snow RW: **Call to action: priorities for malaria elimination.** *Lancet* 2010, **376:**1517-1521.
4. Hay SI, Rogers DJ, Toomer JF, Snow RW: **Annual Plasmodium falciparum entomological inoculation rates (EIR) across Africa: literature survey, Internet access and review.** *Trans R Soc Trop Med Hyg* 2000, **94:**113-127.
5. Kelly-Hope LA, McKenzie FE: **The multiplicity of malaria transmission: a review of entomological inoculation rate measurements and methods across sub-Saharan Africa.** *Malaria journal* 2009, **8:**19.
6. Yukich JO, Briet O, Bretscher MT, Benett A, Lemma S, Berhane Y, Eisele TP, Keating J, Smith TA: **Estimating *Plasmodium falciparum* transmission rates in low-endemic settings using a combination of community prevalence and health facility data.** *PLoS ONE* 2012, **7:** e42861.
7. Ross R: *The Prevention of Malaria.* London: Murray; 1911.
8. Smith DL, Battle KE, Hay SI, Barker CM, Scott TW, McKenzie FE: **Ross, macdonald, and a theory for the dynamics and control of mosquito-transmitted pathogens.** *PLoS Pathog* 2012, **8:**e1002588.
9. Smith T, Maire N, Ross A, Penny M, Chitnis N, Schapira A, Studer A, Genton B, Lengeler C, Tediosi F, et al: **Towards a comprehensive simulation model of malaria epidemiology and control.** *Parasitology* 2008, **135:**1507-1516.
10. Eckhoff P: **Mathematical models of within-host and transmission dynamics to determine effects of malaria interventions in a variety of transmission settings.** *Am J Trop Med Hyg* 2013, **88:**817-827.
11. Griffin JT, Hollingsworth TD, Okell LC, Churcher TS, White M, Hinsley W, Bousema T, Drakeley CJ, Ferguson NM, Basanez MG, Ghani AC: **Reducing Plasmodium falciparum malaria transmission in Africa: a model-based evaluation of intervention strategies.** *PLoS Med* 2010, **7**.
12. Dietz K, Molineaux L, Thomas A: **A malaria model tested in the African savannah.** *Bull World Health Organ* 1974, **50:**347-357.
13. Alonso PL, Eubank S, Ghani A, Sinden R, Hay SI, Smith DL, Smith TA, White LJ, Tanner M: **A research agenda to underpin malaria eradication: modeling.** *PLoS Med* 2011, **8:**e1000403.
14. Reiner RC, Jr., Perkins TA, Barker CM, Niu T, Chaves LF, Ellis AM, George DB, Le Menach A, Pulliam JR, Bisanzio D, et al: **A systematic review of mathematical models of mosquito-borne pathogen transmission: 1970-2010.** *J R Soc Interface* 2013, **10:**20120921.
15. Mandal S, Sarkar RR, Sinha S: **Mathematical models of malaria--a review.** *Malar J* 2011, **10:**202.
16. Patil AP, Okiro EA, Gething PW, Guerra CA, Sharma SK, Snow RW, Hay SI: **Defining the relationship between Plasmodium falciparum parasite rate and clinical disease: statistical models for disease burden estimation.** *Malaria journal* 2009, **8:**186.

17. Molineaux L, Muir DA, Spencer HC, Wernsdorfer WH: **The epidemiology of malaria and its measurement.** In *Malaria : principles and practice of malariology.* Edited by Wernsdorfer WH, McGregor I. Edinburgh ; New York: Churchill Livingstone; 1988: 999-1089
18. Carneiro I, Roca-Feltrer A, Griffin JT, Smith L, Tanner M, Schellenberg JA, Greenwood B, Schellenberg D: **Age-patterns of malaria vary with severity, transmission intensity and seasonality in sub-Saharan Africa: a systematic review and pooled analysis.** *PLoS One* 2010, **5:**e8988.
19. Russell TL, Govella NJ, Azizi S, Drakeley CJ, Kachur SP, Killeen GF: **Increased proportions of outdoor feeding among residual malaria vector populations following increased use of insecticide-treated nets in rural Tanzania.** *Malar J* 2011, **10:**80.
20. Corran P, Coleman P, Riley E, Drakeley C: **Serology: a robust indicator of malaria transmission intensity?** *Trends Parasitol* 2007, **23:**575-582.
21. Drakeley CJ, Corran PH, Coleman PG, Tongren JE, McDonald SL, Carneiro I, Malima R, Lusingu J, Manjurano A, Nkya WM, et al: **Estimating medium- and long-term trends in malaria transmission by using serological markers of malaria exposure.** *Proc Natl Acad Sci U S A* 2005, **102:**5108-5113.
22. Voller A, Draper CC: **Immunodiagnosis and sero-epidemiology of malaria.** *British medical bulletin* 1982, **38:**173-177.
23. Stewart L, Gosling R, Griffin J, Gesase S, Campo J, Hashim R, Masika P, Mosha J, Bousema T, Shekalaghe S, et al: **Rapid assessment of malaria transmission using age-specific sero-conversion rates.** *PLoS One* 2009, **4:**e6083.
24. Stuckey EM, Stevenson J, Cooke M, Owaga C, Marube E, Oando G, Hardy D, Drakeley C, Smith T, Cox J, Chitnis N: **Simulation of malaria epidemiology and control in the highlands of western Kenya.** *Malar J* 2012, **11**.
25. Bousema T, Youssef RM, Cook J, Cox J, Alegana VA, Amran J, Noor AM, Snow RW, Drakeley C: **Serologic markers for detecting malaria in areas of low endemicity, Somalia, 2008.** *Emerg Infect Dis* 2010, **16:**392-399.
26. Cook J, Reid H, Iavro J, Kuwahata M, Taleo G, Clements A, McCarthy J, Vallely A, Drakeley C: **Using serological measures to monitor changes in malaria transmission in Vanuatu.** *Malar J* 2010, **9:**169.
27. Bekessy A, Molineaux L, Storey J: **Estimation of incidence and recovery rates of Plasmodium falciparum parasitaemia from longitudinal data.** *Bull World Health Organ* 1976, **54:**685-693.
28. Muench H: *Catalytic models in epidemiology.* Cambridge: Harvard University Press; 1959.
29. Ross A, Smith T: **Interpreting malaria age-prevalence and incidence curves: a simulation study of the effects of different types of heterogeneity.** *Malar J* 2010, **9:**132.
30. Charlwood JD, Smith T, Lyimo E, Kitua AY, Masanja H, Booth M, Alonso PL, Tanner M: **Incidence of Plasmodium falciparum infection in infants in relation to exposure to sporozoite-infected anophelines.** *Am J Trop Med Hyg* 1998, **59:**243-251.
31. Robert V, Macintyre K, Keating J, Trape JF, Duchemin JB, Warren M, Beier JC: **Malaria transmission in urban sub-Saharan Africa.** *Am J Trop Med Hyg* 2003, **68:**169-176.
32. Beier JC, Killeen GF, Githure JI: **Short report: entomologic inoculation rates and Plasmodium falciparum malaria prevalence in Africa.** *Am J Trop Med Hyg* 1999, **61:**109-113.

33. Gething PW, Patil AP, Smith DL, Guerra CA, Elyazar IR, Johnston GL, Tatem AJ, Hay SI: **A new world malaria map: Plasmodium falciparum endemicity in 2010.** *Malar J* 2011, **10:**378.
34. Smith DL, Dushoff J, Snow RW, Hay SI: **The entomological inoculation rate and Plasmodium falciparum infection in African children.** *Nature* 2005, **438:**492-495.
35. Mueller I, Schoepflin S, Smith TA, Benton KL, Bretscher MT, Lin E, Kiniboro B, Zimmerman PA, Speed TP, Siba P, Felger I: **Force of infection is key to understanding the epidemiology of Plasmodium falciparum malaria in Papua New Guinean children.** *Proc Natl Acad Sci U S A* 2012, **109:**10030-10035.
36. Smith T, Maire N, Dietz K, Killeen GF, Vounatsou P, Molineaux L, Tanner M: **Relationship between the entomologic inoculation rate and the force of infection for Plasmodium falciparum malaria.** *Am J Trop Med Hyg* 2006, **75:**11-18.
37. Hay SI, Okiro EA, Gething PW, Patil AP, Tatem AJ, Guerra CA, Snow RW: **Estimating the global clinical burden of Plasmodium falciparum malaria in 2007.** *PLoS Med* 2010, **7:**e1000290.
38. Okiro EA, Al-Taiar A, Reyburn H, Idro R, Berkley JA, Snow RW: **Age patterns of severe paediatric malaria and their relationship to Plasmodium falciparum transmission intensity.** *Malar J* 2009, **8:**4.
39. Reyburn H, Mbatia R, Drakeley C, Bruce J, Carneiro I, Olomi R, Cox J, Nkya WM, Lemnge M, Greenwood BM, Riley EM: **Association of transmission intensity and age with clinical manifestations and case fatality of severe Plasmodium falciparum malaria.** *JAMA* 2005, **293:**1461-1470.
40. Korenromp EL, Williams BG, Gouws E, Dye C, Snow RW: **Measurement of trends in childhood malaria mortality in Africa: an assessment of progress toward targets based on verbal autopsy.** *Lancet Infect Dis* 2003, **3:**349-358.
41. Trape JF, Rogier C: **Combating malaria morbidity and mortality by reducing transmission.** *Parasitol Today* 1996, **12:**236-240.
42. Cairns M, Roca-Feltrer A, Garske T, Wilson AL, Diallo D, Milligan PJ, Ghani AC, Greenwood BM: **Estimating the potential public health impact of seasonal malaria chemoprevention in African children.** *Nat Commun* 2012, **3:**881.
43. Ross A, Maire N, Molineaux L, Smith T: **An epidemiologic model of severe morbidity and mortality caused by Plasmodium falciparum.** *Am J Trop Med Hyg* 2006, **75:**63-73.
44. Roca-Feltrer A, Schellenberg JR, Smith L, Carneiro I: **A simple method for defining malaria seasonality.** *Malar J* 2009, **8:**276.
45. Paaijmans KP, Read AF, Thomas MB: **Understanding the link between malaria risk and climate.** *Proc Natl Acad Sci U S A* 2009, **106:**13844-13849.
46. Pascual M, Cazelles B, Bouma MJ, Chaves LF, Koelle K: **Shifting patterns: malaria dynamics and rainfall variability in an African highland.** *Proc Biol Sci* 2008, **275:**123-132.
47. Eckhoff PA: **A malaria transmission-directed model of mosquito life cycle and ecology.** *Malar J* 2011, **10:**303.
48. Chitnis N, Hardy D, Smith T: **A Periodically-Forced Mathematical Model for the Seasonal Dynamics of Malaria in Mosquitoes.** *Bulletin of mathematical biology* 2012, **74(5):**1098–1124.
49. Stresman G, Kobayashi T, Kamanga A, Thuma PE, Mharakurwa S, Moss WJ, Shiff C: **Malaria research challenges in low prevalence settings.** *Malar J* 2012, **11:**353.

50. Paull SH, Song S, McClure KM, Sackett LC, Kilpatrick AM, Johnson PT: **From superspreaders to disease hotspots: linking transmission across hosts and space.** *Front Ecol Environ* 2012, **10:**75-82.
51. White MT, Griffin JT, Drakeley CJ, Ghani AC: **Heterogeneity in malaria exposure and vaccine response: implications for the interpretation of vaccine efficacy trials.** *Malar J* 2010, **9:**82.
52. Woolhouse ME, Dye C, Etard JF, Smith T, Charlwood JD, Garnett GP, Hagan P, Hii JL, Ndhlovu PD, Quinnell RJ, et al: **Heterogeneities in the transmission of infectious agents: implications for the design of control programs.** *Proc Natl Acad Sci U S A* 1997, **94:**338-342.
53. Ghani AC, Sutherland CJ, Riley EM, Drakeley CJ, Griffin JT, Gosling RD, Filipe JA: **Loss of population levels of immunity to malaria as a result of exposure-reducing interventions: consequences for interpretation of disease trends.** *PLoS One* 2009, **4:**e4383.
54. Lloyd AL, Zhang J, Root AM: **Stochasticity and heterogeneity in host-vector models.** *J R Soc Interface* 2007, **4:**851-863.
55. Lengeler C, Schellenberg JA, D'Alessandro U: **Will reducing Plasmodium falciparum malaria transmission alter malaria mortality among African children?** *Parasitol Today* 1995, **11:**425; author reply 426.
56. Snow RW, Omumbo JA, Lowe B, Molyneux CS, Obiero JO, Palmer A, Weber MW, Pinder M, Nahlen B, Obonyo C, et al: **Relation between severe malaria morbidity in children and level of Plasmodium falciparum transmission in Africa.** *Lancet* 1997, **349:**1650-1654.
57. Smith TA, Leuenberger R, Lengeler C: **Child mortality and malaria transmission intensity in Africa.** *Trends Parasitol* 2001, **17:**145-149.
58. Chiyaka C, Garira W, Dube S: **Effects of treatment and drug resistance on the transmission dynamics of malaria in endemic areas.** *Theor Popul Biol* 2009, **75:**14-29.
59. White LJ, Maude RJ, Pongtavornpinyo W, Saralamba S, Aguas R, Van Effelterre T, Day NP, White NJ: **The role of simple mathematical models in malaria elimination strategy design.** *Malar J* 2009, **8:**212.
60. Chiyaka C, Tchuenche JM, Garira W, Dube S: **A mathematical analysis of the effects of control strategies on the transmission dynamics of malaria.** *Appl Math Comput* 2008, **195:**641-662.
61. White MT, Griffin JT, Churcher TS, Ferguson NM, Basanez MG, Ghani AC: **Modelling the impact of vector control interventions on Anopheles gambiae population dynamics.** *Parasit Vectors* 2011, **4:**153.
62. Johnston GL, Smith DL, Fidock DA: **Malaria's missing number: calculating the human component of R0 by a within-host mechanistic model of Plasmodium falciparum infection and transmission.** *PLoS Comput Biol* 2013, **9:**e1003025.
63. Gething PW, Elyazar IR, Moyes CL, Smith DL, Battle KE, Guerra CA, Patil AP, Tatem AJ, Howes RE, Myers MF, et al: **A long neglected world malaria map: Plasmodium vivax endemicity in 2010.** *PLoS Negl Trop Dis* 2012, **6:**e1814.

3. Simulation of malaria epidemiology and control in the highlands of western Kenya

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3.1 Abstract

Background

Models of *Plasmodium falciparum* malaria epidemiology that provide realistic quantitative predictions of likely epidemiological outcomes of existing vector control strategies have the potential to assist in planning for the control and elimination of malaria. This work investigates the applicability of mathematical modeling of malaria transmission dynamics in Rachuonyo South, a district with low, unstable transmission in the highlands of western Kenya.

Methods

Individual-based stochastic simulation models of malaria in humans and a deterministic model of malaria in mosquitoes as part of the OpenMalaria platform were parameterized to create a scenario for the study area based on data from ongoing field studies and available literature. The scenario was simulated for a period of two years with a population of 10,000 individuals and validated against malaria survey data from Rachuonyo South. Simulations were repeated with multiple random seeds and an ensemble of 14 model variants to address stochasticity and model uncertainty. A one-dimensional sensitivity analysis was conducted to address parameter uncertainty.

Results

The scenario was able to reproduce the seasonal pattern of the entomological inoculation rate (EIR) and patent infections observed in an all-age cohort of individuals sampled monthly for one year. Using an EIR estimated from serology to parameterize the scenario resulted in a closer fit to parasite prevalence than an EIR estimated using entomological methods. The scenario parameterization was most sensitive to changes in the timing and effectiveness of indoor residual spraying (IRS) and the method used to detect *P. falciparum* in humans. It was less sensitive than expected to changes in vector biting behaviour and climatic patterns.

Conclusions

The OpenMalaria model of *P. falciparum* transmission can be used to simulate the impact of different combinations of current and potential control interventions to help plan malaria control in this low transmission setting. In this setting and for these scenarios, results were highly sensitive to transmission, vector exophagy, exophily and susceptibility to insecticide, and the detection method used for surveillance. The level of accuracy of the results will thus depend upon the precision of estimates for each. New methods for analysing and evaluating uncertainty in simulation results will enhance the usefulness of simulations for malaria control decision-making. Improved measurement tools and increased primary data collection will enhance model parameterization and epidemiological monitoring. Further research is needed on the relationship between malaria indices to identify the best way to quantify transmission in low transmission settings. Measuring EIR through mosquito collection may not be the optimal way to estimate transmission intensity in areas with low, unstable transmission.

3.2 Background

Rationale for work

In order to make informed decisions for malaria control, programme managers require information on the optimal mix of intervention strategies tailored to specific transmission patterns of malaria [1-3]. This information is often unavailable due to the difficulty in measuring rates of malaria transmission and determining the impact of control interventions on transmission. While the efficacy of individual malaria control interventions in reducing morbidity and mortality in western Kenya has been demonstrated by field trials [4, 5], there have been fewer studies investigating the effects across a range of transmission intensities or for combinations of interventions [6, 7].

Since 2008, a number of epidemiological and entomological studies have been carried out in Rachuonyo South, Kenya, as part of the Malaria Transmission Consortium (MTC). The availability of data from these and other studies presents an opportunity for site-specific parameterization of models of malaria transmission. The results of these model simulations can be translated into evidence-based decision making for malaria control programme managers. This project applies individual-based stochastic models of malaria to MTC sites with transmission data to simulate the impact of a range of malaria control strategies.

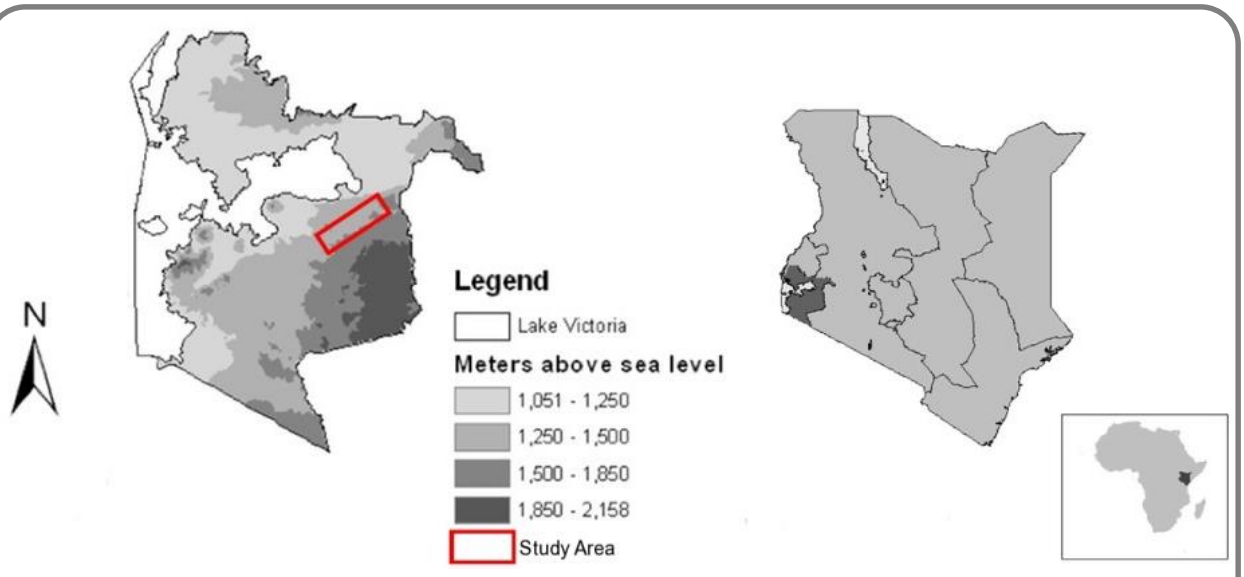

Figure 1: Map of the study area. Map of a) Location and elevation of the study area in Rachuonyo South district; and b) Location of Nyanza Province in relation to Kenya

Study area

Rachuonyo South district is situated in Nyanza province, bordering Lake Victoria in western Kenya (Figure 1) and encompasses an area of 930km^2. The main MTC study site is located in the south west of the district and represents a highland "fringe" area (1,400-1,600 meters above sea level). Ethnicity in Rachuonyo South is predominantly the Luo ethnic group. Residents depend upon farming and cattle and goat herding for subsistence. Homesteads are distributed broadly across a rolling landscape intersected with small streams and rivers. Total annual rainfall in this area averages 1,200 mm per year (Figure 2) while average daily temperatures range from 17-27^{o}C. The area is characterized by generally lo w malaria endemicity with marked seasonal and inter-annual variations in transmission [8, 9].

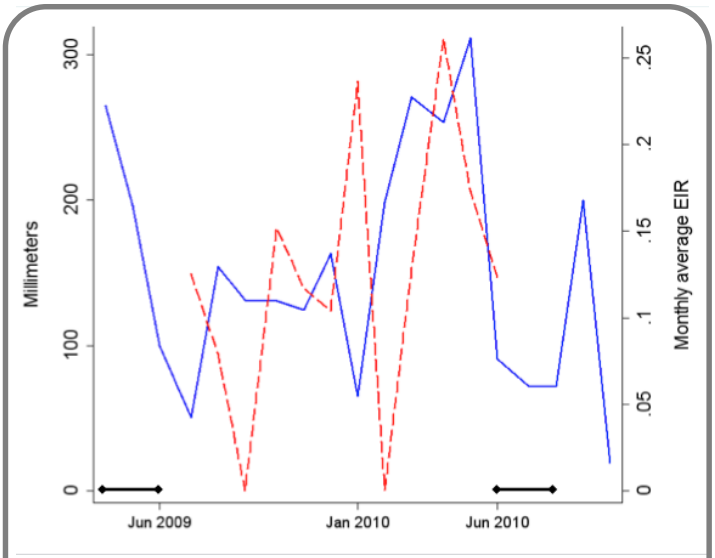

Figure 2: Seasonal patterns of rainfall, estimated EIR, and timing of IRS interventions. The rainfall pattern (solid line) collected by the weather station at Kogalo Primary School, Kowuor Location, Rachuonyo South that informed the estimated seasonal pattern of the EIR (dashed line) in Rachuonyo South district over the period June 2009 – June 2010. The black-capped bars indicate the timing of the 2009 – 2010 deployment of IRS in Rachuonyo South district.

The main malaria vectors in the highlands were previously recorded to be *Anopheles gambiae sensu stricto*, *Anopheles arabiensis* and *Anopheles funestus* [10, 11]. In recent years, there is evidence that *An. gambiae s.s.* is disappearing from lowlands Nyanza leaving *An. arabiensis* as the predominant species within the *An. gambiae sensu lato* complex [12] and *An. funestus* as the primary *Plasmodium falciparum* vector (Stevenson*, personal communication)*. These changes are most likely due to intensive targeting of malaria control interventions, but climatic factors may also have played a role [12-14].

In western Kenya indoor residual spraying (IRS) campaigns were carried out in the Kericho district in the 1940s and Nandi district in the 1950s (using dichlorodiphenyltrichloroethane

(DDT) and dieldrin, respectively). It is thought that malaria transmission was largely eliminated from large portions of the highlands as a result [15, 16]. While epidemics re-emerged in the 1980s [17, 18], it was not until after 2000 that routine, large-scale vector control interventions were introduced in these areas.

The main control methods used today in the epidemic highland areas include mass-distribution of long-lasting insecticide-treated nets (LLINs), IRS with pyrethroids, and prompt and effective treatment of malaria [19] [20, 21]. Artemisinin-based combination therapy (ACT), specifically artemether-lumefantrine (AL) was adopted as the first line treatment drug in 2006 following a decline in efficacy of sulphadoxine-pyrimethamine (SP) and amodiaquine, the previous first and second line treatments, respectively [19]. In 2006 and 2011 Rachuonyo South was included within the Kenyan national mass distribution LLIN campaign and distribution continues through antenatal clinics, child welfare clinics, and comprehensive care clinics for people living with HIV. Since 2005 Rachuonyo South has been targeted for universal coverage of IRS once per year in advance of the main transmission season. Different formulations of pyrethroid insecticide have been used over the years with lambdacyhalothrin (ICON) used in 2009, alphacypermethrin (FENDONA) used in 2010, ICON again in 2011, and 2012 started with ICON and then switched to deltamethrin.

3.3 Methods

OpenMalaria transmission model

A team at the Swiss Tropical and Public Health Institute (Swiss TPH) and Liverpool School of Tropical Medicine (LSTM) has developed stochastic simulation models of transmission of malaria based on the simulation of infection in individuals that are able to simulate the impact (cost-effectiveness, clinical, epidemiological and entomological) of numerous intervention strategies for malaria control [22-26]. These models form part of the OpenMalaria platform that makes the considerable code base written in C++ freely available online [27]. Users are able to carry out predictive simulations either via a downloadable stand-alone programme or via a volunteer grid computing resource and semi-automated experiment design and analysis platform capable of handling entire experiments of 10,000-100,000 scenarios.

Individual infections are simulated by stochastic series of parasite densities, which determine an individual's morbidity and mortality risks as well as their infectiousness to vectors [22, 27]. The simulated infections are nested within simulations of individuals in human populations, and linked to a model of transmission of malaria between humans and mosquitoes and to models of interventions [22, 23, 27]. The transmission model is based on a periodically-forced difference equation model for malaria mosquitoes feeding on, infecting and getting infected from a heterogeneous population of hosts [26]. These dynamics are calibrated by a seasonal pattern of EIR for each mosquito species assuming that in the absence of interventions EIR seasonality is fixed across years [26]. Simulations are run for one human life span to induce an "equilibrium" level of immunity in the population. Subsequent dynamics are used to predict available malaria outcomes, such as patterns of infection in humans or patterns of disease by age and season, which can then be compared to field data.

The details of the methods to build and parameterize the transmission model used in this project have been published elsewhere [22-26] and therefore are not covered in this paper. In this paper the model components described above are employed to an ensemble of 14 model variants for malaria in humans to address stochasticity and model uncertainty [25]. Simulations were repeated with multiple random seeds to address parameter uncertainty.

Model parameterization

The models included in the OpenMalaria platform were initially parameterized from published data from Namawala, Tanzania [22-28]; 61 data sets were used to optimize certain parameters [22-26]. To update the parameterization for the Rachuonyo South scenario, data collected as part of the MTC project in the study area was the first choice to use for the model parameters. A description of these studies and how they were used to parameterize the model can be found in Additional file 1.

MTC field studies

A number of field studies were carried out in Kisii and Rachuonyo South districts between 2009

and 2011 with the goal of establishing an evidence base to help malaria control programme managers monitor malaria transmission and implement and adjust malaria control interventions. Data from these studies are currently being analysed and will be described in detail in forthcoming publications. For the purposes of the modelling work described in this paper, the datasets used are described in Table 1.

Table 1. Use of datasets from MTC Field Studies

Study	Timeframe	Study population	Type and purpose of data used
Community-based cohort	May 2009 – June 2010	3235 people of all ages above 6 months	Monthly malaria prevalence for model validation, coverage levels of LLINs and IRS for model simulation
Community-based cross sectional	February 2009	2607 individuals	Coverage levels of LLINs and IRS for district-level sensitivity analysis
Community-based cross sectional	July 2009	3587 individuals	
4 x 4 Latin square entomological	2009 - 2010	8 households	Vector species distribution for transmission model
Pyrethrum spray catch entomological	September 2009 - present	200 households	Indoor vs. outdoor vector biting behavior in areas with or without indoor residual spraying and/or insecticide treated nets
Weather station	Continuous	Kogalo Primary School, Kowuor Location, Rachuonyo South	Seasonality of rainfall and temperature to adjust entomological parameters

Where data were not available from MTC surveys, parameter inputs were identified via a literature review of publications using the PubMed electronic database using the key words "Kenya, Nyanza, Rachuonyo, western Kenya, malaria, *Plasmodium falciparum*, transmission, antimalarials, artemether- lumfantrine, insecticide residual spraying, insecticide-treated nets, larviciding, intermittent preventive treatment, modelling, malaria incidence, treatment seeking, mosquito resting duration, extrinsic incubation period, Anopheles." An internet review was also conducted on the websites for the Kenyan Ministry of Health, Division of Malaria Control, the National Bureaus of Statistics, and the National Demographic Health Surveys. The sources were

prioritized in the following strata in order of precedence: study area districts MTC data collection, study area districts existing literature, study area provincial data, national level data, existing model parameterization. Where more than one data source was found within any one stratum the study with the closest site characteristics or, where applicable, date of data collection closest to that of the MTC studies was used.

To determine the annual average EIR, the transmission parameter in the model, seroconversion rates using the MSP-1 antigen were estimated from the July 2009 cross-sectional survey as described in Drakeley et al. 2005 [29] and derived EIR equivalents were calculated as described in Corran et al. 2007 [30]. The average monthly EIR values used to calibrate the seasonal pattern of transmission in the scenario were calculated by separating the annual average EIR from existing literature for a neighboring district into the monthly proportion of rainfall in Rachuonyo South recorded by the Kogalo weather station so that the peak malaria transmission month corresponded to one month later than the peak rainfall month (Figure 2). Because the annual average EIR is based on serology, the model incorporates the overall temperature and humidity effects but excludes the seasonality of these effects.

In practice, many of the entomological and health system parameters were based on data from elsewhere used in other modelling exercises [26-32] as they are thought to be fairly standard across anopheline species and anti-malarials. However, because several entomological parameters are sensitive to temperature, particularly the extrinsic incubation period (EIP) and mosquito resting duration [33, 34], these values were adjusted for each study area based on the average annual temperature collected by the Kogalo weather station. Also, the latest data from the study site challenges the assumption that vectors are normally predominantly endophilic and endophagic [35]. For the purposes of this experiment, emphasis was placed on overall vector biting behaviour rather than simulating individual species. This was due to the design of the entomological field studies for which results were available at the time of model parameterization that focused on indoor/outdoor species composition and trap evaluation rather than the biting behaviour within individual species. The efficacy of LLINs and IRS were adjusted to affect the indoor mosquitoes but not the outdoor mosquitoes and the proportion of bites on a human compared to other mammals was reduced for the outdoor mosquitoes.

The monitoring measures serving as the outputs simulated by the model were chosen based on the indicators of malaria transmission measured by the field studies described above.

Simulation

Before the main simulation, the scenario was run for one human life span to ensure each simulated individual acquired the expected natural immunity for his or her age. The fitting of the dynamic EIR in the transmission model to the pre-intervention calibration EIR was done during the last five years of the life span simulation. A subpopulation was considered as a cohort and received mass drug administration (MDA) at the beginning of the main simulation, to "mimic" the MTC cohort study conditions, where participants were given a course of the first-line malaria treatment upon enrollment into the study to clear any existing malaria parasites. Finally, the effect of interventions on epidemiological outcomes of malaria in the full population of the study area was simulated for two years.

Validation and sensitivity analysis

The project addresses uncertainty on three levels: stochasticity, model uncertainty, and parameter uncertainty. Each simulation was repeated by the OpenMalaria simulator on an ensemble of 14 model variants using ten random seeds in order to address model uncertainty and stochasticity. Results in the form of graphs from the ensemble of model variants were visually analysed and compared to observed data from the study areas using Stata (version 11; College Station, TX, USA). Further analysis of the scenario simulation and observed data for the selected impact measures was conducted using Stata. The proportion of simulation results falling within the 95% confidence intervals of the observed cohort data was measured in order to assess goodness of fit.

A sensitivity analysis to address parameter uncertainty was driven by results of the visual comparison of stochasticity. Elements of the model central to the epidemiology and control of malaria in this particular study area were identified based on whether there was uncertainty about parameter estimates and their potential impact on the composition and behaviour of

vectors, effectiveness of interventions, and population-level monitoring. These included effectiveness of IRS, indoor versus outdoor biting behaviour of the vectors, the detection limit of the survey method used for malaria in humans, annual average EIR, and climate and weather patterns affecting vector biology parasite development in the vector. Parameters were altered one at a time and results analysed by comparing the simulated number of cases per person per year for each scenario to those of the baseline parameterization.

3.4 Results

Model design and baseline scenario parameterization

The following parameter estimates are based on currently unpublished data from the MTC studies described above in Table 1. The key entomological feature of the scenario involves one primary malaria vector that bites and rests outdoors 62% of the time. At the time of enrollment into the cohort, 30.3% of the cohort population slept under a net the previous night and 69.3% of survey households received IRS. The IRS deployment schedule happened yearly over a period of two months as described above in the Background section. The annual mean temperature in Rachuonyo South from 2009 to 2010 was recorded as 20.3 degrees Celsius, setting the estimate of the extrinsic incubation period of *An. gambiae* at 14 days and the resting duration 3 days. Malaria transmission is highly variable following two distinct rainy seasons. The EIR is unstable with a last recorded value from an entomological survey of 0.4 infectious bites per person per year [10]. This study was conducted in neighboring Kisii district before LLIN and IRS scale-up in 2006. More recent results from the July 2009 MTC cross sectional study estimate an EIR of 1.5 infectious bites per person per year based on serological data (Table 2).

Table 2. Malaria transmission parameter values*

Month	Average EIR	Month	Average EIR
January	0.003	July	0.079
February	0.129	August	0
March	0.261	September	0.152
April	0.173	October	0.117
May	0.123	November	0.104
June	0.125	December	0.236
Annual average EIR		1.5**	

**All values based on Shililu 1998[36], Ndenga 2006[10] and data from the Kogalo weather station unless otherwise noted*

***Annual average EIR based on seroconversion rates as described in Drakeley et al 2005[29] of samples from a cross sectional survey of 3,587 individuals of all ages conducted in the study area in June 2009. EIR equivalents were derived as described in Corran et al 2007[30].*

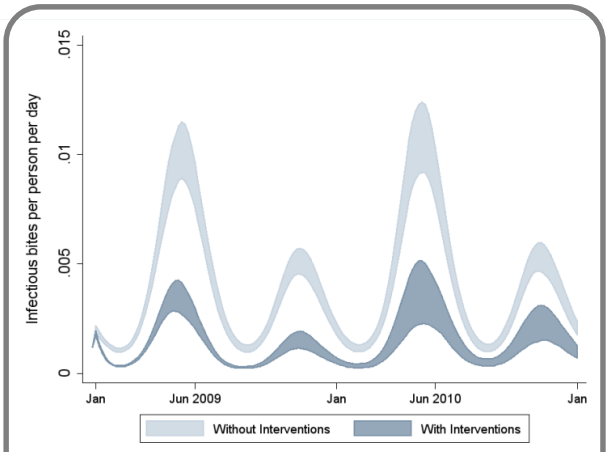

Figure 3 Simulated seasonal transmission dynamics with and without interventions. Baseline model simulation of EIR on a population of 10,000 individuals for two years using 10 random seeds for each of the 14 OpenMalaria model variants with (dark blue shaded area) and without (light blue shaded area) interventions in Rachuonyo South district. The daily EIR is calibrated from monthly EIR values that are smoothed out with a Fourier transform to only include an annual and biannual cycle as described in Chitnis et al. 2012 [26]. The shaded areas represent the range of results from the 140 simulations.

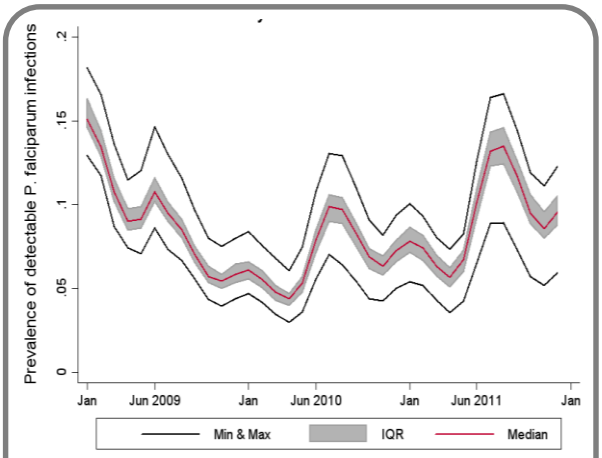

Figure 4: District-level simulation of prevalence of detectable *P. falciparum* infections. Simulated number of *P. falciparum* infections as detected by a rapid diagnostic test (RDT) in a population of 10,000 individuals. The simulation ran for two years using 10 random seeds for each of the 14 OpenMalaria model variants. The center line shows the median value of the 140 simulations at each time point. The shaded area shows the interquartile range, and the two outside lines show the maximum and minimum value at each time point.

For OpenMalaria to simulate dynamics of the study population, code was included in the scenario to select a cohort representing 15% of the total population over one year old matching the cohort enrollment criteria, all of whom received a course of anti-malarials at the start of the survey period. The validation of the model uses the model outputs from only this cohort, while the remaining simulations represent the larger study area population of 10,000 individuals. The details of the values used to parameterize the model along with their sources can be found in Additional Files 2, 3, 4, 5, 6, 7.

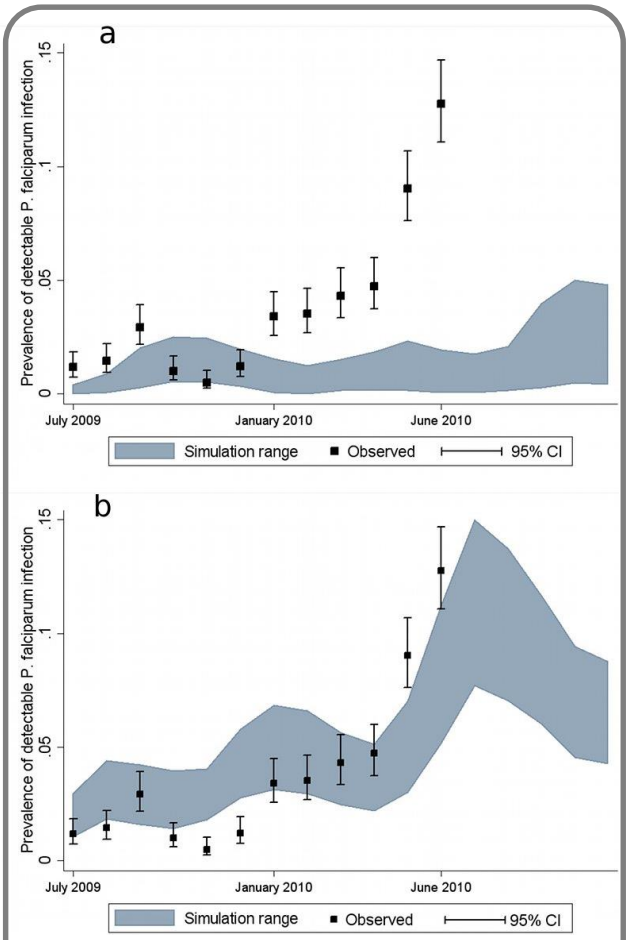

Figure 5 Model validation with observed cohort prevalence data. Simulated vs. observed proportion of a cohort of 1,655 individuals in Rachuonyo South District with detectable P. falciparum infection for EIR values derived from a) entomological studies (0.4 infectious bites per person per year, seasonality from neighboring district; and b) serology (1.5 infectious bites per person per year from one primary vector, seasonality from study site weather station). All simulations ran for three years for each of the 14 OpenMalaria model variants. The squares represent the mean number of patent infections observed in the cohort at each time point. The capped bars represent the upper and lower 95% confidence intervals of the observed mean. The shaded area represents the range of results from the 140 simulations. The source of observed data is the MTC cohort study described in the Methods section.

Simulation and validation

OpenMalaria is able to simulate the seasonality and level of the EIR for the Rachuonyo South scenario with greater stochasticity in the peak months and in the scenario with observed interventions (Figure 3). Simulations show prevalence between 5.58% and 10.81% in Rachuonyo South's peak transmission month and between 2.99% and 6.04% in the lowest transmission month (Figure 4).

The Figures 5a and 5b compare the simulation of *P. falciparum* prevalence in the population with observed data from the MTC cohort study conducted from June 2009 – June 2010 in Rachuonyo South District as detected by a rapid diagnostic test (RDT) using EIR values derived from entomological studies (0.4 infectious

bites per person per year, seasonality from neighboring district, Table 2) versus serology (1.5 infectious bites per person per year, seasonality from study site weather station). The prevalence was especially high in June of 2010, possibly due to a combination of more rainfall than normal during the rainy season and rollout of IRS at a later month compared to the previous year.

While the model is able to predict the level of prevalence in both scenarios, using an EIR from serology and seasonality from weather station data represents a visually better fit with both level of overall and seasonal prevalence compared to using an EIR and seasonality from entomology. With a benchmark for comparing simulation results defined as the proportion of simulation runs falling within the 95% confidence intervals of the observed cohort data, the final scenario was able to improve both the number of months (six months with more than 30% of simulations runs predicted compared to three months, n=12) and the proportion of total simulation runs (29.9% vs. 14.6%, n=1,680).

Sensitivity analysis

Indoor residual spraying

The two main malaria control measures in the study area are distribution of LLINs and IRS. While net use is assumed constant over the time frame of the simulation, IRS is a timed intervention that occurred between April and May of 2009 and June and July of 2010 (Figure 2). To simulate the impact of IRS effectiveness at killing and deterring vectors and the rate at which the insecticide decays on model predictions, scenarios were created to simulate very high and very low IRS effectiveness (Table 3).

Table 3. IRS scenario variables

Variable	Description	Level
IRS description	IRS decay half-life	**Baseline: 4 months**
		Highly effective: 9 months
		Insecticide resistance: 2 months
	IRS deterrent effect	**Baseline: 0.1116**
		Highly effective: 0.8632125
		Insecticide resistance: 0.1
	IRS postprandial killing effect	**Baseline: 0.2772**
		Highly effective: 0.8
		Insecticide resistance: 0.1

Compared to the baseline, increasing the duration and effectiveness of IRS had the effect of greatly reducing the simulated number of patent infections (Figure 6b). While prevalence is greatly reduced, transmission is never completely interrupted even in the scenario simulating highly effective IRS.

Biting behaviour

To study the effects of changes in vector diversity and biting behaviour, different scenarios of proportion of indoor vs. outdoor biting are considered. The baseline scenario assumes one primary vector species which bites outdoors 64% of the time and indoors 36% of the time. The experiment includes one scenario with increased exophagy with 74% of transmission occurring outdoors and 26% of transmission occurring indoors and a second scenario with transmission is split equally indoors and outdoors. This is modeled by reducing the effectiveness of vector control interventions.

Table 4. Detection Limit scenario variables

Variable	Description	Level
Detection Limit	Parasites per microliter	PCR: 10
		Skilled microscopy: 100
		Baseline (RDT): 200
		Low-quality diagnostic: 500

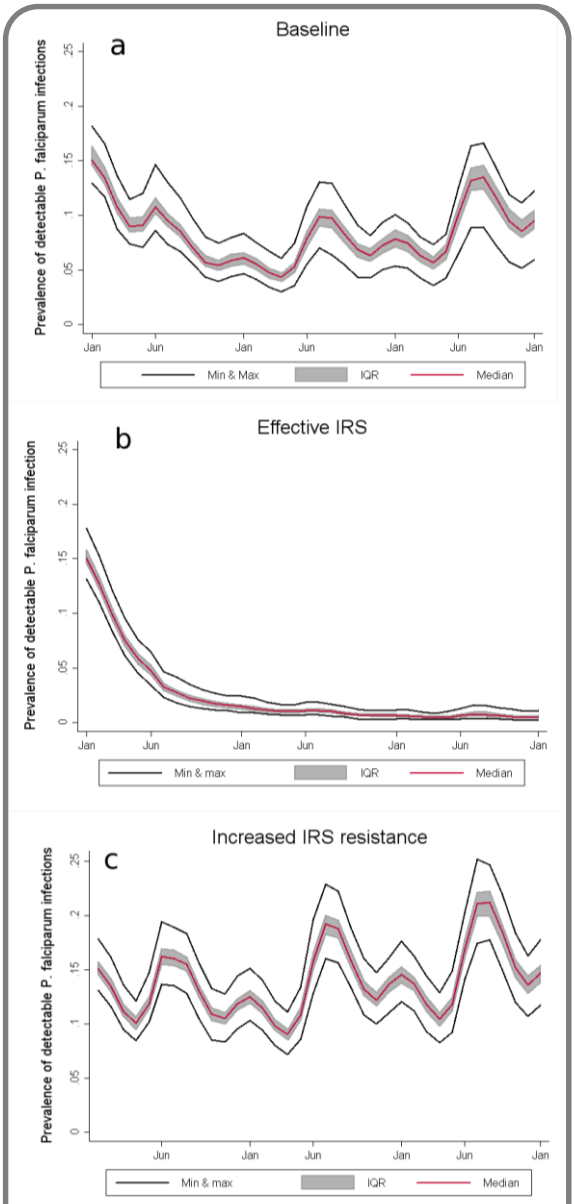

Figure 6: Sensitivity analysis of IRS effectiveness. Effect of b) highly effective IRS intervention with a half-life decay of 9 months and a killing effect of 80% and c) ineffective IRS intervention with a half-life decay of 2 months and a killing effect of 10% on the simulated number of *P. falciparum* infections as detected by RDT in a cohort of 10,000 individuals in Rachuonyo South district compared to a) baseline model with half-life decay of 4 months and a killing effect of 27.72%. The simulation ran for two years using 10 random seeds for each of the 14 OpenMalaria model variants. The center line shows the median value of the 140 simulations at each time point. The shaded area shows the interquartile range, and the two outside lines show the maximum and minimum value at each time point.

The scenario in which the biting behaviour of a single vector species is altered and a greater proportion of EIR is due to indoor biting (increased from 36% to 50%) shows a reduction in prevalence (Figure 7c). This is because the indoor mosquitoes would be affected by the IRS campaigns conducted in April – May of the first year and June – July of the second year. The scenario with a greater proportion of transmission from outdoor biting shows a similar level of transmission during the low season but greater amplitude in peak months (Figure 7b).

Survey detection limit

To address the model's sensitivity to the ability of a given test to detect a *P. falciparum* infection, an experiment was created to mimic the detection limits of polymerase chain reaction (PCR), skilled microscopy, and a low-quality diagnostic such as a poor-quality RDT or unskilled microscopy (Table 4). The number of simulated infections decreases with higher detection limits, as does the stochasticity of the predictions (Figure 8). This indicates a population that has a considerable proportion of infections occurring characterized by low parasitaemia.

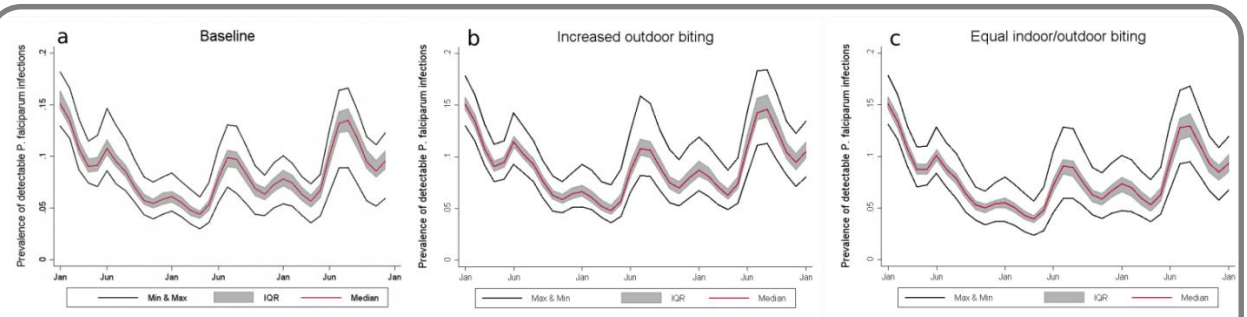

Figure 7: Sensitivity analysis of biting behavior. Effect of changing biting behavior on the simulated number of *P. falciparum* infections as detected by RDT in a population of 10,000 individuals for a) baseline model with one primary vector species 64% exophagy and 36% endophagy, b) increased exophagy (74%) and c) equal exo- and endophagy. The simulation ran for two years using 10 seeds for each of the 14 OpenMalaria model variants. The center line shows the median value of the 140 simulations at each time point. The shaded area shows the interquartile range, and the two outside lines show the maximum and minimum value at each time point.

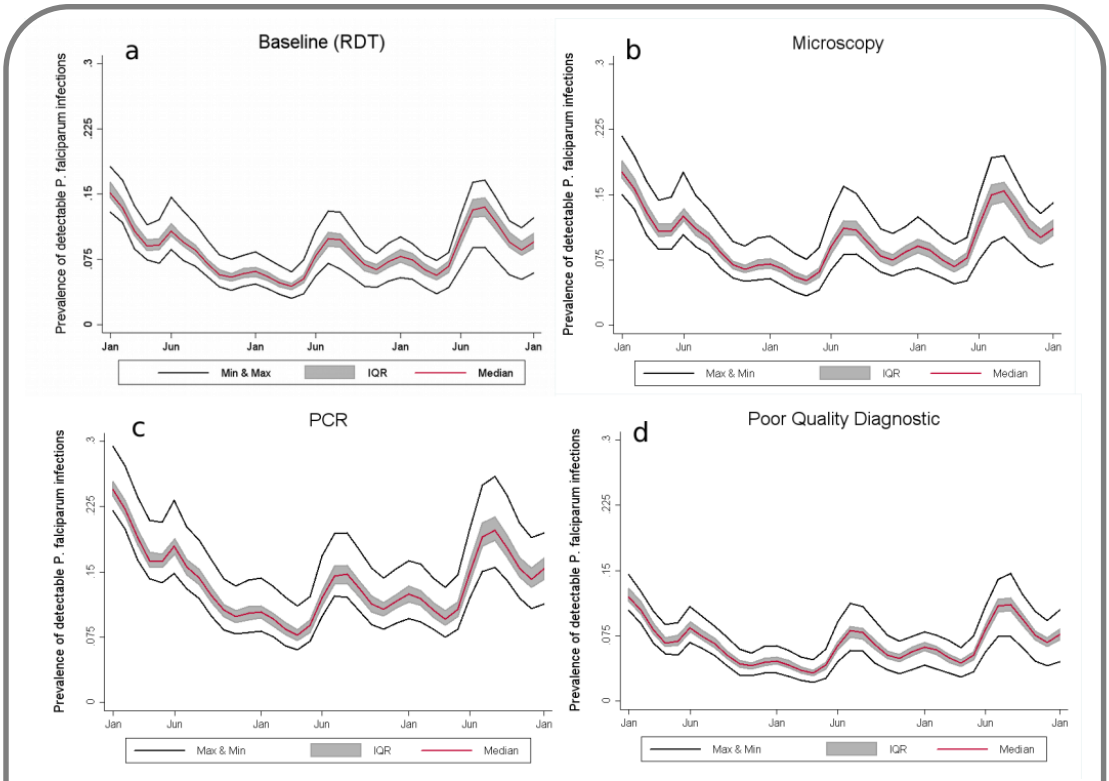

Figure 8: Sensitivity analysis of detection limit of monitoring methods. Effect of changing the detection limit (number of parasites per microliter) at which the survey is able to detect *P. falciparum* infection on the simulated number of *P. falciparum* infections in a population of 10,000 individuals for a) baseline model with a detection limit of 200, equivalent to RDT; b) detection limit of 40, equivalent to PCR; c) detection limit of 100, equivalent to skilled microscopy; and d) detection limit of 500, equivalent to a poor quality diagnostic. The simulation ran for two years using 10 seeds for each of the 14 OpenMalaria model variants. The center line shows the median value of the 140 simulations at each time point. The shaded area shows the interquartile range, and the two outside lines show the maximum and minimum value at each time point.

EIR and climatic patterns

In order to account for differences in collection and calculation method as well as micro-variations in EIR within the study area, an experiment was conducted with varying levels of the annual average EIR while keeping the seasonal pattern the same over the baseline. This includes a scenario with a low EIR value that was measured in an neighbouring district a slightly higher altitude before large-scale control programmes were implemented in 2006, two scenarios with medium EIR (one equal to double the recorded value and one equal to the recorded value in the neighboring lowland districts), and a larger EIR. OpenMalaria is able to simulate the scenarios with EIRs of 7 and 20 with less stochasticity than the scenarios with smaller EIRs.

To examine model sensitivity to changes in the entomological parameters that could occur as a result of different climate patterns an experiment was created to simulate decreased rainfall, increased rainfall, decreased temperature, increased temperature, and two long rainy periods instead of the long and short rains the study area currently experiences. Compared to the baseline, simulating increased rainfall in the same seasonal pattern did not have as great an effect on number of patent infections as did the scenario which increased the short rainy season to match the longer rains. Simulating temperature changes by altering the extrinsic incubation period and resting duration did not have a visible impact on the predicted number of patent infections (Figure 9).

Figure 9 demonstrates the overall results of the one-way sensitivity analysis in relation to the baseline scenario for Rachuonyo South.

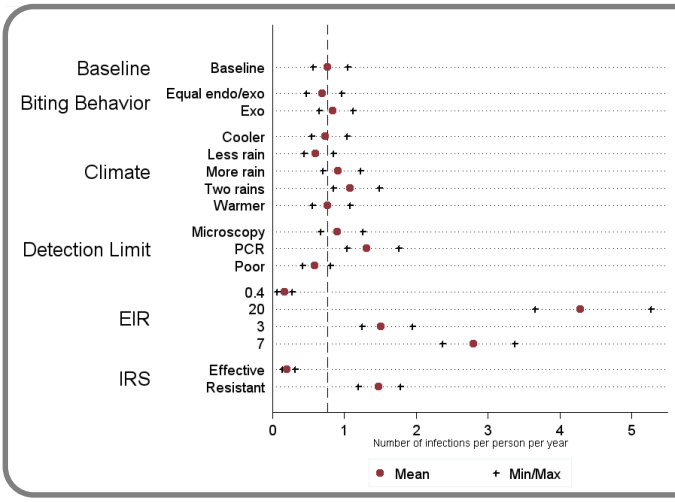

Figure 9: Summary sensitivity analysis compared to baseline model. Summary statistics for the effect of changing key parameters on the simulated number of *P. falciparum* infections per person per year averaged across all model variants during the study period of the MTC cohort study (July 2009 – June 2010) as detected by RDT in a population of 10,000 individuals. The simulation ran for two years using 10 seeds for each of the 14 OpenMalaria model variants. The circles represent the mean and the plus signs represent the minimum and maximum. The dotted line represents the baseline mean as a measure of comparison.

3.5 Discussion

Validation and model analysis

The scenario parameterized for Rachuonyo South district is able to replicate the overall level of prevalence in the given population for the majority of the months out of the year. However, the timing of the peak transmission month is delayed and the depth of the trough in November of the first year of simulations is not captured. Thus, the number of runs simulating the number of patent infections falling within the 95% confidence intervals (CIs) of the observed number of patent infections is lower than optimal. This could be due to several factors, such as inter-annual variation in transmission in the study area.

A main challenge for transmission models is calibration and validation with data from the field. The OpenMalaria transmission model is calibrated primarily by the intensity of malaria transmission, or EIR, for each vector. There are several methods to measure EIR in the field, and the method used varies by location depending on the implementer of the study [37]. Usually the types of surveys necessary to quantify transmission are not done on a regular basis, and in low transmission settings where mosquito densities are low, the longitudinal studies required to estimate EIR are intensive and inherently expensive. Entomological studies with the aim of identifying sporozoite-positive mosquitoes, while important for monitoring vector biting behavior, are not suitable for developing a seasonality pattern for a given total EIR in this area of low, unstable transmission. Perhaps monthly or even weekly studies measuring mosquito

density and changes in vector biting behavior over one or multiple years would be a way of determining the seasonality pattern of transmission. Despite a clearer picture of overall annual transmission, serology is not able to characterize seasonality of transmission, and without a baseline is unable to give an indication of pre- vs. post- intervention exposure. Serology combined with a seasonality pattern from rainfall data offered a more accurate picture than entomological data alone. While this information can be approximated from weather station data and from remote sensing in areas lacking a weather station, a challenge is relating the amount and seasonality of transmission to the amount of rainfall as their relationship is not linear [38].

The method of evaluation used in this study was to analyse the number of simulation runs which fall within the 95% CIs of the observed data. There is not yet any consensus on how to evaluate uncertainty and goodness-of-fit for model ensembles [39]. The merits of different methods have been discussed for models used in meteorology, climate change and macroeconomics, but questions remain on whether model averaging is appropriate and how to quantify an acceptable level of stochasticity for basing programmatic decisions on model predictions [40]. A consensus should be achieved on these criteria if quantitative projections from such models are to become an integral part of the range of decision-making tools for malaria control.

Implications of the sensitivity analysis

The sensitivity analysis highlights the robustness of the OpenMalaria transmission model for simulating a range of entomological and epidemiological scenarios. The majority of the simulation results for extreme scenarios of the entomological and biological components of the model remain similar to the simulation results for the baseline scenario, suggesting that small changes in these parameters are unlikely to have a large impact on prevalence, while changes in EIR and effectiveness of IRS have a greater impact on the estimated prevalence in the study area (Figure 9).

IRS

Pyrethroid resistance has already been documented in western Kenya and elsewhere and much depends on the effectiveness of these insecticides [41-43]. In the study area there are not yet reports of pyrethroid knockdown resistance (kdr) mutations due to the lack of presence of *An. gambiae s.s.,* but there may be other resistance mechanisms present, for example metabolic resistance, given the high numbers of *An. funestus* in the study area. The results of the sensitivity analysis suggest that malaria incidence and prevalence are likely to increase as this resistance continues to rise. As noted in the background section, the Kenya DOMC has alternated deployment of different types of pyrethroid insecticides for different years. While this could potentially have the effect of discouraging resistance to any one formulation, until new insecticides are developed the continued use of only pyrethroids has the potential to encourage resistance.

Biting behavior

Initial results of entomological surveys (Cooke, *personal communication)* show evidence of a shift in the relative importance of outdoor biting compared to what has been observed in the neighbouring highland district in the past [10, 44]. It is unclear whether this is a behavioral change in response to high LLIN and IRS coverage or whether there have been alterations in overall species composition. For Rachuonyo South there are no baseline data to compare this to. Evidence from lowland districts within Nyanza indicate that both composition and biting behaviour of the malaria vectors has changed over the past five years, coinciding with a substantial scaling up of vector control interventions [12]. Entomological surveys conducted in 2009 – 2011 (Stevenson, *personal communication*) show that *An. arabiensis* is now seen more frequently inside and outside dwellings than *An. gambiae s.s.,* the previously-documented major vector in Kisii district [10, 44]. Preliminary data from the study sites also indicate that *An. funestus* or other species may be playing an ever increasingly important role on malaria transmission in the area [35].

The observed data more closely resemble the scenario with indoor/outdoor biting profile based on 2009 – 2011 data, which supports the hypothesis of a greater proportion of outdoor biting. If this is the case, there is a limit to the effectiveness of the current vector control interventions in Rachuonyo South (IRS and LLINs) at controlling *P. falciparum* because they target the shrinking proportion of the infective bites occurring indoors. While these interventions will still offer an important level of deterrency, interventions that have a killing effect on exophagic mosquitoes may be an appropriate addition to existing indoor interventions [45]. Larviciding, area repellents, and even interventions targeting the human-stage of the parasite could also be taken into consideration to complement existing methods. Implementation of a number of these methods is currently being piloted in Rachuonyo South (Bousema, *personal communication)*.

Survey detection limit

The outcome simulated in this scenario is proportion of patent infections as measured by a Paracheck® rapid test kit manufactured by Orchid Biomedical Systems. The 2010 WHO malaria case management guidelines recommend treatment after parasite-based diagnosis [46]. Quality assurance measures for these tests are based on their ability to detect either 100 or 200 parasites per microliter, not because of the limitations of the RDT technology but rather because of limited accuracy and error of expert microscopy, the "gold" standard in malaria diagnosis in the absence of PCR [47, 48]. In addition, there is evidence for changes in the accuracy of diagnosis by RDTs in the East African highlands both over time and across age groups [49].

The implication of the sensitivity of the model to a change in survey detection limit is that if RDTs used in surveys perform poorly, whether the result of low quality manufacturing or improper storage conditions or use, according to simulation results up to 50% of infected individuals would be misclassified. When put in a broader public health context, there are a number of scenarios applicable to the study area when decision-making can be affected by detection limit. These range from a health worker deciding to administer an anti-malarial drug

following malaria diagnosis in an individual, to country-wide planning in the public sector health system for estimating quantities of antimalarial drugs required for a given year, to deciding the appropriate time to change the vector control strategy if transmission is based on an estimate of prevalence.

When approaching a situation where transmission is interrupted, attention must be paid to the type of screening strategy (active vs. passive case detection) and screening method used to detect the last remaining parasitaemia in the population. In these cases the higher presence of asymptomatic, sub-patent infections representing the infectious reservoir of parasites in the population indicates the PCR method would be preferable over a less sensitive method. While molecular diagnostic tools such as PCR and loop-mediated isothermal amplification (LAMP) are both able to detect infections at a much lower parasite density than microscopy or RDTs and may be appropriate in study settings, studies show these methods are not currently suitable for routine diagnosis at a community level [50, 51]. However, even the most sensitive PCR diagnostic does not detect all infections in a population. If a large proportion of infections occur at a high parasite density the detection limit of the diagnostic would not be as important a consideration. This sensitivity analysis shows that observed prevalence depends on the method used for detection, a point relevant for study design and modelling alike.

EIR and climatic patterns

The sensitivity analysis results show that an increase in EIR corresponds to an increase in cases of malaria. The OpenMalaria transmission model is dependent on the length of the gonotrophic cycle of the vector, which is in turn affected by environmental changes. The mosquito resting duration and EIP both decrease as the ambient temperature decreases [33, 52, 53]. If the EIP duration decreases, a vector infected with *P. falciparum* becomes infectious more quickly. A shorter gonotrophic cycle means both increased biting frequency and increased daily mortality of the vector. The highlands of western Kenya have variable seasonal temperature and rainfall changes; for example, in the late 1990s the study area experienced a resurgence of malaria not seen for decades [54]. Simulation results indicate that changes in temperature resulting in a

change in EIP or resting duration and changes in the overall volume of rainfall resulting in a slight change in EIR are not likely to affect the impact of IRS deployment or result in a shift in *P. falciparum* prevalence in the population. In addition, there is preliminary evidence that in the study area increased relative humidity is associated with an increased number of anophelines (Cooke, *personal communication)*. However, even taking into account the caveats for the relationship between malaria transmission and rainfall, changing the pattern of transmission to simulate the effect of an extension of the historically short rainy season to match the rainfall profile of the longer rainy season could result in greater amplitude of incidence in the peak months.

Limitations

Data

Many parameters in the model remain from the initial Tanzanian model parameterization [55], for example the parameters for the mosquito feeding cycle (Additional File 1) and treatment-seeking behaviour (Additional File 2), because there are not yet site-specific studies with this focus. While ample entomological data were collected in the study area, there was less available information on treatment-seeking behaviour and its consequences outside the public sector.

Coartem® was given to all MTC cohort study participants to clear any prevalent *P. falciparum* parasitaemia making it possible to measure malaria incidence at each follow-up. The study excluded pregnant women from the cohort due to the limited data on use in pregnancy and contraindication in the 1st trimester pregnancy of artemether-lumefantrine [19], the active ingredients of Coartem®. Infection with *P. falciparum* during pregnancy has been shown to be associated with increased parasitaemia of the mother due to a weakened immune system as well as an increased likelihood of manifestation of clinical disease in addition to adverse effects on the fetus and newborn [56]. Although this is unlikely to have a major effect on transmission in the population as a whole, the patent infections and uncomplicated episodes in the age groups for women of childbearing age could be underestimated.

Model

Since the OpenMalaria transmission model was developed to examine the effect of moderate to high transmission, it does not include a mechanism to account for inter-annual variation in EIR as driven by climatic factors. Thus, every year is treated as the same, which is not the case in the study area. In the western Kenyan highlands sharp increases in incidence occur every few years [54] and are likely to be driven by climate variability; the higher than usual transmission in the cohort following heavy rains during the time of the survey provides an example of such a sharp increase. As a result of the validation using one year's data in this area of substantial year-to-year variation, firm conclusions are unable to be drawn about the longer-term seasonal transmission in the population.

Nyanza province has the highest prevalence of HIV in Kenya at 15.1% of the population [57, 58]. HIV infection increases an individual's susceptibility to malaria infection and severity of clinical outcomes and decreases immunity [59, 60]. A limitation of the transmission model is that it does not account for the interaction between malaria and HIV.

The models analysed here do not explicitly take spatial associations into account. Variation in proximity to breeding sites could be a factor driving the difference in epidemic profile of the study area. The parameterizations used in this study do not take into account the rate of imported cases from lowland areas, as there is frequent travel between the highland Kisii and Nyamira districts and the lowland areas of Rachuonyo North, Nyando and Kisumu districts. Heterogeneity in availability to vectors and imported cases should be taken into account in future simulations of the study area.

3.6 Conclusions

Individual-based stochastic simulations of malaria can be used as a tool to assist decision making for malaria control programmes by testing assumptions about the seasonal pattern of transmission, vector diversity and behaviour, and intervention effectiveness in district-level settings. Efforts should be made to ensure models aiding in the understanding of site-specific

transmission dynamics are more accessible to programme managers. The sensitivity analysis shows that in order to simulate malaria in the Rachuonyo South highlands, attention must be paid to vector biting behaviour, their susceptibility to IRS, and the detection method used for human surveys. These features will have an impact on predicting the impact of interventions in areas with low and/or variable *P. falciparum* transmission. The sensitivity analysis also demonstrates the accuracy of the model and can lend confidence to end users of these results in informing control options. New methods and tools for analysing and evaluating simulation results will enhance the usefulness of simulations for malaria control decision-making. Measuring EIR through mosquito collection may not be the optimal way to define transmission in areas with low, unstable transmission. Further research into the relationship between different measures of malaria is needed to better quantify transmission in low transmission settings.

3.7 Author contributions

EMS designed the experiments, performed the literature review for model parameterization, analysed results and drafted the manuscript. JS participated in parameterization of the model and designed, supervised and conducted the MTC field studies. MC provided field implementation and sample analysis for the MTC entomological field studies. CO and EM supervised and coordinated the field collection of samples. GO was responsible for data management. DH programmed the simulation software. CD provided serological analysis for the MTC field studies. TAS and JC conceived of and designed the study. NC participated in designing the experiments, analysing the results, and drafting the manuscript. All authors read and approved the final manuscript.

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3.9 References

1. Hay SI, Rogers DJ, Toomer JF, Snow RW: **Annual Plasmodium falciparum entomological inoculation rates (EIR) across Africa: literature survey, Internet access and review.** *Trans R Soc Trop Med Hyg* 2000, **94:**113-127.
2. **A research agenda for malaria eradication: vector control.** *PLoS medicine* 2011, **8:**e1000401.
3. Chitnis N, Schapira A, Smith T, Steketee R: **Comparing the effectiveness of malaria vector-control interventions through a mathematical model.** *The American journal of tropical medicine and hygiene* 2010, **83:**230-240.
4. Hawley WA, ter Kuile FO, Steketee RS, Nahlen BL, Terlouw DJ, Gimnig JE, Shi YP, Vulule JM, Alaii JA, Hightower AW, et al: **Implications of the western Kenya permethrin-treated bed net study for policy, program implementation, and future research.** *The American journal of tropical medicine and hygiene* 2003, **68:**168-173.
5. Pluess B, Tanser FC, Lengeler C, Sharp BL: **Indoor residual spraying for preventing malaria.** *Cochrane database of systematic reviews* 2010**:**CD006657.
6. Guyatt HL, Corlett SK, Robinson TP, Ochola SA, Snow RW: **Malaria prevention in highland Kenya: indoor residual house-spraying vs. insecticide-treated bednets.** *Tropical medicine & international health : TM & IH* 2002, **7:**298-303.
7. Hamel MJ, Otieno P, Bayoh N, Kariuki S, Were V, Marwanga D, Laserson KF, Williamson J, Slutsker L, Gimnig J: **The combination of indoor residual spraying and insecticide-treated nets provides added protection against malaria compared with insecticide-treated nets alone.** *The American journal of tropical medicine and hygiene* 2011, **85:**1080-1086.
8. Mabaso ML, Craig M, Ross A, Smith T: **Environmental predictors of the seasonality of malaria transmission in Africa: the challenge.** *Am J Trop Med Hyg* 2007, **76:**33-38.
9. Kristan M, Abeku TA, Beard J, Okia M, Rapuoda B, Sang J, Cox J: **Variations in entomological indices in relation to weather patterns and malaria incidence in East African highlands: implications for epidemic prevention and control.** *Malar J* 2008, **7:**231.
10. Ndenga B, Githeko A, Omukunda E, Munyekenye G, Atieli H, Wamai P, Mbogo C, Minakawa N, Zhou G, Yan G: **Population dynamics of malaria vectors in western Kenya highlands.** *J Med Entomol* 2006, **43:**200-206.
11. Okara RM, Sinka ME, Minakawa N, Mbogo CM, Hay SI, Snow RW: **Distribution of the main malaria vectors in Kenya.** *Malaria journal* 2010, **9:**69.
12. Bayoh MN, Mathias DK, Odiere MR, Mutuku FM, Kamau L, Gimnig JE, Vulule JM, Hawley WA, Hamel MJ, Walker ED: **Anopheles gambiae: historical population decline associated with regional distribution of insecticide-treated bed nets in western Nyanza Province, Kenya.** *Malar J* 2010, **9:**62.
13. Minakawa N, Sonye G, Mogi M, Githeko A, Yan G: **The effects of climatic factors on the distribution and abundance of malaria vectors in Kenya.** *Journal of medical entomology* 2002, **39:**833-841.
14. Zhou G, Githeko AK, Minakawa N, Yan G: **Community-wide benefits of targeted indoor residual spray for malaria control in the western Kenya highland.** *Malar J* 2010, **9:**67.

15. White GB: **The Anopheles gambiae complex and malaria transmission around Kisumu, Kenya.** *Trans R Soc Trop Med Hyg* 1972, **66:**572-581.
16. John CC, Riedesel MA, Magak NG, Lindblade KA, Menge DM, Hodges JS, Vulule JM, Akhwale W: **Possible interruption of malaria transmission, highland Kenya, 2007-2008.** *Emerging infectious diseases* 2009, **15:**1917-1924.
17. Malakooti MA, Biomndo K, Shanks GD: **Reemergence of epidemic malaria in the highlands of western Kenya.** *Emerging infectious diseases* 1998, **4:**671-676.
18. Shanks GD, Biomndo K, Hay SI, Snow RW: **Changing patterns of clinical malaria since 1965 among a tea estate population located in the Kenyan highlands.** *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2000, **94:**253-255.
19. DOMC: **National Guidelines for Diagnosis, Treatment and Prevention of Malaria in Kenya.** (Management DoMCC ed.2006.
20. Fillinger U, Ndenga B, Githeko A, Lindsay SW: **Integrated malaria vector control with microbial larvicides and insecticide-treated nets in western Kenya: a controlled trial.** *Bull World Health Organ* 2009, **87:**655-665.
21. DOMC, KNBS, Macro I: **2010 Kenya Malaria Indicator Survey.** Nairobi, Kenya2011.
22. Smith T, Killeen GF, Maire N, Ross A, Molineaux L, Tediosi F, Hutton G, Utzinger J, Dietz K, Tanner M: **Mathematical modeling of the impact of malaria vaccines on the clinical epidemiology and natural history of Plasmodium falciparum malaria: Overview.** *Am J Trop Med Hyg* 2006, **75:**1-10.
23. Chitnis N, Smith T, Steketee R: **A mathematical model for the dynamics of malaria in mosquitoes feeding on a heterogeneous host population.** *Journal of Biological Dynamics* 2008, **2:**259 - 285.
24. Smith T, Maire N, Ross A, Penny M, Chitnis N, Schapira A, Studer A, Genton B, Lengeler C, Tediosi F, et al: **Towards a comprehensive simulation model of malaria epidemiology and control.** *Parasitology* 2008, **135:**1507-1516.
25. Smith T, Ross A, Maire N, Chitnis N, Studer A, Hardy D, Brooks A, Penny M, Tanner M: **Ensemble modeling of the likely public health impact of a pre-erythrocytic malaria vaccine.** *PLoS medicine* 2012, **9:**e1001157.
26. Chitnis N, Hardy D, Smith T: **A Periodically-Forced Mathematical Model for the Seasonal Dynamics of Malaria in Mosquitoes.** *Bulletin of mathematical biology* 2012, **74(5):**1098–1124.
27. **OpenMalaria** [http://code.google.com/p/openmalaria/wiki/Start]
28. Owusu-Agyei S, Smith T, Beck HP, Amenga-Etego L, Felger I: **Molecular epidemiology of Plasmodium falciparum infections among asymptomatic inhabitants of a holoendemic malarious area in northern Ghana.** *Tropical medicine & international health : TM & IH* 2002, **7:**421-428.
29. Drakeley CJ, Corran PH, Coleman PG, Tongren JE, McDonald SL, Carneiro I, Malima R, Lusingu J, Manjurano A, Nkya WM, et al: **Estimating medium- and long-term trends in malaria transmission by using serological markers of malaria exposure.** *Proc Natl Acad Sci U S A* 2005, **102:**5108-5113.
30. Corran P, Coleman P, Riley E, Drakeley C: **Serology: a robust indicator of malaria transmission intensity?** *Trends Parasitol* 2007, **23:**575-582.

31. Briet OJ, Hardy D, Smith TA: **Importance of factors determining the effective lifetime of a mass, long-lasting, insecticidal net distribution: a sensitivity analysis.** *Malaria journal* 2012, **11:**20.
32. Ross A, Penny M, Maire N, Studer A, Carneiro I, Schellenberg D, Greenwood B, Tanner M, Smith T: **Modelling the epidemiological impact of intermittent preventive treatment against malaria in infants.** *PLoS One* 2008, **3:**e2661.
33. Minakawa N, Omukunda E, Zhou G, Githeko A, Yan G: **Malaria vector productivity in relation to the highland environment in Kenya.** *Am J Trop Med Hyg* 2006, **75:**448-453.
34. Macdonald G: *Malariology: A comprehensive survey of all aspects of this group of diseases from a global standpoint.* Philadelphia: W.B. Saunders Company; 1957.
35. Stevenson J, St. Lauernt B, Lobo N, Cooke M, Kahindi S, Oriango R, Harbach R, Cox J, Drakeley C: **Novel vectors of malaria parasite in the western highlands of Kenya [letter].** *Emerg Infect Dis* 2012 Sept, **[serial on the Internet]**.
36. Shililu JI, Maier WA, Seitz HM, Orago AS: **Seasonal density, sporozoite rates and entomological inoculation rates of Anopheles gambiae and Anopheles funestus in a high-altitude sugarcane growing zone in Western Kenya.** *Trop Med Int Health* 1998, **3:**706-710.
37. Kelly-Hope LA, McKenzie FE: **The multiplicity of malaria transmission: a review of entomological inoculation rate measurements and methods across sub-Saharan Africa.** *Malaria journal* 2009, **8:**19.
38. Paaijmans KP, Wandago MO, Githeko AK, Takken W: **Unexpected high losses of Anopheles gambiae larvae due to rainfall.** *PLoS One* 2007, **2:**e1146.
39. Knutti R: **The end of model democracy? An editorial comment.** *Climactic Change* 2010, **102:**395-404.
40. Stainforth DA, Allen MR, Tredger ER, Smith LA: **Confidence, uncertainty and decision-support relevance in climate predictions.** *Philosophical Transactions of the Royal Society* 2007, **365:**2145-2161.
41. Ranson H, Abdallah H, Badolo A, Guelbeogo WM, Kerah-Hinzoumbe C, Yangalbe-Kalnone E, Sagnon N, Simard F, Coetzee M: **Insecticide resistance in Anopheles gambiae: data from the first year of a multi-country study highlight the extent of the problem.** *Malaria journal* 2009, **8:**299.
42. Ombok MO, G; Bayoh, N; Vulule, J; Gimnig, J; Walker, E: **Entomological monitoring of the indoor residual spraying (IRS) program in western Kenya.** In *Kenya National Malaria Forum* Nairobi, Kenya2011.
43. Kawada H, Dida GO, Ohashi K, Komagata O, Kasai S, Tomita T, Sonye G, Maekawa Y, Mwatele C, Njenga SM, et al: **Multimodal pyrethroid resistance in malaria vectors, Anopheles gambiae s.s., Anopheles arabiensis, and Anopheles funestus s.s. in western Kenya.** *PLoS One* 2011, **6:**e22574.
44. Githeko AK, Adungo NI, Karanja DM, Hawley WA, Vulule JM, Seroney IK, Ofulla AV, Atieli FK, Ondijo SO, Genga IO, et al: **Some observations on the biting behavior of Anopheles gambiae s.s., Anopheles arabiensis, and Anopheles funestus and their implications for malaria control.** *Exp Parasitol* 1996, **82:**306-315.

45. Killeen GF, Chitnis N, Moore SJ, Okumu FO: **Target product profile choices for intra-domiciliary malaria vector control pesticide products: repel or kill?** *Malaria journal* 2011, **10:**207.
46. WHO: **Guidelines for the Treatment of Malaria, Second Edition.** Geneva2010.
47. WHO: **The role of laboratory diagnosis to support malaria disease management: focus on the use of RDTs in areas of high transmission. .** Geneva: WHO Technical Consultation; 2004.
48. WHO: **Malaria Rapid Diagnostic Test Performance: Results of WHO product testing of malaria RDTs: Round 2 (2009).** (Organization WH ed. Geneva2009.
49. Abeku TA, Kristan M, Jones C, Beard J, Mueller DH, Okia M, Rapuoda B, Greenwood B, Cox J: **Determinants of the accuracy of rapid diagnostic tests in malaria case management: evidence from low and moderate transmission settings in the East African highlands.** *Malaria journal* 2008, **7:**202.
50. Han ET, Watanabe R, Sattabongkot J, Khuntirat B, Sirichaisinthop J, Iriko H, Jin L, Takeo S, Tsuboi T: **Detection of four Plasmodium species by genus- and species-specific loop-mediated isothermal amplification for clinical diagnosis.** *Journal of clinical microbiology* 2007, **45:**2521-2528.
51. Poschl B, Waneesorn J, Thekisoe O, Chutipongvivate S, Karanis P: **Comparative diagnosis of malaria infections by microscopy, nested PCR, and LAMP in northern Thailand.** *The American journal of tropical medicine and hygiene* 2010, **83:**56-60.
52. Macdonald G: *The Epidemiology and Control of Malaria.* London: Oxford University Press; 1957.
53. Rogers DJ, Randolph SE: *Advances in Parasitology.* San Diego2006.
54. Githeko A, Ndegwa W: **Predicting malaria epidemics in the Kenyan highlands using climate data: a tool for decision makers.** *Global Change & Human Health* 2001, **2:**10.
55. Chitnis N, Hardy D, Smith T: **A Periodically-Forced Mathematical Model for the Seasonal Dynamics of Malaria in Mosquitoes.** *Bulletin of mathematical biology* 2012.
56. Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, Newman RD: **Epidemiology and burden of malaria in pregnancy.** *Lancet Infect Dis* 2007, **7:**93-104.
57. Montana L, Neuman M, Mishra V, Hong R: **Spatial Modeling of HIV Prevalence in Cameroon, Kenya, and Tanzania.** 2005.
58. Montana L, Neuman M, Mishra V: **Spatial Modeling of HIV Prevalence in Kenya.** In *Demographic and Health Research*2007.
59. Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF: **HIV infection as a cofactor for severe falciparum malaria in adults living in a region of unstable malaria transmission in South Africa.** *AIDS* 2004, **18:**547-554.
60. Whitworth J, Morgan D, Quigley M, Smith A, Mayanja B, Eotu H, Omoding N, Okongo M, Malamba S, Ojwiya A: **Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study.** *Lancet* 2000, **356:**1051-1056.

Additional File 1: Parameter values for the model of the mosquito feeding cycle

Table S1: Parameter values for the model of the mosquito feeding cycle

Parameter	Value
Initial proportion of vectors infected	0.078
Initial proportion of vectors infectious	0.015[1]
Extrinsic incubation period	14**[2-4]
Human blood index	0.97[5]
Proportion of mosquitoes host-seeking on the same day as oviposting	0.313
Probability that the mosquito successfully bites chosen host	0.95
Probability that the mosquito escapes host and finds a resting place after biting	0.95
Probability of a mosquito successfully laying eggs given that it has rested	0.88
Probability of mosquito successfully resting after finding a resting site	0.99
Duration of the resting period of the vector	3[4, 6]
Maximum proportion of day spent host-seeking by vector	0.33
Probability that the mosquito survives the feeding cycle	0.623
Probability that the mosquito successfully bites chosen non-human host	0.95
Probability that the mosquito escapes non-human host and finds a resting place after biting	0.95
Probability of mosquito successfully resting after finding a resting site	0.99
Proportion of encounters on un-protected animals vs. protected animals	1

**Note: detailed description of parameters used in the entomological model can be found in Chitnis 2008[7] and Chitnis 2012[4]. All values based on Chitnis 2012[4] unless otherwise noted.*

References

1. Ndenga B, Githeko A, Omukunda E, Munyekenye G, Atieli H, Wamai P, Mbogo C, Minakawa N, Zhou G, Yan G: **Population dynamics of malaria vectors in western Kenya highlands.** *J Med Entomol* 2006, **43:**200-206.

2. Eling W: **Tropical temperatures can inhibit development of the human malaria parasite Plasmodium falciparum in the mosquito** *Proc Exper Appl Entomol, NEV Amsterdam* 2001, **12:**151 - 156.

3. Noden BH, Kent MD, Beier JC: **The impact of variations in temperature on early Plasmodium falciparum development in Anopheles stephensi.** *Parasitology* 1995, **111 (Pt 5):**539-545.

4. Chitnis N, Hardy D, Smith T: **A Periodically-Forced Mathematical Model for the Seasonal Dynamics of Malaria in Mosquitoes.** *Bulletin of mathematical biology* 2012, **74(5):**1098–1124.

5. Githeko AK, Service MW, Mbogo CM, Atieli FK, Juma FO: **Origin of blood meals in indoor and outdoor resting malaria vectors in western Kenya.** *Acta tropica* 1994, **58:**307-316.

6. Armstrong JA, Bransby-Williams WR: **The maintenance of a colony of Anopheles gambiae, with observations on the effects of changes in temperature.** *Bull World Health Organ* 1961, **24:**427-435.

7. Chitnis N, Smith T, Steketee R: **A mathematical model for the dynamics of malaria in mosquitoes feeding on a heterogeneous host population.** *Journal of Biological Dynamics* 2008, **2:**259 - 285.

Additional File 2: Health system parameter values

Table S2: Health system parameter values

Parameter	Value	Source
National guidelines for first line antimalarial	Coartem	DOMC 2006[1]
National guidelines for inpatient antimalarial	Quinine	DOMC 2006[1]
National guidelines for second line antimalarial	Quinine	DOMC 2006[1]
Initial cure rate in the absence of resistance, first line (%)	0.96	Juma 2008[2]
Initial cure rate in the absence of resistance, inpatient (%)	0.998	Ross 2008[3]
Initial cure rate in the absence of resistance, second line (%)	0.998	Ross 2008[3]
Initial cure rate in the absence of resistance, self-treatment (%)	0.63	Ross 2008[3]
Population complying to drug regimine, ACT (%)	0.892	Kabanywanyi 2010[4]
Population complying to drug regimine, self-treatment (%)	0.85	Ross 2008[3]
Effectiveness of treatment of non-compliers, first line (%)	0.8544	Fogg 2004[3]
Effectiveness of treatment of non-compliers, self-treatment (%)	0	Ross 2008[3]
Probability that a patient with newly incident uncomplicated disease seeks official care per timestep	0.04	Ross 2008[3]
Probability that a patient with uncomplicated disease self-treats per timestep	0.0212	Sumba 2008[5]
Probability that a patient with recurrence of uncomplicated disease seeks official care per timestep	0.04	Ross 2008[3]
Probability that a patient with severe disease obtains appropriate care per timestep	0.48	Ross 2008[3]
Probalility of sequelae in inpatients per timestep, for individuals under 5 years old	0.0132	Ross 2008[3]
Probalility of sequelae in inpatients per timestep, for individuals over 5 years old	0.005	Ross 2008[3]

References

1. DOMC: **National Guidelines for Diagnosis, Treatment and Prevention of Malaria in Kenya.** (Management DoMCC ed.; 2006.

2. Juma EA, Obonyo CO, Akhwale WS, Ogutu BR: **A randomized, open-label, comparative efficacy trial of artemether-lumefantrine suspension versus artemether-lumefantrine tablets for treatment of uncomplicated Plasmodium falciparum malaria in children in western Kenya.** *Malar J* 2008, **7:**262.

3. Ross A, Penny M, Maire N, Studer A, Carneiro I, Schellenberg D, Greenwood B, Tanner M, Smith T: **Modelling the epidemiological impact of intermittent preventive treatment against malaria in infants.** *PLoS One* 2008, **3:**e2661.

4. Kabanywanyi AM, Lengeler C, Kasim P, King'eng'ena S, Schlienger R, Mulure N, Genton B: **Adherence to and acceptability of artemether-lumefantrine as first-line anti-malarial treatment: evidence from a rural community in Tanzania.** *Malar J* 2010, **9:**48.

5. Sumba PO, Wong SL, Kanzaria HK, Johnson KA, John CC: **Malaria treatment-seeking behaviour and recovery from malaria in a highland area of Kenya.** *Malar J* 2008, **7:**245.

Additional File 3: Description of model demographic parameters

Table S3: Description of model demographic parameters and source

Age Group	<1	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Distribution (%)[1]	2.6	13.1	15.2	13.8	10	8.6	702	6	4.7	4.1	3.5	2.9	2.2	1.9	1.3	1.1	0.6	1	0.1
Distribution (#)*	510	2,567	2,979	2,705	1,960	1,685	1,411	1,176	921	804	686	568	431	372	255	216	118	196	20

Case Fatality Rate**	<3 months: 0.09189	18-30 months: 0.0689189	4.5-7.5 years: 0.0459459
	3-8 months: 0.0810811	2.5-3.5 years: 0.0675676	7.5-12.5 years: 0.0945946
	9-17 months: 0.0648649	3.5-4.5 years: 0.0297297	12.5-14 years: 0.1243243

*Proportion at national level applied to census total population of study area, 19,598 individuals
**Deaths among hospitalized cases of severe malaria. Schellenberg, 1999[2]

References

1. Kenya National Bureau of Statistics (KNBS) and ICF Macro. 2010. **Kenya Demographic and Health Survey 2008-09.** Calverton, Maryland: KNBS and ICF Macro.

2. Schellenberg D, Menendez C, Kahigwa E, Font F, Galindo C, Acosta C, Armstrong Schellenberg J, Aponte JJ, Kimario J, Urassa H, Mshinda H, Tanner M, Alonso P: **African children with malaria in an area of intense *Plasmodium falciparum* transmission: features on admission to the hospital and risk factors for death.** *Am J Trop Med Hyg* 1999, **63:**431 – 438.

Additional File 4: Vector control intervention effective length of protection parameter values

Table S4: Vector control intervention effective length of protection parameter values*

Parameter	Mean	Sigma	L	Function	k
ITN Hole Rate	0	0.8	-	-	-
ITN Rip Rate	2.7	0.8	-	-	-
ITN Initial Insecticide	1	0	-	-	-
ITN Insecticide Decay	0	0	3[1]	exponential[2]	-
ITN Attrition	-	-	15.57941	constant	18
IRS Decay	-	-	0.33	exponential[2]	-

**Note: all values are based on Chitnis 2010[13] updated with the model described in Briët 2012[3] unless otherwise noted.*

References

1. Chitnis N, Smith T, Schapira A: **Parameter Values for Transmission Model. Unpublished work.** pp. 1 - 17. Basel: Swiss TPH; 2010:1 - 17.

2. Ombok MO, G; Bayoh, N; Vulule, J; Gimnig, J; Walker, E: **Entomological monitoring of the indoor residual spraying (IRS) program in western Kenya.** In *Kenya National Malaria Forum* Nairobi, Kenya; 2011.

3. Briet OJ, Hardy D, Smith TA: **Importance of factors determining the effective lifetime of a mass, long-lasting, insecticidal net distribution: a sensitivity analysis.** *Malaria journal* 2012, **11:**20.

Additional File 5: Vector control intervention effectiveness parameter values

Table S5: Vector control intervention effectiveness parameter values*

Parameter	Deterrency	Preprandial Killing Effect	Postprandial Killing Effect
ITN Base Factor	-	0	0
ITN Hole Factor	1	0	0
ITN Hole Scaling Factor	1	0	0
ITN Insecticide Factor	8416	972	972
ITN Insecticide Scaling Factor	0.001	0.001	0.001
ITN Interaction Factor	1	0	0
IRS Pyrethroid Insecticide	0.1116	0	0.2772

**Note: all values are based on Chitnis 2010[1] updated with the model described in Briet 2012[2] unless otherwise noted. Please note that all figures for "IRS Pyrethroid Insecticide" in this table have been adjusted from their original levels to account for the proportion of exposure in the study area occurring outdoors. Unadjusted initial values for these parameters by species can be found in the sources noted above.*

References

1. Chitnis N, Smith T, Schapira A: **Parameter Values for Transmission Model. Unpublished work.** pp. 1 - 17. Basel: Swiss TPH; 2010:1 - 17.

2. Briet OJ, Hardy D, Smith TA: **Importance of factors determining the effective lifetime of a mass, long-lasting, insecticidal net distribution: a sensitivity analysis.** *Malaria journal* 2012, **11:**20.

Additional File 6: Vector control intervention implementation parameter values

Table S6: Vector control intervention implementation parameter values*

Intervention	Usage	Target age (years)	Timing	Coverage
ANC	1	0.0833[1]	0	0.8[1]
Mass	-	-	0	0.3026
			2009 April	
IRS	-	-	2010 June	0.693
MDA	-	cohort	2009 June	0.15

**Note: all values are based on MTC cohort data unless otherwise noted.*

References

1. Chitnis N, Smith T, Schapira A: **Parameter Values for Transmission Model. Unpublished work.** pp. 1 - 17. Basel: Swiss TPH; 2010:1 - 17.

Additional File 7: Model parameterization source overview

Table S7: Model parameterization source overview	
Total inputs	123
Site-specific MTC data	12 (10%)
Regional/national lit review	41 (33%)
Previous model parameterization	70 (57%)

Additional File 8: Rachuonyo South baseline model parameterization, District-level

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4. Modeling the cost effectiveness of malaria control interventions in the highlands of western Kenya

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4.1 Abstract

Introduction

Tools that allow for *in silico* optimization of available malaria control strategies can assist the decision-making process for prioritizing interventions. The OpenMalaria stochastic simulation modeling platform can be applied to simulate the impact of interventions singly and in combination as implemented in Rachuonyo South District, western Kenya, to support this goal.

Methods

Combinations of malaria interventions were simulated using a previously-published, validated model of malaria epidemiology and control in the study area. An economic model of the costs of case management and malaria control interventions in Kenya was applied to simulation results and cost-effectiveness of each intervention combination compared to the corresponding simulated outputs of a scenario without interventions. Uncertainty was evaluated by varying health system and intervention delivery parameters.

Results

The intervention strategy with the greatest simulated health impact employed long lasting insecticide treated net (LLIN) use by 80% of the population, 90% of households covered by indoor residual spraying (IRS) with deployment starting in April, and intermittent screen and treat (IST) of school children using Artemether lumefantrine (AL) with 80% coverage twice per term. However, the current malaria control strategy in the study area of LLIN use of 56% and IRS coverage of 70% was the most cost effective at reducing disability-adjusted life years (DALYs) over a five year period.

Conclusions

All the simulated intervention combinations can be considered cost effective in the context of available resources for health in Kenya. Increasing coverage of vector control interventions has a larger simulated impact compared to adding IST to the current implementation strategy, suggesting

that transmission in the study area is not at a level to warrant replacing vector control to a school-based screen and treat program. These results have the potential to assist malaria control program managers in the study area in adding new or changing the implementation of current interventions.

4.2 Introduction

Important progress has been made in the past decade in reducing malaria morbidity and mortality in Kenya, but it is not obvious which additional tools and strategies should be the next priority to include in the package of malaria control interventions in a given area to keep transmission levels low, especially given the threat of resistance of the parasite and vectors to antimalarial drugs and insecticides [1, 2]. Application of mathematical models for use in simulations of malaria epidemiology and control can help estimate the impact of interventions singly and in combination to support this goal.

OpenMalaria, a stochastic simulation modeling platform [3], has previously been applied to Rachuonyo South District, Nyanza Province, Kenya in order to describe the epidemiology of malaria and control area and identify uncertainty in key parameters pertaining to the study area [4]. Results indicate that the OpenMalaria model, as parameterized for Rachuonyo South District, can be extended to simulate the epidemiologic and economic impact of combinations of a range of existing and potential future malaria control interventions, singly and in combination, implemented in the study area [4]. This study addresses the cost effectiveness of feasible malaria control interventions in Rachuonyo South District for a five year time horizon.

Study area

Rachuonyo South District in Homa Bay County of Nyanza Province, Kenya is a highland fringe area with altitude between 1,400 and 1,600 meters. Ethnicity is predominantly Luo and homesteads are distributed broadly across a rolling landscape intersected with small streams and rivers. The area is characterized by generally low malaria endemicity with marked seasonal and inter-annual variations in transmission [5, 6]. As a result of a 2009 survey, community level parasite prevalence was estimated to be 4.5% and transmission was measured with an entomological inoculation rate of 1.5

infectious bites per person per year [4], but subsequent surveys in the study area showed community-level parasite prevalence to be as high as 15.5% [7]. This is in the range of the reported 2010 national average parasite prevalence of 12%, but low compared to prevalence in the neighboring lowland districts bordering Lake Kisumu that reach 38% in children under 15 [8]. Malaria transmission peaks twice each year following rainfall patterns with a long rainy season between March and June and a shorter season in October and November. Recent studies indicate that *Plasmodium falciparum* is transmitted not only by *Anopheles funestus* and *An arabiensis*, but also by another, as yet unidentified secondary vector with outdoor-active, early-biting behavior, potentially challenging the effectiveness of current vector control interventions targeting indoor biting mosquitoes [9].

The main malaria control methods are currently mass-distribution of LLINs, annual indoor residual spraying (IRS) with pyrethroids, and prompt and effective treatment [8, 10, 11]. Kenya's health system relies heavily on user fees and other out-of-pocket payments, with exemptions for children under five, the poor, and special conditions and services such as malaria and tuberculosis, in both the formal public and private sector [12]. The latter provides a substantial proportion of primary care services (31%) [13].

Rachuonyo South is one of a number of field sites of the Malaria Transmission Consortium (MTC), a project with the goal of enabling operational program managers to achieve optimal implementation of transmission-reducing malaria control techniques. Active between 2009 and 2012, MTC surveys provided detailed entomological studies of species composition and biting behavior [9], transmission estimation and community evaluation of LLINs and IRS versus LLINs alone. To complement these studies, a trial to assess the effect of hotspot-targeted interventions in populations living both inside and outside hotspots has recently been implemented [14]. Targeted interventions of this trial included distribution of LLINs, IRS, larviciding and intermittent screening and treatment.

4.3 Methods

Ethics approval

The study proposal received ethics approval from the Ethical Review Committee (ERC) of the Kenya Medical Research Institute (KEMRI) Nairobi under proposal number SSC 2163, the London School of Hygiene & Tropical Medicine ethics committee (#6111), and from Centers for Disease Control and Prevention (with exempt status).

OpenMalaria modelling platform

A team at the Swiss Tropical and Public Health Institute (Swiss TPH) and Liverpool School of Tropical Medicine (LSTM) developed the OpenMalaria platform comprising stochastic simulation models of transmission of malaria based on the simulation of infection in individuals. These models are able to evaluate the impact (cost-effectiveness, clinical, epidemiological and entomological) of numerous intervention strategies for malaria control [3, 15-19]. The details of the methods to build and parameterize the transmission model used in this project have been published elsewhere [3, 15-19]. Briefly, individual infections in humans are simulated by stochastic series of parasite densities, which determine an individual's morbidity and mortality risks as well as their infectiousness to vectors [3, 15]. These simulated infections are linked to a model of transmission of malaria between humans and mosquitoes and to models of interventions [3, 15, 16].

Model parameterization and experiment design

The scenario describing the current intervention mix was parameterized using a previously-published model of malaria epidemiology and control in Rachuonyo South District, validated with observed data from the site-specific MTC studies described above [4]. Parameterization of this baseline scenario included the characteristics of vector composition and biting behavior, seasonality of transmission, treatment seeking behavior and existing malaria control interventions in the study area as described above.

Combinations of interventions for the experiment were chosen in collaboration with malaria control personnel in the study area to correspond to a 2011-2012 intervention evaluation trial [14]. LLIN use the previous night was simulated at the proportion observed in the population (56%) and an increased level (80%) with one mass distribution at the beginning of the study period. Proportion of houses receiving IRS with a pyrethroid was simulated at the proportion observed in the population (70%) and an increased level (90%). The implementation schedule for IRS was simulated at the observed once-yearly schedule of alternating start dates in April and then June, as well as consistent implementation starting in April, May, and June. Intermittent screen and treatment of school aged children with Artemether lumefantrine (AL) was simulated at low (40%) and high (80%) coverage, and a frequency of either once (January, May and September) or twice (initial months plus March, July and November) per school term. These combinations, as well as their coverage levels and implementation schedules, are described in **Table 1**.

Model Implementation

Each intervention strategy was simulated in a population of 100,000 individuals. To simulate the status quo prior to interventions simulations were run for one human life span to induce an "equilibrium" level of immunity. Forward simulations of each intervention combination were made using an ensemble of 14 model variants for malaria in humans to address model uncertainty [18], with each model variant repeated with five random seeds to address stochasticity. Each intervention combination was simulated for a period of five years assuming 28% of fevers receive an antimalarial [8]. Simulations were run over the malariacontrol.net volunteer computing platform (www.malariacontrol.net).

Table 1. Experiment design of the combinations and coverage levels of interventions simulated for the study.

	LLIN use (%)	IRS coverage (%)	IRS deployment month	School-based IST coverage (%)	IST frequency (per school term)	Fevers receiving an antimalarial (%)
Current strategy*	56	70	Alternating April/June			28
No intervention						28
Increase coverage	80	90	Alternating April/June			28
Add school-based IST	56	70	April	80	2	28
	80	90	April	80	2	28
Change timing of IRS	56	70	April			28
	56	70	May			28
	56	70	June			28
Change timing and increase coverage of IRS	56	90	April			28
	56	90	May			28
	56	90	June			28
IRS alone, change coverage		70	Alternating April/June			28
		90	Alternating April/June			28
LLINs alone	56					28
	80					28
IST alone				40	1	28
				40	2	28
				80	1	28
				80	2	28

*Represents the base case scenario as parameterized in Stuckey et al. 2012 [4].

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Estimating the cost of malaria case management and interventions

Case management costing model

Malaria case management costs were based on a societal perspective; direct costs to the health systems are considered, as well as direct expenditures associated with malaria episodes at the household level. Indirect costs, including productivity loss due to illness, were not accounted for. While the latter tend to dominate the economic cost of illness [20-23], including these in cost-effectiveness analysis would result in double counting of intervention benefits [24-26].

Treatment costs are evaluated following a model of malaria case management developed for endemic settings and is described elsewhere [25]. Briefly, the entry point to the model is an acute malaria episode from where treatment seeking is described in terms of the formal and informal sector, and then by level of care compliance with the recommended first-line antimalarial, and further by type of treatment and adherence and drug quality of that treatment. Defined in this manner, the methodology captures patterns in health seeking behavior in a given setting that reflect the underlying health systems infrastructure, quality of health care delivery as well as individual preferences and beliefs about and understanding of clinical outcomes associated with the illness. The methodology to evaluate effectiveness of malaria service delivery using data from national surveys and literature is detailed elsewhere [27]. While the proportion of fevers in Kenya that access medical care is estimated at 61.8% based on demographic health and surveillance (DHS) data [28], effective coverage will be much lower due to poor adherence to drug regimen, intake of counterfeit antimalarials, and drug resistance [27].

On the provider side, cost per episode covers drugs, diagnosis, medical personnel, facility charges, and other consumables. In addition to the first-line antimalarial as per national malaria guidelines, a portion of uncomplicated cases were assigned to treatment with sulfadoxine pyrimethamine (SP) given evidence on moderate uptake of AL, the first line artimisinin combination therapy (ACT) in the study area [29, 30]. Drug costs associated with severe illness include intravenous and oral quinine with length of regimen varied by outcome. Kenya's national policy of treating severe illness with intra venous (IV) artesunate had not been implemented at the time of

the study and was therefore not included in the costing model. For hospitalizations leading to recovery, costs included an initial dose of IV quinine, followed by three further days of IV quinine and four days oral quinine. For severe cases that develop into neurological sequelae, costs included an initial dose of IV quinine, followed by 4.5 days of further IV quinine treatment, and subsequent 5.5 days of oral quinine therapy. Severe fatal events were assumed to occur within 48 hours of hospital admission and therefore involve only the initial loading dose of IV quinine and two more days of IV quinine treatment [31]. Drug costs were calculated according to age and weight appropriate regimens [22]. Cost of diagnosis with RDT were calculated proportionally to the fraction of fever cases tested. Facility, personnel, linens, consumables and other outpatient "hotel" charges were obtained from the WHO-CHOICE project [32]. Costs by facility type including health centers with beds, health centers with no beds, and hospital outpatient and inpatient departments were then matched with respective probability of seeking care at a given level estimated from the 2009 Kenyan DHS survey [28]. The DHS patterns in health seeking behavior for febrile illness are likely representative of uncomplicated malaria in countries with high levels of transmission, and somewhat biased in countries with low EIR to the extent that mothers are able to differentiate malaria from other febrile illnesses and care for their children differently. For severe episodes treated in inpatient settings, facility charges were scaled to account for length of hospitalization: 4.5 days for severe episodes that recover, 10 days for severe episodes that develop into neurological sequelae, and 2 days for terminal episodes [31]. Costs were inflated to 2012 using the average annual consumer price index (CPI) estimated over the 2008-2011 year period [33] and can be found in **Text S1**.

Direct patient costs associated with a malaria episode include travel expenses to and from healthcare facility and other consumables (i.e. water, food, etc) and were based on the multi-country literature review. Spending on consumables is generally considered negligible; only a few studies recorded these data with an average of $0.20 per visit [25, 34, 35]. For treatment outside of the formal sector including pharmacy, shop, and other sources of care based on self-diagnosis, it is assumed that patients do not incur any additional costs to purchase the drug because these providers are generally close to the patient's home. Thus only drug costs were added for treatments in informal sector.

Both average and marginal health system costs were calculated for each outcome. The average cost includes all costs involved in delivering a health intervention, including the use of spare capacity or slack in the system, health care resources diverted from other uses, and existing health sector resources shared with other health programs. In the marginal analysis only costs of drugs, diagnosis, and patient spending per visit were considered, as broader savings to the health system including labour and capital costs would not be immediately affected by changes in consumption of medical services due to lower diseases burden achieved by control interventions [31, 36].

A sensitivity analysis was conducted for the costs of test and cost per ACT dose by varying costs by -50%/+100%, and for proportion of fevers that access medical care by varying access -/+50% (**Table 2**).

Costing interventions

A general approach for costing malaria interventions using secondary data was applied as outlined by Kolaczinski et al [37]. Current cost of commodities including LLINs, insecticide, and drugs were sourced from the Global Fund to Fight AIDS, Tuberculosis and Malaria Price and Quality Reporting Tool [38]. Costs associated with delivery of interventions and intervention mixes were estimated by reviewing Kenyan field trials predominately from around the study area as identified in a recent systematic review of costs of malaria interventions [39] (**Table 3**). These non-tradable costs were expressed in Kenyan Shillings, inflated to 2012 via Kenyan GDP deflator [33], and converted into USD at reference year exchange rates [40]. Ingredient costs considered in the marginal analysis include commodities, training and distribution. A sensitivity analysis was conducted for the intervention costs by varying costs by -50%/+100% (**Table 3**).

Table 3. Costing and sensitivity analysis of malaria control interventions in Kenya.

					Sensitivity analysis	
Intervention	**Unit**	**Distribution method**	**Economic cost per unit**	**Marginal economic cost per unit**	**Lower value**	**Upper value**
Long lasting insecticide-treated bednets (LLIN)	Net delivered	Mass campaign through community organizations [55]	$8.52	$8.37	$4.26	$17.04
Indoor residual spraying (IRS)	Person protected	Annual mass campaign [55]	$0.73	$0.34	$0.34	$1.46
School-based intermittent screen and treat (IST)	Child screened	School-based distribution [56]	$6.32	$2.89	$3.16	$12.63

All costs are in 2012 USD.
doi:10.1371/journal.pone.0107700.t003

Analysis

Epidemiological outcomes

The simulated effectiveness of malaria control interventions and intervention combinations was evaluated by calculating the mean and inter-quartile range (IQR) of all model variants and seeds for each intervention combination for the difference in disease burden over a five year period from the start of intervention deployment compared to the mean of the simulations of the base case scenario with no interventions other than the existing case management system. Outcomes evaluated include decrease in parasite prevalence, number of uncomplicated episodes, hospitalizations and deaths averted in the general population. In addition to indicators for severity of illness, the overall population burden averted in terms of disability adjusted life years (DALYs) is calculated by combining mortality and morbidity measures as described by Murray and Lopez [25, 41]. Following standard methodology for cost effectiveness analysis presented by Drummond and colleagues [24], years of life lost to illness (YLLs) are calculated assuming age-specific life expectancies based on the life-table from Butajira, Ethiopia, with an average life expectancy of 46.6 years at birth [42].

Cost effectiveness calculation

Estimates of effectiveness of control interventions and intervention mixes are combined with the added costs of implementing these control measures. Treatment cost savings, or the reduction in cost to the health system due to the reduction in cases seen by the system, achieved by implementing the control strategy, are used to offset implementation costs and thus cost effectiveness ratios are calculated based on net rather than total intervention costs.

The cost savings to the case management system and households (CM) associated with implementing each intervention combination (IC) instead of a scenario without interventions (NO) are computed as DC_{cmNO}-DC_{cmIC}, where DC_{cmNO} are the direct costs (DC) of case management in the scenario without interventions and DC_{cmIC} are the direct costs of case management in the case of each intervention combination. These cost savings are subtracted from the direct cost of implementing each intervention combination (DC_{int}) to give a net intervention combination cost (NC) computed as follows: $NC = DC_{int} –(DC_{cmNO}-DC_{cmIC})$. Cost effectiveness is evaluated in two ways. The first is by calculating the average cost effectiveness ratio (ACER), as the net cost (NC) of the intervention divided by the net effects (NE) of the intervention. The second is by calculating the incremental cost effectiveness ratio (ICER), which follows the same methodology for calculating the ACER, except the net costs and net effects of each intervention combination are calculated against the currently implemented strategy.

Both marginal and average cost-effectiveness ratios over a five year reference period are reported to illustrate the likely short-term financial impact of the intervention, as well as the longer-term impact associated with the intervention including structural changes in health care delivery in response to lower disease burden achieved by the program. Cost effectiveness ratios are reported without discounting of future costs and benefits due to the short implementation time frame of the study and the recommendation from the revised GBD study [43]. Cost effectiveness ratios are calculated for a range of policy relevant outcomes including cost per case, hospitalization, death, and DALYs averted.

4.4 Results

Epidemiological outcomes

Compared to an intervention scenario with no malaria control outside of routine case management, and after five years of implementation, unsurprisingly, the intervention combination with the highest levels of intervention coverage (includes LLIN use by 80% of the population, 90% of households covered by IRS with deployment starting in April, and IST of school children using AL with 80% coverage twice per term) had the best health outcomes (simulated reduction in all-age parasite prevalence (99%, IQR 99.1-99.3%), average averted cases of uncomplicated malaria per person (7.46, IQR 7.44-7.48), hospitalizations averted (thousands)(3.96, IQR 3.95, 3.98), deaths averted (1,541, IQR 1,535, 1,551), and DALYs averted (thousands) (77.6, IQR 77.3-78.2)) (**Table 4**).

Simulation results indicate that increased coverage of vector control has a larger impact than adding an IST intervention to the current control strategy. However, adding the highest IST coverage and frequency to the current strategy could reduce parasite prevalence by an additional nine percentage points (**Figure 1**). Despite high coverage levels of all interventions, the scenario with the largest simulated epidemiological impact only resulted in one fewer uncomplicated case per person over the course of five years compared to the level observed in the study area with the current strategy (**Table 4**). Changing the timing of IRS deployment did not result in a reduction in simulated parasite prevalence either at observed coverage levels or when coverage was increased to 90% (**Table 4**).

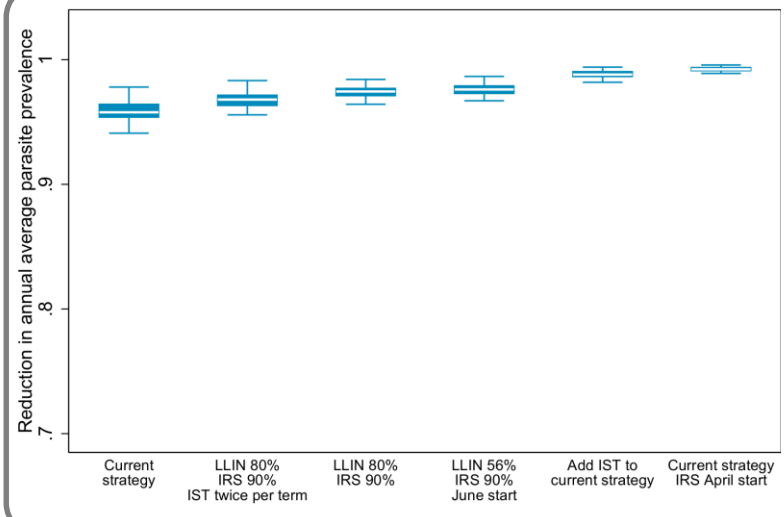

Figure 1: Simulated reduction in all-age annual average parasite prevalence by intervention combination compared to a scenario with no intervention. White lines represent the simulated median value, blue boxes represent the inter-quartile range, and capped bars represent the upper and lower adjacent values for simulated results for each intervention combination using an ensemble of 14 model variants and five random seeds. Choice of intervention combinations is based on the criteria of simulated reduction in parasite prevalence greater than the strategy currently implemented in the study area.

Table 4. Simulated effect of intervention combinations.

	Proportion reduction in all-age parasite prevalence, year 5		Uncomplicated episodes averted per person		Hospitalizations averted (thousands)		Deaths averted		DALYs averted (thousands)	
	Mean	**IQR**	**Mean**	**IQR**	**Mean**	**IQR**	**Mean**	**IQR**	**Mean**	**IQR**
Current strategy										
LLIN 56%+IRS 70%	0.96	(0.95, 0.96)	7.04	(6.97, 7.10)	3.78	(3.74, 3.83)	1.42	(1.40, 1.44)	71.48	(70.77, 2.37)
Increase coverage										
LLIN 80%+IRS 90%	**0.99**	**(0.98, 0.99)**	**7.43**	**(7.40, 7.45)**	**3.96**	**(3.94, 3.97)**	**1.52**	**(1.51, 1.53)**	**76.27**	**(75.93, 6.75)**
Add school-based IST										
LLIN 56%+IRS 70%+IST 80% twice per term	**0.98**	**(0.97, 0.98)**	**7.16**	**(7.08, 7.22)**	**3.82**	**(3.79, 3.87)**	**1.46**	**(1.45, 1.48)**	**73.68**	**(73.07, 4.47)**
LLIN 80%+IRS 90%+IST 80% twice per term	**0.99**	**(0.99, 0.99)**	**7.46**	**(7.44, 7.48)**	**3.96**	**(3.96, 3.98)**	**1.54**	**(1.54, 1.55)**	**77.57**	**(77.26, 8.16)**
Change timing of IRS										
LLIN 56%+IRS 70% April start	**0.97**	**(0.96, 0.97)**	**7.09**	**(7.01, 7.15)**	**3.80**	**(3.76, 3.86)**	**1.43**	**(1.42, 1.45)**	**71.85**	**(71.27, 2.83)**
LLIN 56%+IRS 70% May start	0.95	(0.95, 0.96)	6.98	(6.90, 7.05)	3.75	(3.71, 3.82)	1.40	(1.39, 1.42)	70.48	(69.81, 1.50)
LLIN 56%+IRS 70% June start	0.96	(0.96, 0.97)	**7.08**	**(7.01, 7.13)**	**3.80**	**(3.77, 3.84)**	**1.43**	**(1.41, 1.44)**	**71.79**	**(71.09, 2.80)**
Change timing and increase coverage of IRS										
LLIN 56%+IRS 90% April start	0.76	(0.73, 0.78)	6.12	(5.85, 6.25)	3.26	(3.06, 3.45)	1.21	(1.14, 1.27)	61.31	(58.17, 4.18)
LLIN 56%+IRS 90% May start	**0.97**	**(0.96, 0.97)**	**7.07**	**(7.01, 7.13)**	**3.79**	**(3.75, 3.84)**	**1.43**	**(1.41, 1.45)**	**71.79**	**(71.19, 2.88)**
LLIN 56%+IRS 90% June start	**0.97**	**(0.97, 0.98)**	**7.16**	**(7.09, 7.22)**	**3.84**	**(3.81, 3.88)**	**1.45**	**(1.43, 1.46)**	**72.78**	**(72.20, 3.63)**
IRS alone, change coverage										
IRS 70%	0.53	(0.50, 0.55)	2.89	(2.06, 3.33)	1.66	(1.35, 1.97)	0.60	(0.49, 0.74)	30.33	(25.56, 7.05)
IRS 90%	0.66	(0.63, 0.67)	3.63	(2.95, 3.99)	2.10	(1.86, 2.37)	0.74	(0.66, 0.85)	37.62	(33.56, 2.63)
LLINs alone										
LLIN 56%	0.95	(0.95, 0.96)	7.00	(6.93, 7.05)	3.76	(3.72, 3.82)	1.41	(1.39, 1.43)	70.86	(70.11, 1.95)
LLIN 80%	0.94	(0.93, 0.94)	**7.15**	**(7.08, 7.22)**	**3.80**	**(3.76, 3.86)**	**1.44**	**(1.42, 1.46)**	**72.65**	**(71.76, 3.68)**
School-based IST alone										
IST 40% once per term	0.09	(0.05, 0.16)	0.28	(−0.83, 1.05)	0.16	(−0.17, 0.63)	0.07	(−0.04, 0.26)	3.40	(−2.12, 12.75)
IST 40% twice per term	0.14	(0.11, 0.20)	0.46	(−0.66, 1.20)	0.25	(−0.08, 0.68)	0.10	(−0.001, 0.32)	5.21	(−0.33, 14.80)
IST 80% once per term	0.16	(0.13, 0.21)	0.53	(−0.59, 1.27)	0.29	(−0.05, 0.74)	0.12	(−0.01, 0.35)	5.93	(−0.84, 16.08)
IST 80% twice per term	0.22	(0.19, 0.27)	0.78	(−0.27, 1.46)	0.42	(0.08, 0.82)	0.16	(0.05, 0.36)	8.14	(2.34, 18.06)

Compared to a scenario with no interventions outside the existing case management system, the mean and inter-quartile range of the impact of different intervention combinations (**Table 1**) on epidemiological outcomes in a population of 100,000 individuals over a time period of five years*. **Bold** figures indicate mean results improved from the current strategy.
**Unless otherwise indicated.*

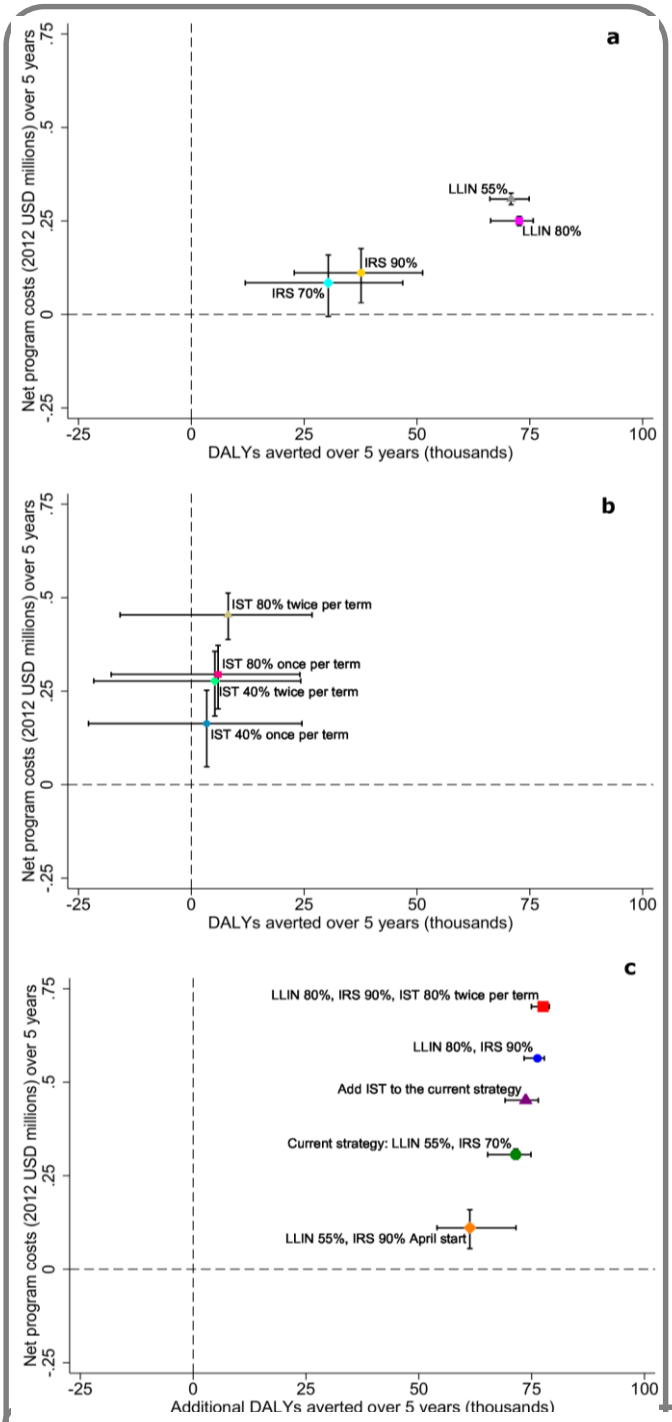

Figure 2: Relationship between cost and simulated health impact. Simulated cumulative DALYs averted after five years compared to the no intervention scenario by net program costs for different implementation strategies of **a**) vector control interventions, **b**) intermittent screen and treat in school children, and **c**) combinations of interventions. Symbols represent the mean simulation results across 14 model variants and five random seeds. Horizontal capped bars represent range of simulated DALYs averted. Vertical capped bars represent range of simulated net program costs. Negative DALYs averted indicate simulated interventions that have a worse health outcome than the no intervention scenario. Negative net program costs indicate simulated interventions where the savings to the health system are greater than the delivery costs.

Despite moderate levels of self-reported LLIN use, simulations indicate LLINs, and not IRS, account for the majority of impact on parasite prevalence. Removing LLINs and continuing only with a higher level of IRS coverage resulted in a similar number of averted uncomplicated cases compared to the IST interventions (**Table 4**). With higher LLIN use, simulations indicate IRS adds only a limited additional benefit above that provided by the nets (**Figure1, Figure 2c**).

Depending on coverage level and frequency, without vector control interventions, simulations suggest IST could reduce annual average parasite prevalence in the population by 9-22% (**Table 4**). In the absence of vector control interventions, when starting with the IST 40% coverage once per term scenario, and compared to a scenario with no interventions, keeping the same coverage and increasing doses to twice per term showed a similar reduction in parasite prevalence as keeping the same frequency and increasing IST coverage to 80% (**Figure 2**).

Costing

Total delivery costs and net health system costs for implementing each intervention combination can be found in **Table S1**. Program costs always exceeded savings in case management. The top contributor to uncertainty in the highest coverage intervention combination scenario was the cost per LLIN distributed, followed by cost per child screened, ACT cost, cost per person protected by IRS, and access to treatment (**Figure 3**). Because of a low proportion of fevers tested for malaria with an RDT (12%), test cost did not contribute greatly to overall uncertainty.

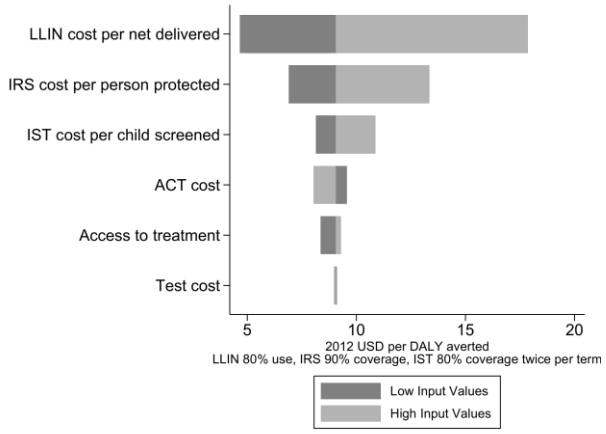

Figure 3. Sensitivity analysis. Tornado diagram of the change in the ACER of an intervention with 80% LLIN use, 90% IRS coverage, and 80% IST coverage twice per term in relation to variation in component costs.

Intervention combination cost effectiveness

Five intervention combinations simulated more averted DALYs than the currently-implemented intervention combination (**Table 4, Figure 4**). All of these intervention combinations involve increasing coverage of LLINs, of IRS, or both, with the exception of one which adds IST to the current strategy (**Table 4, Figure 4**). However, none of these options were simulated to be more cost effective than the current strategy (**Table 5**). All interventions can be considered very cost effective health interventions. The currently implemented intervention combination has a simulated ACER of 4.29 USD per DALY averted, but even the intervention combination with the highest cost per additional DALY averted (IST at 80% coverage twice per term, LLIN use 80%, IRS coverage 90%), has a simulated ACER of only 9.06 USD (**Table 5**).

Table 5. Cost effectiveness of different intervention combinations for a population of 100,000 over five years of implementation (2012 US$).

	Average ACER		Marginal ACER		Average ICER	Marginal ICER
	Mean	*IQR*	*Mean*	*IQR*	*Mean*	*Mean*
Current strategy						
Current strategy: LLIN 55%, IRS 70%	4.29	(4.22, 4.33)	6.30	(6.28, 6.31)		
Change timing and increase coverage of IRS						
LLIN 55%, IRS 90% May start	5.27	(5.21, 5.31)	6.75	(6.74, 6.75)	235.46	111.58
LLIN 55%, IRS 90% June start	5.11	(5.06, 5.13)	6.62	(6.61, 6.62)	50.24	24.27
Add IST						
Add IST to the current strategy	6.13	(6.09, 6.14)	7.02	(7.01, 7.03)	66.03	30.55
Increase coverage						
LLIN 80%, IRS 90%	7.39	(7.38, 7.40)	8.92	(8.92, 8.92)	53.75	48.06
Add IST, increase coverage						
LLIN 80%, IRS 90%, IST 80% twice per term	9.06	(9.04, 9.05)	9.59	(9.58, 9.60)	65.05	48.27

The mean and inter-quartile range of the average cost effectiveness ratios (ACER) compared to a scenario with no interventions outside the existing case management system, and incremental cost effectiveness ratios (ICER) compared to the currently implemented strategy for different intervention combinations with more simulated DALYs averted than the currently implemented strategy. ACERs and ICERs are calculated using costs reported in **Table S1** and effectiveness reported in **Table 1**. Interventions are displayed in ascending order of simulated DALYs averted (**Table 1**). IQR represents mean costs values applied to the inter-quartile range of simulated health effects.

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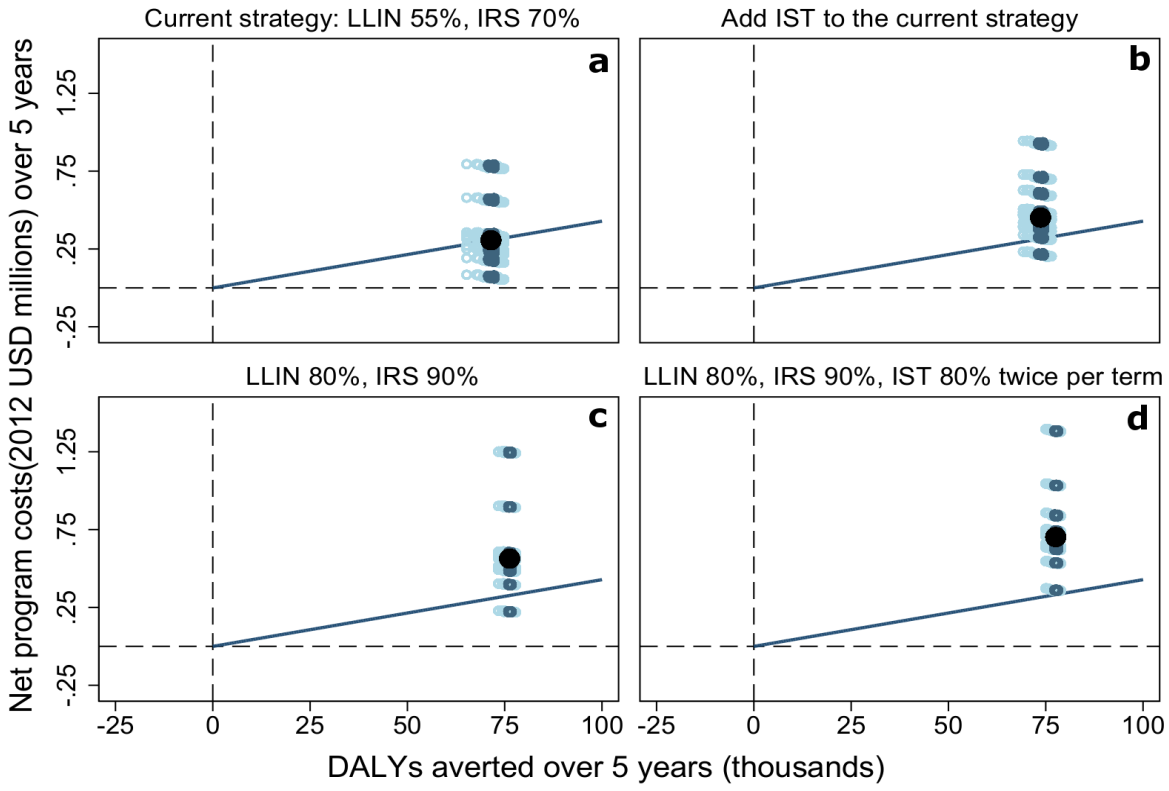

Figure 4. Cost effectiveness planes. Simulated cumulative DALYs averted in a population of 100,000 individuals after five years compared to the no intervention scenario by net program costs for the intervention combinations with a better simulated health outcome than the currently implemented malaria control strategy, ranked in descending order of ACER. Black dots represent the mean simulation results across 14 model variants and five seeds. Circles represent the simulated DALYs averted by net program costs with different assumptions of input costs of the case management system and malaria control interventions in the study area represented in Table 2 and Table 3. Dark blue circles are within the inter-quartile range of simulated DALYs averted and the light blue circles are outside the range. Negative DALYs averted indicate simulated interventions that have a worse health outcome than the no intervention scenario. Negative net program costs indicate simulated interventions where the savings to the health system are greater than the delivery costs. Diagonal lines correspond to the ratios of mean (4.29 USD per DALY averted) ACER of the currently implemented intervention combination in the study area (LLIN use 56%, IRS coverage 70%).

4.5 Discussion

Cost effectiveness analyses based on health outcomes simulated by transmission models can compare many more intervention effects than can static models or field trials. In these simulations, interventions simulate a decrease in vector population and a corresponding decrease in transmission that allows for mass community effects of interventions. In particular, such models can explore the effects of intervention scenarios by transmission level and coverage level whereas in single field studies all the effects of different interventions cannot be captured.

Increased coverage and use of vector control interventions has a larger simulated impact on all malaria indicators than adding IST to the currently implemented control strategy. There could be additional impact of IST programs not captured in this analysis, including improved school performance and decreased anemia [44]. While results from a cluster-randomized trial of once per term IST in school children in the south coast of Kenya at similar coverage levels did not show an impact on parasitaemia [45], effectiveness of the program will depend on baseline parasitaemia and results may be different in Rachuonyo South District. Results suggests that, at least at transmission levels comparable to those in the study area, it would not be warranted to take focus away from vector control in favor of a school-based IST program even at a deployment frequency of twice per term, assuming such a level exists where this would be advisable. The simulated screen and treat campaign in this study was limited to school children, and incorporating a focal- or mass screen and treat program in the community may have very different results. However, should Rachuonyo South District decide to implement an IST program, simulations indicate adding this intervention to the existing malaria control program could still be a cost-effective intervention with a mean simulated ICER of only 66 USD above the currently implemented strategy (**Table 5**).

Despite moderate observed use in the population, simulations show LLINs and not IRS account for the majority of impact on disease burden. Changing the timing of IRS implementation did not have a large impact on parasite prevalence. This could be due to the simulation experiment design, which models implementation of IRS programs rolled out over a 60 day period culminating in the target proportion of individuals protected. Because the start date of implementation was varied by 30 days at a time, implementation could overlap enough to prevent observing a

substantial difference between scenarios. Rather than changing the timing or coverage of IRS, the study area may benefit from adding new vector control interventions, particularly those targeting exophagic and exophilic vectors.

Limitations

While interventions were chosen to correspond to those in the hotspot-targeted intervention study, simulated implementation was assumed for the whole population rather than target hot spots because OpenMalaria does not incorporate an explicit spatial element. Therefore results cannot be matched against intervention trial results for validation purposes. However, findings from this experiment can help put the trial results in the broader context of what could be expected from community-wide implementation of combinations of interventions.

While simulations of the scenarios describing the effects of the intervention combinations in reducing malaria burden account for uncertainty by employing an ensemble of 14 model variants and multiple random seeds, uncertainty in the costing model is limited to a one-way sensitivity analysis. A probabilistic sensitivity analysis exposing the model to changes in assumptions of inputs to the case management and intervention unit costs is being conducted for publication elsewhere, and will assist in clarifying the uncertainty inherent in these predictions.

Despite vector behavior in the study area favoring outdoor biting, IRS had a lower health impact than expected when simulated as a stand-alone intervention when compared to LLINs. The IRS model parameterization has deterrency and killing effects of half that of LLINs, due to simulated action only on post-prandial indoor resting mosquitoes, in contrast to the both pre- and post-prandial killing effect of LLINs. A model update will allow the effect of IRS to be simulated on both states of the mosquito feeding cycle, and the parameters for effectiveness of IRS should be updated based on experimental hut data. It is also worth noting the lower cost per sachet of insecticide assumed in the costing model compared to the average unit costs reported in the recently released UNITAID report on malaria vector control commodities [46], due to the economies of scale achieved through a multi-country procurement by the IRS implementing partner [47].

Implications of results for health systems

Results of this experiment have the potential to assist malaria control program managers in the study area in deciding on adding new or changing the implementation of current interventions. All the simulated intervention combinations can be considered cost effective in the context of levels of health expenditure in Kenya. Malaria is the number six contributor to burden of disease in Kenya, both overall and in children under five [48]. The low cost per DALY averted by the malaria control interventions with a higher simulated number of DALYs averted than the current strategy represents a small portion of the total health expenditure per capita of 42 USD [13] and could be a cost effective option for reaching the country's development strategies. In comparison with estimates from a recent systematic review on costs and cost effectiveness of malaria control interventions [39], these results are on the low end of the range of previous estimates. Similarly, compared to WHO-CHOICE estimates for the AFR-E region, while the simulated DALYs averted per year for the currently-implemented strategy are comparable to WHO estimates for 50% coverage of vector control interventions (14,296 simulated, 14,711 observed), the simulated cost per DALY averted are substantially lower than the regional averages when converted to 2012 USD (4.29 2012 USD simulated, 50 2005 International Dollars (I$) observed) [49]. This puts malaria prevention interventions in the study area in the range of regional estimates for tuberculosis (6-15 2005 I$ per DALY averted [50] and HIV prevention communication (3-4 2005 I$ per DALY averted) [51].

Findings from this study indicate that there are several combinations of interventions that could result in a greater health impact per dollar spent than the currently implemented strategy. However, increasing LLIN use and IRS coverage and initiating a school-based IST program will require investment in several elements not included in this analysis. Firstly, the unit costs of scaling up or introducing some programs will vary by implementation strategy more than others. For example, the majority of the economic cost of the LLIN program implemented by training existing community organizations on distribution is represented by the marginal cost of procuring nets (**Table 3**). Therefore a change in strategy may not result in a large change in cost per net delivered due to increased or decreased non-commodity costs. The reverse is true for a school-based IST

program where marginal costs are under half the cost per child screened (**Table 3**), and could therefore be far more sensitive to changes in program design.

Secondly, additional costs will be incurred by determining the appropriate strategy for achieving programmatic goals. Several scenarios in this experiment assume LLIN use of 80%, which is an ambitious target that will depend not only on universal coverage but a large behavior change communications component. Understanding of the behavioral determinants for why nets existing in households currently remain unused will be critical to achieving this goal. In addition to increased personnel and commodities, increasing coverage of IRS will require continued monitoring of insecticide resistance in the vector population, as well as understanding why households remain unsprayed, whether it is due to rejection by household members or the inability to logistically access hard to reach households. Implementing a school-based IST program as intensive as twice per school term over an extended period of time could result in a change in adherence rates as well as an increased risk of selecting for drug resistance, elements which may impact the effectiveness of the intervention if community acceptability is not assessed.

Thirdly, the study does not allow for any economies or diseconomies of scale for the costs of commodities and program delivery, assuming costs will grow linearly with scale up. In practice this will likely not be the case; increasing intervention coverage from 70% to 80% may be more expensive than scaling up from 50% to 60%.

Assessing the epidemiologic impact and cost effectiveness of different intervention combinations is a necessary element in considering a change of malaria control policy, but it is by no means the only criteria with which to base a recommendation for policy change. Changes in implementation, whether this includes new strategies to increase coverage and use of existing interventions or the addition of a new intervention, will have implications on acceptability by the individuals and communities receiving the interventions, the personnel involved in service delivery, the natural environment into which increased insecticides could be introduced, and the systems of surveillance and monitoring for indicators of malaria and other febrile illnesses, to name a few. Conducting a health impact assessment, drawing on existing frameworks [52, 53], may strengthen the success of any change in strategy.

4.6 Author contributions

EMS designed the experiments, performed the literature review for model parameterization, analysed results and drafted the manuscript. KG designed the costing model and participated in analyzing the results and drafting the manuscript. JC, CD, JS helped with parameterization of the model and manuscript preparation. TB, AYB and SK designed the field studies. JS, AYB and WO supervised and conducted the intervention field trial and were responsible for data management. TS and JC conceived and designed the modeling study. NC participated in designing the experiments, analyzing the results, and drafting the manuscript. All authors read and approved the final manuscript.

4.7 Acknowledgements

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References

1. Feachem RG, Phillips AA, Targett GA, Snow RW: **Call to action: priorities for malaria elimination.** *Lancet* 2010, **376:**1517-1521.

2. WHO: **World Malaria Report 2012.** Geneva: World Health Organization; 2013.

3. **OpenMalaria.** Available: http://code.google.com/p/openmalaria/wiki/Start. Accessed 2013 Jul 2.

4. Stuckey EM, Stevenson J, Cooke M, Owaga C, Marube E, Oando G, Hardy D, Drakeley C, Smith T, Cox J, Chitnis N: **Simulation of malaria epidemiology and control in the highlands of western Kenya.** *Malar J* 2012, **11**.

5. Mabaso ML, Craig M, Ross A, Smith T: **Environmental predictors of the seasonality of malaria transmission in Africa: the challenge.** *Am J Trop Med Hyg* 2007, **76:**33-38.

6. Kristan M, Abeku TA, Beard J, Okia M, Rapuoda B, Sang J, Cox J: **Variations in entomological indices in relation to weather patterns and malaria incidence in East African highlands: implications for epidemic prevention and control.** *Malar J* 2008, **7:**231.

7. Stevenson JC, Stresman GH, Gitonga CW, Gillig J, Owaga C, Marube E, Odongo W, Okoth A, China P, Oriango R, et al: **Reliability of school surveys in estimating geographic variation in malaria transmission in the western Kenyan highlands.** *PLoS One* 2013, **8:**e77641.

8. Department of Malaria Control, Kenya national Bureau of Statistics, ICF Macro (2011) 2010 Kenya Malaria Indicator Survey. Nairobi, Kenya.

9. Stevenson J, St. Lauernt B, Lobo N, Cooke M, Kahindi S, Oriango R, Harbach R, Cox J, Drakeley C: **Novel vectors of malaria parasite in the western highlands of Kenya [letter].** *Emerg Infect Dis* 2012 Sept, **[serial on the Internet]**.

10. Fillinger U, Ndenga B, Githeko A, Lindsay SW: **Integrated malaria vector control with microbial larvicides and insecticide-treated nets in western Kenya: a controlled trial.** *Bull World Health Organ* 2009, **87:**655-665.

11. Kenya Division of Malaria Control: **National Guidelines for Diagnosis, Treatment and Prevention of Malaria in Kenya.** In: Management DoMCC ed.; 2006.

12. Chuma J, Okungu V: **Viewing the Kenyan health system through an equity lens: implications for universal coverage.** *Int J Equity Health* 2011, **10:**22.

13. Government of Kenya: **Comprehensive Public Expenditure Review 2013.** Nairobi, Kenya: Government of Kenya, Ministry of Devolution and Planning; 2013.

14. Bousema T, Stevenson J, Baidjoe A, Stresman G, Griffin JT, Kleinschmidt I, Remarque EJ, Vulule J, Bayoh N, Laserson K, et al: **The impact of hotspot-targeted interventions on malaria transmission: study protocol for a cluster-randomized controlled trial.** *Trials* 2013, **14:**36.

15. Smith T, Killeen GF, Maire N, Ross A, Molineaux L, Tediosi F, Hutton G, Utzinger J, Dietz K, Tanner M: **Mathematical modeling of the impact of malaria vaccines on the clinical epidemiology and natural history of Plasmodium falciparum malaria: Overview.** *Am J Trop Med Hyg* 2006, **75:**1-10.

16. Chitnis N, Smith T, Steketee R: **A mathematical model for the dynamics of malaria in mosquitoes feeding on a heterogeneous host population.** *Journal of Biological Dynamics* 2008, **2:**259 - 285.

17. Smith T, Maire N, Ross A, Penny M, Chitnis N, Schapira A, Studer A, Genton B, Lengeler C, Tediosi F, et al: **Towards a comprehensive simulation model of malaria epidemiology and control.** *Parasitology* 2008, **135:**1507-1516.

18. Smith T, Ross A, Maire N, Chitnis N, Studer A, Hardy D, Brooks A, Penny M, Tanner M: **Ensemble modeling of the likely public health impact of a pre-erythrocytic malaria vaccine.** *PLoS medicine* 2012, **9:**e1001157.

19. Chitnis N, Hardy D, Smith T: **A Periodically-Forced Mathematical Model for the Seasonal Dynamics of Malaria in Mosquitoes.** *Bulletin of mathematical biology* 2012, **74(5):**1098–1124.

20. Akazili J, Aikins M, Binka F: **Malaria treatment in Northern Ghana: What is the treatment cost per case to households?** *African Journal of Health Sciences* 2007, **14:**70-79.

21. Conteh L, Sicuri E, Manzi F, Hutton G, Obonyo B, Tediosi F, Biao P, Masika P, Matovu F, Otieno P, et al: **The cost-effectiveness of intermittent preventive treatment for malaria in infants in Sub-Saharan Africa.** *PLoS One* 2010, **5:**e10313.

22. WHO: **Guidelines for the Treatment of Malaria, Second Edition.** Geneva 2010.

23. Wiseman V, Kim M, Mutabingwa TK, Whitty CJ: **Cost-effectiveness study of three antimalarial drug combinations in Tanzania.** *PLoS Med* 2006, **3:**e373.

24. Drummond MF, MJ S, GW T, BJ OB, GL S: *Methods for the Economic Evaluation of Health Care Programmes 3 ed.* Oxford, United Kingdom: Oxford University Press; 2005.

25. Tediosi F, Maire N, Smith T, Hutton G, Utzinger J, Ross A, Tanner M: **An approach to model the costs and effects of case management of Plasmodium falciparum malaria in sub-saharan Africa.** *Am J Trop Med Hyg* 2006, **75:**90-103.

26. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB: **Recommendations of the Panel on Cost-effectiveness in Health and Medicine.** *JAMA* 1996, **276:**1253-1258.

27. Galactionova K, Penny M, Tediosi F, de Savigny D, Smith T: **Impact of Health System Factors on Health Benefits and Cost-Effectiveness of a Malaria Vaccine.** In *The 9th World Congress on Health Economics: Celebrating Health Economics*; *July 8, 2013; Sydney, Australia*

28. Kenya National Bureau of Statistics, ICF Macro: **Kenya Demographic and Health Survey 2008-09.** Calverton, Maryland: KNBS and ICF Macro; 2010.

29. Watsierah CA, Jura WG, Oyugi H, Abong'o B, Ouma C: **Factors determining anti-malarial drug use in a peri-urban population from malaria holoendemic region of western Kenya.** *Malar J* 2010, **9:**295.

30. Nyandigisi A, Memusi D, Mbithi A, Ang'wa N, Shieshia M, Muturi A, Sudoi R, Githinji S, Juma E, Zurovac D: **Malaria case-management following change of policy to universal parasitological diagnosis and targeted artemisinin-based combination therapy in Kenya.** *PLoS One* 2011, **6:**e24781.

31. Goodman C, Coleman P, Mills A: **Economic analysis of malaria control in Sub-Saharan Africa.** Global Forum for Health Research; 2000.

32. World Health Organization: **CHOosing interventions that are cost-effective: country-specific unit costs.** Geneva, Switzerland: World Health Organization; 2011.

33. World Bank: **Implicit Price Deflators for Gross Domestic Product.** 2013.

34. Batwala V, Magnussen P, Hansen KS, Nuwaha F: **Cost-effectiveness of malaria microscopy and rapid diagnostic tests versus presumptive diagnosis: implications for malaria control in Uganda.** *Malar J* 2011, **10:**372.

35. Malaria Vaccine Initiative: **Estimating the economic burden of malaria in Nigeria.** Malaria Vaccine Initiative; 2012.

36. Kirigia JM, Snow RW, Fox-Rushby J, Mills A: **The cost of treating paediatric malaria admissions and the potential impact of insecticide-treated mosquito nets on hospital expenditure.** *Trop Med Int Health* 1998, **3:**145-150.

37. Kolaczinski J, Hanson K: **Costing the distribution of insecticide-treated nets: a review of cost and cost-effectiveness studies to provide guidance on standardization of costing methodology.** *Malar J* 2006, **5:**37.

38. Global Fund to fight AIDS, TB and Malaria: **Price and Quality Reporting Tool.** 2013.

39. White MT, Conteh L, Cibulskis R, Ghani AC: **Costs and cost-effectiveness of malaria control interventions--a systematic review.** *Malar J* 2011, **10:**337.

40. Oanda: **Historical Exchange Rates.** Available: http://www.oanda.com/. 2013.

41. Murray CJ, Lopez AD: **The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 to 2020.** Cambridge, MA, USA: Harvard University Press; 1996.

42. INDEPTH Network: **Model life tables for Sub-Saharan Africa.** Aldershot, United Kingdom: INDEPTH Network; 2004.

43. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, et al: **Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010.** *Lancet* 2012, **380:**2197-2223.

44. Brooker S, Okello G, Njagi K, Dubeck MM, Halliday KE, Inyega H, Jukes MC: **Improving educational achievement and anaemia of school children: design of a cluster randomised trial of school-based malaria prevention and enhanced literacy instruction in Kenya.** *Trials* 2010, **11:**93.

45. Halliday KE, Okello G, Turner EL, Njagi K, Mcharo C, Kengo J, Allen E, Dubeck MM, Jukes MC, Brooker S: **Impact of Intermittent Screening and Treatment for Malaria among School Children in Kenya: A Cluster Randomised Trial.** *PLoS Med* 2014, **11:**e1001594.

46. UNITAID: **Malaria Vector Control Commodities Landscape.** Geneva: WHO; 2013.

47. RTI International: **Indoor Residual Spraying (IRS) 2 for Malaria Control. Task Order 1 - Final Report.** Research Triangle Park, NC: RTI International; 2013.

48. WHO: **The global burden of disease: 2012 .** Geneva: WHO; 2014.

49. WHO-CHOICE: **AFR-E: Cost effectiveness results for Malaria**. Geneva: WHO; 2005

50. WHO-CHOICE: **AFR-E: Cost effectiveness results for Tuberculosis**. Geneva: WHO; 2005

51. WHO-CHOICE: **AFR-E: Cost effectiveness results for HIV/AIDS**. Geneva: WHO; 2005

52. Mikkelsen-Lopez I, Wyss K, de Savigny D: **An approach to addressing governance from a health system framework perspective.** *BMC Int Health Hum Rights* 2011, **11:**13.

53. International Association for Impact Assessment: **Health Impact Assessment: International Best Practice Principles.** In *Special Publication Series*. Fargo, ND 2006.

54. Management Sciences for Health: **International Drug Price Indicator Guide.** Cambridge, MA: MSH 2011.

55. Guyatt HL, Kinnear J, Burini M, Snow RW: **A comparative cost analysis of insecticide-treated nets and indoor residual spraying in highland Kenya.** *Health Policy Plan* 2002, **17:**144-153.

56. Drake TL, Okello G, Njagi K, Halliday KE, Jukes M, Mangham L, Brooker S: **Cost analysis of school-based intermittent screening and treatment of malaria in Kenya.** *Malar J* 2011, **10:**273.

Text S1: Costing the Kenya malaria case management system, interventions, and cost effectiveness

Table S1: Costing model parameterization of access to and cost of the Kenya case management system

Parameter	Value	Cost (2012 USD)
Proportion of the most recent episode of fevers within 2 week recall seeking medical care	0.618 [1]	
Proportion of fevers treated at a formal health facility	0.486 [1]	
Health center without beds	0.556 [1]	1.59 [2]
Health center with beds	0.209 [1]	1.97 [2]
Hospital outpatient	0.235 [1]	2.29 [2]
Hospital inpatient		6.96 [2]
Coartem (ACT)	0.439	
(6 x 2 tablets co-pack) 20mg + 120mg tab-cap	**Table A2**	0.0898*[3]
Proportion of ACT treatments with full adherence	0.771	
Quinine (QN)		
Intravenous (IV), Day 1	**Table A2**	0.1324* [3]
Intravenous (IV), Day 2	**Table A2**	
Oral, Day 3	**Table A2**	0.0524* [3]
Sulfadoxine-Pyrimethamine (SP)	0.214	0.0299* [3]
Proportion of children under 5 with fever tested for malaria in any setting		
Paracheck® rapid diagnostic test (RDT)	0.12 [4]	0.62 [5]
Cost of travel to seek treatment		0.40**
Cost of consumables while seeking treatment		0.20 [6-8]

*Median supplier price **Multi-country literature review

Table S2: Drug dosing per full course per age group for treatment of uncomplicated and severe illness as per 2010 WHO malaria treatment guidelines [9]

	ACT dose	**Quinine Dose**		
	20mg + 120mg tab-cap	*Day 1 (IV, per 300 ampule)*	*Day 2 (IV, per 300 ampule)*	*Day 3 (oral, per 300mg tablet)*
Years of age		20 mg/kg over 4 hours	10 mg/kg every 8 hours	10 mg/kg every 8 hours
<1	6	180	270	270
1 - 3	6	240	360	360
3 - 5	12	360	540	540
5 - 6	12	420	630	630
6 - 10	12	600	900	900
10 – 12	18	840	1260	1260
12 - 16	24	1080	1620	1620
> 16	24	1200	1800	1800

Table S3: Source for methodology followed in the costing exercise

Methodology	**Source**
Costing of case management system	Tediosi et al. [6]
Costing of malaria control interventions	Kolaczinski et al. [10], White et al. [11]
Calculating the burden of disease (DALYs)	Murray and Lopez [12,13]
Cost-effectiveness analysis	Drummond et al. [14]

Table S4: Total costs and cost savings of different intervention combinations for a population of 100,000 over five years of implementation (2012 US$)

	Total intervention costs (thousands)				Net program costs (thousands)			
	Average		Marginal		Average		Marginal	
	Mean	IQR	Mean	IQR	Mean	IQR	Mean	IQR
Current strategy								
LLIN 55.63% + IRS 70%	732.54	(731.60, 733.21)	587.23	(586.29, 587.94)	306.42	(309.52, 301.68)	450.17	(450.93, 448.93)
Increase coverage								
LLIN 80% + IRS 90%	1014.21	(1013.47, 1014.87)	826.04	(825.32, 826.64)	564.00	(564.23, 562.91)	680.49	(680.16, 680.46)
Add IST								
LLIN 55.63% + IRS 70% + IST 80% twice per term	884.93	(882.85, 886.09)	657.13	(656.05, 657.94)	451.59	(452.73, 448.63)	517.34	(517.45, 516.71)
LLIN 80% + IRS 90% + IST 80% twice per term	1154.39	(1153.03, 1155.64)	890.31	(889.41, 891.25)	702.44	(701.58, 702.36)	744.06	(743.44, 744.50)
Change timing of IRS								
LLIN 55.63% + IRS 70% April start	806.81	(805.63, 807.85)	622.29	(621.21, 623.31)	377.39	(379.12, 373.81)	484.06	(484.26, 483.53)
LLIN 55.63% + IRS 70% May start	732.59	(731.60, 733.56)	587.27	(586.33, 588.22)	310.43	(314.45, 304.52)	451.58	(452.43, 450.21)
LLIN 55.63% + IRS 70% June start	732.81	(731.43, 734.05)	587.49	(586.10, 588.66)	303.94	(306.63, 300.55)	449.47	(449.82, 448.99)
Change timing and increase coverage of IRS								
LLIN 55.63% + IRS 90% April start	474.27	(473.20, 475.18)	465.91	(464.85, 466.81)	110.76	(128.79, 97.26)	350.38	(357.94, 346.37)
LLIN 55.63% + IRS 90% May start	806.66	(805.73, 807.74)	622.14	(621.24, 623.22)	378.53	(381.11, 374.27)	484.34	(484.72, 483.57)
LLIN 55.63% + IRS 90% June start	806.21	(805.07, 806.97)	621.71	(620.58, 622.47)	371.82	(373.65, 368.32)	481.75	(482.09, 480.97)
IRS alone, change coverage								
IRS 70%	258.50	(258.42, 258.59)	121.53	(121.50, 121.58)	84.36	(124.58, 55.88)	68.00	(83.86, 57.26)
IRS 90%	332.45	(332.38, 332.52)	156.30	(156.27, 156.34)	111.29	(148.43, 82.71)	87.83	(102.31, 78.02)
LLINs alone								
LLIN 55.63%	732.53	(731.70, 733.43)	587.20	(586.47, 588.12)	308.88	(313.14, 304.45)	450.97	(451.85, 449.97)
LLIN 80%	682.05	(681.41, 682.80)	670.03	(669.40, 670.76)	250.58	(254.95, 246.24)	530.95	(532.55, 529.93)
IST alone								
IST 40% once per term	179.14	(171.79, 184.35)	81.98	(78.62, 84.36)	163.31	(207.20, 123.63)	77.32	(94.88, 61.24)
IST 40% twice per term	302.59	(290.01, 311.97)	138.47	(132.71, 142.76)	277.25	(311.14, 242.31)	130.90	(146.33, 116.94)
IST 80% once per term	323.87	(310.19, 333.80)	148.21	(141.95, 152.75)	294.53	(325.73, 4.3401)	139.46	(154.61, 26.01)
IST 80% twice per term	497.76	(477.02, 516.82)	227.78	(218.30, 236.51)	454.06	(477.80, 433.41)	214.38	(226.50, 206.64)

References

1. Kenya National Bureau of Statistics, ICF Macro (2010) Kenya Demographic and Health Survey 2008-09. Calverton, Maryland.
2. WHO-CHOICE (2008) Unit Costs Estimates for Service Delivery - Estimation File. Geneva.
3. Management Sciences for Health (2011) International Drug Price Indicator Guide. Cambriage, MA: MSH.
4. Department of Malaria Control, Kenya Bureau of Statistics, ICF Macro (2011) 2010 Kenya Malaria Indicator Survey. Nairobi, Kenya.
5. Global Fund to Fight AIDS, TB and Malaria (2013) Price and Quality Reporting Tool.
6. Tediosi F, Maire N, Smith T, Hutton G, Utzinger J, et al. (2006) An approach to model the costs and effects of case management of Plasmodium falciparum malaria in sub-saharan Africa. Am J Trop Med Hyg 75: 90-103.
7. Batwala V, Magnussen P, Hansen KS, Nuwaha F (2011) Cost-effectiveness of malaria microscopy and rapid diagnostic tests versus presumptive diagnosis: implications for malaria control in Uganda. Malar J 10: 372.
8. Malaria Vaccine Initiative (2012) Estimating the economic burden of malaria in Nigeria. Malaria Vaccine Initiative.
9. WHO (2010) Guidelines for the Treatment of Malaria, Second Edition. Geneva.
10. Kolaczinski J, Hanson K (2006) Costing the distribution of insecticide-treated nets: a review of cost and cost-effectiveness studies to provide guidance on standardization of costing methodology. Malar J 5: 37.
11. White MT, Conteh L, Cibulskis R, Ghani AC (2011) Costs and cost-effectiveness of malaria control interventions--a systematic review. Malar J 10: 337.
12. Murray CJ, Lopez AD (1996) The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 to 2020. Cambridge, MA, USA: Harvard University Press.
13. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, et al. (2012) Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380: 2197-2223.
14. Drummond MF, Sculpher M, Torrance G, O'Brien B, Stoddart G (2005) Methods for the Economic Evaluation of Health Care Programmes 3 ed. Oxford, United Kingdom: Oxford University Press.

5. Interrupting malaria transmission in Southern Province, Zambia: a short report on modeling the effects of mass screen and treat and mass drug administration campaigns

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5.1 Summary

Following scale-up of vector control interventions, preliminary results from the evaluation of a mass screen and treat (MSAT) program in Zambia's Southern province suggest a benefit of MSAT using artemether-lumefantrine (AL) at reducing the malaria parasite prevalence. We use OpenMalaria, a discrete-time individual-based stochastic model of malaria, parameterized for Zambia's Southern province, to simulate antimalarial administration for interruption of transmission in the study area. Simulations were run on scenarios created for a range of drug combinations, coverage levels, target age groups, distribution frequencies, and levels of transmission and evaluated based on the proportion of simulations runs leading to interruption of transmission. Simulations suggest MSAT with the use of an antimalarial drug with a longer prophylactic effect such as dihydroartemisinin-piperaquine (DHP) and MSAT with DHP combined with a drug with a gametocytal effect such as primaquine (PQ) will be only marginally more effective than the existing strategy of MSAT with AL. However, including a drug preventing transmission such as ivermectin in a mass drug administration (MDA) with DHP+PQ has the potential to further reduce transmission in the study area. Results suggest a high proportion of low density infections missed by RDT diagnosis that are treated and cleared with MDA. The optimal implementation strategy for treatment-based interventions will vary by background level of parasitaemia and coverage level, and success of any MSAT or MDA campaign will depend on sustained coverage of vector control interventions to ensure sustained gains in reduction of disease burden.

5.2 Background

Malaria control is based on both preventing transmission and obtaining prompt and effective treatment of infection. Many countries have made significant progress in preventing malaria, focusing largely on vector control through long lasting insecticide-treated nets (LLINs) and indoor residual spraying (IRS) of insecticides. With reduced levels of transmission, supplementing vector control with mass administration of drugs that kill both malaria parasites and mosquitoes has the potential to interrupt transmission. In response to the need to plan next steps following a scale up of vector control interventions, the Zambia National Control Center in partnership with PATH MACEPA is conducting an evaluation of a malaria testing and treatment campaign in Southern province to contribute to a marked reduction of community level malaria. In addition to the existing implementation strategy of targeting all ages with three rounds of AL, an additional set of operational and chemotherapeutic options are currently under institutional review board review. These changes to the design include replacing AL with DHP which clears asexual blood stages of current infections and has a longer prophylactic period against future malaria infection [8], as well as use of PQ which has a strong gametocytocidal effect [9]. Ivermectin, which is toxic to mosquitoes that subsequently bite the human [10], is additionally being considered for future inclusion in the intervention. The goal of this report is to assess the effectiveness of changing the operational strategy of the malaria testing and treatment campaign as simulated by the OpenMalaria model.

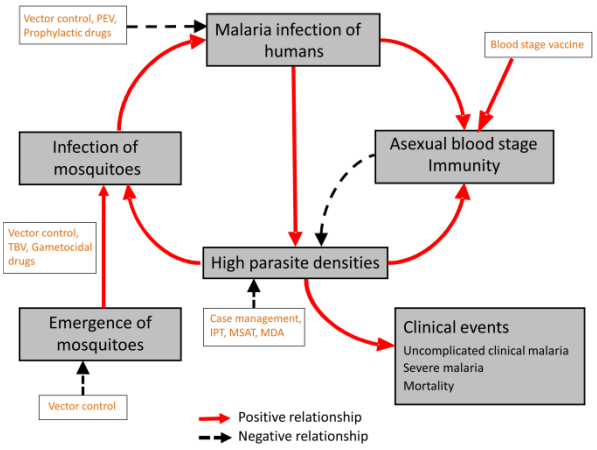

Figure 1: Schematic of the OpenMalaria transmission model [1-3] with positive feedback shown by solid lines and negative feedback by dashed lines. Emergent mosquitoes biting on humans with high parasite densities are more likely to become infected and subsequently infectious if they live long enough. They, in turn, can infect humans, leading to high parasite densities and the buildup of acquired immunity. Acquired immunity tends to moderate parasite densities, which can lead to clinical events, such as uncomplicated malaria, severe malaria, and death.

5.3 Methods

Model

The OpenMalaria modeling platform combines a stochastic individual-based simulation model for malaria in humans with a periodically-forced deterministic model for malaria in mosquitoes, shown in a simple schematic in Figure 1 [1-3]. The model includes multiple aspects of the dynamics of malaria in humans, including human demography, acquired immunity and superinfection [11, 12], variations in parasite densities and infectiousness to mosquitoes [13, 14], and the clinical effects of malaria [15-18], and has been fit to multiple field data sets. The model for malaria transmission in mosquitoes [19] includes multiple mosquito species, nonhuman hosts, and a periodically varying emergence rate [20]. The model platform consists of an ensemble of fourteen model variants with varying assumptions such as heterogeneity in exposure and decay of immunity to help quantify the effects of uncertainty in model formulation [21]. It has been used to investigate the effects of case management [22], vaccines [23-26], intermittent preventive treatment [27], mass screen and treat [28] and vector control interventions [29-32] in reducing malaria transmission and disease.

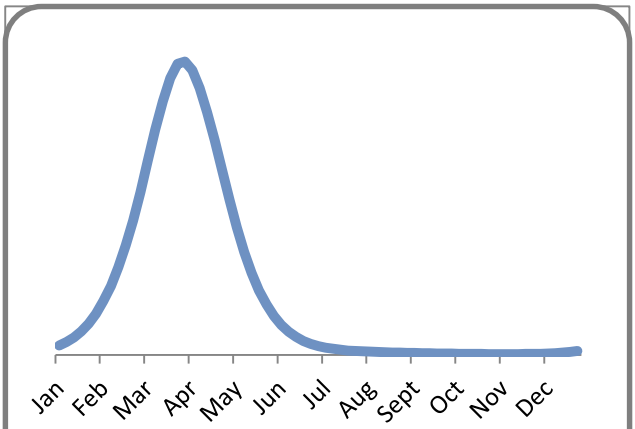

Figure 2: Seasonal pattern of malaria transmission used to parameterize the baseline model for Southern Province. This pattern was repeated for each scenario for a range of six values of annual average EIR.

In each simulation, the human population is forced with a specified periodically-varying entomological inoculation rate (EIR), or infectious bites per person per year, for one human life span to build immunity in the human population. Following this warm-up period, the mosquito emergence rate that gives rise to the specified EIR was estimated. The human and mosquito models are then connected so that infections in the human population give rise to infections in the mosquito population

which in turn infect the human population and so on, such that the EIR varies dynamically in response to interventions.

Model parameterization and validation

A review of published literature and available data from field studies in the study area was conducted to identify a set of parameter values representing the demography, seasonal pattern of malaria transmission (**Figure 2**), entomology, existing malaria control interventions (**Figure 3**), and case management for Southern province in Zambia. Details of the baseline parameter values can be found in the Appendix.

This baseline scenario was simulated on a population of 10,000 individuals over the time frame of the MSAT trial. Simulation results from the baseline scenario were validated against observed RDT positivity rates by facility catchment area following the scale up of an MSAT program using AL [5].

Baseline scenario assumptions

- 57.52% of population sleeping under an LLIN the previous night [4], out of 71.8% households owning at least one ITN
- EIR: 80% from *Anopheles arabiensis*, 20% from *An funestus [6, 7]*
- 18% coverage of IRS
- 21.8% of under 5 fevers in the last two weeks accessing an antimalarial [4]
- 75% compliance to MSAT drug regimen

Experiment design

To investigate the effects of operational considerations and drug regimen on health outcomes, assuming the baseline MSAT implementation as illustrated in **Figure 3**, the following scenarios were included in the experiment and altered one at a time (<u>baseline scenario underlined</u>):

i) three profiles of targeting based on age: <u>all ages</u>, children under five years[1], and adults 25-49 years;

[1] In this experiment, targeting of specific age groups leads to lower coverage of the overall population; the intervention affects only 40% of individuals in the targeted age groups.

ii) four profiles of frequency of the three campaign rounds: eight weeks apart, four weeks apart, three weeks apart, and two weeks apart;

iii) three profiles of coverage of the health facility catchment areas present in the study area: 40%, 72%, and 100%;

iv) four profiles of drug combinations: MSAT with AL, MSAT with DHP, MSAT with DHP + PQ, and MDA with DHP + PQ + ivermectin.

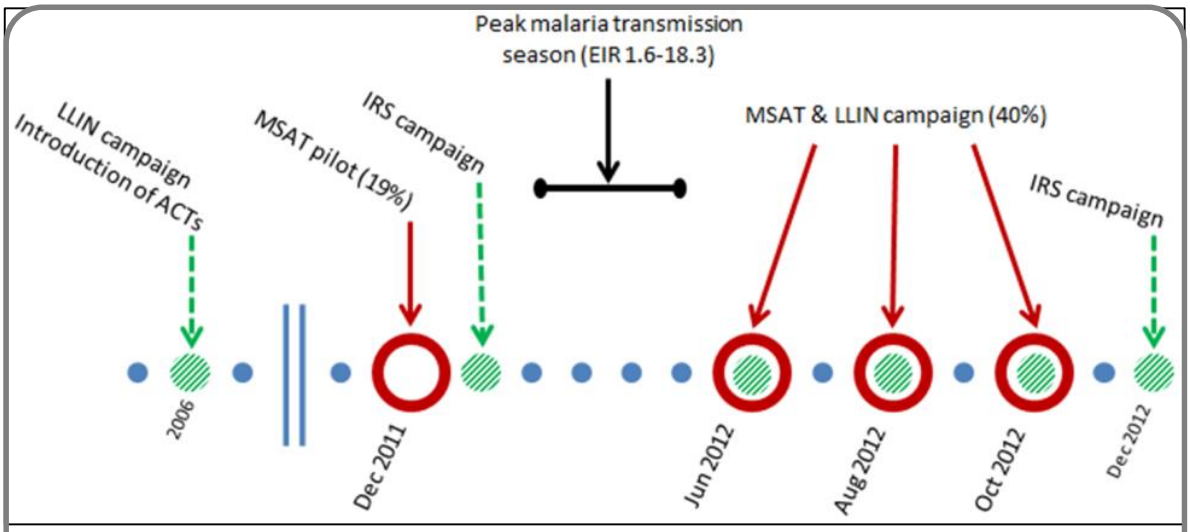

Figure 3: Schematic of malaria control interventions existing in Southern province, Zambia from 2006-2012 that served to inform the baseline scenario used for this experiment.

To analyze the sensitivity of the intervention to changes in model parameters for transmission and implementation, and to account for model uncertainty and stochasticity, the following variations were applied to each of the scenarios described above:

i) fourteen model variants, which vary in their assumptions about malaria epidemiology

ii) three random seeds to account for the effects of stochasticity

iii) six levels of pre-intervention entomological inoculation rate (EIR), at 1.5, 3, 9, 18, 26, and 36.6 infectious bites per person per year [7], with a rate of ten imported cases per 1,000 individuals in EIR values 9 and below

Based on these additions, each scenario was run for a total of 252 different model runs. Scenarios were evaluated based on the proportion of simulations runs leading to

interruption of transmission defined as zero clinical cases (ZCC) in month three following the final intervention deployment [33, 34], and the simulated reduction in mean all-age mean parasite prevalence (MPP) compared to the baseline scenario.

5.4 Results and discussion

Validation

The model was able to simulate the range of observed prevalence of health facility catchment areas at each of the three MSAT deployment rounds, in each of the three strata of parasite prevalence rate at the time of the December 2011 pilot survey (**Figure 4**).

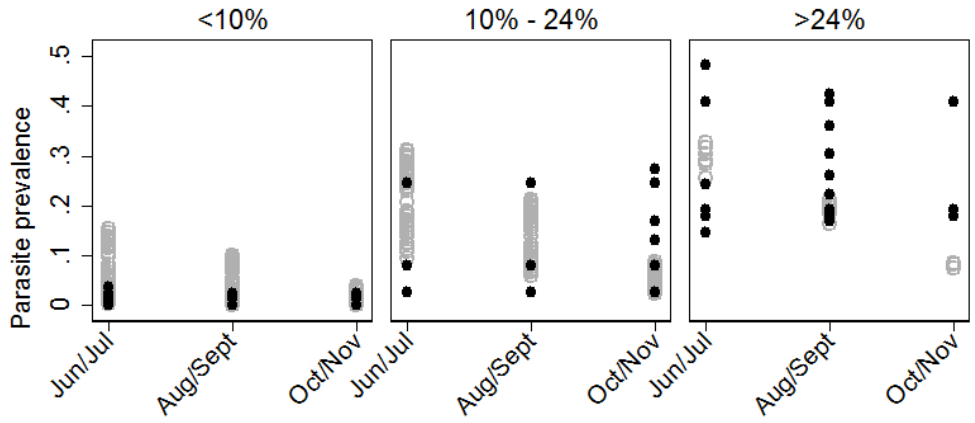

Figure 4: Validation of the baseline scenario parameterization. Simulated vs. observed effect of three rounds of MSAT using AL, by parasite prevalence at pilot conducted in December 2011 [5]. Black circles represent observed parasite all age prevalence rates in health facility catchment areas. Grey circles represent simulated parasite rates.

However, for the health facility catchment areas representing the highest parasite prevalence rate, no simulation runs estimated a prevalence rate of greater than 35% in the June/July intervention round, while during the same time period the observed prevalence rates reached as high as 48.2% (**Figure 4**) [5]. This effect of the simulated intervention having a greater impact than observed on areas of high prevalence could be due to the model assumptions that imported cases only factor in to scenarios with an EIR of 9 and below, with results indicating that even areas with higher prevalence could witness a proportion of cases resulting from imported infections.

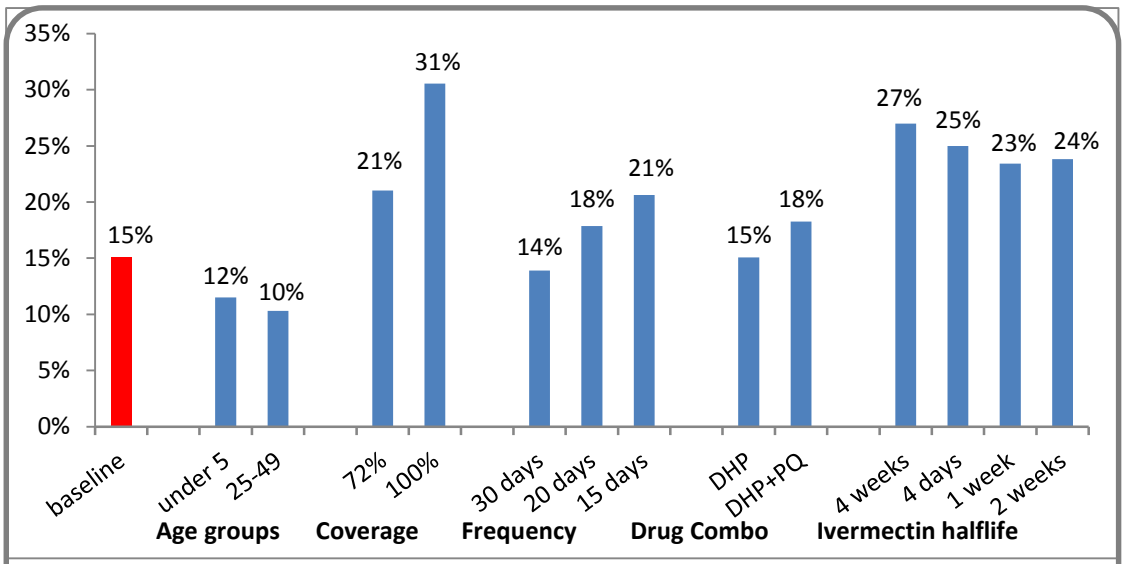

Figure 5: Proportion of simulations predicting zero clinical cases three months after intervention

Implementation combinations

Out of the 252 simulation runs for the baseline scenario, in the timestep corresponding to the third month following the final simulated MSAT round, 15% (n=38) showed ZCC. 37 of the 38 simulation runs predicting interruption of transmission were scenarios with parasite prevalence of <10% at the time of the December 2011 pilot survey, with only one in the category of parasite prevalence between 10% and 24%.

Age groups

Limiting implementation of MSAT to children under five or adults aged 25-49 does not show an improvement either in terms of ZCC (12% and 10%, respectively) (**Figure 5**) or in terms of reduction in MPP (-40% and -17%, respectively) compared to targeting all age groups (**Figure 6**). Results of parasite prevalence rates presented at the recent Malaria Elimination Symposium at the Zambia National Health Research Conference showed a higher parasite prevalence rate among the 5-16 age group (Silumbe, *personal communication)*. Based on these results it is clear that neither of these two age groups taken alone are principle drivers of transmission in the study area and therefore it is not surprising that this method of targeting did not have a greater impact than targeting the whole population.

Coverage

Increasing MSAT coverage to 72% results in an additional 6% ZCC and a 23% reduction in MPP compared to the baseline, while 100% coverage more than doubled the number of simulation runs estimating interruption of transmission to 31%, and a 36% reduction in MPP compared to the baseline. These results indicate that subsequent rounds of MSAT conducted during the 2013 and 2014 dry season where 72% and 100% of health facility catchment areas targeted, respectively, will likely see a greater health impact than the first round of MSAT with 40% coverage.

Frequency of implementation

Shortening time between MSAT rounds has the potential to increase the effectiveness of the intervention. Cutting the interval between rounds in half to 30 days did not show an improvement over baseline (14% vs. 15% ZCC), likely the result of 30 days being too long to catch the end of the prophylactic period of AL. A 20 day interval was marginally more effective in interrupting transmission (18% vs. 15% ZCC) but not at reducing MPP (4% reduction compared to the baseline).

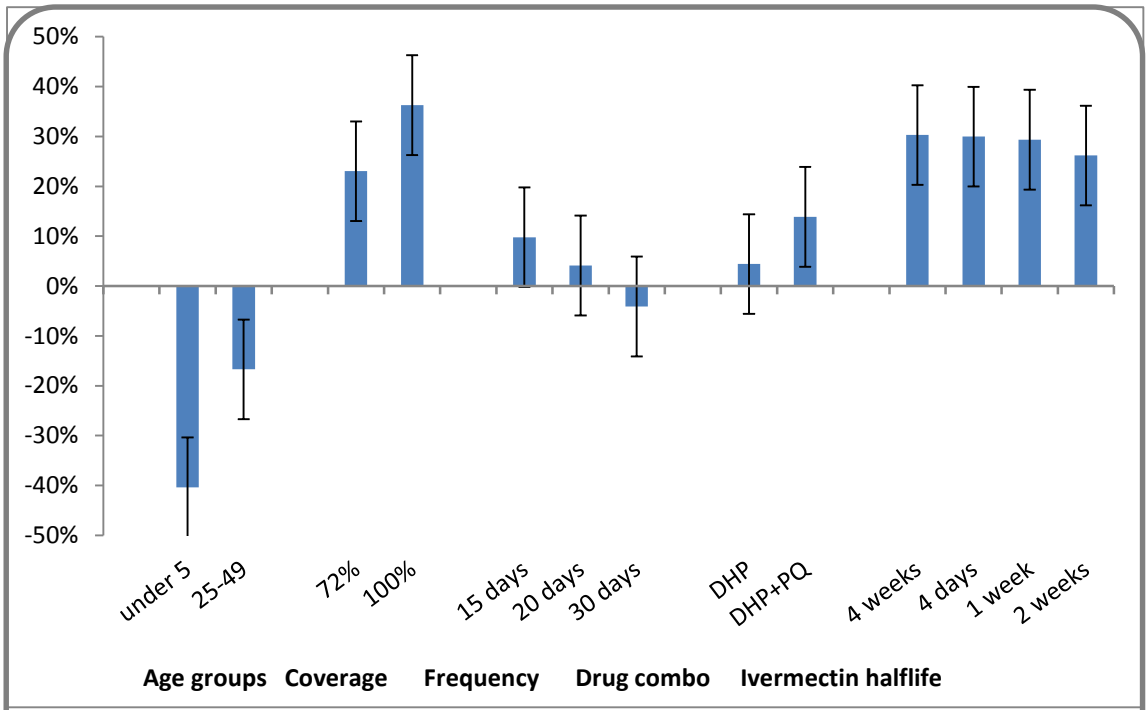

Figure 6: Simulated reduction in parasite prevalence in all ages compared to baseline scenario as measured in June 2013, the peak transmission month following MSAT implementation.

Interestingly, conducting the three rounds of MSAT 15 days apart resulted in the ZCC as increasing coverage to 72% (21% ZCC), but did not have as great an impact in parasite prevalence (10% reduction in MPP compared to the baseline scenario). This indicates that extending the prophylactic period by a shorter, more intense exposure to the antimalarials has more of an impact on transmission from mosquitoes to humans than to the overall parasite reservoir in the population.

Drug combinations

Despite the longer prophylactic period, MSAT with DHP did not perform better than AL at interrupting transmission or reducing MPP (both 15% ZCC, 4%). Adding PQ to the DHP regimen had a similar effect of interrupting transmission as shortening the interval between rounds to 20 days (18% ZCC) but had a larger effect on reducing MPP (14%). Conducting MDA with DHP + PQ + ivermectin had the largest impact of any combination of drugs or frequency of implementation with 27% ZCC and a 30% reduction in MPP over the baseline.

Ivermectin halflife

Varying the halflife of efficacy of Ivermectin between 4 days, 1 week, 2 weeks and 4 weeks did not result in a difference in reduction of parasite prevalence (26%-30%) or interrupting transmission (23%-27% ZCC). One possible explanation for this lack of variation could be due to the life span of the vector and the parasite. Ivermectin with a short halflife could be most effective on newly-infected mosquitoes, while ivermectin with a long halflife could be most effective on newly-infectious mosquitoes, in both cases preventing onward transmission.

Limitations

In the OpenMalaria model, there is no inter-annual variation in seasonality in EIR. This assumption is of little consequence when simulating the impact of interventions, but it can have an impact when validating studies that attempt to simulate the dynamics of malaria in a given location over a period of multiple years.

The OpenMalaria model does not explicitly take spatial associations into account. Variation in proximity to breeding sites could be a factor driving the difference in epidemic

profile of the study area. This can be captured by introducing heterogeneity in availability to mosquitoes in humans. However, targeting vector control interventions according to this availability cannot be modelled. Additionally, focal screen and treat (FSAT) programs, which may be an appropriate strategy in many settings, are not included in the portfolio of simulations.

Validation results showing a larger simulated round-to-round MSAT impact than observed in health facility catchment areas with MPP of greater than 24% at time of the pilot survey suggest a level of imported cases existing in these higher transmission catchment areas. This will need to be taken into account in refining the parameterization of Southern Province for future simulation experiments. A longer time period of simulated MSAT/MDA implementation may also clarify the impact of the program.

While the dosage level of ivermectin used in onchocerciasis control programs lasts approximately six days [35], increasing the dose used in an MDA program for malaria control may provide a longer duration of mosquito mortality [36]. To clarify these issues, conducting a comprehensive sensitivity analysis on the duration of effectiveness of ivermectin under different conditions will be an essential addition to this study, as will investigating the effect of different levels of compliance to the drug regimen. Additional focus needs to be placed on the effect of timing of ivermectin and parasite-vector dynamics to better apply appropriate targeting for inclusion of ivermectin in an MDA campaign.

5.5 Implications for future MSAT implementation in Southern Province

The optimal implementation strategy for MSAT/MDA in Southern Province will vary by background level of parasitaemia and coverage level, and success of the intervention depends on continued coverage of vector control interventions to ensure sustained gains in reduction of disease burden. Simulation results suggest a high proportion of low density infections missed by RDT diagnosis that are treated and cleared with MDA. Clarifying the relationship between sub-patent parasitaemia and transmission will be helpful to inform future program implementation.

Despite the marginal simulated initial benefit of switching to DHP, utilization of a different drug than the first line malaria treatment could have benefits for avoiding drug resistance that will only become clear after multiple years of implementation. While simulations with single low dose PQ also did not have a large effect at being added to a regimen of MSAT with DHP, this does not exclude PQ playing a role in malaria control and elimination. Integration of PQ into the first line treatment regimen for clinical cases or into active case detection or FSAT programs could be an effective use of the drug. Safety trials will need to be conducted and options for integrating a test for G6PD deficiency investigated. Strategies targeting Ivermectin have the potential to be a useful intervention in the study area. An additional benefit of ivermectin not reflected by simulation results may be to protect ACTs from additional resistance pressure due to mass treatment. If drug resistant parasites evolve in a person treated with ivermectin, ivermectin's effect of killing vectors prevents onward transmission of those resistant parasites. Simulations aimed at identifying the optimal mix of dosage and operational strategy can further clarify the role of ivermectin.

Direction for future OpenMalaria simulations

- Analysis of results stratified by level of parasite prevalence
- Sensitivity analysis of compliance to drug regimen
- Effectiveness and coverage levels for targeting children 5-15 with MSAT/MDA
- Effectiveness of MSAT/MDA in the contexts of Western Kenya, Ethiopia and Senegal
- Effectiveness of DHP, DHP+PQ, and DHP+PQ+ivermectin at different coverage levels and frequency of implementation
- Cost effectiveness analysis to determine the net health benefits of different operational strategies
- Simulated benefit of treating cattle with avermectin to target partially zoophagic vectors

5.6 Acknowledgements

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5.7 References

1. **OpenMalaria [http://code.google.com/p/openmalaria/wiki/Start]**
2. Smith T, Killeen GF, Maire N, Ross A, Molineaux L, Tediosi F, Hutton G, Utzinger J, Dietz K, Tanner M: **Mathematical modeling of the impact of malaria vaccines on the clinical epidemiology and natural history of Plasmodium falciparum malaria: Overview.** *Am J Trop Med Hyg* 2006, 75:1-10.
3. Smith T, Maire N, Ross A, Penny M, Chitnis N, Schapira A, Studer A, Genton B, Lengeler C, Tediosi F, et al: **Towards a comprehensive simulation model of malaria epidemiology and control.** *Parasitology* 2008, 135:1507-1516.
4. ZMOH: **Zambia National Malaria Indicator Survey 2010.** Lusaka2011.
5. PATH/MACEPA: **Malaria Test and Treat Campaign Summary - NMCC Briefing document.** Lusaka, Zambia: PATH/MACEPA; 2013.
6. Fornadel CM, Norris LC, Glass GE, Norris DE: **Analysis of Anopheles arabiensis blood feeding behavior in southern Zambia during the two years after introduction of insecticide-treated bed nets.** *Am J Trop Med Hyg* 2010, 83:848-853.
7. Kent RJ, Thuma PE, Mharakurwa S, Norris DE: **Seasonality, blood feeding behavior, and transmission of Plasmodium falciparum by Anopheles arabiensis after an extended drought in southern Zambia.** *Am J Trop Med Hyg* 2007, 76:267-274.
8. Lwin KM, Phyo AP, Tarning J, Hanpithakpong W, Ashley EA, Lee SJ, Cheah P, Singhasivanon P, White NJ, Lindegardh N, Nosten F: **Randomized, double-blind, placebo-controlled trial of monthly versus bimonthly dihydroartemisinin-piperaquine chemoprevention in adults at high risk of malaria.** *Antimicrob Agents Chemother* 2012, 56:1571-1577.
9. Sutanto I, Suprijanto S, Kosasih A, Dahlan MS, Syafruddin D, Kusriastuti R, Hawley WA, Lobo NF, Ter Kuile FO: **The effect of primaquine on gametocyte development and clearance in the treatment of uncomplicated falciparum malaria with dihydroartemisinin-piperaquine in South sumatra, Western indonesia: an open-label, randomized, controlled trial.** *Clin Infect Dis* 2013, 56:685-693.
10. Foy BD, Kobylinski KC, da Silva IM, Rasgon JL, Sylla M: **Endectocides for malaria control.** ***T****rends Parasitol* 2011, 27:423-428.
11. Maire N, Smith T, Ross A, Owusu-Agyei S, Dietz K, Molineaux L: **A model for natural immunity to asexual blood stages of Plasmodium falciparum malaria in endemic areas.** *Am J Trop Med Hyg* 2006, 75:19-31.
12. Smith T, Maire N, Dietz K, Killeen GF, Vounatsou P, Molineaux L, Tanner M: **Relationship between the entomologic inoculation rate and the force of infection for Plasmodium falciparum malaria.** *Am J Trop Med Hyg* 2006, 75:11-18.
13. Killeen GF, Ross A, Smith T: **Infectiousness of malaria-endemic human populations to vectors.** *Am J Trop Med Hyg* 2006, 75:38-45.
14. Ross A, Killeen G, Smith T: **Relationships between host infectivity to mosquitoes and asexual parasite density in Plasmodium falciparum.** *Am J Trop Med Hyg* 2006, 75:32-37.
15. Ross A, Maire N, Molineaux L, Smith T: **An epidemiologic model of severe morbidity and mortality caused by Plasmodium falciparum.** *Am J Trop Med Hyg* 2006, 75:63-73.
16. Ross A, Smith T: **The effect of malaria transmission intensity on neonatal mortality in endemic areas.** *Am J Trop Med Hyg* 2006, 75:74-81.
17. Smith T, Ross A, Maire N, Rogier C, Trape JF, Molineaux L: **An epidemiologic model of the incidence of acute illness in Plasmodium falciparum malaria.** *Am J Trop Med Hyg* 2006, 75:56-62.
18. Carneiro IA, Smith T, Lusingu JP, Malima R, Utzinger J, Drakeley CJ: **Modeling the relationship between the population prevalence of Plasmodium falciparum malaria and anemia.** *Am J Trop Med Hyg* 2006, 75:82-89.

19. Chitnis N, Smith T, Steketee R: **A mathematical model for the dynamics of malaria in mosquitoes feeding on a heterogeneous host population.** *Journal of Biological Dynamics* 2008, 2:259 - 285.

20. Chitnis N, Hardy D, Smith T: **A Periodically-Forced Mathematical Model for the Seasonal Dynamics of Malaria in Mosquitoes.** *Bulletin of mathematical biology* 2012, 74(5):1098–1124.

21. Smith T, Ross A, Maire N, Chitnis N, Studer A, Hardy D, Brooks A, Penny M, Tanner M: **Ensemble modeling of the likely public health impact of a pre-erythrocytic malaria vaccine.** *PLoS medicine* 2012, 9:e1001157.

22. Tediosi F, Maire N, Smith T, Hutton G, Utzinger J, Ross A, Tanner M: **An approach to model the costs and effects of case management of Plasmodium falciparum malaria in sub-saharan Africa.** *Am J Trop Med Hyg* 2006, 75:90-103.

23. Maire N, Aponte JJ, Ross A, Thompson R, Alonso P, Utzinger J, Tanner M, Smith T: **Modeling a field trial of the RTS,S/AS02A malaria vaccine.** *Am J Trop Med Hyg* 2006, 75:104-110**.**

24. Maire N, Tediosi F, Ross A, Smith T: **Predictions of the epidemiologic impact of introducing a pre-erythrocytic vaccine into the expanded program on immunization in sub-Saharan Africa.** *Am J Trop Med Hyg* 2006, 75:111-118**.**

25. Penny MA, Maire N, Studer A, Schapira A, Smith TA: **What should vaccine developers ask? Simulation of the effectiveness of malaria vaccines.** *PLoS One* 2008, 3:e3193.

26. Smith TA, Chitnis N, Briet OJ, Tanner M: **Uses of mosquito-stage transmission-blocking vaccines against Plasmodium falciparum.** *Trends in parasitology* 2011, 27:190-196.

27. Ross A, Penny M, Maire N, Studer A, Carneiro I, Schellenberg D, Greenwood B, Tanner M, Smith T: **Modelling the epidemiological impact of intermittent preventive treatment against malaria in infants.** *PLoS One* 2008, 3:e2661.

28. Crowell V, Briet OJ, Hardy D, Chitnis N, Maire N, Di Pasquale A, Smith TA: **Modelling the cost-effectiveness of mass screening and treatment for reducing Plasmodium falciparum malaria burden.** *Malar J* 2013, 12:4.

29. Briet OJ, Hardy D, Smith TA: **Importance of factors determining the effective lifetime of a mass, long-lasting, insecticidal net distribution: a sensitivity analysis.** *Malaria journal* 2012, 11:20.

30. Briet OJ, Penny MA, Hardy D, Awolola TS, Van Bortel W, Corbel V, Dabire RK, Etang J, Koudou BG, Tungu PK, Chitnis N: **Effects of pyrethroid resistance on the cost effectiveness of a mass distribution of long-lasting insecticidal nets: a modelling study.** *Malar J* 2013, 12:77.

31. Chitnis N, Schapira A, Smith T, Steketee R: **Comparing the effectiveness of malaria vector-control interventions through a mathematical model.** *The American journal of tropical medicine and hygiene* 2010, 83:230-240.

32. Stuckey EM, Stevenson J, Cooke M, Owaga C, Marube E, Oando G, Hardy D, Drakeley C, Smith T, Cox J, Chitnis N: **Simulation of malaria epidemiology and control in the highlands of western Kenya.** *Malar J* 2012, 11.

33. Feachem RG, Phillips AA, Hwang J, Cotter C, Wielgosz B, Greenwood BM, Sabot O, Rodriguez MH, Abeyasinghe RR, Ghebreyesus TA, Snow RW: **Shrinking the malaria map: progress and prospects.** *Lancet* 2010, 376:1566-1578.

34. **WHO: Global malaria control and elimination: report of a technical review.** Geneva: WHO; 2009.

35. Sylla M, Kobylinski KC, Gray M, Chapman PL, Sarr MD, Rasgon JL, Foy BD: **Mass drug administration of ivermectin in south-eastern Senegal reduces the survivorship of wild-caught, blood fed malaria vectors.** *Malar J* 2010, 9:365.

36. Chaccour CJ, Kobylinski KC, Bassat Q, Bousema T, Drakeley C, Alonso P, Foy BD: **Ivermectin to reduce malaria transmission: a research agenda for a promising new tool for elimination.** *Malar J* 2013, 12:153.

Appendix: Baseline OpenMalaria parameterization for Southern Province, Zambia

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6. Seasonally dependent relationships between indicators of malaria transmission and disease provided by mathematical model simulations

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6.1 Abstract

Background

Evaluating the effectiveness of malaria control interventions on the basis of their impact on transmission as well as impact on morbidity and mortality is becoming increasingly important as countries consider pre-elimination and elimination as well as disease control. Data on prevalence and transmission are traditionally obtained through resource-intense epidemiological and entomological surveys that become difficult as transmission decreases. This work employs mathematical modeling to examine the relationships between malaria indicators allowing more easily measured data, such as routine health systems data on case incidence, to be translated into measures of transmission and other malaria indicators. Simulations of scenarios with different levels of malaria transmission, patterns of seasonality and access to treatment were run with an ensemble of models of malaria epidemiology and within-host dynamics, as part of the OpenMalaria modeling platform. For a given seasonality profile, regression analysis mapped simulation results of malaria indicators, such as annual average entomological inoculation rate, prevalence, incidence of uncomplicated and severe episodes, and mortality, to an expected range of values of any of the other indicators. Results were validated by comparing simulated relationships between indicators with previously published data on these same indicators as observed in malaria endemic areas. These results allow for direct comparisons of malaria transmission intensity estimates made using data collected with different methods on different indicators. They also address key concerns with traditional methods of quantifying transmission in areas of differing transmission intensity and sparse data. Although seasonality of transmission is often ignored in data compilations, the models suggest it can be critically important in determining the relationship between transmission and disease. Application of these models could help public health officials detect changes of disease dynamics in a population and plan and assess the impact of malaria control interventions.

6.2 Author summary

While malaria is still a major public health problem in many parts of the world, control programs have greatly reduced the burden of disease in recent years and many countries are now considering the goal of elimination. Unfortunately, malaria transmission becomes more difficult to measure when it is low because traditional methods involve capturing mosquitoes; an expensive and time-consuming technique. To measure transmission in areas without adequate field data, we run simulations of a mathematical model of malaria over a range of transmission intensities and seasonal patterns to examine how different measurements of malaria (prevalence, clinical disease, and death) relate to each other, how they relate to transmission, and if the relationships are likely to vary by seasonal pattern of transmission. These simulated relationships allow us to translate easily measured data, such as clinical case incidence seen at health facilities, into estimates of transmission. This technique can help public health officials plan and assess the impact of malaria control interventions, even in areas without intense research activities.

6.3 Introduction

Evaluating the effectiveness of malaria control interventions on the basis of their impact on transmission is increasingly important as countries consider elimination as well as malaria control. However, direct measurement of transmission, such as by the entomological inoculation rate (EIR) (a measure of human exposure defined by the number of infective mosquito bites per human in a given time period), involves mosquito capture. This is extremely labor-intensive, and is only reliable in high transmission areas and seasons [1]. In areas of low transmission, or during dry seasons, identifying a sufficient number of sporozoite-positive mosquitoes makes this exercise excessively time- and resource- intense, often precluding collection of a full year's worth of data and making estimates of seasonality challenging. Alternatives are to estimate transmission rates from sero-conversion rates [2,3] or by calculating force of infection (FOI) from combining information on prevalence and treatment [4]. Estimating both the exposure to infectious mosquitoes and subsequent FOI from parasite

prevalence in areas of high transmission is difficult due to superinfection and immunity. Mathematical models are useful in examining relationships between malaria indicators, allowing translation of routine health center data into measures of transmission and addressing concerns with previously implemented methods of measuring transmission [5].

Understanding the seasonal pattern of malaria transmission is important for planning control interventions, for example the timing of deploying indoor residual spraying (IRS) and seasonal malaria chemoprophylaxis (SMC) which are implemented ahead of the peak transmission months. Given the wide range of seasonal patterns combined with transmission intensities that exist in areas of the world with malaria transmission, and due in large part to the absence of robust field data, the effect of seasonality on the relationship between malaria indicators has not been studied in great detail. Attempts have been made to define [6, 7] and quantify [8] the relationship between seasonally varying covariates and transmission based on available studies on malaria transmission and disease burden, but results for the latter were only found to be reliable in areas of very high transmission (EIR > 100 infectious bites per person per year) [6].

One approach for quantifying transmission in areas without EIR data is to use simulation models to analyze how different malaria indicators (parasite prevalence, prevalence of uncomplicated and severe episodes, mortality) relate to each other, and how they relate to transmission measured by EIR [5]. To validate such models, a straightforward approach would be to compare the simulated relationships between indicators to those observed in the field. However, when relationships between indicators differ in places with disparate patterns of seasonality, such an approach becomes challenging. This study uses simulation models to analyze whether relationships between malaria indicators are likely to vary by intensity and pattern of seasonality. Analysis of these simulation results can help identify the best way of quantifying transmission for the purposes of specifying the seasonal patterns to drive the existing models of *Plasmodium falciparum* dynamics. This in turn will assist in planning for malaria control by allowing for the selection of interventions tailored to the level of

transmission in a given location, and monitoring the effectiveness of those interventions by their impact on transmission.

6.4 Methods

OpenMalaria transmission model simulation

This experiment utilizes an ensemble of simulation models of transmission of malaria developed by a team at the Swiss Tropical and Public Health Institute (Swiss TPH) and Liverpool School of Tropical Medicine. These models form part of the OpenMalaria platform that makes the considerable code base written in C++ accessible to the public through an online wiki [9]. Based on a stochastic series of parasite densities for individual infections, stochastic individual-based models of malaria in humans [10-12] are linked to a periodically-forced model of malaria in mosquitoes [13] in order to simulate the dynamics of malaria transmission and the impact of intervention strategies for malaria control. Details of the methods to create and parameterize the transmission model used in this project have been previously published [10-13] and therefore are not covered in this paper. Models are fitted to 10 objectives using 61 standard scenarios as described in Smith et al. 2008 [11]. The transmission model is calibrated by the seasonal pattern of the EIR with units of infectious bites per person per year. Simulations were run for one human life span to induce a stable level of immunity in the population. Each simulation was repeated on an ensemble of 14 model variants with varying assumptions on mass action, heterogeneity of exposure, decay of acquired immunity, co-morbidities, and access to treatment as described in Smith et al. 2012 [12] to address model uncertainty, with five random seeds to address stochasticity.

Study design

The overall objective of estimating transmission in areas without EIR data was addressed by applying the OpenMalaria modeling platform to simulate malaria with different levels of transmission and patterns of seasonality observed in malaria-affected locations, and deriving

outputs for all other malaria indicators. **Table 1** describes the indicators chosen as simulation outputs that were evaluated in this study. Relationships between all indicators for the different values of EIR and different seasonality profiles were estimated from simulation results (described below) using Stata v12 (College Station, TX). For this process the indicators were calculated for the whole population, with the exception of the relationships involving mortality which were limited to children under five due to a lack of data in older age groups for validation purposes.

Table 1. Malaria indicators described in this study and their definitions for the purposes of this study.

Indicator name	Definition	Transformation*
Entomological Inoculation Rate (EIR)	Annual average number of infectious bites received from a malaria vector per person	Logarithmic
Parasite prevalence	Proportion of the population (all ages) with detectable parasitaemia (greater than 100 parasites per microliter)	Logit
Uncomplicated episodes	Annual average number of uncomplicated clinical episodes of malaria per person (all ages)	Logarithmic
Severe episodes	Annual average number of severe clinical episodes of malaria per 1,000 people (all ages)	Logarithmic
Mortality	Annual average number of deaths due to malaria in children under 5 per 1,000 people	Logarithmic

* Transformation used in fractional polynomial analysis.
doi:10.1371/journal.pcbi.1003812.t001

Scenario Design

The baseline scenario used in these experiments was based on a scenario previously parameterized for the Rachuonyo South district in the highlands of western Kenya [14]. The model assumes no interventions beyond standard case management through the health system as described in Tediosi et al. [15], a main vector of *A. gambiae* s.s., and artimisinin combination therapy (ACTs) as the first line antimalarial. Simulations were run on a population of 100,000 individuals over three years with monthly surveys of malaria outcomes.

Seasonality Index

To quantify the "amount" of seasonality in a location a seasonality index (φ) was defined in order to describe the variations in transmission within one year in a given location. The methodology presented here is general and can be used for any measure of transmission, but

the example below is used with EIR.

We let *T* denote the period (1 year) and let *f (t)* be a positive continuous periodic function that denotes transmission at time *t*, with $f(t+T) = f(t) > 0$ for all $t \geq 0$. The mean level of transmission (over 1 year) is,

$$\Theta = \frac{1}{T}\int_0^T f(t)dt$$

In a similar manner to the coefficient of variation in statistics, we define φ as the normalized square root of the integral of the squared difference between *f(t)* and its mean,

$$\varphi = \frac{1}{\Theta}\sqrt{\frac{1}{T}\int_0^T (f(t)-\Theta)^2 dt}$$

This seasonality index, φ, allows us to quantify the level of seasonality of transmission in a given location with one positive real number, differentiating between "amounts" of seasonality for transmission patterns with the same number of peaks. Because malarious areas in general have either one or two peak transmission seasons, there could be seasonality patterns in different locations that lead to the same seasonality index, φ. We therefore label the seasonality profile with both the seasonality index and the number of peaks.

Seasonality profiles

The simulations described here treat transmission in the absence of interventions as periodic with a one year period [13]. One scenario with a seasonality pattern of constant annual transmission (φ =0) and five scenarios with varying seasonal transmission patterns (φ =1, one peak; φ =1, two peaks; φ =0.5, two peaks; φ =1.5, one peak; φ =1.5, two peaks) were created, described in **Table 2** and **Figure 1**.

Table 2. Seasonality patterns of transmission observed malaria-endemic areas.

Seasonality pattern ID	Seasonality index (φ)	Number of peaks	Description
0, 0	0	0	No seasonality – constant transmission throughout the year
1, 1	1	1	Medium seasonality, one transmission season
1, 2	1	2	Medium seasonality, two transmission seasons
0.5, 2	0.5	2	Low seasonality, two transmission seasons
2, 1	2	1	High seasonality, one transmission season
2, 2	2	2	High seasonality, two transmission seasons

doi:10.1371/journal.pcbi.1003812.t002

These six patterns were chosen to represent the range of seasonal patterns of malaria transmission existing in the malaria endemic world, namely because there are usually not more than two peak transmission seasons. The seasonality profiles with φ =1.5 exhibit large variations in seasonality. For φ =1.5 with one peak, 86% of annual transmission is focused in the three peak transmission months, while for φ =1.5 with two peaks, the peak is narrower with 95% of annual transmission occurring in the three months of the higher peak. The results of what this means for prevalence and morbidity over one year can be found in **Figure S1** in **Text S1**. Seasonality patterns were repeated for eleven values of annual average EIR from 0.5 to 365.

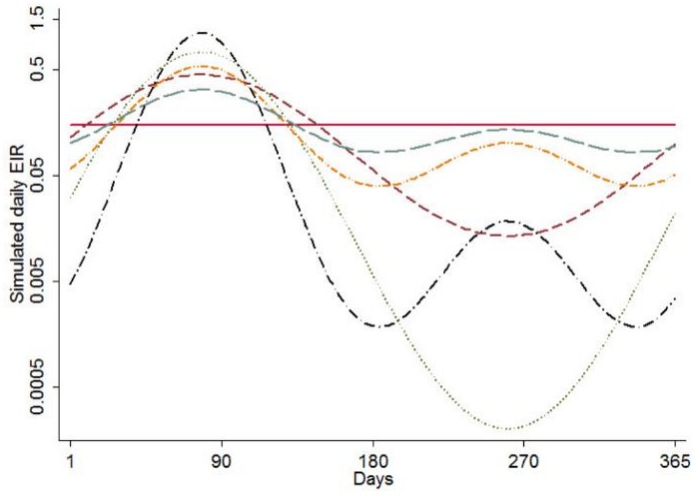

Figure 1: **Annual pattern of transmission, defined as the simulated daily EIR, for each seasonality profile as described by the seasonality index (φ, number of peaks).** Unbroken red line represents (0,0). Brown dashed line represents (1,1). Orange dotted-dashed line represents (1,2). Green dotted line represents (1.5,1). Black dotted-dashed line represents (1.5,2). Blue dashed line represents (0.5,2)

Complete details of the methods behind the experiment creation can be found in **Text S1**. The relationships between malaria indicators were estimated using fractional polynomial regression as described in more detail in **Text S2**.

Model validation

In order to gauge the model's ability to reproduce field data, a validation exercise was completed by comparing simulation results to data not used in

the original process of model fitting from previously published studies. The relationships for validation, the datasets used and how they relate to model fitting are described in **Table S1**.

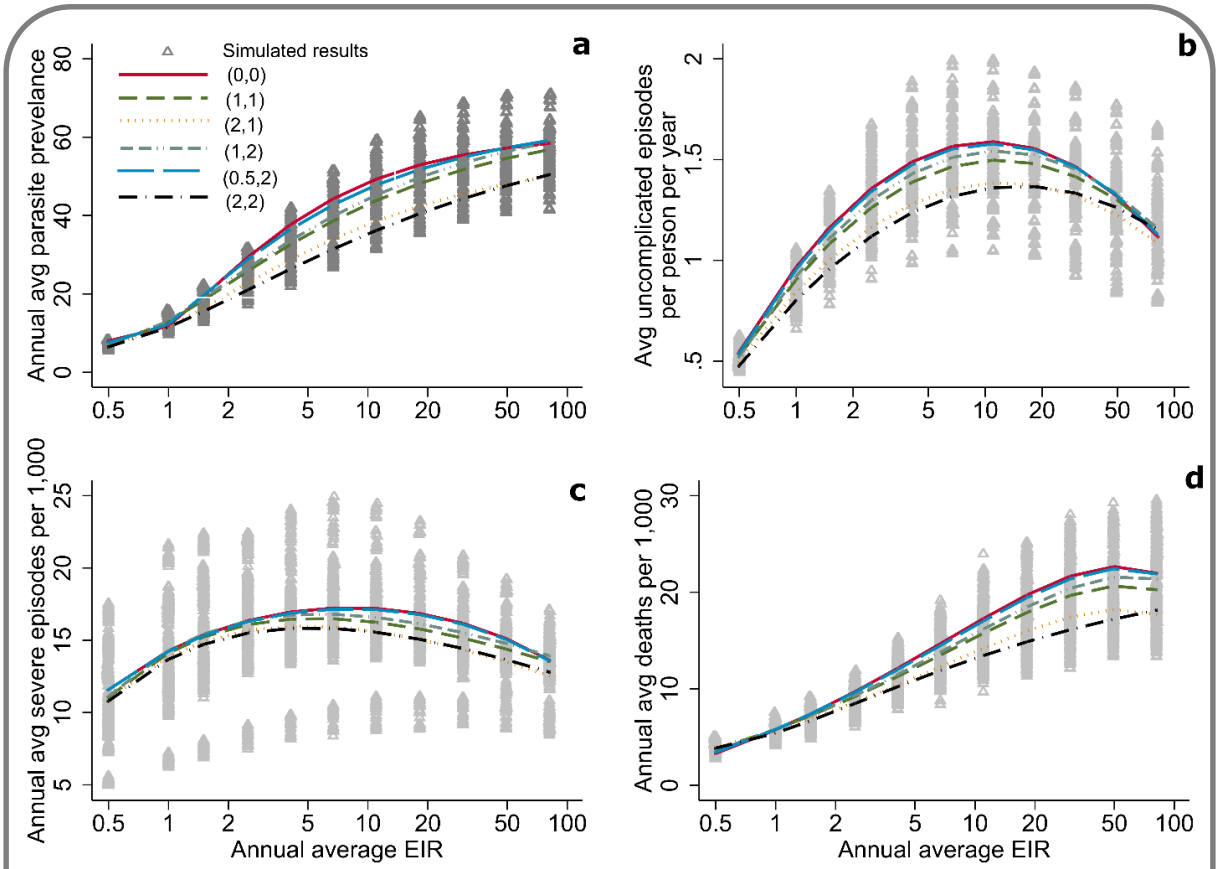

Figure 2: Relationship of parasite prevalence (a), uncomplicated episodes (b), severe episodes (c), and mortality (d) to annual average EIR by seasonality index (φ). Triangles represent simulated results. The lines show the estimated relationship between indicators from the simulation runs, fitted using fractional polynomial regression, for each pattern of seasonality as described by the seasonality index (ϕ, number of peaks) (**Figure 1**). Unbroken red line represents (0,0). Brown dashed line represents (1,1). Orange dotted-dashed line represents (1,2). Green dotted line represents (2,1). Black dotted-dashed line represents (2,2). Blue dashed line represents (0.5,2).

While the annual average EIR in the scenarios used for estimating the relationships between malaria indicators were capped at a value of 81.4, scenarios for validation were simulated up to an average of 365 infectious bites per person per year. This tailors the analysis to low- to mid-range values of annual average EIR where this tool will be the most applicable, while still allowing for a more comprehensive range of annual average EIRs that appear in the validation datasets.

6.5 Results

Indicators as a function of entomological inoculation rate (EIR)

When analyzing the relationship between EIR and other malaria indicators, the differences between seasonality profiles are greatest at moderate levels of EIR (**Figure 2a-d**). Results are similar between seasonality profiles at both ends of the EIR spectrum for uncomplicated and severe disease, but seasonality impacts the relationship with prevalence and mortality more at higher values of EIR (**Figure 2a-d**).

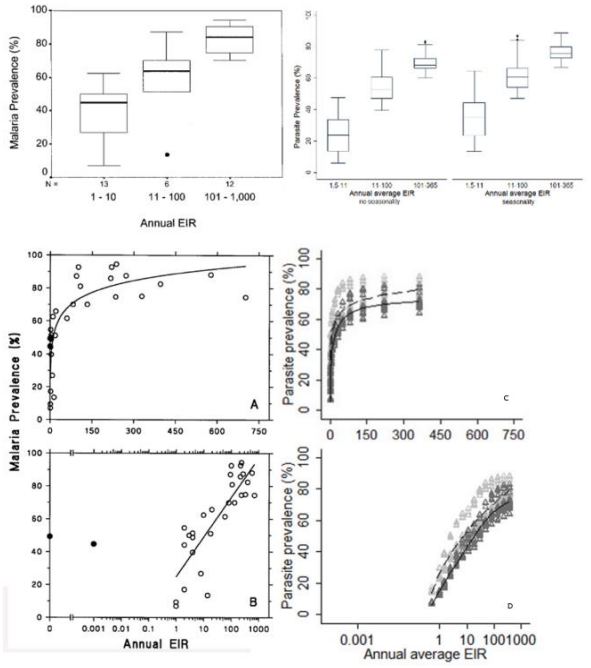

Figure 3: The relationship between prevalence (defined as the maximum recorded parasite prevalence rate in any given age group) and EIR from Beier et. al [17] (3.1 a, 3.2 a-b) and OpenMalaria simulations (3.1 b, 3.2 d). In **3.1** the mean value is shown as a line inside the box, the 25th to 75th percentile is shown by the box, and the range of values is shown by the lines outside the box. In **3.2** grey triangles represent simulation results without (light gray) and with (dark gray) seasonality as described by the seasonality index (ϕ, number of peaks) (**Figure 1**). The lines show the estimated relationships with seasonality (2,2) (dashed) and without seasonality (0,0) (unbroken) using fractional polynomial regression. Figures **3.1a** and **3.2a-b** have been reproduced from Beier et al. [17] with permission.

The Beier et al. dataset, describing the relationship between EIR and parasite prevalence in children under five in sites across Africa, has been applied for a previous validation of the OpenMalaria model [16]. One site out of 31 as published separately was used to fit the model for incidence of asexual blood stage infection, as indicated in **Table S1**. Compared to the results presented in Beier et al. [17], simulation results are within the range of observed values for low and medium values of EIR, but predict a slightly lower prevalence in extremely high EIR settings, especially in a setting with no seasonality (**Figure 3**). Perhaps this is because observed results reach up to 1,000 infectious bites per person per year while the simulated scenarios were capped at 365. While the observed relationship is fitted as log-linear, the simulated relationship starts levelling off at an EIR of 100.

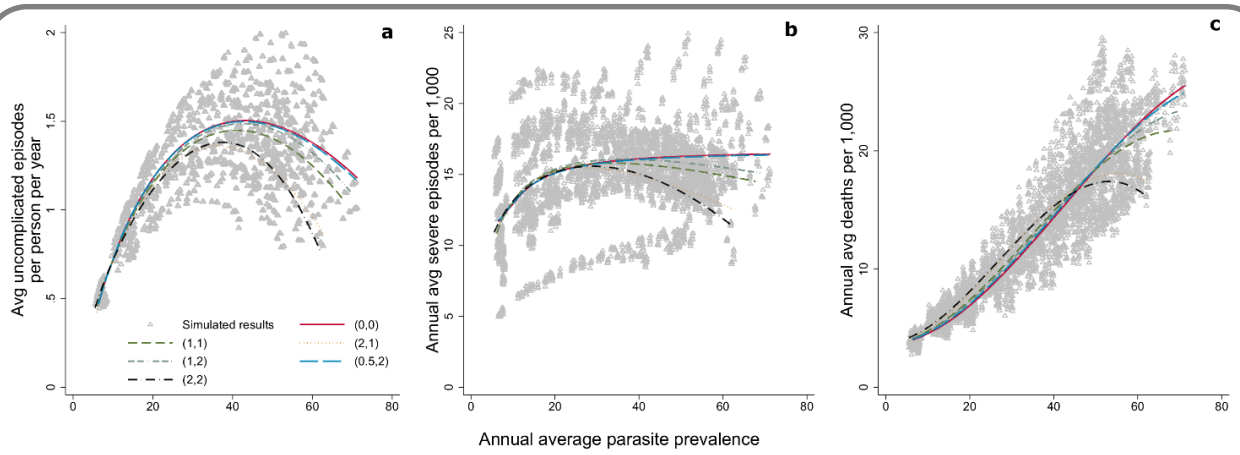

Figure 4. Relationship of uncomplicated episodes (a), severe episodes (b), and mortality (c) to parasite prevalence by seasonality index. Triangles represent simulated results. The lines show the estimated relationship between indicators from the simulation runs, fitted using fractional polynomial regression, for each pattern of seasonality as described by the seasonality index (ϕ, number of peaks) (**Figure 1**). Unbroken red line represents $(0,0)$. Brown dashed line represents $(1,1)$. Orange dotted-dashed line represents $(1,2)$. Green dotted line represents $(1.5,1)$. Black dotted-dashed line represents $(1.5,2)$. Blue dashed line represents $(0.5,2)$.

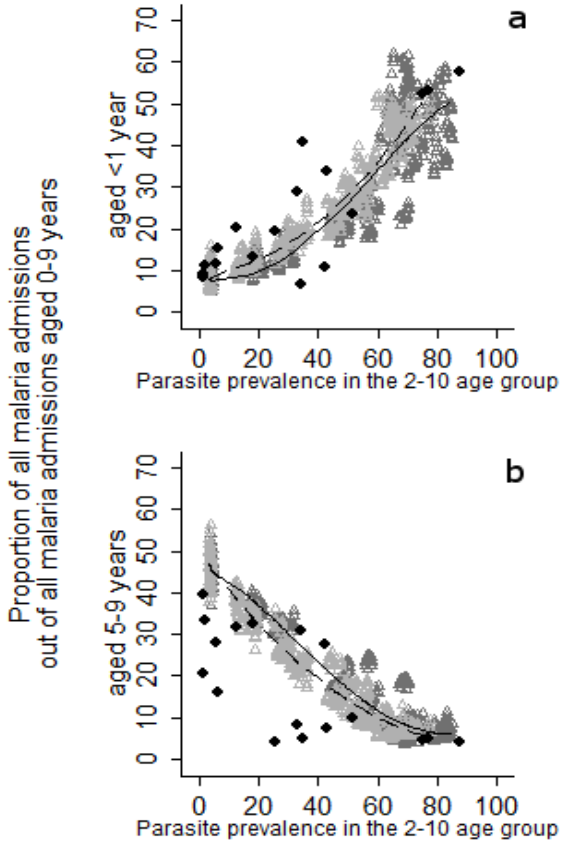

Figure 5: Relationship between the proportion of paediatric severe malaria in children under 1 year (a) and children aged 5-9 years (b) and parasite prevalence in the 2-1- age group from Okiro et al, [18] (black circles) and OpenMalaria simulations (grey triangles). Triangles represent simulation results with (dark gray) and without (light gray) seasonality. Lines show the estimated relationships with (dashed) and without (unbroken) seasonality using fractional polynomial regression.

Indicators as a function of parasite prevalence

The relationship between parasite prevalence and uncomplicated episodes is non-monotonic (**Figure 4a**) for all values of φ. It can be noted that the simulated relationship between parasite prevalence and severe disease shows more stochasticity than the other relationships with parasite prevalence in areas of lower prevalence (**Figure 4b**). This variation can be attributed to model uncertainty, in particular differing assumptions about access to treatment, rather than to the effect of seasonality. For uncomplicated disease, severe disease and mortality, the effect of seasonality is greater in areas of higher parasite prevalence; the variation increases once prevalence reaches 40% (**Figure 4a-c**).

Compared to the results presented in Okiro et al. [18] the model is able to reproduce the general pattern of the relationship between severe pediatric malaria and prevalence in children aged 2-10 in children under 1 year as well as children aged 5-9, with the burden of malaria moving to older age groups as prevalence is reduced (**Figure 5**).

Compared to the results presented in Korenromp et al. [19], which describes the relationship between parasite prevalence and both malaria-specific and all-cause mortality in children under 5, the model is able to capture the general pattern for the relationship between malaria- specific mortality in children under five for low and moderate prevalence settings (**Figure 6**).There appears to be variation across sites in the observed data that may be explained by the ability of verbal autopsy to capture indirect deaths due to malaria in different settings [20]. Nine sites (for which EIR estimates were available) out of the 28 sites included in the study were used to fit the model of direct malaria mortality in relation to EIR, as indicated in **Table S1**.

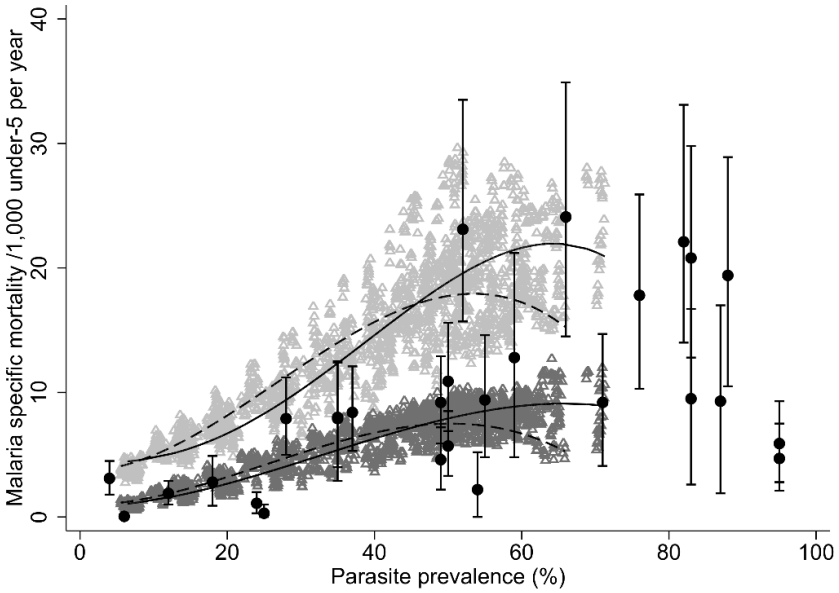

Figure 6: **Relationship between mortality in children under 5 and average all-age parasite prevalence as described in (black dots) Korenromp et. al [19] (black circles) and OpenMalaria simulations (triangles) for all deaths (light gray) and direct deaths only (dark gray).** Lines show the simulation-based estimated relationships with seasonality (φ=1.5, 2 peaks) (dashed) and without seasonality (φ=0, 0 peaks) (unbroken) using fractional polynomial regression. The observed values from Korenromp et. al are results of verbal autopsy which do not specify direct malaria deaths as opposed to indirect malaria deaths.

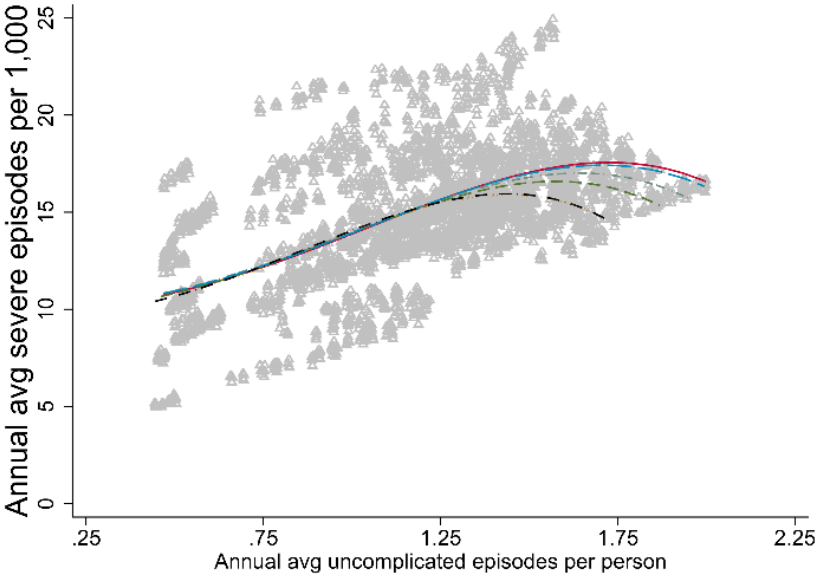

Figure 7. **Relationship of severe episodes to uncomplicated episodes by seasonality index**. Triangles represent simulated results. The lines show the estimated relationship between indicators from the simulation runs, fitted using fractional polynomial regression, for each pattern of seasonality as described by the seasonality index (φ, number of peaks) (**Figure 1**). Unbroken red line represents (0,0). Brown dashed line represents (1,1). Orange dotted-dashed line represents (1,2). Green dotted line represents (1.5,1). Black dotted-dashed line represents (1.5,2). Blue dashed line represents (0.5,2).

Indicators as a function of uncomplicated episodes

At lower numbers of uncomplicated episodes per person per year, seasonality does not play a role in the relationship with severe episodes (**Figure 7**). The curves separate at levels above 1.25 uncomplicated episodes per person per year with two-peak scenarios φ =1 and φ =1.5 diverging from the other values of φ (**Figure 7**). The scatter plot of simulation results showed no discernible relationship between mortality and either uncomplicated or severe episodes, and are therefore not shown here.

Age prevalence curves by indicator

Age prevalence curves are validated by comparing simulation results to those presented in Carneiro et al, which report on the age distribution of children with clinical malaria, hospital admissions with malaria and malaria-diagnosed mortality for different categories of intensity and seasonality of malaria transmission identified from a systematic review epidemiological studies [6].

It should be noted that there are differences in the classification of degree of seasonality between the observed and simulated data. Carneiro and colleagues describe settings with marked seasonality as those with greater than or equal to 75% of episodes concentrated less than or equal to 6 months of the year. In the OpenMalaria simulations, Marked seasonality is defined as the setting with φ =1.5.

The reported estimated median ages and inter-quartile ranges (defined as the 50th percentile of the best-fitting distribution for each outcome and transmission scenario) from these fitted models for each level of transmission and level of seasonality are compared to estimates from fitted OpenMalaria simulation results to validate age prevalence curves of the malaria indicators mentioned above. In all cases, the results of the OpenMalaria simulations are comparable to the previously published results (**Figure 9**).

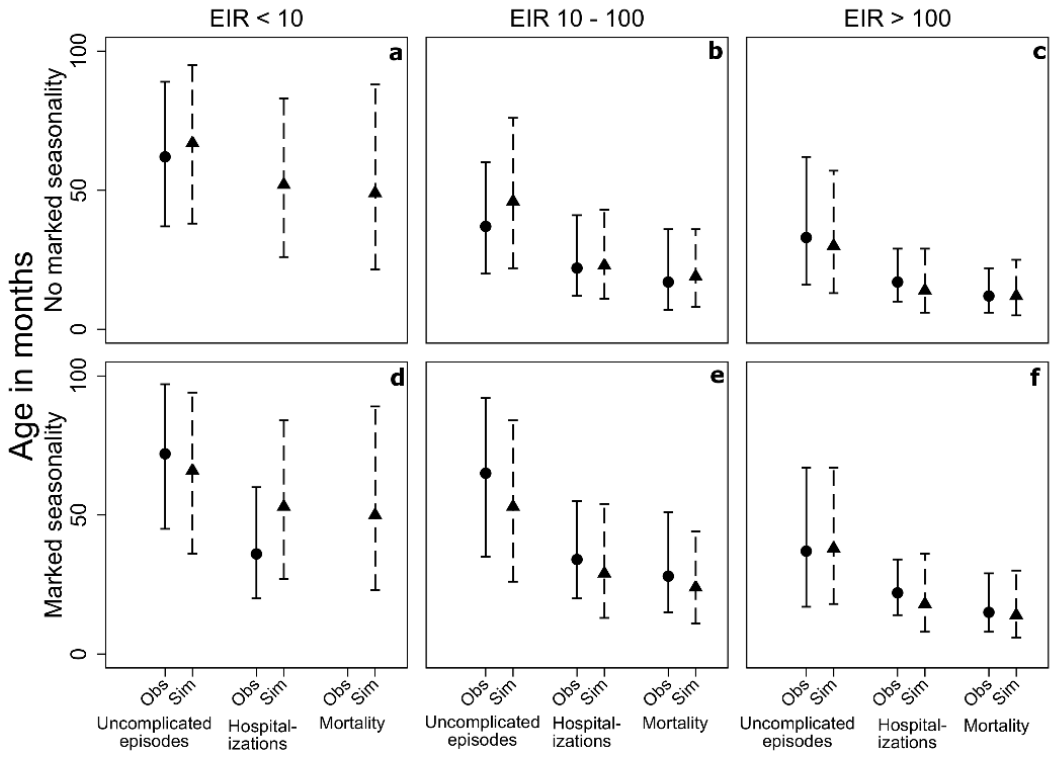

Figure 8: Median ages and inter-quartile range age prevalence curves in months of age by annual average EIR levels of <10 (a,d), 10-100 (b, e), and >100(c,f), and seasonality patterns (φ=1.5, 2 peaks (a-c) and φ=0, 0 peaks (d-f) for uncomplicated episodes, malaria hospitalizations, and mortality as observed in Carneiro et al. [6] (circles, unbroken lines) and simulated by the OpenMalaria model (triangles, dashed lines).

6.6 Discussion

Due to the lack of understanding of the relationship between EIR and other malaria indicators based on challenges in measuring EIR from entomological studies, modeling is able to further define the relationships between indicators and help clarify details of what cannot measured from field studies but is nonetheless necessary knowledge about malaria indicators. This is of value for malaria control program managers because it provides insight on transmission without substantial field studies. These models can be used to simulate the likely range of values in areas without access to adequate field data.

Empirical studies of the relationships between different malaria indicators are challenging because these relationships may in principle be affected by many, often poorly characterized, contextual factors, with the degree of seasonality being possibly one of the most important. The original fitting of the OpenMalaria model parameters to multiple field datasets used a standard pattern of seasonality of transmission from Namawala, Tanzania; effects of seasonality observed in these results are thus not an artifact of the fitting process. Simulations suggest that with equal levels of average annual transmission, the level of seasonality, i.e. whether malaria transmission is fairly constant over the course of a year versus peaks in certain months, affects the relationship between malaria indicators. An increase in the degree of seasonality has a greater impact on outcomes with moderate levels of EIR and prevalence. There is greater stochasticity in simulation results for scenarios with higher amplitude of the annual cycle compared to scenarios with a constant level of transmission.

There have been previous attempts to create a measure for the seasonality of malaria transmission [21-23], mainly relying only on rainfall and/or vector abundance to describe the proportion of transmission occurring within a certain number of months. The approach to developing the seasonality index presented here is in response to the need to provide a quantitative metric for differences between seasonal patterns. Results indicate that this index does not distinguish well between patterns that have a different number of peaks (**Figure 2**); therefore the number of peaks should also be noted in any analysis of studies that employ this

index. Areas with seasonal malaria transmission typically have substantial variation in rainfall and transmission with numerous small peaks, but normally only have one or two main seasons. The total number of peaks can thus be assumed to be limited to a maximum of two.

The difference in results for different patterns within the same seasonality index calls into question the assumptions behind the drivers of the relationships between malaria indicators. Scenarios with a higher degree of seasonality, regardless of number of peaks, return lower levels of prevalence, disease and mortality for a given level of transmission. An important driver is multiple concomitant events; when two illness episodes occur at the same time they are only considered as one, which may occur more frequently in high seasonality scenarios. At more mild patterns of seasonality, this phenomenon is only seen at higher levels of transmission. These results also potentially indicate an effect on acquisition of immunity in these settings, a consideration when modeling the relationship between transmission and the acquisition of immunity in a population. Several model variants differ in their assumptions about immunity [12], and while outside the scope of this paper, an important question for future investigation would be the impact of this aspect of the model variants and effect, if any, that occurs for different seasonal patterns of transmission.

Results indicating the impact of seasonality on the relationship between malaria indicators is relevant to malaria epidemiology because, as has been described in Carneiro et al [6], areas with similarly high average annual prevalence result in less frequent cases of malaria in highly seasonal settings. A focused empirical analysis of this effect would be another welcome addition to the understanding of the subject.

Access to treatment has the potential to impact the relationships between transmission and other malariological indicators such as severe disease and mortality. The higher the proportion of malaria cases that are treated with effective antimalarials the more the parasite reservoir in the human host population is suppressed, the fewer gametocytes are available, and the less likely it is that mosquitoes are infected. The authors are not aware of any empirical studies of the relationship between access to treatment and population-level health outcomes. However, work by Briët and Penny investigates the impact of access to treatment on the

OpenMalaria model [24]. The relationships between severe episodes and other indicators (**Figures 2c, 4b, 7**) may depend more on access to effective case management, indicated by the stochasticity in simulation results which is due to model uncertainty rather than the effect of seasonality.

There are direct implications on control programs for the relationship between seasonality and the expected number of uncomplicated cases for a given level of parasite prevalence. Locations with poor monitoring and surveillance systems resulting from complex emergencies or insufficient reach of the public sector may have readily-available parasite prevalence data as a result of research activities. These results may impact how routine data from the case management system in these locations are able to be used to inform study design for the implementation of seasonality-dependent interventions such as IRS and SMC.

Two sources mentioned in this model validation were also used in the original model fitting [12]. However, as indicated in the Results section and in **Table S1**, the relationships used here for validation were not the same relationships (Korenromp et al.) or subsets of data (Beier et al.) used for fitting. Although both help parameterise the model, because this process was independent to the relationships being validated, they can therefore be treated as available for validation.

Each simulation result is a point in multidimensional space with each dimension corresponding to one malaria indicator. However, to determine the relationship between any two indicators, all simulation points are projected onto a two-dimensional space where the relationship is estimated through fractional polynomial regression. Due to this projection, when two indicators have a monotonically-increasing relationship with a third indicator, they may not necessarily have a monotonically-increasing relationship with each other. For example, while simulated parasite prevalence and mortality both increase with increasing annual average EIR, the same effect will not necessarily be seen on mortality in conditions of increasing prevalence. Similarly, the effects of seasonality appear to decrease as EIR increases, but increase as prevalence increases.

While the range of transmission levels and patterns represented in this study are designed to cover a large proportion of malaria endemic areas, there are areas with contexts that will fall outside the scope of this work. There remain areas with extremely high transmission beyond an annual average EIR of 81.4 at which this analysis is capped, but these programs are unlikely to be at a stage of malaria control to benefit from applying the methods described in this paper for fine-tuning malaria control interventions as vector control interventions can be effectively utilized to substantially reduce malaria transmission to moderate levels and transmission can be accurately measured with entomological methods.

Simulated results were limited to annual average EIR values greater than 0.5. In very low transmission settings infections are sporadic and could be better captured with epidemic models. At very low annual average transmission rates malaria can be sustained by regular importation or the presence of hotspots. The relationships between malaria indicators then depend critically on the degree of transmission heterogeneity and interactions between sub-populations. In these settings, estimating transmission through using serology to estimate EIR or force of infection through may be more suitable. Although not currently available in the OpenMalaria transmission model, force of infection and serology will be important components to add to future versions to better simulate the current practice of measuring transmission at low values of EIR. With the inclusion of these indicators, the new model can be calibrated with data on incidence but validated with other indicators (i.e. prevalence or serology).

Because of the strong effect of seasonality on the relationships between malaria indicators, it follows that obtaining accurate estimates of transmission across a range of seasonal patterns, not just transmission intensities, is critical for tailoring malaria control and elimination programs to specific country contexts. An accurate map describing seasonal patterns of transmission to attach to maps of transmission intensity and other indicators would be a useful tool. While obtaining this information may not be straightforward, there is a need for research studies designed with measuring not only transmission but also other malaria indicators to ensure the annual pattern of transmission is accounted for. Therefore, goals for reduction in transmission and burden of disease can be further tailored to specific sites.

The methods described here will be able to be compiled into a lookup tool that will allow malaria control professionals to enter the data they have on one index and see the range of likely results for other measures of malaria. In addition to estimates, an essential requirement would be providing a means to display uncertainty around simulation results. Examples of how this might be achieved are discussed in **Text S3** and shown in **Figures S2-S5** in **Text S3**. Such a tool could aid in the planning process of tailoring malaria control interventions to the appropriate level of transmission.

6.7 Acknowledgements

The authors would like to thank our colleagues in the Swiss TPH Health Systems Research and Dynamical Modeling Unit for valuable discussions, and Emelda Okiro for providing the data presented in Figure 5. We acknowledge Olivier Briët for his helpful comments on an earlier draft of the manuscript, Michael Tarantino for assistance with setting up and submitting scenarios for simulation, and the MalariaControl.net participants for volunteering computing resources to run OpenMalaria simulations.

6.8 Author contributions

Conceived and designed the experiments: EMS TS NC. Performed the experiments: EMS. Analyzed the data: EMS NC. Wrote the paper: EMS TS NC. Study concept and design: TAS

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References

1. Hay SI, Rogers DJ, Toomer JF, Snow RW: **Annual Plasmodium falciparum entomological inoculation rates (EIR) across Africa: literature survey, Internet access and review.** *Trans R Soc Trop Med Hyg* 2000, **94:**113-127.
2. Corran P, Coleman P, Riley E, Drakeley C: **Serology: a robust indicator of malaria transmission intensity?** *Trends Parasitol* 2007, **23:**575-582.
3. Drakeley CJ, Corran PH, Coleman PG, Tongren JE, McDonald SL, Carneiro I, Malima R, Lusingu J, Manjurano A, Nkya WM, et al: **Estimating medium- and long-term trends in malaria transmission by using serological markers of malaria exposure.** *Proc Natl Acad Sci U S A* 2005, **102:**5108-5113.
4. Yukich JO, Briet O, Bretscher MT, Benett A, Lemma S, Berhane Y, Eisele TP, Keating J, Smith TA: **Estimating *Plasmodium falciparum* transmission rates in low-endemic settings using a combination of community prevalence and health facility data.** *PLoS ONE* 2012, **7:** e42861.
5. Stuckey EM, Smith TA, Chitnis N: **Estimating malaria transmission through mathematical models.** *Trends Parasitol* 2013.
6. Carneiro I, Roca-Feltrer A, Griffin JT, Smith L, Tanner M, Schellenberg JA, Greenwood B, Schellenberg D: **Age-patterns of malaria vary with severity, transmission intensity and seasonality in sub-Saharan Africa: a systematic review and pooled analysis.** *PLoS One* 2010, **5:**e8988.
7. MARA: **Duration of Malaria Transmission Season.** Available: [http://www.mara.org.za]. Accessed 19 January, 2014.
8. Roca-Feltrer A, Schellenberg JR, Smith L, Carneiro I: **A simple method for defining malaria seasonality.** *Malar J* 2009, **8:**276.
9. **OpenMalaria** [http://code.google.com/p/openmalaria/wiki/Start]
10. Smith T, Killeen GF, Maire N, Ross A, Molineaux L, Tediosi F, Hutton G, Utzinger J, Dietz K, Tanner M: **Mathematical modeling of the impact of malaria vaccines on the clinical epidemiology and natural history of Plasmodium falciparum malaria: Overview.** *Am J Trop Med Hyg* 2006, **75:**1-10.
11. Smith T, Maire N, Ross A, Penny M, Chitnis N, Schapira A, Studer A, Genton B, Lengeler C, Tediosi F, et al: **Towards a comprehensive simulation model of malaria epidemiology and control.** *Parasitology* 2008, **135:**1507-1516.
12. Smith T, Ross A, Maire N, Chitnis N, Studer A, Hardy D, Brooks A, Penny M, Tanner M: **Ensemble modeling of the likely public health impact of a pre-erythrocytic malaria vaccine.** *PLoS medicine* 2012, **9:**e1001157.
13. Chitnis N, Hardy D, Smith T: **A Periodically-Forced Mathematical Model for the Seasonal Dynamics of Malaria in Mosquitoes.** *Bulletin of mathematical biology* 2012, **74(5):**1098–1124.
14. Stuckey EM, Stevenson J, Cooke M, Owaga C, Marube E, Oando G, Hardy D, Drakeley C, Smith T, Cox J, Chitnis N: **Simulation of malaria epidemiology and control in the highlands of western Kenya.** *Malar J* 2012, **11**.

15. Tediosi F, Maire N, Smith T, Hutton G, Utzinger J, et al: **An approach to model the costs and effects of case management of Plasmodium falciparum malaria in sub-saharan Africa.** *Am J Trop Med Hyg* 2006, **75**: 90-103.
16. Maire N, Smith T, Ross A, Owusu-Agyei S, Dietz K, Molineaux L: **A model for natural immunity to asexual blood stages of Plasmodium falciparum malaria in endemic areas.** *Am J Trop Med Hyg* 2006, **75:**19-31.
17. Beier JC, Killeen GF, Githure JI: **Short report: entomologic inoculation rates and Plasmodium falciparum malaria prevalence in Africa.** *Am J Trop Med Hyg* 1999, **61:**109-113.
18. Okiro EA, Alegana VA, Noor AM, Mutheu JJ, Juma E, Snow RW: **Malaria paediatric hospitalization between 1999 and 2008 across Kenya.** *BMC Med* 2009, **7:**75.
19. Korenromp EL, Williams BG, Gouws E, Dye C, Snow RW: **Measurement of trends in childhood malaria mortality in Africa: an assessment of progress toward targets based on verbal autopsy.** *Lancet Infect Dis* 2003, **3:**349-358.
20. Adjuik M, Smith T, Clark S, Todd J, Garrib A, Kinfu Y, Kahn K, Mola M, Ashraf A, Masanja H, et al: **Cause-specific mortality rates in sub-Saharan Africa and Bangladesh.** *Bull World Health Organ* 2006, **84:**181-188.
21. Briet OJ, Vounatsou P, Amerasinghe PH: **Malaria seasonality and rainfall seasonality in Sri Lanka are correlated in space.** *Geospat Health* 2008, **2:**183-190.
22. Mabaso ML, Craig M, Ross A, Smith T: **Environmental predictors of the seasonality of malaria transmission in Africa: the challenge.** *Am J Trop Med Hyg* 2007, **76:**33-38.
23. Mabaso ML, Craig M, Vounatsou P, Smith T: **Towards empirical description of malaria seasonality in southern Africa: the example of Zimbabwe.** *Trop Med Int Health* 2005, **10:**909-918.
24. Briet OJ, Penny MA: **Repeated mass distributions and continuous distribution of long-lasting insecticidal nets: modelling sustainability of health benefits from mosquito nets, depending on case management.** *Malar J* 2013, **12:**401.

Table S1. Datasets used for model validation and their relationship to fitting of OpenMalaria parameters

Source	Relationship	Dataset description	Relationship to model fitting
Beier et al. 1999 [1]	EIR and parasite prevalence	Observed prevalence in children less than five years of age in 31 sites across Africa. EIR estimated by mosquito capture.	One site as published separately [2] was used to fit the model for incidence of asexual blood stage infection [3].
Korenromp et al. 2003 [4]	Mortality and parasite prevalence	Malaria-specific and all-cause mortality rates as reported by verbal autopsy in children under five in 28 sites across Africa. Parasite prevalence among children under five years in the catchment population of the hospital.	Nine sites (for which EIR estimates were available) were used to fit the model of direct malaria mortality in relation to EIR [5].
Okiro et al. 2009 [6]	Severe disease and parasite prevalence	Community derived parasite prevalence and the age and clinical presentation of paediatric malaria in children aged 0–9 years admitted to hospital in 13 hospitals across Africa.	None
Carneiro et al. 2010 [7]	Age-prevalence curves in patterns of differing seasonality	Systematic review of age distribution in children under 10 for clinical malaria, hospital admissions with malaria, and malaria-diagnosed mortality, stratified by level and pattern of transmission.	Some datasets were used for model fitting, but not explicitly considering seasonality of transmission.

References

1. Beier JC, Killeen GF, Githure JI (1999) Short report: entomologic inoculation rates and Plasmodium falciparum malaria prevalence in Africa. Am J Trop Med Hyg 61: 109-113.
2. Beier JC, Oster CN, Onyango FK, Bales JD, Sherwood JA, et al. (1994) Plasmodium falciparum incidence relative to entomologic inoculation rates at a site proposed for testing malaria vaccines in western Kenya. The American journal of tropical medicine and hygiene 50: 529-536.
3. Maire N, Smith T, Ross A, Owusu-Agyei S, Dietz K, et al. (2006) A model for natural immunity to asexual blood stages of Plasmodium falciparum malaria in endemic areas. Am J Trop Med Hyg 75: 19-31.
4. Korenromp EL, Williams BG, Gouws E, Dye C, Snow RW (2003) Measurement of trends in childhood malaria mortality in Africa: an assessment of progress toward targets based on verbal autopsy. Lancet Infect Dis 3: 349-358.
5. Ross A, Maire N, Molineaux L, Smith T (2006) An epidemiologic model of severe morbidity and mortality caused by Plasmodium falciparum. Am J Trop Med Hyg 75: 63-73.
6. Okiro EA, Al-Taiar A, Reyburn H, Idro R, Berkley JA, et al. (2009) Age patterns of severe paediatric malaria and their relationship to Plasmodium falciparum transmission intensity. Malar J 8: 4.
7. Carneiro I, Roca-Feltrer A, Griffin JT, Smith L, Tanner M, et al. (2010) Age-patterns of malaria vary with severity, transmission intensity and seasonality in sub-Saharan Africa: a systematic review and pooled analysis. PLoS One 5: e8988.

Text S1: Experiment creation

Seasonality index

In the OpenMalaria transmission model, daily EIR at each time point $EIR_d(t)$ based on a given annual average EIR is specified by five Fourier coefficients representing the cycle's average (a_0), annual cycle (a_1, b_1), and bi-annual cycle (a_2, b_2) as described by:

$$EIR_d(t) = e^{a_0 + a_1 \cos(\omega t) + b_1 \sin(\omega t) + a_2 \cos(2\omega t) + b_2 \sin(2\omega t)},$$

where:

$$\omega = \frac{2\pi}{T},$$

and T=1 year.

The values a_1, b_1, a_2, b_2 are picked to provide a given seasonal profile as described in Table S1.1. For a given annual average EIR, EIR_a, a_0 is

$$a_0 = \ln\left(\frac{EIR_a}{\sum_{t=1}^{T} e^{a_1 \cos(\omega t) + b_1 \sin(\omega t) + a_2 \cos(2\omega t) + b_2 \sin(2\omega t)}}\right)$$

<u>Parameterization of models of seasonality</u>

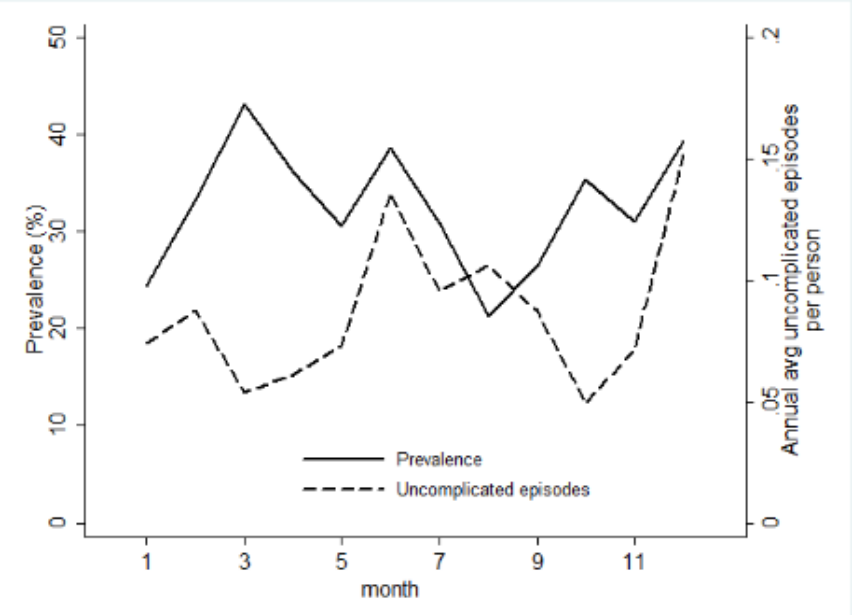
1. For simulations of no seasonality in transmission of malaria, values of $a_1=a_2=b_1=b_2=0$ were assigned. Simulations were run for the following values of annual average EIR: [0.5, 1, 1.5, 2.5, 4.1, 6.7, 11, 18.2, 30, 49.4, 81.4, 134.3, 221.4, 365].
2. For each annual average EIR, simulations were run for each of six patterns of seasonality (**Table S1, Table 2 of the main manuscript**). Each of these was parameterized with a vector of Fourier coefficients calculated to give the chosen value φ [1,2]. The six patterns were selected so as to cover the range of seasonality patterns observed in malaria-endemic areas.

Table S2

Seasonality pattern ID	0	1,1	1.5,1	1,2	0.5,2	1.5,2
Seasonality index (φ)	0	1	1.5	1	0.5	1.5
Number of peaks	0	1	1	2	2	2
a_1	0	1.76256	4.10688	0.836862	0.437636	2.05344
a_2	0	0	0	0.836862	0.437636	2.05344
b_1	0	0	0	0	0	0
b_2	0	0	0	0	0	0

Figure S1. Relationship between parasite prevalence and uncomplicated episodes.

Simulated annual pattern of parasite prevalence (unbroken line) and uncomplicated episodes (dashed line) for the seasonality pattern φ =2, 2 peaks and an annual average EIR of 11. Lines represent the mean over all model variants and multiple random seeds.



References

1. Chitnis N, Hardy D, Smith T (2012) A Periodically-Forced Mathematical Model for the Seasonal Dynamics of Malaria in Mosquitoes. Bulletin of mathematical biology 74(5): 1098–1124.
2. Bracewell RN (2000) The Fourier transform and its applicaitons: McGraw-Hill Higher Education. 258-285 p.

Text S2: Methods fitted regression models for the relationships between malaria indicators

Statistical model design and fit

The relationships between malaria indicators were investigated by regression analysis using Stata v12 (College Station, Texas). Linear regression models were used for each relationship, based on better fit than Poisson or negative binomial models (as assessed using the Akaike information criteria (AIC)). Final models were fitted using the second-degree fractional polynomial method described in Royston et al. [1] and Sauerbrei et al. [2] where models are of the form:

$$y = \beta_0 + \beta_1 x^p + \beta_2 x^q \quad ,$$

where *x* and *y* are the two malaria indicators being investigated, transformed as indicated in Table 1 of the manuscript and *p* and *q* are any of (-2, -1, -0.5, 0, 0.5, 1, 2, 3) with $p \neq q$ and x^0 representing ln(*x*).

In the case *q*=*p*:

$$y = \beta_0 + \beta_1 x^p + \beta_2 x^p \ln(x) .$$

Table S3. Fitted regression models for the relationships between malaria indicators, φ =0

Variable to estimate*	Input variable		Form	Coefficient	95% CI
EIR	Parasite prevalence	$ß_1$	$(X+2.68)^3$-9.07	0.41	0.39,0.44
		$ß_2$	$(X+2.68)^3$*ln(X+2.68)-6.67	-0.24	-0.26,-0.22
		$ß_0$		1.65	
	Mortality	$ß_1$	ln(X)-.91	-14.70	-16.76,-12.65
		$ß_2$	$X^{0.5}$-1.58	27.27	24.47,30.06
		$ß_0$		1.75	
Parasite prevalence	EIR	$ß_1$	(X+0.71)-2.61	1.21	1.18,1.24
		$ß_2$	$(X+0.71)^2$-6.83	-0.13	-0.13,-0.12
		$ß_0$		-0.28	
	Mortality	$ß_1$	X^3-15.56	0.44	0.42,0.46
		$ß_2$	X^3*ln(X)-14.23	-0.28	-0.30,-0.27
		$ß_0$		-0.47	
Uncomplicated episodes	EIR	$ß_1$	(X+0.71)-2.61	0.79	0.77,0.82
		$ß_2$	(X+0.71)*ln(X+0.71)-2.51	-0.39	-0.40,-0.37
		$ß_0$		0.43	
	Parasite prevalence	$ß_1$	(X+2.68)-2.09	0.92	0.87,0.97
		$ß_2$	$(X+2.68)^2$-4.35	-0.19	-0.20,-0.18
		$ß_0$		0.37	
	Severe episodes	$ß_1$	X^3-20.02	0.32	0.25,0.38
		$ß_2$	X^3*ln(X)-20.00	-0.21	-0.26,-0.16
		$ß_0$		0.24	
	Mortality	$ß_1$	X^2-6.23	0.96	0.91,1.01
		$ß_2$	X^2*ln(X)-5.70	-0.64	-0.68,-0.61
		$ß_0$		0.41	
Severe episodes	EIR	$ß_1$	$(X+0.71)^{0.5}$-1.62	0.34	0.30,0.38
		$ß_2$	$(X+0.71)^3$-17.85	-0.004	-.004,-.003
		$ß_0$		2.83	
	Parasite prevalence	$ß_1$	(X+2.68)-2.09	0.28	0.22,0.35
		$ß_2$	$(X+2.68)^2$-4.35	-0.05	-0.07,-0.03

	Uncomplicated episodes	$ß_0$		2.76	
		$ß_1$	$(X+0.76)^3$-0.89	0.38	0.33,0.42
		$ß_2$	$(X+0.76)^3$*ln(X+0.76)+0.03	-0.59	-0.71,-0.47
	Mortality	$ß_0$		2.72	
		$ß_1$	ln(X)-.91	3.94	3.16,4.72
		$ß_2$	$X^{0.5}$-1.58	-4.86	-5.92,-3.79
		$ß_0$		2.79	
Mortality	EIR	$ß_1$	(X+0.71)-2.61	0.58	0.56,0.59
		$ß_2$	$(X+0.71)^3$-17.85	-0.01	-0.01,-.009
	Parasite prevalence	$ß_0$		2.67	
		$ß_1$	$(X+2.68)^2$-4.35	0.43	0.41,0.46
		$ß_2$	$(X+2.68)^2$*ln(X+2.68)-3.20	-0.22	-0.24,-0.21
		$ß_0$		2.52	

*Variables are defined and transformed as per **Table 1** of the main manuscript.

Table S4. Fitted regression models for the relationships between malaria indicators, φ =2, 2 peaks

Variable to estimate*	Input variable		Form	Coefficient	95% CI
EIR	Parasite prevalence	$ß_1$	$(X+2.84)^3$-6.351870522	0.60	0.57,0.63
		$ß_2$	$(X+2.84)^3$*ln(X+2.84)-3.91	-0.40	-0.42,-0.37
		$ß_0$		1.77	
	Mortality	$ß_1$	$X^{-0.5}$-.66	64.17	57.09,71.26
		$ß_2$	ln(X)-.84	28.63	26.13,31.14
		$ß_0$		1.78	
Parasite prevalence	EIR	$ß_1$	(X+0.71)-2.612658873	0.925	0.89,0.96
		$ß_2$	$(X+0.71)^2$-6.83	-0.08	-0.09,-.07
		$ß_0$		-0.79	
	Mortality	$ß_1$	X^3-12.59	0.47	0.43,0.50
		$ß_2$	X^3*ln(X)-10.64	-0.31	-0.33,-0.28
		$ß_0$		-0.92	
Uncomplicated episodes	EIR	$ß_1$	(X+0.71)-2.61	0.70	0.67,0.73
		$ß_2$	X*ln(X+0.71)-2.51	-0.32	-0.33,-0.30
		$ß_0$		0.26	
	Parasite prevalence	$ß_1$	(X+2.84)-1.85	0.76	0.73,0.79
		$ß_2$	$(X+2.84)^3$-6.35	-0.05	-0.05,-0.05
		$ß_0$		0.26	
	Severe episodes	$ß_1$	X^3-18.30	0.33	0.26,0.41
		$ß_2$	X^3*ln(X)-17.74	-0.24	-0.29,-0.18
		$ß_0$		0.11	
	Mortality	$ß_1$	X-2.33	2.76	2.54,2.98
		$ß_2$	X^2-5.41	-0.52	-0.57,-0.47
		$ß_0$		0.20	
Severe episodes	EIR	$ß_1$	(X+0.71)-2.61	0.33	0.29,0.38
		$ß_2$	(X+0.71)*ln(X)-2.51	-0.18	-0.20,-0.15
		$ß_0$		2.74	
	Parasite prevalence	$ß_1$	$(X+2.84)^2$-3.43	0.20	0.17,0.23
		$ß_2$	$(X+2.84)^2$*ln(X+2.84)-2.11	-0.17	-0.19-0.14

	Uncomplicated episodes	$ß_0$		2.73	
		$ß_1$	ln(X+0.81)+0.13	0.08	0.06,0.11
		$ß_2$	$(X+0.81)^2$-0.78	0.14	0.10,0.18
	Mortality	$ß_0$		2.64	
		$ß_1$	$X^{0.5}$-1.53	9.36	7.30,11.41
		$ß_2$	$X^{0.5}$*ln(X)-1.29	-3.24	-3.99,-2.49
		$ß_0$		2.70	
Mortality	EIR	$ß_1$	(X+0.71)-2.61	0.57	0.55,0.59
		$ß_2$	$(X+0.71)^2$-6.83	-0.05	-0.06,-0.05
	Parasite prevalence	$ß_0$		2.46	
		$ß_1$	$(X+2.84)^2$-3.43	0.48	0.46,0.51
		$ß_2$	$(X+2.84)^2$*ln(X+2.84)-2.11	-0.29	-0.31,-0.27
		$ß_0$		2.39	

*Variables are defined and transformed as per **Table 1** of the main manuscript.

References

1. Royston P, Altman DG (1994) Regression Using Fractional Polynomials of Continuous Covariates: Parsimonious Parametric Modelling. Journal of the Royal Statistical Society Series C (Applied Statistics) 43: 429-467.
2. Sauerbrei W, Roston P (1999) Building multivariable prognostic and diagnostic models: transformation of the predictors by using fractional polynomials. Journal of the Royal Statistical Society Series A 162: 71-94.

Text S3. Model choice and presentation of simulation results

When presenting results of stochastic simulation models, it is important not only to demonstrate the general trends, but to adequately express uncertainty inherent in stochastic simulations. Evaluating goodness of fit and uncertainty for simulation results of model ensembles remains a challenge [1], as does presentation of these results. There are numerous options for analysing and presenting simulation results, including aggregation into averages, ranges and standard deviations, elimination of poor-performing models, and weighting models based on their structure similarity or performance during the fitting process. The following examples represent analysis of simulation results from the OpenMalaria model ensemble of 14 model variants as described in Smith et. al [2].

In the context of this study the options relevant options include:

1. As presented in the main manuscript, scatter plot range of results with the fitted regression model over all model variants of each pattern of seasonality (**Figure S2**)
2. Shaded range of results with the median over all model variants of each pattern of seasonality (**Figure S3**)
3. Shaded range of results with the median over all seeds for each model variant, for each pattern of seasonality (**Figure S4**)
4. Shading range of results with the mean of all model variants and the fitted regression model over all model variants, for each pattern of seasonality (**Figure S5**)

There are benefits to displaying results by model variant if the goal of analysis is to understand the effect differences in assumptions of model structure have on results. For example, model variants 670, 674 and 678 have different assumptions about susceptibility to co-morbidity and access to treatment [2], which may be of interest when examining the relationship between malaria mortality and EIR (**Figure S4**). However, if model variants are not to be examined individually, there are benefits of displaying results of means or medians across all model variants as the overall uncertainty is more relevant to analysis of results than the uncertainty due to any one model variant.

While a shaded area gives an easily-identifiable range of simulation results encompassing areas not explicitly simulated in the experiment, (**Figure S3**), a scatter plot is able to identify outliers in directions of both independent and dependent variables as well as give

an indication of the density of simulation results in a given area (**Figure S2**), more easily showing patterns in the overall results and how they relate to the summary smoothing functions.

In the case of the relationship between mortality and EIR, the uncertainty in simulation results is due more to model variant than to pattern of seasonality, as can be ascertained by comparing **Figure S3** and **Figure S4**. However, this is not the case for all relationships between indicators presented in this study.

Fractional polynomial regression has the flexibility to fit the range of non-linear, non-monotonic relationships seen between these indicators and has the advantage of being able to exclude predictions less than zero through the algorithms used by defining the origin. Despite criticisms about the fractional polynomial approach to model selection and potential inflation of type one error [3], choosing to present results of regression analysis allows a methodology for applying these equations to make predictions in areas outside the range of simulations, which means and medians of simulation results cannot. The fitted models will diverge from resembling the means for relationships that are increasingly non-linear.

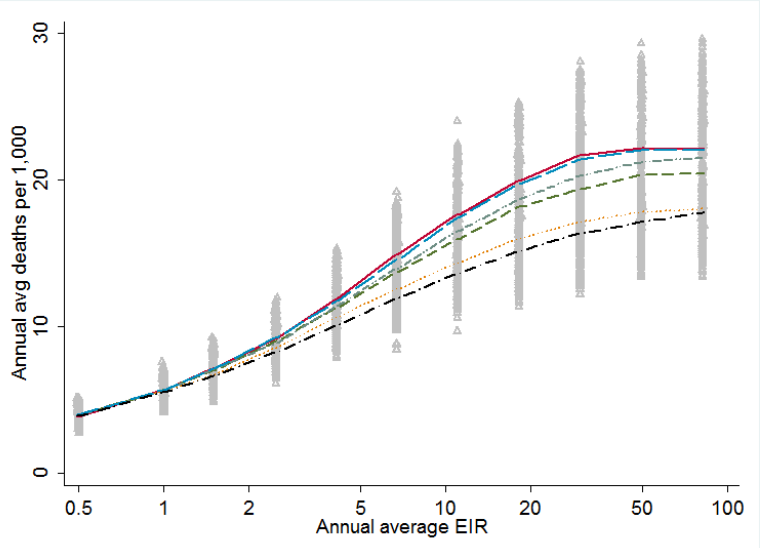


Figure S2. Fitted regression models for each pattern of seasonality over scatter range of simulation results. Circles represent simulated results of the relationship between mortality and eir over 14 model variants, six random seeds and five patterns of seasonality. Lines represent, for each pattern of seasonality as described in Figure 1 and Table 2, the fractional polynomial regression model fitted over 14 model variants as described in Smith et. al [2] and five random seeds. Unbroken red line represents φ =0. Brown dashed line represents φ =1, one peak. Orange dotted-dashed line represents φ =1, two peaks. Green dotted line represents φ =2, one peak. Black dotted-dashed line represents φ =2, two peaks. Blue dashed line represents φ =0.5, two peaks.

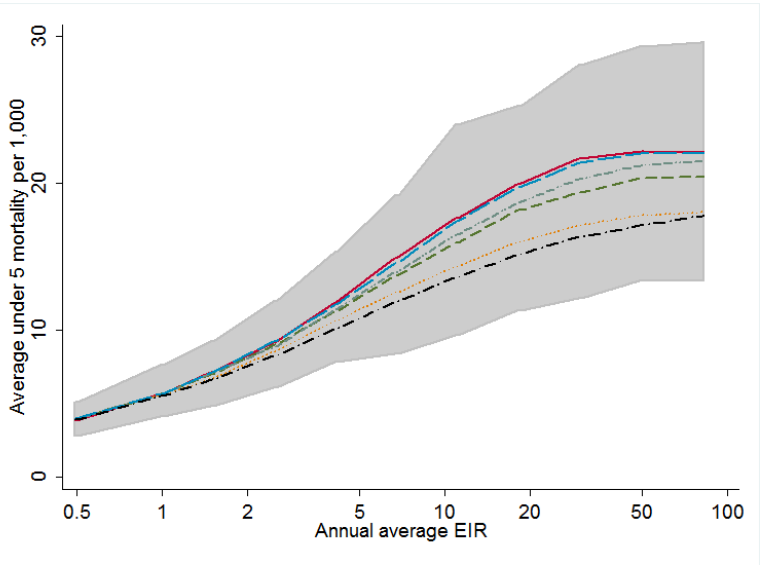


Figure S3. Median of each pattern of seasonality over shaded range of simulation results. Shaded area represents range of simulated results of the relationship between mortality and EIR over 14 model variants, five random seeds and six patterns of seasonality. Lines represent, for each pattern of seasonality as described in **Figure 1** and **Table 2**, the median of 14 model variants as described in Smith et. al [2] and five random seeds. Unbroken red line represents φ =0. Brown dashed line represents φ =1, one peak. Orange dotted-dashed line represents φ =1, two peaks. Green dotted line represents φ =2, one peak. Black dotted-dashed line represents φ =2, two peaks. Blue dashed line represents φ =0.5, two peaks.

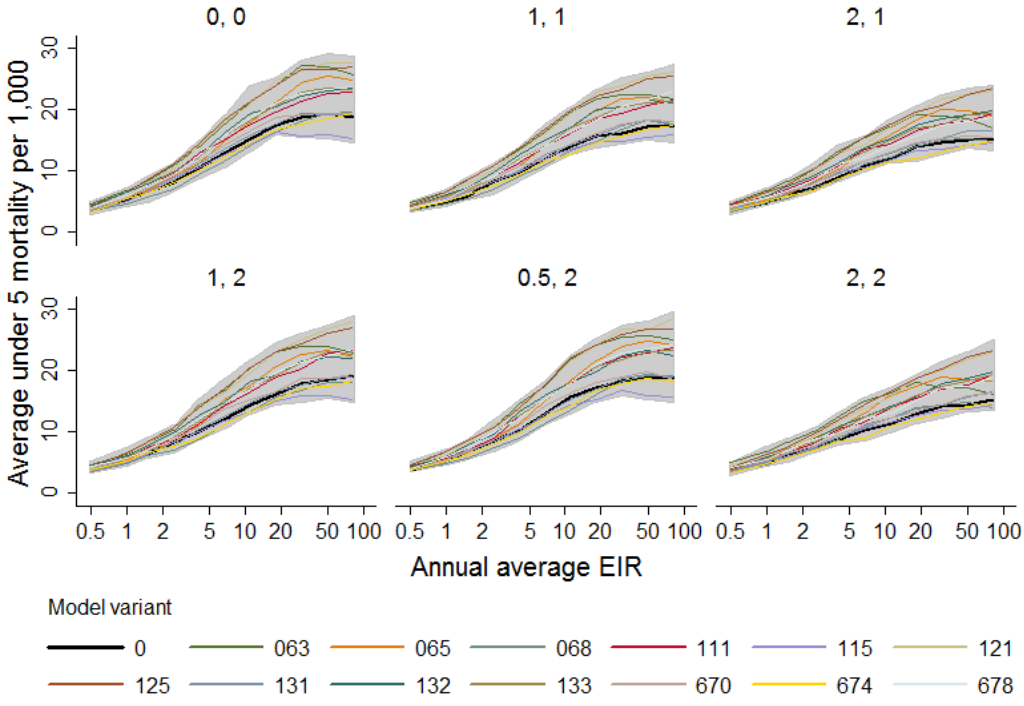


Figure S4. Median of each model variant over shaded range of simulation results, by pattern of seasonality. Shaded areas represent the range of simulated results of the relationship between mortality and eir over 14 model variants and five random seeds. Lines represent the median of each of the 14 model variants as described in Smith et. al [2] over five random seeds. Panels represent the patterns of seasonality as described in **Figure 1** and **Table 2**.

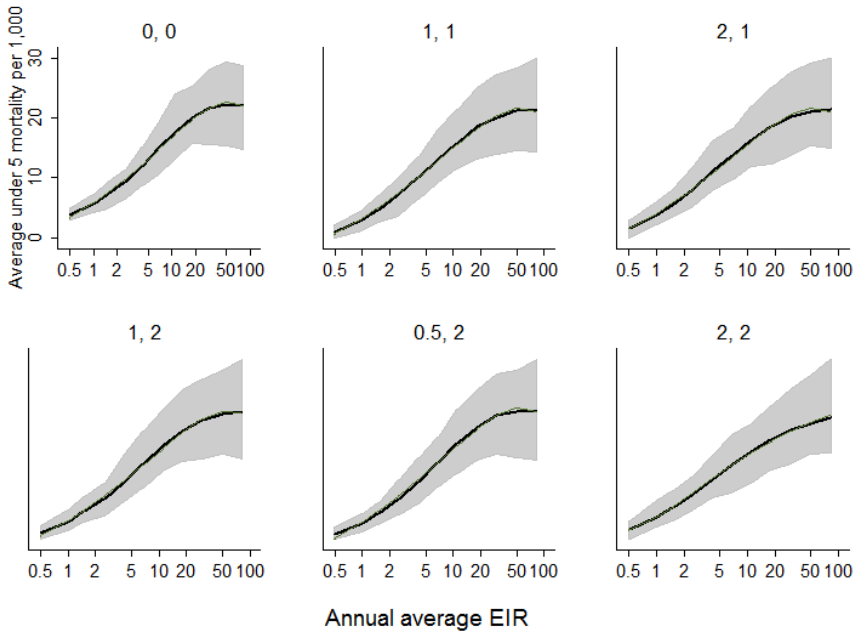


Figure S5. Mean and fitted regression model over shaded range of simulation results, by pattern of seasonality. Shaded areas represent the range of simulated results of the relationship between mortality and EIR over 14 model variants and five random seeds. Black lines represent the mean of 14 model variants as described in Smith et. al [2] and five random seeds. Green lines represent the fractional polynomial regression model fitted over 14 model variants and five random seeds. Panels represent the patterns of seasonality as described in **Figure 1** and **Table 2**.

References

1. Knutti R (2010) The end of model democracy? An editorial comment. Climactic Change 102: 395-404.
2. Smith T, Ross A, Maire N, Chitnis N, Studer A, et al. (2012) Ensemble modeling of the likely public health impact of a pre-erythrocytic malaria vaccine. PLoS medicine 9: e1001157.
3. Strasak AM, Umlauf N, Pfeiffer RM, Lang S (2011) Comparing penalized splines and fractional polynomials for flexible modelling of the effects of continuous predictor variables. Computational Statistics & Data Analysis 55: 1540-1551.

7. Discussion

7.1 Summary

The overall aim of this thesis was to applying individual-based stochastic models of malaria to field sites to better understand malaria transmission dynamics in these settings and to explore possible scenarios with different control interventions and strategies. This is demonstrated by the two main areas of application for infectious disease modeling presented in this thesis.

The first application is to gain a better epidemiological understanding. This is achieved by examining the simulated relationships between malaria indicators in different intensities and patterns of seasonality, and by developing an alternative method of quantifying malaria transmission in areas with scarce data. The second application is to explore intervention effectiveness, which is achieved by simulating malaria dynamics in Rachuonyo South District, Kenya and in Southern Province, Zambia. After validating these results with observed data, the simulated impact of intervention combinations is investigated and, in the case of Rachuonyo South, attached to a costing model to put simulated results in the context of longer-term implications for malaria control programs.

This discussion contextualizes these two approaches of applied modeling, and summarizes limitations and future research opportunities for OpenMalaria. Following this, it will discuss the current and potential future role of applied mathematical modeling for informing policy decisions, and the ways through which this role can be achieved by the malaria modeling community.

Findings of site-specific simulations

The studies in Chapters 3, 4 and 5 demonstrate the first comprehensive site-specific applications of OpenMalaria outside of the model development's initial fitting process incorporating parameterization, sensitivity analysis, validation, estimation of new interventions, and a cost effectiveness analysis.

Results of the application of OpenMalaria for simulation of malaria epidemiology and control in Rachuonyo South District in the highlands of western Kenya indicate that estimating the annual pattern of EIR using entomological studies involving mosquito capture, while important for monitoring vector biting behaviour, may be unsuitable in areas of low, unstable transmission. Despite a trend in the District's vectors towards outdoor, early evening biting, the sensitivity analysis in Chapter 3 of the site-specific parameterization indicates that small changes in entomological and biological components may be unlikely to have a large impact on prevalence in the study area. This finding is important for the study area to further understand the potential impact the changing vector composition and behavior may have [1, 2], and to highlight the potential limit to the effectiveness of current vector control interventions in Rachuonyo South at controlling indoor *Plasmodium falciparum* transmission [3]. Continuous entomological monitoring will be essential in this area as use of pyrethoids continues.

The cost effectiveness analysis in Chapter 4 is a helpful exercise for putting simulation results in the context of impact on the overall health sector. All of the simulated intervention combinations, which involved LLINs, IRS, and school-based intermittent screen and treat (IST), were shown to be cost effective given the substantial contribution of malaria to the burden of disease in Kenya and compared to the country's per capita health spending of 42 USD [4]. Simulated results indicate that in the study area, scenarios involving increased coverage and use of vector control interventions are more cost effective than introducing a school-based IST program to the current strategy, which showed a very minor simulated epidemiological impact. While a cost-effectiveness analysis alone is not sufficient for decision-making for the optimal intervention mix in the study area, given the desire for innovative solutions for the next step in malaria control, this study helps to identify a negative study outcome (IST) that can be passed over in favor of interventions that may have a greater impact (increased LLIN use).

Chapter 5 shows that there are operational strategies that could impact the health outcomes of the MSAT trial in Southern Province, Zambia. Increasing coverage of the intervention showed a greater simulated reduction in parasite prevalence than the current strategy, but targeting specific age groups and increasing the campaign frequency to anything longer than 15 days are unlikely to result in a greater impact than the current strategy. While

MSAT with Dihydroartimisinin-Piperaquine (DHP) + Primaquine, a combination with a long prophylactic effect and a gametocytal effect, did not have the desired simulated effect on transmission and disease burden, simulations indicate Ivermectin, an endectocide, could be a viable addition to MDA programs. Further investigation in trial settings is urgently needed on the halflife of effectiveness and the optimal dose of Ivermectin. Current dosage of Ivermectin is based on the MDA deployment for lymphatic filariasis and onchocerciasis control programs, and the optimal dose in terms of both safety and efficacy may be different for malaria control. Because the drug is broadly approved for mass distribution, the timeline for adoption of the drug for a new strategy has the potential to function on a shorter time frame than that of a new compound. Modeling has a clear role in this process for helping decide what to test and where in the field to do so.

Given the results of the intervention combinations simulated in the contexts of the two study areas represented in this thesis, the question arises about whether there is a point where a shift to human-based interventions are warranted at the same time as a shift away from vector control. There are many reasons this may appear to be an attractive option given limited resources available for global malaria control and the threat of insecticide and drug resistance. The cost of malaria control per case averted will be higher in areas of low transmission compared to areas of higher transmission. Simulated results suggest LLINs are most cost effective at an annual average EIR of 4 [5], and the cost per case for identification and treatment increases as the number of cases decreases. Simulation results in Chapters 3-5 show that even in areas considered low transmission vector control continues to play an essential role in disease prevention. This finding supports the empirical evidence seen in of the resurgence of malaria following the cessation of IRS in Sri Lanka and other countries after the Global Malaria Eradication Program in the mid-20th century [6]. It is clear that sustaining vector control long into the elimination phase of any area will be essential.

Findings of simulated relationships between malaria indicators for transmission estimation

The Rachuonyo South District simulation experiment in Chapter 3 directly demonstrates the challenges with traditional methods of estimation of transmission described in Chapter 2.

Accurate measures of transmission are helpful in terms of monitoring, yet at the same time are more difficult to collect as transmission is reduced, and measures of transmission cannot be standardized across all settings.

Results from an experiment simulating the relationship between malaria indicators and across different patterns of seasonality of transmission indicated that not only the amount but also the pattern of seasonality of transmission in a given place is important, particularly in settings with low to moderate transmission. The simulated impact of the amount and pattern of seasonality on relationships between malaria indicators shows the need for field trial design and analysis to consider variability, which is not currently the case in practice. Therefore further development of a seasonality index is required to take into account not only the level of seasonality but also the number of peaks. Further examination of the relationship between seasonality and acquisition of immunity could further clarify these results and shed light on the mechanisms driving the relationships between those indicators.

This method of transmission estimation represents a contribution to the field by adding a new tool to fill the gap identified by site-specific micro-simulations in areas of low transmission. These results demonstrate how mathematical modeling can contribute to evidence-based decision-making in the malaria control community by filling in knowledge gaps, even in areas without substantial observational studies.

Limitations of OpenMalaria

Details of the methods for applying OpenMalaria to site-specific scenarios, and current options for running OpenMalaria software and an evaluation of their applicability are detailed in Appendix 1. There are technological limitations to the individual-based stochastic simulation approach including the large amount of computing resources required to run simulations and the limitation of available methods for experiment creation and analysis of results. Efforts to develop new and to update existing user interfaces for experiment creation and simulation have been challenged by the continuously-updated code base. The OpenMalaria model requires a large number of data points as inputs, with a trend towards greater complexity as the model has

continued to develop over time. With any model, this represents a tradeoff. Adding additional detail to an already-complex set of models makes it more difficult to identify and understand the key drivers of results and potentially decreases the chance for broad use of and trust in model outputs.

The OpenMalaria transmission model was developed to examine areas of moderate to high transmission, and does not include a mechanism to account for the inter-annual variation in EIR as driven by climatic factors common in areas of unstable transmission. Thus, every year is treated as the same, which is not the case in all study areas. Other stochastic models of malaria exist which are instead driven by vector ecology linked to rainfall, temperature and other climatic factors [7-9], with EIR limited to a model output rather than both an input and an output. In addition to the challenge of the non-linear relationship of the amount and seasonality of transmission to the amount of rainfall [8], this approach also fails to highlight the importance of the impact of the case management system and within-host dynamics.

Analysis from site-specific simulations (Chapters 3-5) indicates that heterogeneities in transmission dominate in low transmission settings. The OpenMalaria model does not explicitly take spatial associations into account, making micro-simulations in areas of very low transmission challenging since variation in proximity to breeding sites can be a factor driving the difference in epidemic profile in many areas. This heterogeneity in availability to vectors, as well as the role of imported cases in malaria transmission, should be taken into account in future simulations of low transmission areas. On the other hand, dynamics in higher transmission settings are characterized by a different set of factors including heterogeneities in exposure, acquisition of immunity, and within host dynamics. OpenMalaria is well placed to answer questions about their role on malaria transmission and disease burden. Improved measurement tools and increased primary data collection will enhance model parameterization and epidemiological monitoring in all transmission settings.

The endpoint evaluated by the experiment in Chapter 5 was interruption of transmission. For the purposes of this experiment, interruption of transmission was defined as scenarios with no clinical cases in the same point in time three months after the intervention.

The impact of these programs on interruption of transmission depends heavily upon how this endpoint is specified. For modeling purposes, this should be clarified in greater detail than is currently available from the WHO elimination framework and the malERA agenda [10, 11].

It should be noted that there are important costs that cannot be accounted for in the type of cost-effectiveness analysis presented in Chapter 4. These include research costs, economies or diseconomies of scale, and any costs that may be incurred for technical assistance in LLIN distribution, for example from the Alliance for Malaria Prevention. A systems approach to investigating changing intervention strategy could help identify these and other areas outside the traditional case management system that incur costs, and can strengthen the chances for success of introducing a new intervention. During the literature review of previously-published costing studies of malaria control interventions, it was noted that many studies used different endpoints for evaluating costs of the same intervention. Moving forward, it would be helpful for costing of studies to employ a standard methodology, such as either cost per person protected or cost per net delivered LLINs. Until then, it will continue to be challenging to apply a standard cost-effectiveness analysis methodology across all potential settings.

7.2 Future strategy for OpenMalaria simulations

The opportunity for the greatest potential short term impact of OpenMalaria is for trial design and intervention evaluation, as described in Chapter 5. Starting with simulations of an intervention or combinations of interventions in a single site and validated with observed data, effects of an intervention can then be applied to different implementation strategies in an operational research approach, and even to other trial contexts under consideration. A specific example includes expanding the experiment simulating MSAT and MDA strategies in Zambia to other potential study areas in Senegal, Ethiopia, and the western Kenyan lowlands, and even to epidemic settings in West Africa. There is a clear opportunity to combine these studies with a costing model, as in Chapter 4, and as with the country-specific evaluation of cost effectiveness of the RTS,S vaccine conducted with PATH Malaria Vaccine Initiative (MVI) [12, 13]. In addition to the strategy of Chapter 4 of simulating discrete combinations of interventions, another

possible strategy would be to simulate the incremental cost of scale up of interventions, such as the approach described in Crowell et. al [14].

Results of the studies described above demonstrate the ability of OpenMalaria to not only simulate the dynamics of malaria epidemiology and control, but to apply these dynamics to answer research questions to aid policy makers and program managers in survey design and programmatic decision-making. However, given the challenges in parameterizing and validating site-specific scenarios, it is natural to ask what is gained from this approach, and what should be the characteristics and limit of sites to be simulated, in comparison to focusing on broad-based simulations covering a theoretical context?

It is tempting to identify the main factors impacting the relationship between transmission and disease burden, run simulations for a full-factorial experiment covering a plausible range for all of these factors, and base decisions on these results; caution should be taken with such an approach. The obvious factors to include are level of transmission, amount and pattern of seasonality, vector control coverage, access to treatment, insecticide and drug resistance, the proportion of indoor vs. outdoor transmission and heterogeneity in exposure. Several factors favor the site-specific approach to complement the more general experiments. Firstly, many studies are concentrated in areas with a high burden of malaria and are often conducted in the highest transmission months, leaving out areas of low transmission and dry season months. These omissions are especially relevant for studies on effectiveness of interventions. As such it will be challenging to link such an extremely large database of results with validated field data.

Another benefit of the site-specific approach is that this application of OpenMalaria has acted as a catalyst for model development. For example, application of OpenMalaria to an MSAT intervention highlighted a limitation in the way interventions were previously described and deployed in the schema that prevented the field scenario from being adequately described, that may not have been identified in an experiment with general deployment of a theoretical trial. As a result of code changes, the flexibility of OpenMalaria increased allowing the platform

to be more responsive to requests for answers to questions driving study design and program implementation, and therefore more applicable to end users.

7.3 The current status of applying modeling for decision-making

While the field of mathematical modeling of malaria has continued to develop over the course of the past century, advances in model design and increased computing power in recent years have ushered in an increase in decision-making based on evidence from stochastic model outputs. This has been accompanied by an increase in investment in the technology and tools required to make this possible, for instance the Vector-Borne Disease Network (VecNet) [15] funded by The Bill and Melinda Gates Foundation (BMGF). How models are applied, and at what level decisions informed by models are made, will be influenced by the priorities and approach of the source of funding.

It is difficult to quantify to what extent malaria control decisions are currently being made based on modeling. Donors, rather than national malaria control programs, may still be the main group applying modeling into decision-making in a systematic way, but this could be shifting. For example, the National Malaria Control Program of Tanzania has utilized NetCALC cost and coverage software (see http://www.networksmalaria.org/networks/netcalc) as an integral part of the creation of their LLIN keep up strategy by examining the effect of different coverage levels of LLINs under various distribution scenarios [16].

The field has been naturally moving towards more collaboration between modeling groups, driven by the call for answers via multiple approaches to understand structural uncertainty. An example includes the collaboration between the Swiss TPH, Imperial College London (ICL), Intellectual Ventures (IV), and Glaxo-Smith Kline (GSK) following separate simulation exercises for cost-effectiveness of the RTS,S vaccine as commissioned by the GAVI Alliance through MVI [12]. Collaboration between independently-developed models at the point of predictions has many benefits, including a better understanding of the assumptions and simulation process, and communicating clear messages when models agree.

In the broader field of applied modeling for infectious disease control, simulation results are now routinely used to detect and control epidemics such as influenza [17, 18], hoof and mouth disease [19], and, increasingly, hospital-acquired infections [20]. In terms of endemic diseases, modeling consortia have recently been created for a variety of infectious diseases including HIV (2011, see http://www.hivmodelling.org/), tuberculosis (2012, see http://tb-mac.org/), and, most recently, neglected tropical diseases (NTDs) (2013, see http://www.ntdmodelling.org/). The TB and HIV consortia receive funding from the BMGF, and the NTD Consortium has also been invited by the BMGF to submit a proposal. These coordinating bodies present an opportunity both for strategic allocation of resources and for increased collaboration on research questions. It is unclear, given the number and scope of existing malaria models, and the investment in malaria research by the BMGF – PATH MVI alone has received a grant commitment of $456 million USD [21] - why malaria has not yet been added to this list.

7.4 Proposed role for modeling in malaria control

Malaria dynamics display a high degree of spatial and temporal heterogeneity, and appropriate tailoring of control programs impacts malaria control success. Mathematical models can play an important role in the development and evaluation of policies for control of a range of infectious diseases, inferring the values of parameters that cannot be evaluated experimentally or are too expensive to implement. The role for mathematical modeling of malaria control has been examined in terms of individual interventions [22] and in the elimination research agenda [23, 24], and general guidelines for understanding and using models have been helpfully outlined [25]. However, the developers and end users of these models perhaps do not share the same understanding of the specific role for modeling decision-making in the current context of how decisions are made for research and program implementation. Clarifying this relationship and process will make it easier to tailor tools and design the level of flexibility of models to the intended end user, increasing the chance of success.

Mathematical models should indeed be used to decide in advance which interventions to test in the field. Using models to work out exactly what to test would make it more likely that

trials will lead to improvements in public health practice. A key role and opportunity for applying modeling to malaria control implementation is to help provide a quantitative demonstration of why an intervention may work in one context and not another to those involved in trial design and on the ground implementation. This should entail modeling realistic coverage and deployment options in settings comparable to those in the field to maximize the applicability of modeling exercises.

Several specific thematic areas for prioritization can be identified through analysis in this thesis. Linking costing to simulation results, as described in Chapter 4, as has also been applied for vaccines and case management [26-28]. A cost effectiveness analysis of different operational strategies of MSAT simulations could clarify policy decisions, especially when involving new compounds. Simulating the effect of different target product profiles for development of novel vector control interventions targeting outdoor biting such as odor baited traps and endectocides, such as the analysis demonstrated in Killeen et. al [3, 29], could be helpful in settings such as Rachuonyo South District where vector biting behavior is shifting to outdoors and earlier in the evening.

A particularly challenging application of mathematical models is their use to predict the success of elimination programs [24, 30], motivated by the lack of comprehensive data in many locations. Parameterizing transmission patterns in unstable, low transmission settings for application to stochasitc simulation models has been indicated as a priority by the Malaria Elimination Group [11], yet standardized methods of doing so have not yet been comprehensively proposed. This approach to elimination has demonstrated success with viral diseases, such as predicting the impact of vaccination and elimination scenarios for measles in Italy and elsewhere [31-33]. The challenge of simulating malaria elimination is much greater due to heterogeneity in transmission intensity leading to high-transmission foci that can remain undetected. The minimum population size necessary for malaria to persist is unclear, but it is certainly much smaller than for diseases like measles, meaning parasites can circulate indefinitely within small foci. It is essential for any elimination program to address this challenge.

Chapter 2 indicates that when approaching a situation where transmission is interrupted, attention must be paid to the type of screening strategy (active vs. passive case detection) and screening method used to detect the last remaining parasitaemia in the population. Without an improvement of case-management systems, the case-fatality rate per infection increases as transmission decreases. This makes prompt and effective treatment the key to achieving near-zero deaths and further emphasizes the need for quality surveillance response as transmission is reduced. More empirical and theoretical analyses focused on optimizing surveillance–response systems will aid in accomplishing this goal. A spatially-explicit model would be preferable for this type of experiment, and with appropriate settings for imported infections and a clear operational definition of the end point, estimating probability of interruption of transmission is a useful application.

Limitations of applied modeling

It is difficult to place too much emphasis on the importance of communicating a) the most appropriate and constructive ways to apply simulation results, b) the underlying assumptions of both the models and the method of application of interventions, and c) the uncertainty in model predictions. A misunderstanding about the implications of a model's predictions can lead to loss of confidence in model results, jeopardizing future collaboration.

An illustration is the 2001 United Kingdom foot and mouth disease epidemic. Extensive culling policies informed by mathematical models were criticized, with claims that "use and abuse of mathematical models" led to the slaughter of far more animals than was necessary to control the epidemic [34]. In this case, difficulties in understanding the model assumptions and in interpreting the available data led to questioning of the role models can and should play in informing policy for control of any epidemic [19].

Another is the recent MSAT trials. Modeling studies [35, 36] have shown that, even in favorable settings, MSAT programs must achieve very high coverage of the total population sustained at high frequency to result in a worthwhile impact on infection rates. The limited impact on infection predicted at operationally feasible frequency and coverage levels has now

been borne out by field trials in interventions targeting the whole community [37] and school-aged children [38]. However, despite the substantial differences in the design of the trials in the field compared to those supported by the modeling studies, it was claimed that models failed to predict the disappointing trial results, casting doubt about the underlying assumptions of models [39]. This gave readers the incorrect impression that over-optimistic predictions from mathematical models were a driver behind the testing of an intervention that proved ineffective. In addition to demonstrating the importance of dialogue between modelers and field experts, this highlights the importance of understanding that the way interventions are deployed predict success just as much if not more so than the initial effect of the medicine, or insecticide.

It bears repeating that no simulation, no matter how complex the interaction between its parts, reproduces exactly what happens in 'real life.' Models are only one aspect to providing advice, and must be combined with experimental investigation and the collection and analysis of epidemiological data.

7.5 Communication and interaction with end users: tools, knowledge management and the way forward

This thesis proposes several practical applications and areas for future simulation experiments to inform study design and analysis. However, a gap remains in describing how this 'informing' process is conducted beyond insisting on collaboration. In each case of model application presented in this thesis, there are individual connecting the modelers and the trial designers who understand both the realities of the field and the advantages of consulting models. The consultation process by no means happens organically, and there is little existing infrastructure to facilitate this interaction. There are pros and cons to this approach, for while it may be criticized for its current ad-hoc nature, it is still extremely helpful for both sides so that model potential and limitations can be communicated to implementers, and field realities can be communicated to modelers.

A positive example of such interaction is highlighted by the process of creating the report in Chapter 5. PATH/MACEPA and the Zambia National Malaria Control Center

collaborated with the modeling groups from IV, ICL, and the Swiss TPH to investigate the impact of different MSAT/MDA strategies in Southern Province, Zambia. While each group took a different approach to simulating combinations of drugs and implementation strategies, one clear shared message was shared: in the study area, adding Primaquine (PQ) to Coartem® or DHP did not show a substantial simulated impact on parasite prevalence. Because the modeling groups were all invited to present in a conference symposium and participate in the protocol development meeting, these messages were able to be incorporated into the next phase of the trial.

It is also important to highlight the interaction with LSHTM for the Rachuonyo South OpenMalaria project where the simulation experiment was designed at the same time as the roll out of field trials and updated based on the changing contexts of both the models and the trials. This afforded not only continuous flow of results between the field experiments and the modeling, but also afforded an understanding of what is possible with the model, what inputs were necessary for model parameterization, and the presentation of simulation results that would be most helpful for the study area.

This demonstrates how such collaboration can improve public health practice. Not only the creation, but also the application of mathematical modeling for infectious disease control is indeed better served through collaborations between epidemiologists, policy makers and experts from the field. In order to facilitate success and increase the frequency and quality of interactions, there is a need for flexible structures that connect modelers and users.

Prioritizing the research questions pertinent to disease control and elimination that can be addressed by applied modeling will require understanding what different modeling groups are already doing to inform disease control programs, what researchers and program managers want from models and vice versa, providing a space for dialogue about the underlying assumptions of the models and the value of different modeling approaches, and providing a forum for fostering collaboration. Who is responsible for doing so should be clarified.

Implementation of interventions, at the ground level, is often removed from the dynamics of why, where and when an intervention would be effective. Publishing results in

technical journals is far from sufficient. As a first step, dissemination of examples of linkages between modeling and program design could be consolidated for reference.

As mentioned above, the most important point is for modelers to clearly communicate uncertainty in terms of the range of possible results. A straightforward and non-technical presentation of results is often the most effective, but must describe uncertainty in forecasts to avoid over-stating confidence of model predictions. It is important to consistently and effectively communicate the spectrum of results and implications suggested by model simulations; this will avoid the temptation to focus on one element of model results that seems to confirm an expectation rather than placing the complete results in context. This is not straightforward to present, but there are a number of ways communicating results could be made easier; examples of options for how to do so are described in Appendix 4 of Chapter 6.

A priority should be made to ensure models that aid in the understanding of site-specific transmission dynamics are more accessible to malaria control decision makers. There has been a call to tailor models and the tools to use them to the end user. In the past, this lack of accessibility has acted as a barrier to achieving the goals of applying OpenMalaria to site-specific settings. Training occurred for new users in MTC sites on the model and the process of applying the models to sites using OpenMalariaTools in 2011 before the web-based portals were developed. While these efforts were ultimately unable to produce outputs beyond the stage of site parameterization, they were successful in increasing the visibility of and access to applied modeling within program implementation and research. There are a number of reasons why the training and collaborating efforts did not have the desired effects. These include competing demands from the full time jobs of the participants, frequent upgrades/updates of OpenMalaria (four within the timeframe of one year) resulting in changes to the xml structure and the type of inputs needed, lack of funding for software troubleshooting, and the difficulties inherent in technical training and support in disparate geographical locations.

Tools need to be tailored to the various end users, reinforcing another reason to more strategically clarify the process of applied mathematical modeling of malaria and identify where to focus effort in this development. Efforts towards this goal include VecNet, which provides a

web-based interface for tools targeted at a range of users from students to program managers to modeling experts [15]. Teaching of applied modeling for decision-making can be integrated into any course on epidemiology and control and will help de-mystify this process for the next generation of public health professionals.

The validation exercise conducted in Chapter 6 showing simulated relationships between indicators are comparable to previously published field data is important to lend confidence to model results. It would be helpful for future exercises to have a standard methodology for evaluation of validation exercises of model ensembles. Relatedly, there is not yet any consensus in the modelling community on how to evaluate uncertainty and goodness-of-fit for model ensembles [40]. The merits of different methods have been discussed for models used in meteorology, climate change and macroeconomics, but questions remain on whether model averaging is appropriate and how to quantify an acceptable level of stochasticity for basing programmatic decisions on model predictions [41]. A consensus should be achieved on these criteria if quantitative projections from such models are to become an integral part of the range of decision making tools for malaria control. New methods for analysing and evaluating uncertainty in simulation results as applied to model validation will enhance the usefulness of simulations for malaria control decision-making.

While such a methodology for evaluation of validation exercises would be helpful, going so far as to prescribe the types of datasets that can and cannot be used is not advisable. This is due not only to the need to tailor validation exercises to the question being asked, but because the type and quality of datasets available will likely vary substantially from place to place. Here, retaining flexibility is important.

Predictions of forecasting models in any field are improved over time as a result of the accumulation of inputs to inform model design and parameterization. It is necessary to keep models up to date with new developments in the field through a continuous process of fitting models to new data as they become available and validating simulated results with observations from the field. This can only happen if funding for malaria research is continued and strategically applied.

7.6 References

1. Stevenson J, St. Lauernt B, Lobo N, Cooke M, Kahindi S, Oriango R, Harbach R, Cox J, Drakeley C: **Novel vectors of malaria parasite in the western highlands of Kenya [letter].** *Emerg Infect Dis* 2012 Sept, **[serial on the Internet]**.
2. Bayoh MN, Mathias DK, Odiere MR, Mutuku FM, Kamau L, Gimnig JE, Vulule JM, Hawley WA, Hamel MJ, Walker ED: **Anopheles gambiae: historical population decline associated with regional distribution of insecticide-treated bed nets in western Nyanza Province, Kenya.** *Malar J* 2010, **9:**62.
3. Killeen GF, Chitnis N, Moore SJ, Okumu FO: **Target product profile choices for intra-domiciliary malaria vector control pesticide products: repel or kill?** *Malaria journal* 2011, **10:**207.
4. Kenya Go: **Comprehensive Public Expenditure Review 2013.** Nairobi, Kenya: Government of Kenya, Ministry of Devolution and Planning; 2013.
5. Briet OJ, Chitnis N: **Effects of changing mosquito host searching behaviour on the cost effectiveness of a mass distribution of long-lasting, insecticidal nets: a modelling study.** *Malar J* 2013, **12:**215.
6. WHO: **Global malaria control and elimination: report of a technical review.** Geneva: WHO; 2009.
7. Eckhoff PA: **A malaria transmission-directed model of mosquito life cycle and ecology.** *Malar J* 2011, **10:**303.
8. Paaijmans KP, Read AF, Thomas MB: **Understanding the link between malaria risk and climate.** *Proc Natl Acad Sci U S A* 2009, **106:**13844-13849.
9. Pascual M, Cazelles B, Bouma MJ, Chaves LF, Koelle K: **Shifting patterns: malaria dynamics and rainfall variability in an African highland.** *Proc Biol Sci* 2008, **275:**123-132.
10. **A research agenda for malaria eradication: monitoring, evaluation, and surveillance.** *PLoS medicine* 2011, **8:**e1000400.
11. Group TME: **Shrinking the Malaria Map: A Prospectus on Malaria Elimination.** (Feachem RG, Phillips AA, Targett GA eds.). San Francisco2009.
12. Alliance G: **Malaria Vaccine Investment Strategy, Background Document #3.** GAVI Alliance; 2013.
13. Nunes JK, Cardenas V, Loucq C, Maire N, Smith T, Shaffer C, Maseide K, Brooks A: **Modeling the public health impact of malaria vaccines for developers and policymakers.** *BMC Infect Dis* 2013, **13:**295.
14. Crowell V, Briet OJ, Hardy D, Chitnis N, Maire N, Di Pasquale A, Smith TA: **Modelling the cost-effectiveness of mass screening and treatment for reducing Plasmodium falciparum malaria burden.** *Malar J* 2013, **12:**4.
15. **Vector-Borne Disease Network** [https://www.vecnet.org/]
16. Koenker HM, Yukich JO, Mkindi A, Mandike R, Brown N, Kilian A, Lengeler C: **Analysing and recommending options for maintaining universal coverage with long-lasting insecticidal nets: the case of Tanzania in 2011.** *Malar J* 2013, **12:**150.
17. **Community Flu 2.0** [http://www.cdc.gov/flu/pandemic-resources/tools/communityflu.htm]

18. Coburn BJ, Wagner BG, Blower S: **Modeling influenza epidemics and pandemics: insights into the future of swine flu (H1N1).** *BMC Med* 2009, **7:**30.
19. Kao RR: **The role of mathematical modelling in the control of the 2001 FMD epidemic in the UK.** *Trends Microbiol* 2002, **10:**279-286.
20. van Kleef E, Robotham JV, Jit M, Deeny SR, Edmunds WJ: **Modelling the transmission of healthcare associated infections: a systematic review.** *BMC Infect Dis* 2013, **13:**294.
21. **Who we are: foundation fact sheet** [http://www.gatesfoundation.org/Who-We-Are/General-Information/Foundation-Factsheet]
22. Eziefula AC, Gosling R, Hwang J, Hsiang MS, Bousema T, von Seidlein L, Drakeley C, Primaquine in Africa Discussion G: **Rationale for short course primaquine in Africa to interrupt malaria transmission.** *Malar J* 2012, **11:**360.
23. **A research agenda for malaria eradication: modeling.** *PLoS medicine* 2011, **8:**e1000403.
24. White LJ, Maude RJ, Pongtavornpinyo W, Saralamba S, Aguas R, Van Effelterre T, Day NP, White NJ: **The role of simple mathematical models in malaria elimination strategy design.** *Malar J* 2009, **8:**212.
25. McKenzie FE, Samba EM: **The role of mathematical modeling in evidence-based malaria control.** *Am J Trop Med Hyg* 2004, **71:**94-96.
26. Maire N, Shillcutt SD, Walker DG, Tediosi F, Smith TA: **Cost-effectiveness of the introduction of a pre-erythrocytic malaria vaccine into the expanded program on immunization in sub-Saharan Africa: analysis of uncertainties using a stochastic individual-based simulation model of Plasmodium falciparum malaria.** *Value Health* 2011, **14:**1028-1038.
27. Tediosi F, Maire N, Penny M, Studer A, Smith TA: **Simulation of the cost-effectiveness of malaria vaccines.** *Malaria journal* 2009, **8:**127.
28. Tediosi F, Maire N, Smith T, Hutton G, Utzinger J, Ross A, Tanner M: **An approach to model the costs and effects of case management of Plasmodium falciparum malaria in sub-saharan Africa.** *Am J Trop Med Hyg* 2006, **75:**90-103.
29. Killeen GF, Moore SJ: **Target product profiles for protecting against outdoor malaria transmission.** *Malaria journal* 2012, **11:**17.
30. Moonen B, Cohen JM, Tatem AJ, Cohen J, Hay SI, Sabot O, Smith DL: **A framework for assessing the feasibility of malaria elimination.** *Malaria journal* 2010, **9:**322.
31. Thacker SB, Millar JD: **Mathematical modeling and attempts to eliminate measles: a tribute to the late Professor George Macdonald.** *American journal of epidemiology* 1991, **133:**517-525.
32. Manfredi P, Williams JR, Ciofi Degli Atti ML, Salmaso S: **Measles elimination in Italy: projected impact of the National Elimination Plan.** *Epidemiology and infection* 2005, **133:**87-97.
33. Gay NJ: **Modeling measles, mumps, and rubella: implications for the design of vaccination programs.** *Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America* 1998, **19:**570-573.
34. Kitching RP, Thrusfield MV, Taylor NM: **Use and abuse of mathematical models: an illustration from the 2001 foot and mouth disease epidemic in the United Kingdom.** *Rev Sci Tech* 2006, **25:**293-311.

35. Gabbay J, le May A: **Evidence based guidelines or collectively constructed "mindlines?" Ethnographic study of knowledge management in primary care.** *BMJ* 2004, **329:**1013.
36. Griffin JT, Hollingsworth TD, Okell LC, Churcher TS, White M, Hinsley W, Bousema T, Drakeley CJ, Ferguson NM, Basanez MG, Ghani AC: **Reducing Plasmodium falciparum malaria transmission in Africa: a model-based evaluation of intervention strategies.** *PLoS Med* 2010, **7**.
37. Tiono AB, Ouedraogo A, Ogutu B, Diarra A, Coulibaly S, Gansane A, Sirima SB, O'Neil G, Mukhopadhyay A, Hamed K: **A controlled, parallel, cluster-randomized trial of community-wide screening and treatment of asymptomatic carriers of Plasmodium falciparum in Burkina Faso.** *Malar J* 2013, **12:**79.
38. Halliday KE, Okello G, Turner EL, Njagi K, Mcharo C, Kengo J, Allen E, Dubeck MM, Jukes MC, Brooker S: **Impact of Intermittent Screening and Treatment for Malaria among School Children in Kenya: A Cluster Randomised Trial.** *PLoS Med* 2014, **11:**e1001594.
39. von Seidlein L: **The Failure of Screening and Treating as a Malaria Elimination Strategy. PLoS Med.** *PLoS Med* 2014, **11:**e1001595.
40. Knutti R: **The end of model democracy? An editorial comment.** *Climactic Change* 2010, **102:**395-404.
41. Stainforth DA, Allen MR, Tredger ER, Smith LA: **Confidence, uncertainty and decision-support relevance in climate predictions.** *Philosophical Transactions of the Royal Society* 2007, **365:**2145-2161.

Appendix 1: Commentary on the use and application of OpenMalaria

The OpenMalaria model explicitly describes many of the parts of the *P. falciparum* life cycle as well as the dynamics that link together human and vector behavior, within-host dynamics, health system structure, and effectiveness and implementation of interventions, allowing for flexibility in options for application. However, the model can only be useful if users are given access and have confidence in results.

1. Site-specific experiment design and scenario parameterization

The OpenMalaria model requires a large number of data points as inputs, with a trend towards greater complexity as the model has continued to develop over time. For the exercise in parameterizing OpenMalaria to the context in Rachuonyo South District using schema version 26, operational in early-mid 2011, the total number of individual data inputs was 106. 9% of these (n=10) were provided by site-specific surveys over the relevant timeframe of the study, 47% (n=50) were acquired through a literature review of previously published national and regional data, and 44% (n=47) were kept from the original model parameterization based on rural Tanzania. This last category were generally cases where there were no other data available, i.e. vector biology, or where there were no site-specific data available, i.e. compliance of drug regimen in the case management system. For the most recent site-specific parameterization conducted for Southern Province, Zambia in mid-2013, changes in the model schema brought the total number of necessary inputs up to almost 200. In this case a much greater proportion of inputs were based on a literature review rather than the original model parameters.

OpenMalaria is open source and designed to be used and applied by a range of users as an accessible tool for malaria control decision-makers. Accessibility in this case can mean interfacing directly with the models to run simulations independently or collaborating with the modeling groups at the Swiss TPH. No matter the process, a clear understanding of the type of information/data required for inputs is essential. For a user to piece apart the interaction between and effect of these parameters can only come with practice and time spent working with the model. It is difficult to initially tell which elements are crucial enough to require site specific inputs

and therefore worth the effort to track down for each location, and which will not impact the results enough to be tailored to each individual experiment.

Out of the very long list of elements affecting the dynamics of malaria in a given locality, only a subset are truly essential in order to tailor the description of a scenario to that place. Major categories include transmission (the level, seasonal pattern, and proportion of transmission that occur indoors versus outdoors), case management system (effectiveness of antimalarial drugs, proportion of fevers seeking care), and malaria control interventions (coverage level, timing of implementation, and effectiveness). Specific inputs for a minimum set of input parameters, as well as their general availability, are proposed in Table A1.1.

To assist in the collection of the site-specific data described in Table A1.1, a library of "pre-parameterized" sections of code would be a useful tool for building scenarios. Sections of code could be compiled and applied to scenario design by users; for example, descriptions of the duration and effect of different insecticide formulations, behaviour and biology of individual or classes *Anopheles* vectors, and descriptions of health systems for different levels of access to care.

The proposed set of necessary inputs described Table A1.1 is specifically tailored to experiments such as those described in Chapters 3, 4 and 5 of this thesis which attempt to describe the context and dynamics of malaria epidemiology and control in a location, given a set of existing interventions. Another use of OpenMalaria, which was used extensively before the site-specific approach, has been to describe a not specific geographical location, but rather to investigate an intervention or phenomenon given a standard set of assumptions about the remaining variables over a range of transmission settings. Examples include modelling vaccine effectiveness [1-4] and cost effectiveness [5, 6], the effectiveness and cost effectiveness of intermittent preventive treatment (IPT) of infants [7] and children [8], the ability of case management to prevent re-establishment of malaria after interruption of transmission [9], the cost effectiveness of mass screen and treat [10], the effects of pyrethroid resistance [11], changing vector behaviour [12], and the level of case management [13] on the effectiveness of LLINs, and comparing the effectiveness of vector control interventions [14]. These types of intervention-specific studies require far more detailed input data found from reports of trials where they are available, rather than following the format described in Table A1.1.

Table A1.1. Proposed minimum input parameters necessary for site-specific application of OpenMalaria models.

	Input	OpenMalaria parameter	Potential sources	Source availability		
				Low	*Med*	*High*
Transmission dynamics (repeated for each vector)	Annual average EIR	scaledAnnualEIR	• Moderate to high transmission: studies involving mosquito capture		X	
			• Low transmission: estimating EIR equivalents via seroconversion rates, or calculating force of infection (FOI) by combining information from prevalence and treatment rates	X		
			• Very low transmission: estimating EIR equivalents via seroconversion rates	X		
	Seasonality pattern of transmission (by month)	monthlyValues	• Moderate to high transmission: monthly studies involving mosquito capture	X		
			• Low transmission: monthly average rainfall data through weather stations			X
	Proportion of transmission occurring indoors	propActive	• Entomological studies	X		
Health system	Proportion of fevers that access care	No direct OpenMalaria input. Need to convert by spline interpolation into 5-day treatment probability	• Demographic and health surveillance (DHS) report			X
	Proportion of fevers seen in public sector	pSeekOfficialCareUncomplicated1	• DHS report • Household surveys		X	X
	Proportion of fevers seen in private sector (or self-treatment)	pSelfTreatUncomplicated	• DHS report • Household surveys	X		X
	Most commonly-used antimalarial drug	drugRegimen firstLine	• Ministry of Health or National Malaria Control Program policy documents			X
			• DHS report			X
	% of parasites cleared by drug #1	initialACR [name] value	• Clinical trials			X
	% of population complying to drug #1	compliance [name] value	• Household surveys	X		
	Second most commonly-used antimalarial drug		• DHS report • Household surveys	X	X	

	% of parasites cleared by drug #2	initialACR selfTreatment value	• Clinical trials			X
	% of population complying to drug #2	compliance selfTreatment value	• Household surveys	X		
Interventions	% of population who owns an LLIN	timed deploy coverage	• DHS report • Malaria indicator survey (MIS) report		X	X
	% of population who slept under a LLIN the previous night	usage value	• DHS report			X
	Timing of LLIN distribution	timed deploy time	• National Malaria Control Program/ implementing partner documents			X
	% of infants receiving a LLIN through ANC	continuous deploy coverage	• DHS report • MIS report		X	X
	IRS insecticide formulation	IRS name	• National Malaria Control Program/ implementing partner documents			X
	Halflife of decay of insecticide	decay L	• Entomological studies measuring insecticide decay rate	X		
	Proportion of vectors killed by IRS during the resting stage	postprandialKillingEffect value	• Entomological studies measuring 24 hour mortality	X		
	Timing of IRS deployment	timed deploy time	• National Malaria Control Program/ implementing partner documents		X	
	% of population covered by IRS	timed deploy time	• DHS report • MIS report		X	X
	% of population covered by MSAT/MDA	timed deploy coverage (minAge maxAge)	• Household surveys	X		
	Timing of MSAT/MDA deployment	timed deploy time	• National Malaria Control Program/ implementing partner documents	X		
	Minimum parasites per microlitre detectable by the diagnostic test used for screening	diagnostic deterministic minDensity	• WHO report: Malaria rapid diagnostic test performance			X

2. Model validation

In addition to the two study areas described in this thesis, OpenMalaria has been parameterized for a number of other sites including Asembo Bay in the western Kenya lowlands, Dar es Salaam, Tanzania, several sites in Indonesia, Rafin Marke District in Nigeria, and Luangwa and Nyimba Provinces in Zambia (*all unpublished)*. Out of these sites, only the western Kenyan lowlands site was able to be taken through the process of parameterization, validation and simulation of different interventions in order to investigate the impact of intermittent preventive therapy in school children at reducing parasite prevalence in children under five in response to a request from the Center for Disease Control and Prevention (CDC).

The process of model validation involves comparing simulated data to what is known or can be estimated from *in vivo* or *in vitro* observation. This exercise of checking if the assumptions about the inputs translate to what is observed in practice is important for communicating confidence in model results when predictions are made outside the observed range. Examples of site specific validation can be found in Chapters 2, 5 and 6. The methodology for model validation, whether in a site-specific or general application, depends in large part on the question being asked of the overall experiment. The simulation outputs being compared to observed data must relate to those used to answer the research question in order for the exercise to be considered relevant. For example, in an experiment aimed at reducing under-five mortality in a given location, conducting a validation using parasite prevalence is not as applicable as a validation of like to like with observed mortality in the site in question. In order to maximize the success and applicability of this exercise it is essential to identify the validation dataset at the beginning of the experiment design process.

3. Tools and knowledge management

There are currently a variety of options for creating experiments and running OpenMalaria depending on the needs and operating system of the user. Current options for running OpenMalaria and an evaluation of their applicability are described in Table A1.2. Investment of time and resources into further development of the currently available tools have for a time largely been limited awaiting the release of the VecNet infrastructure, a web-based interface for both basic and advanced users [15].

Table A1.2. Available methods for creating and submitting OpenMalaria simulation experiments

Method	Operating system	Experiment creation?	GUI?	Internet connection required?	Visualization of results?	Target user	Pros	Cons
OpenMalariaTools standalone software [16]	Win32 Linux 32-bit	Yes	Yes	Only for download at initial installation	Yes (through integration with LiveGraph software)	Basic	• Automatic schema translation • Includes basic scenario editor	• Not consistently updated to the most recent OpenMalaria schema release • Limited technical assistance available
Binary executable (compiled from source and run via command line)	Win32 OS X Linux 32/64-bit	Yes	No	No	No	Advanced	• Can be used independently by user • Fast for testing integrity of scenarios on small population sizes	• Requires knowledge of command line • Requires custom build • Run time limited by computing power of one machine
Maia cluster at the University of Basel	Win32 OS X Linux 32/64-bit	No	Yes	Yes	No	Advanced	• Very fast • Can be used and monitored independently by user • Technical assistance available	• Only available for Swiss TPH employees • Requires knowledge of command line
BOINC [17]	N/A	No	No	Yes	No	Advanced	• Able to handle very large experiments	• Job submission requires monitoring by Swiss TPH engineers • Separate configuration for continuous outputs
Notre Dame web portal [18]	Win32 OS X Linux 32/64-bit	Limited	Yes	Yes	No	Basic Students Advanced	• Good for teaching • Choice of submission to standalone server or BOINC	• Limited experiment creation (only full factorial experiments, no model ensemble or dependencies) • Can only handle
VecNet portal [15]	*Win32* *OS X* *Linux 32/64-bit*	*Yes*	*Yes*	*Yes*	*Yes*	*Basic* *Students* *Advanced*	• *Both basic and advanced user options*	• *Still undergoing Beta testing* • *No dependencies possible for experiment creation*

This tool will allow the various types of stakeholders, including students, modelers and policy makers, to easily access software to design and run simulation experiments and to analyze results.

The more recent experience of training students on the use and applications of OpenMalaria through the use of the Notre Dame web portal showed this tool to be user friendly and ideal both for highlighting the effects of individual elements of the vector life cycle and for highlighting the effects of and interactions between malaria control interventions. The second year of using the web-portal as a teaching tool will occur in the spring of 2014.

The field of applied modeling draws together a wide range of disciplines, and finding individuals with both the interest and appropriate mix of skills can be a challenge, especially as it is an interdisciplinary medium without a clear training path. On the other hand, this is also a positive feature of the field because users can come from a variety of backgrounds, bringing a richness of perspective to the field. The background of an OpenMalaria user has the potential to be from a background in computer science, mathematics, statistics, epidemiology, public health, economics, entomology, and the list goes on. Specific skills include coding for data analysis software and command line, software installation and customization, vector control, field operations for program implementation, the role of public vs. private sector in access to care, the malaria parasite life cycle and epidemiology at different levels of transmission. This is a tall order in that many of the elements described above require steep learning curves, and the training experience demonstrates that site-specific application requires a full time effort rather than an exercise to be conducted as a side project. To assist in the collection of the site-specific data described in Table A1.1, a library of “pre-parameterized” sections of code would be a useful tool in building scenarios.

A strength of OpenMalaria is its open source status, designed to be used and applied by a range of users. If mathematical models of malaria are to become accessible to malaria control decision-makers, whether accessibility in this case means interfacing directly with the models to run simulations independently or collaborating with the modeling groups, a clear understanding of the type of information/data required for inputs is essential. For a user to piece apart the interaction between and effect of these parameters can only come with practice and time spent working with the model. It is difficult to tell which elements are

crucial enough to require site specific inputs and therefore worth the effort to track down for each location, and which will not impact the results enough to be tailored to each individual experiment.

4. Suggested further model development and applications

The OpenMalaria model is driven by EIR, a quantity that proves challenging to estimate not only in the present time as described in Chapter 2, but also historically. In order to simulate malaria in a given area using OpenMalaria, a pre-intervention EIR must be specified in order for the simulated population to acquire the appropriate level of immunity during the warm up period, after which observed malaria interventions are applied. Historical records of EIR are sparse and of varying quality [19], and when only a current value of EIR is available for a site, additional simulations are necessary before the main experiment is conducted. These extra simulations aim to estimate which pre-intervention EIR results in the observed EIR after interventions are applied, based on what is known about the implementation timing and coverage level. This methodology is problematic not only due to the extra time and computing resources it takes to estimate this parameter, but it makes an assumption that the input parameters for the effectiveness of the interventions are accurate and/or sufficient and acting as they should. This then makes it difficult to conceptually justify validating intervention effectiveness in such an experiment.

An example of addressing heterogeneities is demonstrated by the differences in methodology for model parameterization for the study areas described in Chapters 3-5, which take different approaches to describing malaria transmission and burden in a particular geographic area. The case of western Kenyan highlands assumes a single value for annual average EIR applied to a district level of approximately 10,000 individuals. On the other hand, the experiment focusing on Southern Province Zambia assumes a range of exposure to transmission across the Province where the population is close to 250,000 individuals and results are reported according to different categories of parasite prevalence.

If OpenMalaria continues to inform study design, it would be helpful to have guidance on the methodology for parameterizing experiments in, and the implications for, analyzing simulation results for different administrative levels, whether that is at village, District, or Province level, in different categories of transmission. For example, the design of

an experiment simulating the population dynamics of a cohort of individuals as in western Kenya (Chapters 3-4) will be different than that of one for a cluster-randomized trial covering a much larger geographical areas as that in Zambia (Chapter 5). Much of this will depend on the degree of heterogeneity of exposure, the rate of imported infections, and population density in the area in question. In practice this understanding may develop after experience applying OpenMalaria to more study areas, but the flexibility of OpenMalaria to explicitly indicate the population size of an experiment should make the process straightforward.

A short term gap in validation of OpenMalaria model elements, apart from assembling a larger number of site-specific validations of areas across a variety of transmission settings, is a more updated parameterization of the more recently developed model for IRS and LLIN implementation. Following the substantial scale up of vector control interventions after the creation of the Global Fund for AIDS, TB and Malaria (GFATM), there should now be a larger body of evidence with which to conduct the admittedly complex exercise of validating these updated parameterizations with observed data on the effectiveness of the interventions in a variety of field settings.

References

1. Smith TA, Chitnis N, Briet OJ, Tanner M: **Uses of mosquito-stage transmission-blocking vaccines against Plasmodium falciparum.** *Trends in parasitology* 2011, **27:**190-196.
2. Smith T, Ross A, Maire N, Chitnis N, Studer A, Hardy D, Brooks A, Penny M, Tanner M: **Ensemble modeling of the likely public health impact of a pre-erythrocytic malaria vaccine.** *PLoS medicine* 2012, **9:**e1001157.
3. Brooks A, Briet OJ, Hardy D, Steketee R, Smith TA: **Simulated impact of RTS,S/AS01 vaccination programs in the context of changing malaria transmission.** *PLoS One* 2012, **7:**e32587.
4. Penny MA, Maire N, Studer A, Schapira A, Smith TA: **What should vaccine developers ask? Simulation of the effectiveness of malaria vaccines.** *PLoS One* 2008, **3:**e3193.
5. Tediosi F, Maire N, Penny M, Studer A, Smith TA: **Simulation of the cost-effectiveness of malaria vaccines.** *Malaria journal* 2009, **8:**127.
6. Maire N, Shillcutt SD, Walker DG, Tediosi F, Smith TA: **Cost-effectiveness of the introduction of a pre-erythrocytic malaria vaccine into the expanded program on immunization in sub-Saharan Africa: analysis of uncertainties using a stochastic individual-based simulation model of Plasmodium falciparum malaria.** *Value Health* 2011, **14:**1028-1038.
7. Ross A, Penny M, Maire N, Studer A, Carneiro I, Schellenberg D, Greenwood B, Tanner M, Smith T: **Modelling the epidemiological impact of intermittent preventive treatment against malaria in infants.** *PLoS One* 2008, **3:**e2661.
8. Ross A, Maire N, Sicuri E, Smith T, Conteh L: **Determinants of the cost-effectiveness of intermittent preventive treatment for malaria in infants and children.** *PLoS One* 2011, **6:**e18391.
9. Crowell V, Hardy D, Briet O, Chitnis N, Maire N, Smith T: **Can we depend on case management to prevent re-establishment of P. falciparum malaria, after local interruption of transmission?** *Epidemics* 2012, **4:**1-8.
10. Crowell V, Briet OJ, Hardy D, Chitnis N, Maire N, Di Pasquale A, Smith TA: **Modelling the cost-effectiveness of mass screening and treatment for reducing Plasmodium falciparum malaria burden.** *Malar J* 2013, **12:**4.
11. Briet OJ, Penny MA, Hardy D, Awolola TS, Van Bortel W, Corbel V, Dabire RK, Etang J, Koudou BG, Tungu PK, Chitnis N: **Effects of pyrethroid resistance on the cost effectiveness of a mass distribution of long-lasting insecticidal nets: a modelling study.** *Malar J* 2013, **12:**77.
12. Briet OJ, Chitnis N: **Effects of changing mosquito host searching behaviour on the cost effectiveness of a mass distribution of long-lasting, insecticidal nets: a modelling study.** *Malar J* 2013, **12:**215.
13. Briet OJ, Penny MA: **Repeated mass distributions and continuous distribution of long-lasting insecticidal nets: modelling sustainability of health benefits from mosquito nets, depending on case management.** *Malar J* 2013, **12:**401.
14. Chitnis N, Schapira A, Smith T, Steketee R: **Comparing the effectiveness of malaria vector-control interventions through a mathematical model.** *The American journal of tropical medicine and hygiene* 2010, **83:**230-240.
15. **Vector-Borne Disease Network** [https://www.vecnet.org/]
16. **OpenMalariaTools** [http://code.google.com/p/openmalaria/wiki/openmalariaTools]
17. **malariacontrol.net** [http://www.malariacontrol.net/]
18. Dame UoN, SwissTPH, University JC: **OpenMalaria web portal.** 2013.
19. Kelly-Hope LA, McKenzie FE: **The multiplicity of malaria transmission: a review of entomological inoculation rate measurements and methods across sub-Saharan Africa.** *Malaria journal* 2009, **8:**19.