



UNCERTAINTY QUANTIFICATION OF AGENT-BASED MODELS WITH APPLICATION TO MALARIA INTERVENTION MODELING

PhD Thesis Proposal in Epidemiology

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ABSTRACT

Background: Agent-based models (ABMs) have been used extensively to study the dynamics of malaria transmission as well as the impact of malaria control interventions. Results from these models have provided evidence to guide decision-making in malaria endemic countries. Sub-national models taking into account malaria transmission heterogeneities and tailored interventions require to run malaria simulations at high spatial resolution, at the cost of increased parameter uncertainty. Quantifying uncertainty of these models can help increase the credibility and robustness of ABMs and their predictions. This PhD aims to quantify the uncertainty of agent-based models with application to malaria intervention modeling in two ways: 1) Forward propagation, which aims to provide insights about how parameter variability impacts model outputs; 2) inverse uncertainty quantification, which seeks to improve model parameter inference by comparing observed data with model outputs. Results of uncertainty quantification will have conclusions made for future planning of interventions at the sub-national level.

Objectives: In this PhD project, we aim to understand the drivers of impact of interventions in Ghana, develop a novel inference framework for quantifying and propagating parameter uncertainty in the OpenMalaria Ghana model, and simulate the impact of malaria interventions in order to support decisions for strategic planning at high spatial resolution.

Methods: In Objective 1, a sensitivity analysis for geographic and intervention modeling parameters will be performed where a variance-based approach (Sobol indices) is used to calculate the sensitivity indices of vector composition (relative abundance and biting patterns of mosquito species), intervention coverage and half-life parameters to clinical cases averted and prevalence reduction. Further, we plan to identify the parameters that drive the variance of the model outputs. Results from Objective 1 will provide for Objective 2 the parameters that would require accurate estimates for reliable model predictions and which would be inferred. We will develop an efficient sampling-based framework for inferring multiple parameters and quantifying and propagating uncertainty for malaria interventions applied to Ghana data. Using the findings from objective 2, we will improve model calibration of the ABM OpenMalaria model for Ghana to enhance its credibility and reliability for malaria intervention modeling. Scenarios for sub-national tailoring of interventions for Ghana will be refined and prioritization criteria for combinations of interventions at the district level will be developed. Using the model with quantified parameter uncertainty, we will focus on exploring if the geographic extension of vaccination and/or the switch to Interceptor G2 bednets to help achieve the malaria control targets of the National Malaria Elimination Program (NMEP).

Relevance of thesis: This work aims to provide an efficient inference framework to identify key drivers of intervention impact and present results with their uncertainties. This approach will enhance the reliability of the strategic information provided by models to support decision-making. The NMEP and policymakers will be able to use these intervention model predictions to allocate their limited resources more efficiently and design intervention strategies that are more likely to succeed.

ABBREVIATIONS AND ACRONYMS

HBHI	High Burden to High Impact
GMEP	Global Malaria Eradication Program
PMI	US President's Malaria Initiative
ACT	Artemisinin Combination Therapies
EIR	Entomological Inoculation Rate
EPI	Expanded Programme on Immunization
GTS	Global Technical Strategy
IRS	Indoor Residual Spraying
ITN	Insecticide Treated Nets
LLIN	Long lasting Insecticide-treated Nets
SMC	Seasonal malaria chemoprevention
IPTp-SP	Intermittent Preventive Treatment of malaria in pregnancy with Sulfadoxine-Pyrimethamine
LSM	Larval Source Management
MAP	Malaria Atlas Project
MTR	Mid-Term Review
NMCP	National Malaria Control Programme
NMEP	National Malaria Elimination Programme
NMSP	National Malaria Strategic Plan
<i>PfPR</i>	<i>Plasmodium falciparum</i> Prevalence Rate
RBM	Roll-back Malaria
WHO	World Health Organisation
MVIP	Malaria Vaccine Implementation Program
ABMs	Agent-based models

1. INTRODUCTION AND BACKGROUND

1.1 Epidemiology of malaria and history of interventions in Ghana

Malaria remains a major public health concern as it continues to claim many lives worldwide. In 2022, there were 249 million estimated malaria cases with 608'000 estimated deaths globally. Out of these global estimates, Sub-Saharan Africa accounted for 93.6% of cases and 95.4% of deaths. Overall, 78.1% of all deaths in this region were among children under 5 years of age. Ghana is part of the top 11 countries with the highest malaria burden, and part of the High Burden High Impact (HBHI) initiative [1]. It accounts for 2.1% of the estimated cases in Sub-Saharan Africa and 1.9% of estimated malaria deaths [2,3]. With over 5 million reported cases in a population of 33 million, the disease imposes a substantial burden of morbidity and mortality on the population, particularly among vulnerable groups such as children under five years of age and pregnant women [3–5]. Malaria persists in Ghana at varying intensities, influenced by factors such as climate, geography, human behaviour, and socio-economic conditions [6]. Transmission of malaria varies across the three ecological zones of the country namely: the coastal savannah zone, middle transitional or forest zone and the northern savannah zone. Transmission intensity also fluctuates seasonally, typically peaking during and after the rainy season when mosquito-breeding sites become rampant [7]. However, in certain zones, malaria transmission may be perennial, especially in regions or districts most conducive to mosquito breeding [5]. The predominant parasite species responsible for malaria in Ghana is *Plasmodium falciparum* (96.3%), with mixed infections of *Plasmodium falciparum* and either *Plasmodium malariae* (1.6%) or *Plasmodium ovale* (1%) also being reported. The main vectors for malaria transmission are *Anopheles gambiae*, *Anopheles funestus* and *Anopheles arabiensis* [1,8,9].

Ghana has a long history of malaria control efforts, dating back to the colonial era with initiatives such as the Global Malaria Eradication Program (GMEP) [10]. Since then, several interventions targeting either the parasite in the human host or the mosquito vector have been implemented. These include intermittent preventive treatment of malaria in pregnancy with sulfadoxine-pyrimethamine (IPTp-SP), artemisinin-based combination therapies (ACTs), seasonal malaria chemoprevention (SMC), insecticide-treated bed nets (ITNs), indoor residual spraying (IRS), larval source management, and the recent deployment of the RTS,S malaria vaccine through the malaria vaccine implementation program (MVIP) coordinated by WHO [11]. ITNs, ACTs and IPTp-SP are implemented nationwide whereas IRS, SMC and RTS,S are focused on certain regions and districts of the country. Most of these interventions were implemented in the early 2000s, with the RTS,S vaccine most recently, introduced in 2021 [7]. RTS,S is currently implemented in 93 out of 261 districts [1].

In light of the heterogeneity of malaria burden across the country, reducing this burden requires a differentiated response and a choice of intervention mixes based on subnational data [12]. In 2019, the Ghana National Malaria Elimination Program (NMEP), in collaboration with WHO, Global Fund to fight AIDS, TB and Malaria (GFATM) and the US President's Malaria Initiative (PMI), conducted a malaria burden stratification exercise across the country. This stratification exercise was repeated in 2022 to allow for subnational tailoring of malaria interventions per district [7]. Figure 1 shows a map of the 2022 malaria prevalence in Ghana, by district.

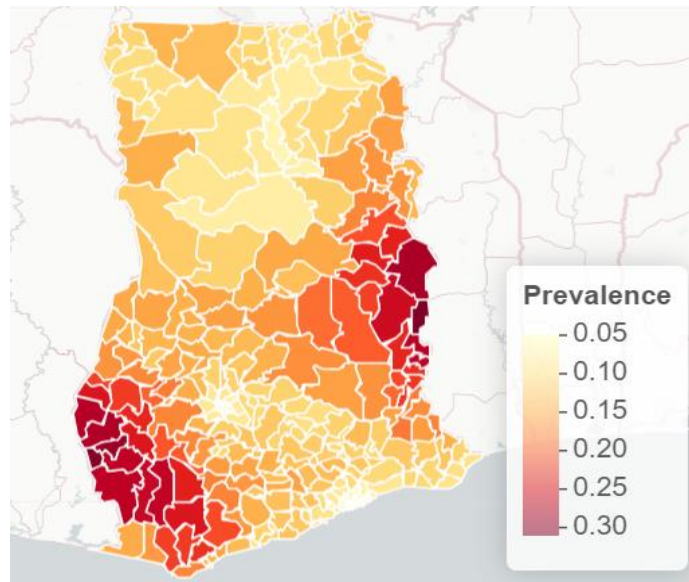


Figure 1: Malaria prevalence map (2022) of Ghana by district

1.2 Context of National Strategic Plan (NSP) in Ghana

Ghana has conducted several malaria control initiatives since the colonial era. Its first initiative was the creation of a malaria control unit within the ministry of health (MOH) in 1957. Apart from the creation of national initiatives, Ghana also committed to other international initiatives such as the Roll Back Malaria (RBM) Initiative, the Abuja Declaration on Roll Back Malaria in Africa, the Millennium Development Goals (MDGs), and the United Nations Sustainable Development Goals (SDGs). The national malaria control program (NMCP) is responsible for developing national malaria strategic plans. It also plans and coordinates malaria surveillance and control activities by adopting the WHO recommendations to the local levels at which interventions will be implemented. In 2022, the name of the NMCP of Ghana was changed to the National Malaria Elimination Programme (NMEP) [1].

The National Malaria Strategic Plan (NMSP) 2021–2025 is Ghana's overarching plan for malaria control and prevention, and it is complemented by additional guidelines and policies such as the National Malaria Control Monitoring and Evaluation Plan 2021–2025 [5]. The NMSP 2021–2025 focuses on achieving three goals: firstly, to decrease malaria mortality by 90%, using 2019 as baseline. Secondly, to reduce malaria case incidence by 50% relative to 2019 levels. Lastly, to attain pre-elimination status for malaria in at least six districts. This strategic plan aims to consolidate the progress made over the preceding eight years while integrating new interventions and strategies. It drew inputs from diverse stakeholders including health partners, community members, research institutions, academia, and non-governmental organizations (NGOs). It provides a roadmap for achieving the objectives of the NMEP in Ghana, guiding partners in channeling their efforts towards accelerated malaria control and pre-elimination initiatives in specific areas [7]. During the period of this strategy, Ghana has made significant progress regarding malaria control. A report on the progress of the NMSP 2021-2025 showed that Ghana had over-achieved most of its national objectives. While the implementation of the NMSP 2021-2025 is still underway, Ghana has recently developed its first National Malaria Elimination Strategic Plan (NMESP) 2024-2028, which aims at eliminating malaria in 21 districts with very low malaria burden by 2028. In addition to the above goal, this NMESP 2024-2028 seeks to reduce malaria mortality by 90% by the year 2028 (using 2022 as baseline) and reduce malaria case incidence by 50% by 2028 [1].

1.3 The usefulness of dynamical disease transmission models towards malaria control and elimination

Dynamical disease transmission models are mathematical frameworks that are used to quantitatively represent the complex interactions between hosts and pathogens in a population

and study the influence of various factors such as interventions on the dynamics of the disease. Mathematical modelling allows us to answer the questions whether the disease persists in the population and how to structure interventions such that the nature of the dynamical system changes on the way to disease elimination [13]. These models can also be used to identify relevant features of the system to better understand and reduce uncertainty when comparing model outputs to epidemiological surveillance data. Finally, mathematical models are impactful to quantify future projections by simulating scenarios informed by implementation constraints, in particular at operationally relevant spatial scales such as health districts. Dynamical disease transmission models have been used to respond to questions posed by NMCPs in line with available National Strategic Plans (NSPs) for disease control [13–16].

In Ghana, these models have been used over the years to understand malaria transmission and the impact of interventions. This includes among others to investigate regional transmission variability and estimate the impact of malaria control interventions [17], estimate the risk of declining funding for malaria [18], to investigate whether partial IRS with pirimiphos-methyl is an effective and cost-saving measure for the control of *Anopheles gambiae* [19], and to estimate the impact of RTS,S/AS01 malaria vaccine allocation strategies [20].

1.3.1 Design and structure of intervention models

Mathematical models address questions that cannot easily be answered with randomized controlled trials (RCTs) or empirical studies: for example, what is the large-scale effectiveness of an intervention in the general population? How can we quantify the effectiveness in complex settings with many different combinations of interventions? Intervention modeling allows simulating various interventions *in silico* and comparing their effectiveness in a population or in subgroups of hosts. It allows for the estimation of the impact of past interventions, simulation of different scenarios of an intervention and comparing different combinations of interventions [21]. The approach to modeling interventions can be either agnostic or mechanistic. The **agnostic approach** focuses primarily on observing the impact of interventions without detailed understanding of underlying mechanisms. Mathematical models or statistical methods are used to analyze pre- and post-intervention data to estimate the impact of interventions on disease parameters, such as the force of infection or effective reproduction number. In a **mechanistic approach**, detailed understanding of intervention mechanisms is required. Complex mathematical models or computer simulation models that incorporate detailed representations of intervention mechanisms and their interactions with disease transmission dynamics are used. These models may include compartmental or agent-based models (ABMs). Compartmental models classify hosts broadly by their disease state and model the temporal dynamics of the compartments' size through differential equations. ABMs on the other hand, allow for more detailed host attributes and can study complex emerging dynamics at the individual level. Compared with compartmental models, ABMs come at the cost of analytic tractability and usually results in less transparency and ease of communication of results. ABMs are also demanding computationally, which can limit the extent of the analysis performed. Modeling interventions requires a combination of epidemiological data, an understanding of intervention mechanisms, and appropriate modeling frameworks to assess their impact on disease transmission dynamics meaningfully.

Some transmission dynamic ABMs for malaria modeling have been developed to simulate malaria epidemiology and control. These are OpenMalaria [22], EMOD [23] and malariasimulation [24]. OpenMalaria, developed by the Swiss Tropical and Public Health Institute, is an individual-based model aiming at simulating the dynamics of malaria transmission and epidemiology, and the impact of interventions on health and economic outcomes. It is an open source program written in C++. Initially designed for modeling malaria vaccines, it employs microsimulations to depict *Plasmodium falciparum* malaria dynamics in human populations. The model simulates various aspects, including the dynamics of malaria parasitemia during infection, the life cycle of mosquitoes, disease transmission between humans and mosquitoes, the development of anti-malaria immunity in human hosts, and the progression to illness and mortality. OpenMalaria simulates malaria in human and vector

populations, and has been used extensively to investigate multiple questions relating to disease dynamics or the use of existing and new interventions [15,25].

1.3.2 Intervention modeling with ABMs for policy making

Effective malaria control demands evidence-based decision-making supported by quantitative analysis. ABMs enable researchers to simulate different intervention scenarios and evaluate their impact on key metrics such as prevalence rates, incidence rates, mortality, and cost-effectiveness. Through modeling, policymakers can identify optimal intervention combinations, resource allocation strategies, and implementation timelines to maximize impact within budget constraints [26]. Securing funding for malaria control programs often requires demonstrating the potential impact of proposed interventions. ABMs generate robust predictions to provide stakeholders with compelling evidence of the anticipated benefits of investments in new interventions. This strengthens funding requests (for example to the GFATM) and increases the likelihood of obtaining support from donors, governments, and other stakeholders. ABMs facilitate the incorporation of spatial data, allowing for region-specific modeling and analysis. By considering local transmission dynamics, vector species, human population characteristics, and healthcare infrastructure, policymakers can optimize intervention strategies to target high-risk areas effectively [15].

The ABM OpenMalaria has been very useful in estimating the potential impact of various interventions. For example, Penny *et al.* used OpenMalaria together with three other malaria models to parameterize the RTS,S vaccine efficacy against infection by fitting the model to phase 3 trial data. Having obtained model estimates of vaccine efficacy, they were able to make projections for wider transmission settings [27]. The recommendation of the Interceptor G2 (IG2), a dual-insecticidal bed net, has been a major milestone to malaria control in malaria endemic areas faced with pyrethroid resistance. The NMCPs and policymakers are now in cycle of careful net replacement strategies and management to preserve the long-term efficacy of different types of nets [28]. OpenMalaria provides a platform where country-specific net replacement strategies can be evaluated in the presence of existing interventions to inform decision-making. OpenMalaria allows scenario modeling to provide estimates of the required coverage and likely impact of interventions that cannot be ascertained from National Strategic Plans or RCTs alone.

1.4 Uncertainty Quantification

Representing a real-world system using a mathematical model entails uncertainty. Uncertainties may stem from several sources including parameter uncertainty, observation uncertainty, stochastic uncertainty, and model uncertainty. **Parameter uncertainty** arises due to the challenge of not knowing the values of the parameters or obtaining inaccurate measurements from the system. **Observation uncertainty** arises when there are inaccuracies in measuring the real-world system. **Stochastic uncertainty** occurs due to randomness in the real-world system. **Model uncertainty** measures the error between model outputs and observed data stemming from model design choices.

Uncertainty quantification can be classified in two forms: **forward uncertainty propagation** (i.e. sensitivity analysis), which investigates the impacts of random input values of model parameters on the outputs of a model, whereas **inverse uncertainty quantification** (i.e. calibration or parameter estimation) is the process of using experimental data to learn about the sources of modelling uncertainty [29]. For example, in malaria intervention modeling, sensitivity analysis might be used to determine which parameters have the most significant impact on the spread of the disease [30], while calibration could adjust the model parameters to align with observed disease trends to estimate these parameters. Apart from understanding factors contributing to a specific model behaviour, sensitivity analysis also helps to identify parameters that require accurate estimates for more robust and reliable model predictions [31]. Taken together, uncertainty quantification helps to make the models more robust and to better inform public health policy [29,32,33].

Various techniques have been developed for quantifying uncertainties in computer models. Sensitivity analysis techniques, such as variance-based methods, gradient-based methods and global sensitivity analysis, assess the relative importance of input parameters in influencing model outputs [34]. These techniques often pair a sampling scheme with a sensitivity measure in order to quantify the relationship between model outputs and parameters. Bayesian inference approaches for inverse uncertainty quantification such as Markov Chain Monte Carlo (MCMC), sequential Monte Carlo (SMC) and Approximate Bayesian Computation (ABC) methods leverage probabilistic frameworks to update model predictions based on observed data, thereby quantifying uncertainties in model parameters [35].

Despite significant progress in uncertainty quantification methodologies, challenges exist in effectively handling uncertainties, particularly in complex ABMs such as the ABM OpenMalaria. Computational efficiency remains a key concern, as traditional uncertainty quantification techniques may become computationally expensive for large-scale simulations. Recent advances in uncertainty quantification include the development of surrogate modeling techniques, such as the use of emulators (eg. Gaussian process emulation), which provide computationally efficient alternatives to traditional Monte Carlo simulations [36]. An emulator approximates a complex mathematical model by establishing statistical associations between high-dimensional model parameter inputs and model outputs of interest (e.g. disease prevalence at a pre-defined time point). Once trained, emulators reduce computational costs and shorten the amount of time needed to implement model runs: instead of running a large amount of simulations under various scenarios, one only needs to evaluate the input parameters under a (e.g. Gaussian) estimator.

1.4.1 Calibration and parameter inference from historical data

Most parameters of transmission-dynamic models of malaria are usually informed country-specific data (e.g. census data, climate data to inform seasonality, data on intervention history including geostatistical effective intervention coverage estimates and entomological data on mosquito species and their contribution to transmission intensity) or taken from literature with only a few unknown parameters being estimated with data on available observed cases. Calibration or fitting the model to data, involves adjusting model parameters to ensure that the model's predictions align as closely as possible with observed data. During the calibration process, unknown parameters of a model are estimated based on observed data [29,32]. Researchers often obtain parameter values with confidence intervals estimated using statistical estimation from literature, but in cases where parameter values cannot be directly estimated from observed data, calibration is used to estimate these parameters. In doing so, the model is run for different parameter sets and the outputs compared with observed data in order to identify the parameter values that achieve a good fit. Calibration heavily relies on the availability and accuracy of historical data hence requires reliable and relevant data sources [33].

Several methods exist for calibrating ABMs and can be categorized into two namely, **point estimation and distributional estimation**. Point estimation methods provide a single parameter combination that best fits the model to data whereas the distributional estimation methods aim to find multiple parameter combinations that fit the model to data over a certain range of values. Obtaining a range of plausible parameter values provides additional information on the uncertainty of parameter values and the outputs of the model [37]. Previous research on calibration methods have shown that methods using sampling algorithms as their parameter-search strategy (i.e. distributional estimation methods), obtain valid estimates of parameter uncertainty. In their recent systematic review of calibration methods, Hazebag *et al.* identified some sampling-based calibration methods that have been used in calibrating ABMs of malaria, including Bayesian Markov chain Monte Carlo (MCMC) and random draw from prior with stepwise calibration [27,38]. The same study recommended the use of methods using sampling algorithms as their parameter-search strategy as they provide valid estimates of parameters as well as their uncertainties [37]. Emulators can be integrated with Bayesian calibration to accelerate the calibration process for computationally expensive models [36].

1.4.2 Uncertainty in intervention modeling

In Ghana, as in many malaria-endemic countries, there is a pressing need for more precise and effective malaria control strategies to achieve a more targeted malaria response. These strategies are often designed and implemented at a sub-national level to address the heterogeneity of malaria transmission. During malaria control intervention planning, the geographical allocation, target population, type of intervention, combination, coverage, timing, distribution scheme are part of the determinants of the success of interventions [15]. Below are some sources of uncertainty in intervention modeling.

1. The **Entomological Inoculation Rate (EIR)** quantifies the risk of malaria transmission by measuring the frequency of infectious mosquito bites per person per year. This is a critical component in designing interventions as a reduction in the EIR shows effectiveness of interventions in reducing malaria transmission. However, the process of estimating the EIR and the subsequent application of this metric in tailoring interventions is filled with uncertainties that can significantly undermine their effectiveness. Most modelling studies take into account this uncertainty and infer the EIR during the model calibration process [39].
2. Another source of uncertainty arises when implementing a vector control intervention such as insecticide treated bed nets (ITNs) in several geographical locations with varying levels of malaria transmission intensity, some areas may receive fewer bed nets than needed while others receive more than necessary, or the bed nets may not be used correctly by the recipients. This uncertainty regarding the extent (coverage) and success (usage or **effective coverage**) of the **ITN** implementation across the different locations adds a layer of complexity to intervention planning. Often **geostatistical effective intervention coverage** estimates are based on survey-point data, which are then smoothed with spatial covariates. Performing such estimates at finer scales (e.g. districts within regions in Ghana) comes at the cost of increased uncertainty reflecting variability within a region (Figure 2: example on using Malaria Atlas Project data) which needs to be taken into account during the calibration process. This uncertainty can lead to under- or over-allocation of resources and may prevent the success of future interventions. By accurately quantifying coverage uncertainty and its impact on intervention effectiveness, programs can optimize resource allocation, prioritize high-risk areas, and tailor interventions to local contexts, ultimately improving malaria control efforts.
3. Another source of uncertainty in intervention modeling is the discrepancy of **seasonal malaria chemoprevention** effectiveness between randomized control trial or pilot study data and large-scale impact evaluation with routine surveillance data. Unlike what is suggested in controlled settings, the effectiveness of SMC is likely not governed by an all-or-nothing uptake but rather the result of a context-specific interplay between **coverage** and **half-life** (in particular adherence) of the treatment efficacy.

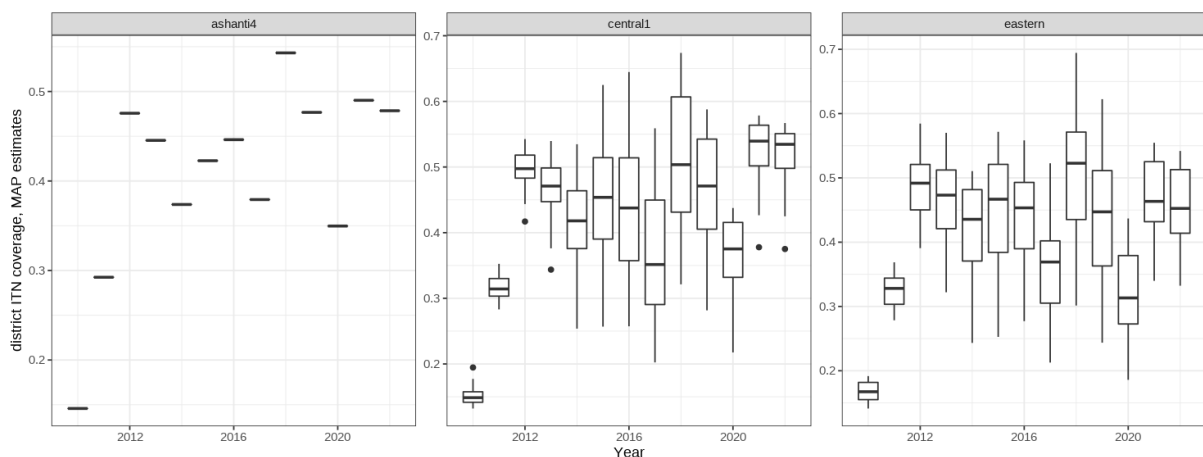


Figure 2: Geospatial estimates for ITN effective coverage at the district level in Ghana provided by Malaria Atlas Project. We show boxplots (median & quartiles) of coverage estimates for three different regions (each represented by a panel). For the region Ashanti4, the parametric (ITN effective coverage) uncertainty is negligible, as all district estimates are located on the median, whereas Central1 and Eastern point towards parametric uncertainty at the regional level, which should be taken into account during the model calibration process.

A recent generic sensitivity study has shown that for specific modeling use cases, health outcome measures such as prevalence reduction are most sensitive to effective **intervention coverage** and **half-life of intervention efficacy** (Figure 3) [25]. This suggests the need to quantify the uncertainty of these parameters during the modeling process.

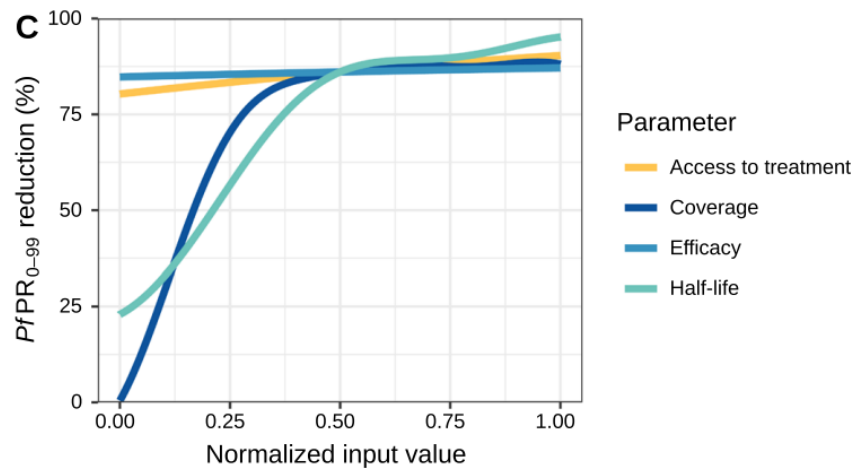


Figure 3: One-parameter sensitivity analysis of intervention characteristics toward *Plasmodium falciparum* prevalence (PfPR) reduction. Adapted from: Figure 3, panel C in Golumbeanu et al. 2022. This figure shows coverage, efficacy and half-life sensitivity for a mosquito sugar bait intervention. The steep curves for coverage and half-life between 0 and 0.5 suggest strong dependence of health outcomes post intervention (e.g. prevalence reduction) on these parameters.

Since determining the exact EIR for every setting at the sub-national level is virtually impossible, the ABM OpenMalaria currently simulates a wide range of EIR values (eg. 1-400 infectious mosquito bites per person per year) and selects the one that fits best the observed past prevalence or incidence. Together with the stochasticity of the model, this calibration step provides confidence intervals for the predictions. Confidence intervals are generated using the method by Ionides et al. (2017) [40]. This calibration approach provides a point estimate and does not provide information on the uncertainty of parameters and the model output. In order to obtain a range of plausible parameter values that provide additional information on the uncertainty of parameter values and the outputs of the model, a sampling-based algorithm is required. In addition, even though the current calibration approach infers the EIR, intervention coverage uncertainty has not been considered. This necessitates a framework that infers multiple parameters at a high-dimensional level. This PhD seeks to develop a sampling-based inference framework for model calibration to quantify and propagate intervention parameter uncertainty (e.g. effective coverage, half-life of efficacy) and its impact on simulating the effect of malaria interventions.

1.5 Relevance of PhD

This PhD focuses on quantifying the uncertainty in agent-based model outputs, particularly in the context of malaria intervention modeling. The primary objective is to assess how parameter uncertainty affects the robustness of model outputs and resulting conclusions made for future planning of interventions at the sub-national level. This work represents the first effort to incorporate and evaluate the uncertainty from various parameters in the OpenMalaria Ghana model, beyond just the entomological inoculation rate (EIR) and to determine the impact of these uncertainties on simulating the effect of malaria interventions at the sub-national level.

Sensitivity analysis for geographic and intervention modeling parameters will be performed where we calculate the sensitivity indices of vector composition (relative abundance and biting patterns of mosquito species), coverage and half-life parameters to clinical cases averted and prevalence reduction and identify the most important parameters for the Ghana model. These indices will tell us how crucial each parameter is to the relevant outcomes. An efficient sampling-based inference framework for multiple parameters will be developed and uncertainty quantification performed for malaria interventions applied to Ghana data. Lastly, scenario modeling for malaria interventions in Ghana will be performed incorporating the parametric uncertainty. This will serve as a guide to the country in efficient resource allocations, and in assessing the impact of interventions.

One of the key elements of the high burden to high impact (HBHI) country-led response is the use of strategic information to drive impact [41]. NMCPs of malaria endemic countries in Sub-Saharan Africa including Ghana rely on support from modeling studies to effectively deploy malaria control interventions for maximum impact. Quantifying uncertainty of key parameters in the Ghana malaria intervention model and assessing the impact of this parametric uncertainty on intervention scenario evaluation will help to understand the robustness of predictions and contribute to more effective malaria control strategies. In pre-elimination settings where resources need to be strategically allocated, uncertainty quantification will help to identify areas where interventions can have the most significant impact and where they might be needed most urgently.

This work will provide an efficient inference framework that will allow for the uncertainty of multiple key parameters to be quantified to enhance the accuracy and reliability of the strategic information provided by models to support decision-making. The NMCP and policymakers will utilize intervention model predictions to allocate their limited resources more efficiently and to design intervention strategies that are more likely to succeed.

2. OBJECTIVES AND RESEARCH AIM

Main Objective:

The main objective of this thesis is to quantify and propagate parameter uncertainty and its impact on intervention scenario modeling.

Specific Objectives:

1. Understand the key drivers of impact of interventions in Ghana.

Perform sensitivity analysis for intervention-specific and geographic-specific parameters and identify the most influential parameters for the impact estimates inferred with the OpenMalaria Ghana model.

2. Develop a novel inference framework for calibrating the OpenMalaria model at a higher spatial resolution.

Develop an efficient sampling-based inference framework to infer multiple parameters and perform uncertainty quantification for malaria interventions applied to the Ghana data.

3. Simulate the impact of malaria interventions in Ghana in order to support decisions for strategic planning.

Perform scenario modeling for malaria interventions in Ghana including parametric uncertainty.

3. RESEARCH PLAN AND METHODS

3.1 Methods Objective 1

Description: For the first objective, sensitivity analyses of intervention coverage and half-life parameters as well as geographic-specific parameters such as vector composition towards relevant specified health outputs such as prevalence reduction (i.e. NSP endpoint of 2027 vs 2024 as reference) and clinical cases averted (i.e. cumulative 2024-2027 with 2023 pre-NSP as reference) will be performed. This will help to identify the key drivers of impact for malaria interventions across different districts of Ghana. In particular, we are interested in parameters that are related to implementation and sampling strategies by the NMEP (*Table 1*). Existing district-level OpenMalaria model calibration for Ghana will be used, and a variance-based (robustness towards global perturbations) approach will be employed to perform the sensitivity analysis. This approach will capture global sensitivity and quantify the contribution of individual and interaction effects of model inputs by decomposing the output variance in a sum of individual input parameter conditional variances. Latin Hypercube Sampling (LHS) will be performed to efficiently sample the input space and Sobol indices calculated to quantify model input–output relationships. *Table 1* shows the parameters to be considered for the sensitivity analysis whereas *Table 2* shows a comparison of sensitivity analysis methods and highlights the approaches that will be used for this objective.

Table 1: Parameters to be considered for sensitivity analysis

Parameters to be considered for variance-based sensitivity analysis	
Geographic-specific Parameters	
Vector Composition	<ol style="list-style-type: none"> 1. Relative abundance and outdoor biting of <i>An. gambiae</i> 2. Relative abundance and outdoor biting of <i>An. funestus</i> 3. Relative abundance and outdoor biting of <i>An. arabiensis</i>
Intervention-specific Parameters	
Intervention Effective Coverage	<ol style="list-style-type: none"> 1. Future ITN coverage 2. Future SMC coverage 3. Future Vaccine coverage
Intervention Efficacy	<ol style="list-style-type: none"> 4. Initial efficacy and half-life of ITN 5. Initial efficacy and half-life of SMC 6. Initial efficacy and half-life of Vaccine

Table 2: Comparison of sensitivity analysis methods [35]. The highlighted method will be used to perform the sensitivity analysis

Sensitivity Analysis Method	Pros	Cons
One-at-a-Time (OAT)	<ul style="list-style-type: none"> - Simple to implement and interpret - Useful for identifying individual parameter effects 	<ul style="list-style-type: none"> - Ignores interactions between parameters - Not comprehensive - Can be computationally expensive if the model has many parameters
Gradient-Based	<ul style="list-style-type: none"> - Efficient for small perturbations - Provides local sensitivity information 	<ul style="list-style-type: none"> - Limited to local perturbations - May miss global interactions - Requires differentiable model
Variance-Based (e.g., Sobol indices)	<ul style="list-style-type: none"> - Comprehensive - Captures global sensitivity 	<ul style="list-style-type: none"> - Computationally expensive

	<ul style="list-style-type: none"> - Quantifies contribution of individual and interaction effects 	<ul style="list-style-type: none"> - Requires large number of model evaluations
Latin Hypercube Sampling (LHS)	<ul style="list-style-type: none"> - Efficient sampling method - Good for covering input space uniformly 	<ul style="list-style-type: none"> - Does not provide sensitivity measures directly - Requires post-analysis (e.g., correlation) to interpret results
Partial Rank Correlation Coefficient (PRCC)	<ul style="list-style-type: none"> - Handles non-linear, non-monotonic relationships - Relatively simple to implement 	<ul style="list-style-type: none"> - May not capture all interactions - Assumes monotonic relationships
Regression-Based Methods	<ul style="list-style-type: none"> - Provides clear, interpretable results - Can handle multiple inputs simultaneously 	<ul style="list-style-type: none"> - Assumes linearity - May not be suitable for highly non-linear models
Low-Rank Approximations [42]	<ul style="list-style-type: none"> - Performs global sensitivity analysis in high dimensions - Reduced computational cost 	<ul style="list-style-type: none"> - issues of convergence may be encountered in certain cases

Technical and data requirement: For Ghana, a recent calibration at the district level until 2022 will be used. This calibration utilizes regional MAP intervention coverage estimates with district-level prevalence estimates of *Plasmodium falciparum* in children aged 2-10 as target. Based on this starting point, databases of OpenMalaria simulation outputs will be created for the sensitivity analysis by using the current workflow coded with the OpenMalariaUtilities R package, for creation and deployment of simulations on the High Performance Computing (HPC) at sciCORE (<http://scicore.unibas.ch/>) scientific computing core facility at University of Basel, as well as for post-processing. To calculate the sensitivity indices, the function *soboljansen* from the R package *sensitivity* will be used. This function estimates the sensitivity indices through Markov Chain Monte Carlo (MCMC) sampling, using a Monte Carlo approximation for computing conditional expectations. R Statistical software version 4.3.0 on the Open OnDemand RStudio-Server will be used for this analysis.

Outputs and deliverables: Results of the analysis from Objective 1 will provide us with model parameters that malaria cases and prevalence in different districts of Ghana are most sensitive to. This will allow us to evaluate the robustness of current malaria control strategies at the district level as currently implemented in the NSP in Ghana. The mid-term review is carried out to evaluate whether the malaria control targets are reached given the current implementation strategy. Results of the sensitivity analysis will help the NMEP to carefully choose intervention re-allocation if needed. For instance, interventions whose impact is particularly sensitive to coverage increase will be prioritized. The sensitivity analysis will be integrated in the OpenMalaria workflow package, which will be publicly available.

Risks and their mitigation: As it is computationally costly to simulate an exhaustive number of simulations to explore the entire parameter space for diverse combinations of interventions, settings, and deployment, we plan to use the Gaussian process emulator for OpenMalaria, which is currently being built by members of the Analytics and Intervention Modeling (AIM) group at Swiss TPH. While efficient sampling techniques such as low discrepancy sequences (e.g. Sobol indices) may give spurious results for non-uniform multivariate distributions (e.g. when considering multiple time points of prevalence outputs), we will investigate more recent approaches such as low-rank approximations [42] to avoid the curse of dimensionality. Low-rank approximations express the model output as a sum of a small number, which are products of univariate functions in each of the input parameters. The number of unknown coefficients in low-rank approximations grows only linearly with the input dimension, which makes it promising for dealing with cases of high dimensionality.

3.2 Methods Objective 2

Description: An efficient sampling-based inference framework for multiple parameters will be developed and inverse uncertainty quantification for malaria applied to Ghana data will be performed (i.e. inference of historical intervention coverages). Results from Objective 1 will provide us with the parameters that would require accurate estimates for robust model predictions and we will infer these parameters. We will employ an efficient sampling algorithm (e.g. Adaptive mixture importance sampling (AMIS)) that has been proven to efficiently calibrate models with high-dimensional parameter spaces to design a framework to perform inverse uncertainty quantification. In the framework detailed in *Retkute et al. 2021* [43], algorithms known as importance sampling are augmented by a proposal function which compares the empirical distribution function of modelled malaria prevalence conditioned on pixel-level geospatial estimates with the modelled prevalence alone. At each iteration, the algorithm samples from a shrinking subset of active pixel sites until no site is active anymore. Here, we will simulate each district separately at appropriate pixel resolution (e.g. 5km²) and infer EIR and ITN coverage levels (for most recent years) based on district aggregated prevalence from 2015-2024. All data (past intervention and prevalence) will be provided through an established partnership with MAP. Table 3 shows various calibration approaches employed in the most common malaria intervention ABMs used for subnational tailoring.

Table 3: Calibration approaches in the state-of-the-art malaria intervention ABMs used for sub-national tailoring. The highlighted method will be adapted to develop the inference framework.

Simulator	Metric	Calibration Method	Pros	Cons
OpenMalaria [22]	gaussian likelihood of prevalence including uncertainty of target	quadratic approximation of profile likelihood	does not require sampling, nor large number of simulations provide uncertainty bounds for inferred parameter	single parameter for inference
OpenMalaria [43]	Effective sample size (ESS)	Adaptive Multiple Importance Sampling	More than one parameter for inference	Computationally expensive if simulations are not easily parallelizable
Malariasimulation [24]	weighted difference between prevalence	1-dimensional minimizer	fast, could be used for inference in higher dimension	no uncertainty for inferred parameter
EMOD-intra host [44]	Effective sample size (ESS)	incremental mixture importance sampling & Wilks' theorem	high dimensional inference	boundary

Technical and data requirement: This objective will require proficiency in programming language R, for implementing the inference framework and analyzing the results. We will need access to Ghana data on malaria transmission dynamics, intervention effectiveness, demographic information, and other relevant parameters available from the NMEP.

Outputs and deliverables: Output from Objective 2 will be a fully implemented, tested, and documented sampling-based inference framework. This framework will be used to calibrate

the OpenMalaria Ghana model. Complete documentation of methodologies, code, and algorithms used in the framework will be publicly available on GitHub.

Risks and their mitigation: This objective is faced with the risk of high computational cost associated with sampling-based calibration methods for large parameter spaces that may require multiple runs to quantify uncertainty. This risk can be mitigated by focusing on adaptive sampling methods that are computationally efficient and are easily parallelizable. We can also use emulator-based approaches that have successfully been applied to OpenMalaria [36].

3.3 Methods Objective 3

Description: In Objective 3, we will use the calibrated model from Objective 2 to refine modeling scenarios for Ghana at the sub-national (district) level and define prioritization criteria for combinations of interventions. Given the putative impact on malaria burden, we will focus on propagating the uncertainty on the impact of ITNs, IRS, SMC and vaccines (RTS,S, R21). In particular, we will focus on exploring if the geographic extension of vaccination, since it is currently implemented in only 93 out of 261 districts and/or the switch to Interceptor G2 bednets will help achieve malaria control targets of the NMEP (see 1.2). As these two interventions are novel, there is a high interest from the NMEP to have relevant and reliable evidence to use for decision-making. Since specific questions have not yet been posed by the NMEP, we will simulate a full factorial experiment (i.e. all intervention combinations) in all districts. This will allow us to not only simulate the strategy of interest for the NMEP once it is defined but also explore alternative options. The current intervention deployment coverages for ITNs, SMC and vaccines will be used as the business-as-usual scenario. Future scenarios with higher coverage levels of the aforementioned interventions will also be simulated for all districts and intervention combinations will be prioritized based on their projected reductions in malaria prevalence and incidence in the year of interest. If the NMEP is interested in considering the cost of interventions, intervention implementation data provided by the NMEP will be used. This will allow us to prioritize interventions without exceeding the budget limit.

Technical and data requirement: The outcomes of Objective 3 will provide robust intervention impact estimation for sub-national models of malaria in Ghana with data preceding the upcoming Global Fund call in 2026. Data will be provided based on our established relationships with MAP and the NMEP.

Outputs and deliverables: Outputs from Objective 3 will provide intervention stratification alternatives at the district level to the Ghana NMEP. Improved calibration and forward propagation of uncertainty will be key to ensure the robustness of intervention impact evaluation. We will also provide detailed reports with particular emphasis on policy implications for non-modelers.

Risks and their mitigation:

To ensure data access but also model results uptake by stakeholders, we need to ensure trustworthy communication between NMEP and the AIM group at Swiss TPH. We plan to have regular meetings in Accra and at international conferences to align our interests and to adapt research questions to the needs of the NMEP. At the moment, parameterization for the new malaria vaccine R21 is not yet available for use in OpenMalaria and so including R21 will depend on getting the parameterization within the period of this PhD.

4. ETHICAL ISSUES

Individual level data will not be required in this project hence there are no ethical issues to declare.

5. LIST OF TENTATIVE TITLES OF MANUSCRIPTS

Objective	Manuscript Title	Authors
1	Determining Most Sensitive Parameters in the Spread of Malaria in Ghana: A Sensitivity Analysis of a Malaria Intervention Model.	Zenabu Suboi, [...], Amanda Ross, Christian Selinger, Emilie Pothin
2	Uncertainty Quantification for Agent-based Models of Malaria Interventions: A Sampling-Based Inference Framework	Zenabu Suboi, [...], Amanda Ross, Christian Selinger, Emilie Pothin
3	Prioritisation of vaccination in Ghana to reach malaria control targets: A modelling study.	Zenabu Suboi, [...], Amanda Ross, Christian Selinger, Emilie Pothin

6. TIMEPLAN WITH MILESTONES

Obj.	Main Activity	2024				2025				2026				2027
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1
	Proposal writing													
1	OpenMalaria training													
	Sensitivity analysis and parameter identification													
	Paper 1													
2	Development and testing of the inference framework													
	Paper 2													
3	Scenario Modeling and analysis													
	Paper 3													
	Thesis writing													

7. COLLABORATION AND SUPPORT

Internal (Swiss TPH):

- Modeling support: Dr. Emilie Pothin, Dr. Christian Selinger
- Epidemiology support: Prof. Dr. Christian Lengeler

External (Ghana):

- Public Health: Prof. Evelyn Ansah (UHAS)
- Mathematics/modeling: Dr. Rhoda Hawkins (AIMS-Ghana)

Data availability:

- Geospatial estimates: Dr. Punam Amratia (MAP-Tanzania), Sammy Oppong (MAP)
- Routine and intervention data: Dr. Keziah Malm, Wahjib Mohammed, NMEP Ghana

8. PHD COMMITTEE

First supervisors

Dr. Emilie Pothin, Swiss TPH

Prof. Dr. Christian Lengeler, Swiss TPH

Dr. Christian Selinger, Swiss TPH

Second supervisor

PD Dr. Amanda Ross, Swiss TPH

External examiner

To be determined

9. SHORT CV

Name	Zenabu Suboi
Date of birth	02.11.1991
Nationality	Ghanaian
Natural languages	Dagaare (mother tongue) English, Akan (proficient)
Phone	+41 766305272
E-mail	zenabu.suboi@swisstph.ch

Employment

10.2021 – Date	Assistant Lecturer at Academic City University College, Ghana
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Selected Research Projects

01.2019 – 12.2020	Calibration of models to data: A comparison of methods (Master thesis)
06.2020	Modeling the effect of mass dog vaccination delivery strategies in rural Western Kenya

Education

01.2019 – 12.2020	Master in Mathematics, Stellenbosch University, South Africa
08.2017 – 06.2018	Master in Mathematical Science, AIMS – South Africa
09.2012 – 06.2016	Bachelor in Statistics, University for Development Studies, Ghana

10. LEARNING AGREEMENT

Domain	Course Title	Semester	ECTS	Completed
SWISS TPH / UNIVERSITY OF BASEL				
Background Knowledge	OpenMalaria Training	May-July 2024	N/A	✓

	Malaria epidemiology and control	SS 2024	2	✓
Methods	Introduction to Bayesian Statistics	SS 2024	2	✓
	Data analysis in epidemiology	SS 2024	3	✓
	Mathematical modelling of infectious diseases	SS 2024	2	✓
	Research data management	TBD	2	
	Introduction to R for epidemiological data analysis	SS 2024	1	✓
	Advances in infection biology, epidemiology and global public health	TBD	1	
Transferable skills	Scientific writing	TBD	2	
	Effective presentation skills	TBD	1	
	Meet the professionals	TBD	1	
SSPH+				
SSPH+	Systematic Reviews and Meta-analysis	TBD	1	
	Writing a journal article and getting it published	TBD	1.5	
Total ECTS			18.5	10
MaModAfrica PhD training School - (AIMS Senegal / SWISS TPH)				
Malaria Modeling	Epidemiological Concepts	Nov / Dec 2023	N/A	✓
	Infectious Disease, Malaria Epidemiology, and Control			✓
	Compartmental Models of Infectious Disease Dynamics			✓
	Model Conception			✓
	Malaria Models			✓
	Simulation Algorithms and Numerics			✓
	Parameter Inference			✓
	Geospatial Modelling			✓
	R Coding for Data Management, Data Analysis, and Data Quality Assessment			✓

11. BUDGET PLAN

Cost item	Year 1 (2024)	Year 2 (2025)	Year 3 (2026)	Total
Annual Salary (gross)	29'400	29'400	29'400	88'200
Conferences Participation Fees	-	500	500	1'000

Health Insurance	900	900	900	2'700
Semester Fee	740	740	740	2'220
Other Costs (Visa, Permit, Software)	300	300	300	900
Travel Costs	3'000	3'000	3'000	9'000
Total	34'340	34'840	34'840	104'020 CHF

This budget will be covered through a grant by the Bill & Melinda Gates Foundation (04/2024-03/2027) led by Dr. Emilie Pothin.

12. REFERENCE LIST

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