Application of microsimulation modeling for malaria control decision-making

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Background
Financing for malaria control has increased substantially over the past decade, funding large scale distribution of malaria control commodities such as long-lasting insecticide-treated nets (LLINs) and artemisinin combination therapy (ACTs). Over the same time period there has been a noted decrease in reported morbidity and mortality due to malaria. According to the 2012 World Malaria Report, 50\% of malaria endemic countries were on track to achieve the goal of 75\% reduction in malaria cases by 2015 \cite{1}. However, this success is being challenged by the lack of sufficient funding for malaria control. Roll Back Malaria estimated a gap of $3.8 billion dollars to fund sufficient malaria commodities over only the period of 2013-2015 \cite{2}. This context justifies the prioritization of identifying and assessing the cost-effectiveness of different mixes of malaria control interventions.

Methods
The goal of this work is to apply individual-based stochastic models of malaria to field sites to better understand transmission dynamics and explore different control interventions and strategies. Simulations were conducted using OpenMalaria, an ensemble of stochastic simulation models of malaria transmission able to simulate the dynamics of \textit{Plasmodium falciparum} in a given population \cite{3}. Based on parasite densities for individual infections, stochastic individual-based models of malaria in humans \cite{4,5} are linked to a periodically-forced model of malaria in mosquitoes \cite{6} in order to simulate the dynamics of malaria transmission and the impact of intervention strategies for malaria control. Models are fitted to 10 objectives using 61 standard scenarios, calibrated by the seasonal pattern of infectious bites per person per year, and run for one human life span to induce a stable level of immunity in the population.

The two study areas include Rachuonyo South District, western Kenya and Southern Province, Zambia. For both study areas, baseline scenarios were parameterized and experiments designed in collaboration with research and implementing partners: the London School of Hygiene and Tropical Medicine, the Centers for Disease Control and Prevention, and the Kenya Medical Research Institute in Rachuonyo South \cite{7,8}, and the Zambia National Malaria Control Centre and PATH/MACEPA in Southern Province \cite{9}. Baseline scenarios were validated by comparing simulation results with observed data collected in the study area. Experiment results were evaluated by comparing simulated results to the simulated baseline scenario.

Results
The experiment set in Rachuonyo South attempted to answer the question of whether there are alternative malaria control strategies that could have a larger impact malaria burden in Rachuonyo South compared to the currently-implemented strategy. Simulation results suggest that while an intervention with 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 Coartem® with 80\% coverage twice per term had the greatest simulated health impact, 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 DALYs over a five year period.

For Southern Province, answering the question of which factors are likely to increase the effectiveness of a mass test and treat (MTAT) campaign, simulation results suggest that the most important determinant of success in reducing prevalence is the coverage of the population
achieved by the campaign. However, even with high coverage of mass drug administration (MDA) in areas with a pre-intervention all-age parasite prevalence of less than 10%, simulations suggest that elimination would require more than one year of campaign implementation. Including single low-dose primaquine, which acts as a gametocide, to the drug regimen did not further reduce prevalence. The addition of an endectocide, such as ivermectin, resulted in a lower simulated parasite prevalence and warrants further investigation.

Discussion
In order to increase the applicability of results and the success of the collaboration, it is essential to have the appropriate use of models to answer a question. Cost-effectiveness analysis is a helpful tool but cannot be the only basis for decision-making; this should take into account logistical feasibility, insecticide and drug resistance, and acceptability of an intervention by the community. For these projects, collaboration between the field and modelers has been essential yet extremely ad hoc. Asking questions that are both epidemiologically relevant and able to be addressed by models requires connections between modelers and the users, who currently are principally funders and academics involved in trial design rather than malaria control program managers. A structure to facilitate these connections does not yet exist, and there is a lack of clarity on who should drive the agenda for questions being asked. Cultivating a broader understanding of the role of models is necessary in order to increase their use in evidence-based decision-making.

Conclusions
OpenMalaria has been demonstrated to aid in the decision-making process for trial design and intervention evaluation when applied to operationally-feasible contexts. Based on this application, it can be concluded that a major role of models is to act as a tool to communicate the interactions between elements of a system, and apply them to specific questions. Results of intervention effectiveness are setting-dependent, and models can play a role in bridging the large gap between global predictions and site-specific recommendations. This role and associated use cases is what should in part drive further development of model features and tools.

References