Malaria Vector Control in Sub-Saharan Africa: Impact and Economic Evaluation of Larviciding

MALARA VECTOR CONTROL IN SUB-SAHARAN AFRICA: IMPACT AND ECONOMIC EVALUATION OF LARVICIDING

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ABSTRACT

The last decade witnessed the important scaled-up of malaria control interventions in sub-Saharan Africa (SSA). There is now renewed impetus to achieve the long-term goal of malaria elimination and reducing vectorial capacity of the *Anopheles* mosquito is a necessary first step towards this objective. Relying solely on the two pillars of malaria vector control (i.e., insecticide-treated nets and indoor residual spraying) will be insufficient to achieve elimination in much of SSA, however. Larval Source Management, and larviciding in particular, could play an important role in areas where breeding habitats are '*few, fixed, and findable*' or where malaria vectors exhibit exophagic and exophilic behaviors, and in settings where insecticide resistance has emerged. Yet, only few contemporary studies have investigated the effectiveness of larviciding for malaria control despite historical success. Using the wealth of data from Dar es Salaam's Urban Malaria Control Program (2004-2008), this dissertation will first assess the impact of a community-based larviciding program on prevalence of malaria infection in 15 urban wards of Dar es Salaam (Tanzania). The cost-effectiveness of this intervention will then be estimated from both a provider and a societal perspective. Finally, in a context of accelerated malaria control, the effect of reducing malaria transmission on disease-related behavior and knowledge will be examined.

Results suggest that the larviciding intervention had a significant protective effect, decreasing by 21% the odds of being infected with malaria. Larviciding was found to be cost-effective for incidences as low as 40 infections per 1,000 individuals per year but the cost-effectiveness ratios were highly dependent on the assumed baseline malaria incidence rates. Such a successful intervention could also bring about further challenges to sustaining gains in reducing malaria transmission as the larviciding intervention was found to negatively affect bednet usage and knowledge of disease symptoms. Collectively, these results imply that larviciding should be considered as part of an Integrated Vector Management approach in SSA, if local eco-epidemiological conditions are suitable, and that there is a need to sustain behavioral change communication following successful vector control interventions.

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INTRODUCTION

During the last decade, the mobilization of important financial resources has led to the scaling-up of malaria control interventions in sub-Saharan Africa (SSA)[1]. Interventions such as insecticide-treated bed nets (ITNs), indoor residual spraying (IRS), rapid diagnostic tests (RDTs), and the introduction of artemisin combination therapy (ACT) are believed to have played a role in mitigating the malaria burden in SSA[2-4]. The reductions in morbidity and mortality that coincided with the scaling-up of such intervention led some to advocate moving beyond control to malaria elimination[5,6]. The impetus provided by a leading philanthropist's call for malaria eradication within his lifetime has spurred several research initiatives in that direction[7,8].

Interventions that reduce vectorial capacity are a necessary first step towards eradication[9]. Sustaining consolidated control in much of SSA still faces important challenges, however. This is especially true in areas where vectors exhibit exophagic and exophylic behaviors[10,11]. Mathematical models suggested that the outdoor biting rate of the main malaria vectors defines what is achievable in terms of malaria reduction with IRS and ITNs[12] - the two pillars of vector control interventions in SSA[13]. Other challenges include the emergence of pyrethroid resistance for the primary malaria vectors in diverse areas of the African continent. Relying solely on IRS and ITNs is believed to be insufficient to achieve malaria elimination in much of SSA[9,14]. Hence, larval source management, and larviciding in particular, may become desirable in areas where transmission is focal and where breeding habitats are easily located and accessible such as in urban settings[15]. Yet, strong empirical evidence on the causal effect of larviciding on malaria infection is difficult to obtain and further studies are needed. This was indeed identified as a priority research area for accelerating

program transition toward malaria elimination at a recent WHO meeting [16].

Second, managers of malaria control programs will need to define context-specific packages of optimum interventions to achieve either low endemicity control or elimination. Despite the availability of interventions of proven efficacy, the challenge remains to define this package of intervention in a sustainable, equitable, and cost-effective way. Cost-effectiveness analysis is a well-established, albeit imperfect, method that can guide this type of evidence-based decision-making. The knowledge base regarding the cost-effectiveness of malaria interventions is relatively scarce, however. To the best of our knowledge, larviciding was the object of only one cost-analysis study[17,18] and the cost-effectiveness of this intervention remains to be quantified.

Finally, additional challenges to elimination could also stem from vector control measures themselves. Larval source management for example, by concomitantly reducing densities of other non-malaria vector nuisance insects, could impact the uptake of other interventions such as ITNs[19-21]. Use of bednet is believed to be a function of night-time temperature, perceived malaria risk (including beliefs about malaria transmission), and density of nuisance biting insects[22-24]. With decreases in malaria transmission and perceived malaria risk, use of mosquito net could be driven primarily by a desire to avoid bites of insects other than anophelines. Few studies of vector control interventions that reduce vector densities and malaria transmission investigated such potential impacts.

This doctoral dissertation is organized around these three main research questions. Specifically, the first paper investigates the effectiveness of large-scale community-based micriobial larvicicidng to reduce prevalence of malaria infections in urban Dar es Salaam (Tanzania)[25-29]. This paper was published in 2013 in *PLoS ONE* [30]. The second paper

estimates the cost-effectiveness of larviciding for urban malaria control and has been published in 2014 in *Malaria Journal*[31]. The third paper examines the impacts of this large-scale larviciding intervention on bednet usage and knowledge of malaria symptoms and transmission. This last paper was also published in *Malaria Journal*[32].

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PAPER #1: IMPACT OF COMMUNITY-BASED LARVICIDING ONTHE PREVALENCE OF MALARIA INFECTION IN DAR ES SALAAM, TANZANIA

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ABSTRACT

Background: The use of larval source management is not prioritized by contemporary malaria control programs in sub-Saharan Africa despite historical success. Larviciding, in particular, could be effective in urban areas where transmission is focal and accessibility to *Anopheles* breeding habitats is generally easier than in rural settings. The objective of this study is to assess the effectiveness of a community-based microbial larviciding intervention to reduce the prevalence of malaria infection in Dar es Salaam, United Republic of Tanzania.

Methods and Findings: Larviciding was implemented in 3 out of 15 targeted wards of Dar es Salaam in 2006 after two years of baseline data collection. This intervention was subsequently scaled up to 9 wards a year later and, to all 15 targeted wards in 2008. Continuous randomized cluster sampling of malaria prevalence and socio-demographic characteristics was carried out during 6 survey rounds (2004-2008), which included both cross-sectional and longitudinal data (N=64,537). Bayesian random effects logistic regression models were used to quantify the effect of the intervention on malaria prevalence at the individual level.Effect size estimates suggest a significant protective effect of the larviciding intervention. After adjustment for confounders, the odds of individuals living in

areas treated with larviciding being infected with malaria were 21% lower (Odds Ratio=0.79; 95% Credible Intervals: 0.66-0.93) than those who lived in areas not treated. The larviciding intervention was most effective during dry seasons and had synergistic effects with other protective measures such as use of insecticide-treated bed nets and house proofing (i.e., complete ceiling or window screens).

Conclusion: A large-scale community-based larviciding intervention significantly reduced the prevalence of malaria infection in urban Dar es Salaam.

INTRODUCTION

The Ross-Macdonald model of malaria transmission suggests that control methods that reduce adult mosquitoes' longevity can achieve greater malaria reduction than strategies that target larval stages. Yet, Larval Source Management (LSM), such as the use of larvicides and the draining of breeding habitats, has historically been a very successful tool to reduce mosquito density [1] – examples include the elimination of *Anopheles arabiensis* from Egypt [2] and Brazil [3], malaria control in the Zambian copperbelt (1930-1950) [4], Dr. Gorga's work during the construction of the Panama canal [5], and the vector control program of the Tennessee Valley Authority [6]. With the discovery of DDT, however, such approaches where disfavored as exemplified by the almost exclusive use of this potent insecticide during the Global Malaria Eradication Program (1955-1969) [7]. In addition, LSM programs were often associated with vertical, authoritarian management. Currently, there are few examples of LSM initiatives in post-colonial Africa [8-10]. LSM is often perceived as a secondary malaria control strategy, labor-intensive, requiring strong managerial support and oversight for monitoring and evaluation [11,12], and often beyond the financial and operational capabilities of most malaria endemic areas in sub-Saharan Africa [13].

Such considerations might explain the insufficient evidence-base of LSM in post-colonial Africa, and the contemporary prioritization of malaria control programs that rely on Insecticide-Treated Nets (ITNs) and Insecticide Residual Spraying (IRS) as the main vector control measures. Nevertheless, a renewal of interest in applications of LSM within the sub-Saharan context has been observed recently [14-18]. In fact, in April of 2012, the World Health Organization (WHO) released an interim position statement [19] on the use of larvicides for malaria control in sub-Saharan Africa, recognizing that larviciding should be considered for

malaria control but only in areas where breeding sites are '*few, fixed and findable*' [19]. Larval control is regarded as being of secondary importance in comparison with IRS and ITNs. Although the WHO acknowledges that larvicides could be effective as one of the leading methods of vector control in urban areas of sub-Saharan Africa, it highlights the lack of recent and sound evidence of its effectiveness. Few contemporary studies have assessed the effectiveness of larvicides on malaria infection. Studies in highland valley communities of Kenya [20] and urban Tanzania [21] demonstrated substantial reduction in malaria prevalence, while no reductions were observed in a study conducted in a rural setting in The Gambia [22]. Strong empirical evidence on the causal effect of larviciding on malaria infection is difficult to obtain since larviciding interventions need to be implemented and scaled-up over large areas, appropriate control groups with similar malaria ecology are difficult to find, and the cost of such trials can be prohibitively expensive [14].

The rationale for adding larvicides to the arsenal of malaria control tools in urban areas is manifold. First, in contrast to rural areas, vector breeding habitats are generally fewer and much easier to reach in highly densely populated areas [10]. Second, the most potent malaria vector in Africa, *An. gambiae*, has been shown to exhibit exophagic behavior in some urban areas - although the majority of bites still take place indoors [23]. If this behavior intensifies over time, and therefore more biting and resting start to occur outside of homes, the efficacy of both IRS and ITNs would be reduced. Mathematical models have provided evidence that the outdoor biting rate defines what is achievable in terms of malaria reduction with IRS and ITNs [24]. LSM is one of the few strategies that could contribute to further reduce malaria when *Anopheles* are partially exophagic [14]. Third, insecticide resistance has emerged for the primary malaria vectors in many areas of the African continent [25-28] and combining IRS and ITN with

larviciding could become more desirable in such settings. Finally, relying solely on IRS and ITNs may be insufficient to achieve malaria elimination in much of sub-Saharan Africa [29,30]. As such, larviciding may be part of an integrated vector management (IVM) approach [31] that could help hinder malaria transmission [18]. Such informed use of larvicides, based on local malaria ecology, is in line with WHO's current position on IVM [31,32].

Africa is the fastest urbanizing continent in the world and its share of urban population is expected to double between 2000 and 2030 [33]. Malaria intensity is generally much lower in urban areas and transmission is highly focal [34,35]. A corollary of this reduced endemicity is that urban dwellers will develop lower levels of clinical immunity to the disease, which can pose public health challenges. It has been estimated that about 28% of the malaria burden in sub-Saharan Africa is attributable to urban malaria [34]. Malaria control in urban settings offers more options than for rural areas because logistical constraints are alleviated by relatively good transportation, education, communication, and health infrastructures [36].

Following this rationale, the Dar es Salaam Urban Malaria Control Program (UMCP) was launched in 2004, targeting 15 of the city's 73 wards, covering 56 km^2 of the city, and a population of more than 610,000 residents [36]. The goal was to develop a sustainable larval control intervention as one of the main components of a malaria control strategy. Regular application of microbial larvicides was initiated in 2006 through vertically managed community-based delivery systems [36]. Initial results, restricted to children under five years of age and comprising data from the first period of larviciding (2006-2007) in three wards of the city (N=4,450), demonstrated that this intervention reduced by 72% the odds of malaria infection [21]. In addition, rigorous monitoring of larval population in the same period showed that

larviciding reduced anopheline larval abundance by 96% [36]. The larviciding intervention was scaled-up to 9 wards in 2007 and to all 15 wards in 2008.

In this paper, we will comprehensively investigate the effectiveness of the larviciding intervention on reducing malaria prevalence using 4.6 years of data, including individuals of all ages, and combining both cross-sectional and longitudinal data (N=64,537). This will provide crucial evidence on the potential contribution of larvicide use for reducing population-level malaria burden in urban areas of sub-Saharan Africa.

MATERIALS AND METHODS

Study site

Dar es Salaam is the largest city and economic capital of the United Republic of Tanzania with an estimated population of 2.7 million in 2005 [37]. The climate is tropical humid with two rainy seasons – the long rains during the months of April and May and the short rains of October and November. Malaria transmission is year-round [38] with peaks in incidence after the two rainy seasons. *Plasmodium falciparum* accounts for more than 90% of cases and the principal vectors involved in malaria transmission are *An. gambiae s.* and *An. funestus* [10]. *An. coustani*'s contribution to malaria transmission is believed to be marginal [21]. Dar es Salaam is composed of three municipalities: Illala, Temeke, and Kinondoni. These municipalities are further divided in 73 wards (Figure 1.1). Each ward is comprised of administrative sub-units called *mtaa* (plural *mitaa*) which are further divided in ten-cell units (TCU) – the smallest administrative unit that contains approximately 10-20 houses, but may also contain as many as 100 [10].

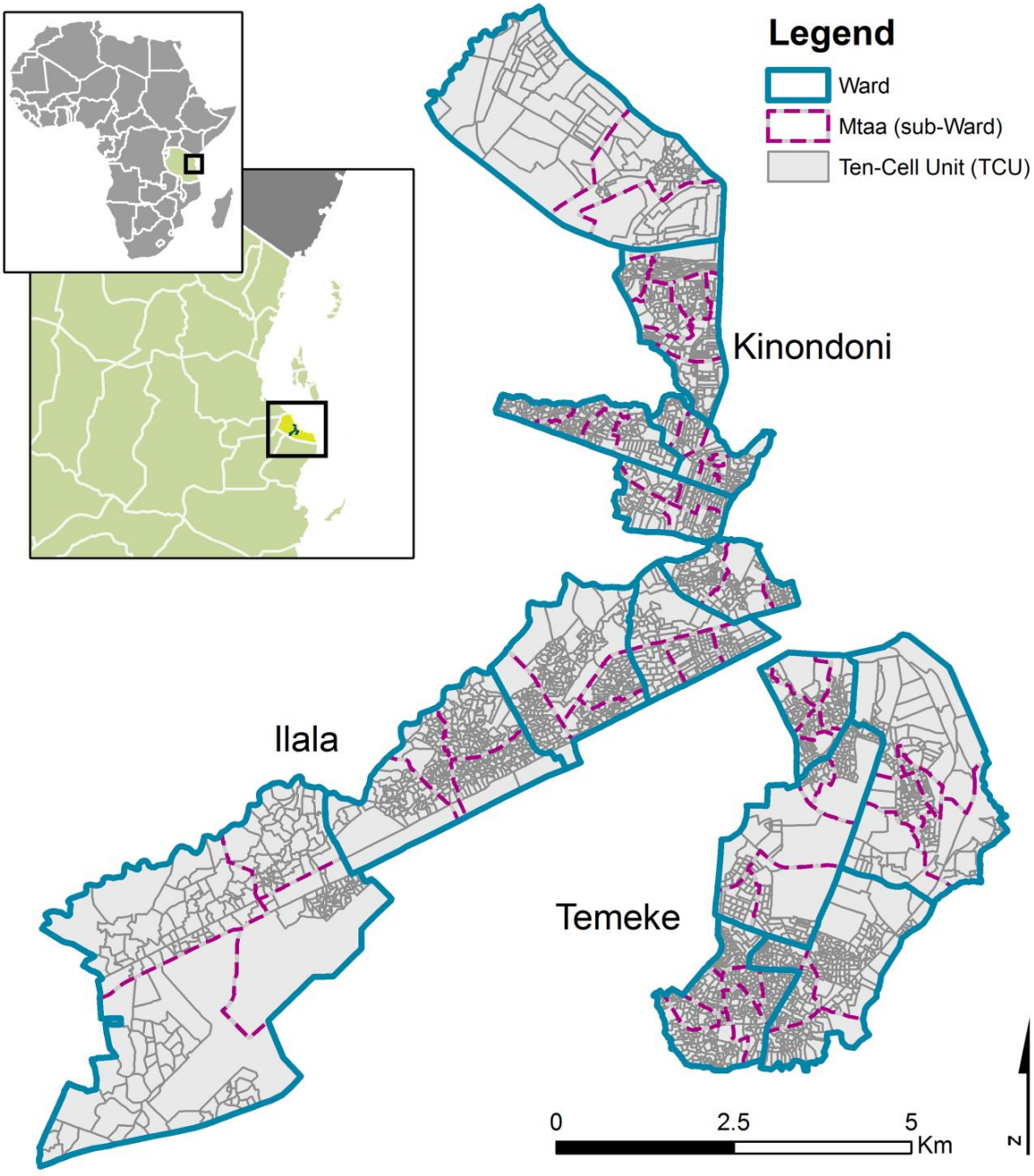

Figure 1.1: Map of the study area and administrative units.

The northern portion belongs to the municipality of Kinondoni, the south-eastern portion to Temeke, and the south-western part to Ilala.

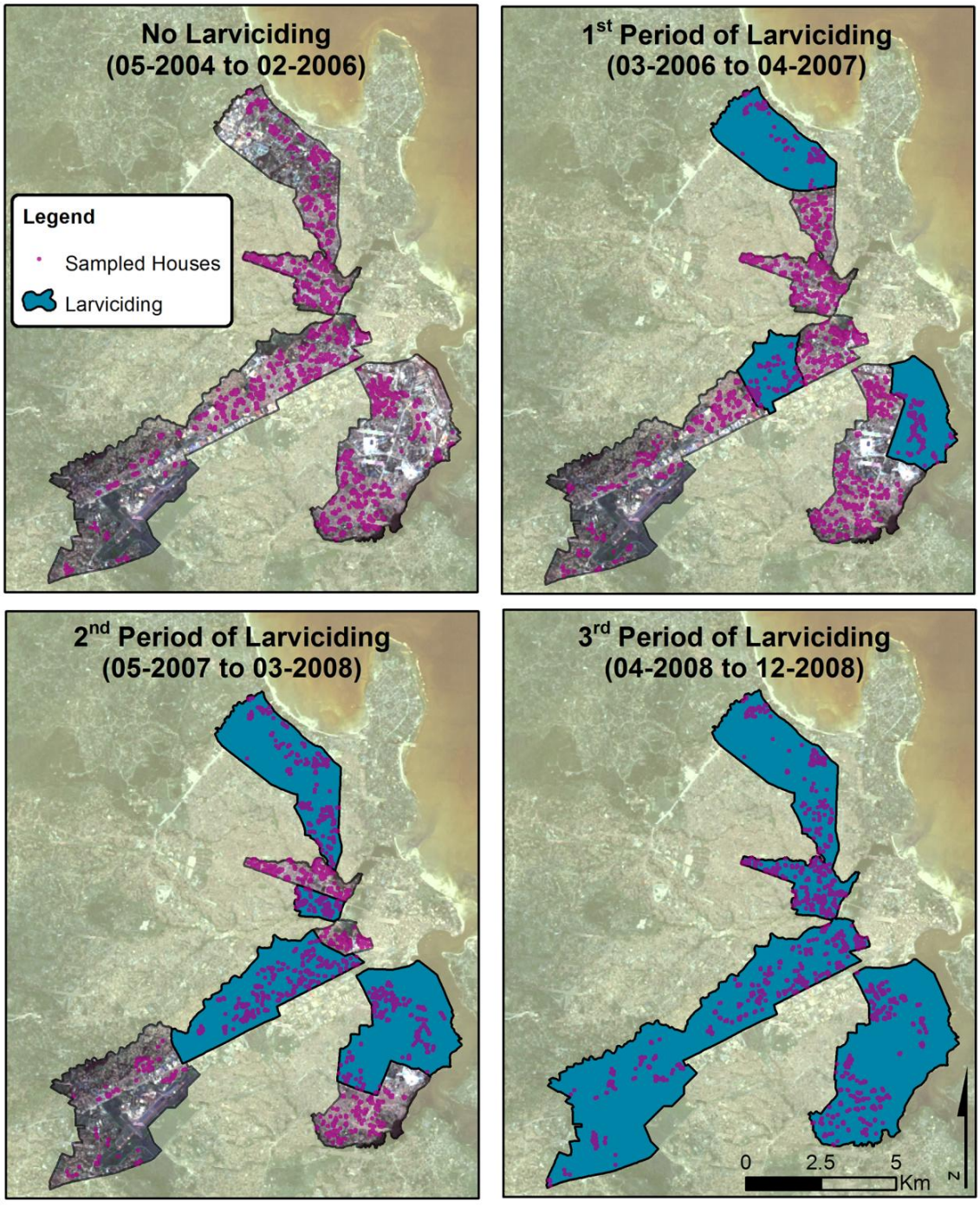

Figure 1.2: Map control and intervention wards and location of sampled households for each larviciding period.

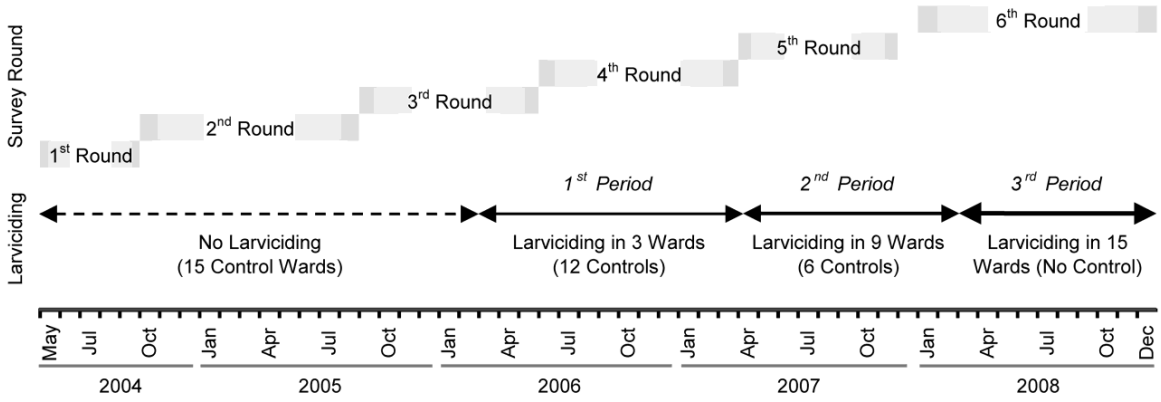

Figure1.3: Timeline of data collection activities and larviciding intervention.

The first survey round was conducted form 05/2004 to 09/2004, the second from 10/2004 to 08/2005, the third from 09/2005 to 05/2006, the fourth from 06/2006 to 03/2007, the fifth from 04/2007 to 11/2007, and the sixth and last survey round from 01/2008 to 12/2008. The first period of the intervention started on March 1st 2006, the second period of larviciding on May 1st 2007, and the last period of larviciding on April 1st 2008.

Design of the larviciding intervention

The Dar es Salaam's UMCP was launched in 2004, and targeted 15 wards, five in each of the three municipalities, totaling 67 *mitaa*. During the first phase of the project (May 2004 to February 2006), systems for extensive mapping [39,40] and surveillance of potential mosquito breeding sites were developed [36]. In 2005, routine surveillance of immature and adult mosquitoes was fully operationalized. Comprehensive larviciding of the identified breeding habitats debuted in March 2006 in three wards (Figure 1.2). The program was community-based but the UMCP remained responsible for vertical management and supervision. This entailed that responsibility for routine mosquito control and surveillance was delegated to modestly paid community members referred to as Community-Owned Resource Person (CORP) [11,12,41]. After 13 months of larviciding in these three wards, operations were extended to six additional wards: two in each municipality, totaling 9 wards covered by larviciding activities. Finally, about 12 months later, in April of 2008, the intervention was scaled-up to all 15 wards of the UMCP. The order in which wards were chosen to receive the larviciding intervention was not randomly allocated. Rather, the choice was the result of careful consideration of the following two criteria: (i) the availability of comprehensive and detailed maps of the ward, and (ii) the proven ability of the ward supervisor and CORPs to efficiently undertake the required tasks.

The biological agents *Bacillus thuringiensis* var. *israelensis* (*Bti*; VectoBac® Valent BioSciences Corporation, VBC, USA) and *Bacillus sphaericus* (*Bs*; VectoLex®, VBC, USA) were used to control the aquatic stages of anopheline mosquitoes.Each *mtaa,* or portion of a *mtaa*, was under the responsibility of a designated CORP who was instructed to treat breeding habitats on a weekly basis. The dosage was 0.04 grams per m^2 and 1 gram per m^2 for *Bti* and *Bs,* respectively. Closed habitats that mainly breed *Culex quinquefaciatus* were treated with *Bs* every

three months by a separate team of CORPs (although *Culex* mosquitoes play no role in malaria transmission, this was a programmatic decision to gain support from the community).

UMCP Data collection

During the study period, a total of six randomized cluster-sampled household surveys were carried out (Figure 1.3). A list of TCUs was assembled for each ward before March of 2004 and was regularly updated throughout the study duration. During the first round of the survey, ten TCUs were randomly sampled from each of the 15 wards. All households located in the sampled TCUs were invited to participate in the survey. From the second round onwards, the TCUs sampled in the first round were followed-up longitudinally, and another ten TCUs per ward were selected for cross-section surveys. Since loss to follow-up is non-negligible in urban areas, starting from the 3rd survey round, the list of subjects to be followed-up also included randomly selected subjects interviewed in previous cross-section surveys. This was implemented in order to guarantee that the minimum required sample size would be met. Sample size calculations used a significance level of 5% and 80% power to detect a 5% absolute difference in malaria prevalence from 10% baseline prevalence. This is equivalent to a ±50% relative risk of infection. Calculations were based on mean TCU population size [21].

Upon consenting to the interview, each household was geo-referenced using a hand-held global positioning system (GPS) device. A detailed questionnaire was administered, collecting information grouped in four modules: (i) house characteristics (e.g., location, conditions, number of habitants); (ii) head of the household (e.g., occupation, education, knowledge of malaria transmission and disease symptoms, assets, agricultural practices); (iii) use of preventive measures (e.g., bednet, mosquito repellent, coil); and (iv) individual characteristics (e.g., age and sex of all household members, occurrence of fever in the past two weeks, treatment-seeking

behavior, use of antimalarial drug, sleeping habits, travel history). A proxy for socio-economic status was constructed using an asset-based index calculated by performing Principal Component Analysis [42] of the households' possession, excluding protective assets such as bednets and window screenings. Table 1.1 describes the variables selected for this study, their type and, if appropriate, the way they were categorized.

Malaria infection status was ascertained for all household members for whom written informed consent was provided. Finger-pricked blood samples were analyzed using Giemsa-stained thick smear microscopy. Quality check was conducted on a 10% sample of blood slides at the Muhimbili University of Health and Allied Sciences – MUHAS (a center of excellence in laboratory analysis), indicating a 94.5% specificity rate and 95.7% sensitivity rate [43]. Individuals found to be infected with malaria were treated with appropriate front-line regimens (sulphadoxine-pyrimethamine until August 2006, after which it was replaced with artesunate-amodiaquine). In order to minimize selection bias and achieve full coverage for each house and TCU, up to three attempts were made to enroll subjects.

Information was collected from a total of 48,525 unique individuals and the great majority of them (39,146) were interviewed once. A total of 5,223 participants were followed up twice, 2,349 three times, 1,236 four times, 472 five times, and 99 subjects participated in every round of the survey. Including follow-up data, our sample is thus composed of 64,537 observations, which were drawn from 913 unique TCU and 6,796 households. The small number of subjects who participated in more than two rounds results from two main factors. First, the high mobility observed among urban dwellers; in the second survey round 25.6% of the subjects had moved or were travelling. Second, 13.9% of those interviewed in round 1 declined to participate in the second survey round. Reasons for refusal included pain inflicted by the finger

prick, misconceptions about malaria transmission, and the mistrust of the malaria counts provided in the precedent survey round. Sensitization efforts addressed these issues and refusal decreased in subsequent survey rounds.

Rainfall data

Rainfall estimates were obtained from the National Oceanic and Atmospheric climate prediction center. This data source combines modeling of satellite-based infrared data collected each 30-minute and station rainfall data to estimate the quantity of daily precipitation over the African continent, and has a spatial resolution of 8 kilometers [44]. Given the biology of the *Anopheles* mosquito and of the *Plasmodium* parasite, the effect of rainfall on malaria transmission is expected to be lagged in time. Previous empirical studies suggested that the effect of rainfall on malaria transmission is lagged by approximately 8 weeks [45-47]. For each observation, we therefore calculated total weekly precipitation (cm) and lagged this estimate by 8 weeks.

Statistical analyses

The main outcome for this study is malaria infection status (a binary variable – Table 1.1) as determined by the Giemsa-stained thick smear. Malaria transmission is most directly related to the density of sporozoites-infected adult anophelines, which are not targeted by the larviciding activities. Therefore, a decline in the prevalence of malaria infection is not expected to be observed until the existing pool of infected mosquitoes dies off, and the overall density of mosquitoes is reduced. Based on observations of entomological indices and malaria incidence, it has been estimated that peaks in vector density are followed by peaks in malaria incidence after approximately 1-2 months [48]. Also, the implementation of larviciding activities requires fine-tuning before CORPs became fully familiar with the routine procedures, which could further lag

any potential impacts. Based on programmatic and biological considerations, a lag of five weeks was deemed most appropriate and is consistent with results from a previous larviciding study in urban Cameroon [49].

The effects of the microbial larviciding activities on malaria occurrence were first examined using univariate statistics. Malaria prevalence was calculated for each survey round, stratifying by larviciding intervention status, if applicable. Confidence intervals for malaria prevalence were constructed using 9,999 bootstrapped replicates. Clustering of standard errors was taken into account by defining the sampling unit as the TCU [50].

Bayesian random effects logistic models where used to take into account clustering of observations at the household and TCU levels in multivariable analyses. We assumed that our binary outcome followed a Bernoulli distribution, $Y_i \sim Bernoulli(p_i)$, where p_i is the probability of an individual harboring malaria parasites, which is itself a function of covariates modeled with a *logit* link. Our model has the following form:

$$\text{logit}(p_{itjk}) = \quad + \quad (\text{Intervention}_{it}) + \quad X_{it} + f(\text{Rainfall}) + f(\text{Time}) + \quad _j + \quad _k + \quad _{itjk}$$

$$\mu_j \sim N(0, \sigma_\mu^2), \upsilon_k \sim N(0, \sigma_k^2), \text{and } \varepsilon_{itjk} \sim N(0, \sigma^2),$$

where p_{itjk} is the probability of individual i at time t living in TCU j and household k to be infected with malaria; β is the coefficient of the larviciding intervention; δ is a vector of coefficients for control variables in vector X (age, sex, sleeping outside of ward in previous weeks, taking antimalarial drug in previous two weeks, individuals treated for malaria in a previous survey round, sleeping under an ITN the night before, living in a house with a complete ceiling, and living in a house with window screens) – in the case of longitudinal observations, many of these variables are time variant; μ_j is a TCU-level random effect; υ_k is an household

random effect; and ε_{itjk} are the residuals. Rainfall was modeled using a smooth function where the spline penalty follows a second-order random walk process (where second-order increments are assumed to be independent with mean of zero and variance σ_t^2). This is appropriate when one wants to model smooth curves with small curvatures [51,52], which is likely to be the case for the relationship between malaria and rainfall. Finally, the time trend was accounted for with *f(.)* and modeled as a first order autoregressive process [53]. It was chosen over other type of process based on the Deviance Information Criterion (DIC) [54], which provides information on the model's fit while penalizing for model complexity.

Potential effect modification of the intervention by other determinants of malaria infection was also investigated for a number of covariates (e.g., age, use of ITN, house proofing, etc.). Variable selection for the final multivariable models was achieved through the consideration of a number of issues: (i) subject-matter knowledge about confounders, (ii) variable exhibiting sufficient variation, and (iii) extent of potential measurement errors.

In order to investigate the robustness of our results to modeling assumptions, we used three additional model specifications by including: (i) individual random effects, (ii) ward fixed effects, and (iii) spatially-structured random effects. We also performed a number of sensitivity analyses. Specifically, we tested for potential spillover effects of the intervention, used different lags for the larviciding intervention and for the rainfall estimates, further covariate adjustments (socio-economic status, educational level, and occupation), and varied the choice of penalty for the semi-parametric time trend (first and second-order random walk). Technical details and results are presented in the Supplemental online material (Text S1).

Models were fitted using Integrated Nested Laplace Approximations (INLA) [55]. A major advantage of INLA is that it calculates posterior marginal distributions in very short

computational time as compared to more traditional Markov Chain Monte Carlo (MCMC) approaches. Further, INLA has been shown to yield very high accuracy that is comparable to MCMC [55,56]. Non-informative priors for the regression parameters and hyperparameters were used (see Supplemental online material for details). All analyses were performed using the R statistical software [57] and estimation of the marginal posterior distribution of the parameters of interest was performed using the *INLA* library [58]. Observations with missing data for age (n=44), place slept in previous two weeks (n=52), occupation of the household head (n=134), and education level of the household head (n=136) were retained in the analysis using the missing indicator method [59].

Ethical considerations

Ethics approval was obtained from the Medical Research Coordination Committee of the National Institute for Medical Research, Ministry of Tanzania (Reference number NIMR/HQ/R.8a/Vol. IX/279 &234). Approval from Harvard School of Public Health Institutional Review Board was also obtained (Protocol # 20323-101). Written informed consent was obtained from all study participants after being provided with information regarding the goal, objectives, risk and benefits of the study. Parents or designated guardians provided signed informed consent on behalf of children under 18 years of age. These procedures were approved by the ethics committees.

RESULTS

Throughout the study period, malaria prevalence exhibited a considerable decline. Malaria prevalence was highest during the first round of data collection in 2004, with 20.8% prevalence (95% CI: 16.8-24.9%). It decreased to 16.9% (95% CI: 15.1-18.8%) in the second survey round, 10.4% (95% CI: 9.7-11.0%) in the third, 6.6% (95% CI: 6.0-7.1%) in the fourth,

4.8% (95% CI: 4.3-5.4%) in the fifth, and 1.7% (95% CI: 1.4-2.1%) in the last survey round. Stratifying malaria prevalence by survey round and larviciding intervention status, we observed that prevalence was slightly lower in the intervention wards as compared to the control ones, with the notable exception of the third survey round (Figure 1.4). Note that the start of the larviciding phases did not precisely coincide with the beginning of the survey rounds due to operational issues (as shown in Figure 1.3, phase 1 of larviciding was launched in March 2006, while the fourth survey round started in June 2006; phase 2 in May 2007; and phase 3 in April 2008). Hence, median dates of interviews in larviciding and control areas do not necessarily coincide, and seasonality in malaria transmission could confound the observed differences in prevalence shown in Figure 1.4.

For each survey round, the socio-demographic characteristics of study participants and households, stratified by larviciding intervention status, are presented in Table 1.1. Use of bednet was highly variable through time and seems to be correlated with rainfall and, probably, abundance of nuisance insects. The proportion of interviews performed during the wet seasons also differs between larviciding and control groups. Interestingly, the proportion of individuals reporting having taken anti-malarial drug in the previous two weeks remained relatively constant through time despite the overall decline in malaria prevalence. Finally, we note that socio-economic status seems to be increasing with time, as exhibited by the rising proportion of individuals in the upper quintiles. Overall, individuals in control and larviciding areas do not seem to differ dramatically in their socio-demographic characteristics. Most differences are observed in either the third or sixth survey rounds where the sample sizes in the larviciding and control groups, respectively, are notably smaller.

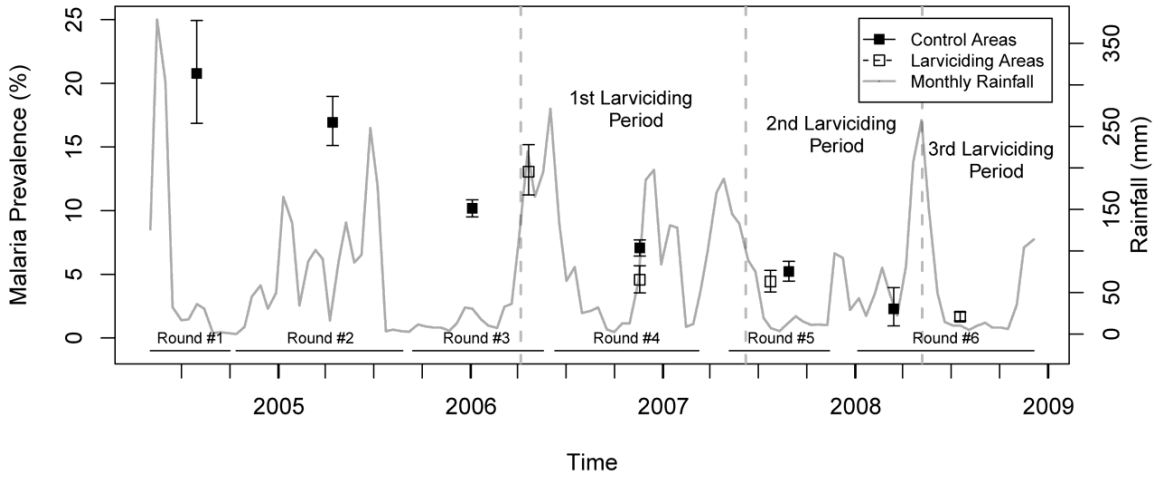

Figure 1.4: Crude prevalence of malaria infection stratified by survey round and larviciding status.

Confidence intervals are based on 9,999 bootstrap replicates and account for clustering at the ten-cell unit level. Monthly rainfall variation is also shown.

Table 1.1: Characteristics of study participants stratified by survey round and intervention group (lagged by 5 weeks).

Variables	Survey round #1	Survey round #2	Survey round #3		Survey round #4		Survey round #5		Survey round #6	
	Control	Control	Control	Larvicide	Control	Larvicide	Control	Larvicide	Control	Larvicide
OUTCOME: Prevalence of malaria infection	20.8%	16.9%	10.2%	13.1%	7.1%	4.6%	5.2%	4.4%	2.3%	1.7%
INDIVIDUAL-LEVEL VARIABLES	**n=5,809**	**n=11,149**	**n=10,791**	**n=697**	**n=9,951**	**n=2,385**	**n=6,461**	**n=5,663**	**n=744**	**n=10,887**
Age										
<5 years of age	16.0%	14.9%	15.3%	15.1%	13.5%	12.7%	12.3%	11.5%	18.4%	10.3%
5-14 years of age	27.7%	27.7%	27.2%	30.1%	28.3%	28.9%	28.0%	31.0%	26.7%	30.3%
15-29 years of age	28.5%	29.2%	28.4%	29.1%	29.0%	29.3%	28.6%	28.6%	30.4%	29.3%
30-44 years of age	15.8%	16.3%	16.8%	14.5%	17.0%	16.6%	19.2%	18.7%	14.7%	18.4%
45-49 years of age	7.1%	7.2%	7.2%	8.3%	7.3%	7.6%	7.8%	6.6%	5.2%	7.5%
≥ 60 years of age	4.9%	4.7%	5.1%	2.9%	4.8%	4.9%	4.2%	3.7%	4.6%	4.2%
Missing	0.2%	0.2%	0.1%	0%	0.1%	0%	0%	0%	0%	0%
Place slept in previous 2 weeks										
Outside the ward	2.9%	2.1%	6.2%	12.1%	8.4%	9.3%	4.7%	8.5%	29.2%	5.1%
Missing	0.1%	0.1%	0.1%	0%	0.2%	0.1%	0%	0%	0%	0.1%
Male sex	36.7%	35.0%	34.5%	35.4%	35.3%	37.0%	36.2%	38.4%	35.2%	39.0%
Slept under a bed net the night before	78.7%	88.9%	85.3%	97.6%	87.8%	78.9%	86.0%	82.2%	94.2%	91.5%
Slept under an ITN the night before	20.5%	23.4%	27.8%	23.7%	24.8%	20.5%	20.9%	20.7%	14.2%	29.3%
Use of coil the night before	4.9%	5.8%	6.6%	8.9%	7.4%	5.1%	8.6%	8.0%	2.2%	5.7%
Use of repellent the night before	0.3%	1.3%	1.6%	4.9%	5.0%	3.4%	3.0%	3.0%	0.5%	3.3%
Use of spray the night before	8.4%	10.5%	15.8%	16.8%	21.0%	18.2%	30.8%	30.6%	6.6%	29.2%
Took malaria drug in previous 2 weeks	7.4%	3.7%	5.4%	3.0%	8.2%	3.9%	4.9%	6.9%	6.3%	2.0%
Interviewed during wet season	10.7%	49.7%	56.2%	100.0%	27.4%	37.5%	64.2%	12.8%	99.5%	46.5%
Follow-up observation	0%	17.0%	26.5%	24.1%	31.2%	32.1%	35.2%	32.8%	17.2%	27.2%

Table 1.1 (Continued): Characteristics of study participants stratified by survey round and intervention group (lagged by 5 weeks).

Variables	Survey round #1	Survey round #2	Survey round #3		Survey round #4		Survey round #5		Survey round #6	
	Control	Control	Control	Larvicide	Control	Larvicide	Control	Larvicide	Control	Larvicide
OUTCOME: Prevalence of malaria infection	20.8%	16.9%	10.2%	13.1%	7.1%	4.6%	5.2%	4.4%	2.3%	1.7%
HOUSEHOLD-LEVEL COVARIATES	**N=1,240**	**N=2,107**	**N=2,038**	**N=124**	**N=1,824**	**N=396**	**N=1,046**	**N=827**	**N=103**	**N=1,549**
Occupation of household head/designated										
Business / Government / Formal sector	63.1%	58.2%	59.8%	67.7%	67.0%	64.4%	60.7%	68.0%	37.9%	76.7%
Farmer / Fisherman	3.3%	1.6%	2.1%	0.0%	0.9%	2.0%	1.4%	0.7%	0%	0.8%
Informal sector	16.9%	17.8%	21.1%	22.6%	19.7%	16.7%	22.8%	17.9%	53.4%	12.5%
Retired / No job / Domestic	15.2%	20.5%	16.3%	9.7%	11.3%	15.2%	13.3%	12.9%	7.8%	9.0%
Missing	1.5%	1.9%	0.8%	0%	1.0%	0.8%	1.7%	0.5%	1.0%	1.0%
Socio-Economic Status										
Lowest quintile	32.0%	32.3%	29.7%	12.9%	20.4%	24.0%	7.3%	7.3%	3.9%	8.4%
Second quintile	29.4%	28.7%	26.2%	20.2%	23.6%	15.4%	20.9%	16.3%	11.7%	15.0%
Third quintile	13.6%	12.1%	16.0%	20.2%	19.9%	18.9%	14.1%	15.7%	57.3%	18.1%
Fourth quintile	12.1%	11.2%	12.5%	21.8%	19.7%	19.9%	29.2%	30.7%	23.3%	29.1%
Highest quintile	12.9%	15.7%	15.5%	25.0%	16.3%	21.7%	28.5%	30.0%	3.9%	29.4%
Education of Household Head/Designated										
Illiterate	6.0%	4.5%	9.4%	0.8%	6.4%	5.3%	2.6%	2.7%	13.6%	1.6%
Primary	64.4%	60.6%	51.0%	50.0%	46.2%	48.0%	35.9%	30.8%	48.5%	35.6%
Secondary	26.9%	28.2%	33.3%	37.9%	42.0%	39.6%	57.4%	60.2%	37.9%	59.3%
Tertiary	1.7%	3.6%	4.9%	11.3%	4.5%	5.8%	3.4%	5.4%	0%	2.9%
Other	0.2%	0.2%	0.4%	0%	0.1%	0.5%	0%	0%	0%	0.1%
Missing	1.0%	2.9%	1.0%	0%	0.9%	0.8%	0.7%	0.8%	0%	0.6%
Know how malaria is transmitted	68.7%	62.4%	78.4%	83.9%	82.9%	84.3%	90.2%	90.1%	81.6%	88.6%
House has window screening	22.0%	19.7%	29.5%	37.9%	23.7%	48.0%	21.5%	28.3%	31.1%	39.1%
House has complete ceiling	27.6%	24.8%	24.1%	35.5%	29.4%	36.4%	42.4%	46.8%	14.6%	33.2%
Own house	51.9%	63.1%	72.4%	66.1%	76.4%	80.3%	81.2%	80.2%	85.4%	85.7%
Household cultivates crops	19.4%	11.0%	10.3%	12.1%	8.7%	11.4%	5.8%	6.8%	13.6%	5.6%

Table 1.2: Univariate and multivariate effect size estimates of the larviciding intervention on malaria prevalence in Dar es Salaam, 2004-2008 (N=64,537).

	Univariate		Multivariable	
	OR*	**95% CrI†**	**OR***	**95% CrI†**
LARVICIDING INTERVENTION	**0.79**	**0.66-0.93**	**0.79**	**0.66-0.93**
Age				
Under five years of age	-	-	1.00	-
≥5 and <15 years of age	-	-	**0.82**	**(0.76-0.90)**
≥15 and <30 years of age	-	-	**0.67**	**(0.61-0.73)**
≥30 and <45 years of age	-	-	**0.60**	**(0.54-0.66)**
≥45 and <60 years of age	-	-	**0.55**	**(0.48-0.63)**
≥60 years of age	-	-	**0.47**	**(0.40-0.56)**
Male sex	-	-	**1.08**	**(1.01-1.15)**
Slept outside ward (previous 2 weeks)	-	-	0.90	(0.77-1.04)
Treated for malaria (previous round)	-	-	**0.65**	**(0.56-0.75)**
Took malaria drug (previous 2 weeks)	-	-	1.02	(0.90-1.16)
ITN used the night before	-	-	**0.93**	**(0.86-0.99)**
House has closed ceiling	-	-	0.93	(0.85-1.01)
House has window screens	-	-	**0.90**	**(0.83-0.98)**
Trend for time (AR1§)		Yes		Yes
Semi-parametric smooth for rainfall		Yes		Yes
Random effects (TCU & Household)		Yes		Yes

Statistically significant results are bolded.
*OR = Odds Ratio
†CrI = Credible Intervals
§AR1 = First Order Autoregressive Process

Table 1.3: Effect modification of the larviciding intervention by selected determinants of malaria prevalence in Dar es Salaam, 2004-2008 (N=64,537).

Effect modification of the larviciding interventionby selected determinants of malaria infection (Odds Ratio and 95% Credible Intervals)*			
	Control	Larviciding	Effect of Larviciding Within Strata
Wet Season	1.00	1.06 (0.84-1.33)	1.06 (0.84-1.33)
Dry Season §	0.97 (0.69-1.10)	**0.57 (0.41-0.77)**	**0.60 (0.47-0.75)**
	Control	Larviciding	Effect of Larviciding Within Strata
No Screen	1.00	0.84 (0.70-1.02)	0.84 (0.70-1.02)
Window Screens	0.93 (0.85-1.02)	**0.80 (0.65-0.99)**	**0.68 (0.54-0.85)**
	Control	Larviciding	Effect of Larviciding Within Strata
Open Ceiling	1.00	0.84 (0.70-1.01)	0.84 (0.70-1.01)
Complete Ceiling	0.97 (0.88-1.06)	**0.78 (0.63-0.97)**	**0.66 (0.53-0.83)**
	Control	Larviciding	Effect of Larviciding Within Strata
No ITN	1.00	**0.83 (0.69-0.99)**	**0.83 (0.69-0.99)**
ITN used	0.96 (0.88-1.04)	**0.77 (0.61-0.96)**	**0.63 (0.48-0.82)**
	Control	Larviciding	Effect of Larviciding Within Strata
Aged ≥5 years	1.00	**0.83 (0.69-0.99)**	**0.83 (0.69-0.99)**
<5 years of age	1.35 (1.23-1.47)	**0.73 (0.56-0.94)**	**0.61 (0.46-0.80)**

Statistically significant results are bolded.
All models are adjusted for age, sex, sleeping outside of the ward (previous 2 weeks), being treated for malaria in a previous round, use of malaria drugs (previous 2 weeks), use of ITN, complete ceiling, window screen, precipitation, time trend. Random effects at household and TCU levels are also included.
§ Dry season is defined as the months of January, February, and June through September

Taking into account the previously stated limitations of our univariate analysis, we present in Table 1.2 the results from the random effects logistic regression models that account for clustering of observations within household and TCU. These analyses suggest a significant protective effect of larviciding, with a point estimate for the odds ratio of 0.79 (95% Credible Intervals (CrI): 0.66-0.93) in both univariate and multivariable analyses. When considering potential effect modification of the larviciding intervention by season, we see that larviciding activities achieved maximum programmatic impact during the dry season (Table 1.3) with an odds ratio of 0.60 (95% CrI: 0.47-0.75). The dry season is defined as the months of January, February, and June through September. The effect of the larviciding intervention also had synergistic effects with other malaria protective measures such as houses with window screens (OR=0.68; 95% CrI: 0.54-0.85), houses with complete ceiling (OR=0.66; 95% CrI: 0.53-0.83), and using an ITN the night before (OR=0.63; 95% CrI: 0.48-0.82). Finally, the effect of the intervention was also heterogeneous among age groups with the larviciding intervention exhibiting a greater protective effect for children under five (OR=0.61; 95% CrI: 0.46-0.80).

Model specifications seem to have little bearing on the estimates of the posterior marginal for the larviciding intervention (see Tables 1.S1 and 1.S2 in the Supplemental online material). Importantly, including fixed effects at the ward level, which would control for any time-invariant measured or unmeasured confounders of the larviciding-malaria relationship, had little impact on the point estimate of the larviciding intervention (adjusted OR=0.80; 95% CrI:0.66-0.97).

Finally, our sensitivity analyses (see Table 1.S3 and 1.S4 in the Supplemental online material) demonstrated that spillover effects were not biasing our effect size estimate towards the null. As expected, effect size estimates were somewhat sensitive to variation in the assumed lag

length between initiation of larviciding activities and malaria transmission but the effect remained statistically significant over lag lengths varying between 28 and 60 days. Results were also robust to changes in other model parameters.

DISCUSSION

This study has shown that a community-based larviciding program, centrally managed by the UMCP, provided significant protection to individuals living in areas covered by the larviciding operations. The strength of association was robust to model specifications and consistently approximated a 21% reduction in the odds of malaria infection. Further, the larviciding intervention achieved maximum effectiveness during the dry season and had synergistic effects with other protective measures such as use of ITN, houses with windows screens, and houses with complete ceilings. In addition, we found no evidence of spillover effects between intervention and control areas.

Our estimated effect size for the larviciding intervention is much lower, but not statistically different, than the one previously reported for the first larviciding period of the UMCP, where the odds ratio of living in areas treated with larvicides and being infected with malaria was estimated to be 0.28 (95% CI: 0.10-0.80) as compared to individuals living in control areas [21]. This can be explained in part by the fact that our study considered all age ranges, while Geissbühler et al [21] restricted their analysis to children under five years of age. While there is no reason to believe that larviciding should be more protective for children than for adults, since the intervention acts at the population level by reducing vector density, children might be more likely to spend evenings and nights at or close to their home, a period of the day when most of malaria transmission occurs. There is thus less potential misclassification of exposure for this age group as compared to adults, who might visit friends or spend time during

evenings near high exposure areas not covered by larviciding activities. Indeed, we found that the product term between the larviciding intervention and age was statistically significant. The estimated odds ratio for the larviciding intervention was of 0.61 (95% CrI: 0.46-0.80) for children under five years of age which is closer to the one reported by Geissbühler et al [21] but insufficient to explain this differential. Another reason which could explain this difference in impact is that our analysis covered all three phases of the intervention with a total of 33 months of larviciding activities, while Geissbühler et al [21] analyzed only the first phase, when the intervention was operational in only three wards for 12 months. Analyses over a longer period may be impacted by programmatic fatigue, coupled with the potential impact that other unmeasured and/or unknown interventions could have on the prevalence of malaria infection and overall transmission dynamics (e.g., artemisin-based combination therapy – ACT started to be the first line of treatment in 2007).

Larviciding during the dry season was shown to be more effective at lowering the prevalence of malaria infection than during the rainy season (when the stratified effect was not significant). This result is especially interesting since 49% of malaria cases were sampled during the dry season. Since larval habitats are less numerous and easier to access when rainfall is low, larviciding activities could have been more effective at suppressing larval production due to operational issues. This highlights one of the key aspects of successful larviciding programs: the ability to locate and access all potential breeding habitats in the targeted area. Also, larviciding should not be deployed alone, but in conjunction with other appropriate vector control activities [60]. The fact that we have estimated larviciding to be more effective than ITNs in Dar es Salaam should not be taken at face value, since the effect size estimate for ITNs does not take into account potential community effects that extend to non-users [61,62], and that the use of

ITNs and other protective measures is likely a function of perceived risk by household members. The combination of different vector control strategies is also supported by our findings of significant synergistic effects between larviciding and use of ITNs, window screens, and houses with a complete ceiling.

With renewed impetus for the long-term goal of malaria eradication [63], the need for tailored programs is imperative, including vector control [30]. Vector control programs should not be established as stand-alone entities. Rather, intersectoral collaboration, health system strengthening, and community mobilization are instrumental to vector control program success. Integrated Vector Management (IVM), as endorsed by WHO [31,64], emphasizes rational decision making processes to efficiently use resources and attain health-based targets [65]. IVM specifically acknowledges that a 'one size fits all' strategy for malaria control will be ineffective. Larviciding should be considered as part of an IVM approach in other urban areas of sub-Saharan Africa, if the local malaria ecology warrants its use. Our study provides a number of important lessons regarding the implementation of larval control: (i) breeding habitats can, and should, be mapped at high resolution using low-cost technology [36], (ii) locally relevant entomological information should be collected to inform operational activities, (iii) monitoring and evaluation systems should be implemented to ensure effective and appropriate delivery and fine-tuning of interventions, and (iv) community involvement and sensitization can be beneficial to programmatic activities. Other strategies included in an IVM approach could facilitate the use of larviciding. For example, in Dar es Salaam 33% of *Anopheles* breeding habitats are found in clogged drains [66]. In this context, the use of environmental management to restore the functionality of drains would result in fewer breeding habitats [43], and therefore reduce the area to be covered with larviciding.

Strengths of this study include its large sample size, longitudinal design, large temporal and spatial extent of larviciding activities that limited potential spillover effects, and availability of reliable baseline information. This study also has some limitations. First, the wards targeted by the UMCP were not randomly allocated to the larviciding intervention. This entails that our effect size estimates for the larviciding intervention could be biased by residual confounding. This is unlikely to be the case as including fixed effects at the ward level, which would control for such time-invariant non-measured confounders, did not impact our results. Second, ACTs were effectively introduced in Dar es Salaam in January 2007. With its gametocidal proprieties, this drug, if used on a large scale, has the potential to significantly reduce the reservoir of malaria in the general population. Although attempts were made at collecting information on ACT use from health facility data, we were not able to assemble reliable temporal information for the targeted 15 wards. Thus, some of the secular decline in the prevalence of malaria infection observed in control areas before the introduction of larviciding may be a result of ACT use (and possibly of other unobserved activities that could potentially impact the risk of malaria transmission).

Our results have important implications for malaria control in sub-Saharan Africa. Specifically, we have provided evidence that a community-based application of microbial larvicides was effective in reducing malaria transmission in urban Dar es Salaam. Microbial larvicides have been shown to be environmentally safe, specific in their action, and highly effective in killing *Anopheles* larvae under field conditions [67-69]. With important projected increases in urban population in sub-Saharan Africa, mosquitoes' behavioral adaptation to current control strategies, and the already recorded emergence of resistance to pyrethroid

insecticides, larval source management, and larviciding in particular, should be given careful consideration by managers of malaria control programs.

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SUPPLEMENTARY APPENDIX 1.1:

IMPACT OF COMMUNITY-BASED LARVICIDING ON THE PREVALENCE OF MALARIA INFECTION IN DAR ES SALAAM, TANZANIA

Mathieu Maheu-Giroux & Marcia C. Castro

INTRODUCTION

In order to assess the robustness of our results three additional model specifications were used and a number of sensitivity analyses were performed. This supplemental material is organized in four sections. First we describe three additional model specifications used for obtaining effect size estimates for the larviciding intervention. Second we present the parameters for which we performed the sensitivity analyses. Third, the different prior distributions for the models' parameters and hyperparameters are defined. Lastly, results from the different models and analyses are briefly discussed.

METHODS

Allowing for different model specifications

As some individuals were followed-up longitudinally in time, we first included a random effect at the individual level as an additional model specification. Further, because the order of the roll-out of the larviciding intervention was not randomized, we cannot eliminate the possibility that ward characteristics are correlated with the intervention. We thus used a second model specification that includes ward fixed effects. Finally, observations may also be spatially dependent given the focal nature of urban malaria. Spatially-structured random effects were hence included in the third model specification to allow for such spatial autocorrelation. Again, we assumed that the binary outcome followed a Bernoulli distribution, $Y_i \sim Bernoulli(p_i)$, where

p_i is the probability of an individual harboring malaria parasites, which is itself a function of covariates modeled with a *logit* link. The three additional models have the following form:

Model (1): TCU, household, and individual levels random effects model

$$\text{logit}(p_{itjk}) = \alpha + \beta(\text{Intervention}_{\text{it}}) + \delta X_{it} + f(\text{Rainfall}) + f(\text{Time}) + \mu_{\text{j}} + \upsilon_k + m_i + \varepsilon_{itjk}$$

$$\mu_j \sim N(0,\sigma_\mu^2), \upsilon_{\text{k}} \sim N(0,\sigma_k^2), m_i \sim N(0,\sigma_i^2), \text{and } \varepsilon_{\text{itjk}} \sim N(0,\sigma^2),$$

where p_{itjk} is the probability of individual i at time t living in TCU j and household k to be infected with malaria; m_i is an individual-level random effect; $\beta$is the coefficient of the larviciding intervention; δ is a vector of coefficients for control variables in vector X; μ_j is a TCU-level random effect; υ_k is an household random effect; and ε_{itjk} are the residuals. Rainfall was modeled using a smooth function where the spline penalty follows a second-order random walk process (where second-order increments are assumed to be independent with mean of zero and variance σ_t^2). Finally, the time trend was accounted for with *f(.)*and modeled as a first order autoregressive process [1]. Individual-level random effects were included to account for subjects followed-up in two or more surveys.

Model (2): Household and TCU random effects with ward fixed effects

$$\text{logit}(p_{itjk}) = \alpha + \beta(\text{Intervention}_{\text{it}}) + \delta X_{it} + f(\text{Rainfall}) + f(\text{Time}) + \omega\ \text{Ward}_{it} + \mu_{\text{j}} + \upsilon_k + \varepsilon_{itjk},$$

$$\mu_j \sim N(0,\sigma_\mu^2), \upsilon_{\text{k}} \sim N(0,\sigma_k^2), \text{and } \varepsilon_{\text{itjk}} \sim N(0,\sigma^2),$$

where p_{itjk} is the probability of individual i at time t living in TCU j and household k to be infected with malaria; ω is a vector of coefficients for the ward fixed effects; and β, δ, *f(.)*, μ_j, υ_k, and ε_{itjk} are similar to those described in Model (1).

Model (3): Household-level and spatial random effects model

For the spatial random effects model, the high number of observations and computing limitations made model fitting problematic. To reduce the dimensionality of the data,

observations were grouped at the household level and a binomial distribution was assumed, $Y_k \sim Binomial(p_k, n_k,)$, where Y_k is the number of malaria cases in household k, $n_k$is the number of individuals in household k, and p_k is the probability being infected with malaria for individuals living in household k. Specifying the model using this binomial logistic regression framework greatly reduced computing time. The trade-off was that we are no longer able to control for individual-level covariates although the effect size estimate for the larviciding intervention can still be interpreted at the individual level. The model was defined as:

$$\text{logit}(p_{kt}) = \alpha + \beta(\text{Intervention}_{kt}) + \delta X_{it} + f(\text{Rainfall}) + f(\text{Time}) + \upsilon_k + \rho_k + \varepsilon_{tk}$$

$$\upsilon_k \sim N(0, \sigma_k^2), \quad \rho_k \left| \rho_{k \neq s} \sim N\left(\frac{\sum_{k \neq s} w_{ks}\rho_k}{\sum_{k \neq s} w_{ks}}, \frac{\sigma_r^2}{\sum_{k \neq s} w_{ks}}\right), \text{ and } \varepsilon_{tk} \sim N(0, \sigma^2)\right.,$$

where p_{kt} is the probability of being infected with malaria for individual living in household k at time t;υ_k is a household random effect; w_{ks} is a binary spatial weight matrix; and ρ_k is a spatial random effect that follows a Gaussian Conditional Autoregressive (CAR) distribution, as proposed by Besag [2]. CAR models have the advantage of providing good approximations of continuous geostatistical processes and are more statistically efficient than geostatistical models [3,4]. CAR models belong to the family of spatial error models, which aim at uncovering causal relationships and assume that spatial dependence occurs because of omitted and spatially correlated variables [1]. In the present case, such omitted variables could be related to mosquito dispersion and behavior, unmeasured human behaviors, unreported programmatic challenges, undocumented local environmental characteristics/changes, or other isolated efforts to control malaria unknown to the UMCP. The neighborhood for the spatial weight matrix is defined based on the distance beyond which residuals are not spatially correlated. Based on visual inspection of Model's (1) residuals and considerations of anophelines dispersion in urban environments, a

distance threshold of 200 meters was deemed most appropriate. Indeed, previous studies have shown that malaria transmission in urban environment is highly focal and that adult anophelines do not disperse more than 200-300 meters from larval habitats in urban settings [5-8]. Further, a study conducted in urban Ouagadougou (Burkina Faso) indicated that *P. falciparum* infections were clustered within 200 meters of larval habitats [9].

Sensitivity analyses

To assess if potential spillover effects were biasing our effect size estimates, two binary variables were created: (i) being in a control ward and within 100 meters of an intervention ward (spillover from intervention to control wards), and (ii) being in an intervention ward and within 100 meters of a control ward (spillover from control to intervention areas). Given the focal transmission of malaria in urban settings and the overall distribution of TCU sizes, a distance threshold of 100 meters in both directions was felt most appropriate. These binary variables were included as covariates along with the larviciding intervention in the regression model.

Further sensitivity analyses were performed by investigating the effect of using different lags for the intervention (28 days, 35 days, 45 days, and 60 days), the influence of the model's choice to account for the time trend (first-order autoregressive, first-order random walk, and second-order random walk), and the impact of different lags for rainfall (7 weeks, 8 weeks, and 9 weeks) on the effect size estimate for the larviciding intervention. Additionally, we present the effect size estimates for the larviciding intervention using further adjustments with the following covariates: quintiles of socio-economic status, occupation of the household head, and education level of the household head.

Prior specifications

All priors for the regression parameters were assumed to have non-informative Gaussian distributions with mean of zero and precision of 0.001 (precision=1/variance). Priors for the precision hyperparameters of the random effects at the individual, household and TCU level and spatially structured random effect were defined on the logarithmic scale and assumed to follow non-informative logGamma (shape = 0.001, scale = 0.001) distributions. The log-precision of the rainfall and time semi-parametric smooth were given logGamma(shape = 1, scale = 1e-5) priors as proposed by Natário and Knorr-Held [10]. The first lag correlation parameter of the first order autoregressive process is defined on the logit scale and was given a Gaussian (mean = 0, precision = 0.4) prior for the first lag correlation parameter (which was defined on the logit scale).

Estimation of the marginal posterior distribution of the parameters of interest was performed using*Integrated Nested Laplace Approximations*[11] and the *INLA* library [12] in R was used for model fitting. Observations with missing data forage (n=44), place slept in previous two weeks (n=52), occupation of the household head (n=134), and education level of the household head (n=136) were retained in the analysis using the missingindicator method[13].

RESULTS AND DISCUSSION

Model's specifications seem to have little bearing on the estimates of the posterior marginal for the larviciding intervention (Table 1.S1). Including a random effect at the individual level had no effect on marginal posterior for the larviciding intervention (Odds Ratio (OR)=0.78; 95% Credible Interval (CrI): 0.66-0.93). Importantly, including fixed effects at the ward level, which would control for any time-invariant measured or unmeasured confounders of the larviciding-malaria relationship, had little impact on the point estimate of the larviciding

intervention (OR=0.81; 95% CrI: 0.67-0.97). The credible interval was somewhat larger, however. This can be explained by the fact that fixed effects disregard the between wards variation in exposure and is thus less statistically efficient than the other models. Finally, allowing for spatially structured random effects did not impact the effect size estimate for the larviciding intervention.

Adjusting these three models for potential confounders of the larviciding-malaria relationship has shown that our effect size estimate was robust to such adjustments (Table 1.S2). Odds ratio for the larviciding intervention ranged from 0.79 (95% CrI: 0.66-0.94) to 0.80 (95% CrI: 0.66-0.97).

Potential spillover effects from either control to larviciding areas or larviciding to control areas would bias our effect size estimates towards the null. After including indicator variables for being within a 100 meters buffer zone in both directions (i.e., control to intervention and intervention to control), we found no evidence of spillover effects as the odds ratio for the larviciding intervention remained virtually unchanged (Table 1.S3).

As expected, our results were somewhat sensitive to the assumed lag length between initiation of larviciding activities and its effect on malaria transmission (Table 1.S4). Nevertheless, the estimated effect size measures were always protective and their credible intervals did not cross the null. Results were much less sensitive to the choice of modeling process for the time trend. The effect of the choice of lag for rainfall had virtually no effect on the effect size estimate of the larviciding intervention. Finally, adding either socio-economic status, occupation of the household head, or education level of the household head did not change the odds ratio for the larviciding intervention.

Table 1.S1: Unadjusted effect size estimates of the larviciding intervention on malaria prevalence in Dar es Salaam, 2004-2008 (N=64,537).

	Model (1)		Model (2)		Model (3)	
	OR*	**95% CrI†**	**OR***	**95% CrI†**	**OR***	**95% CrI†**
LARVICIDING INTERVENTION	**0.78**	**(0.66-0.93)**	**0.81**	**(0.67-0.97)**	**0.78**	**(0.66-0.91)**
Trend for time (AR1§)	Yes		Yes		Yes	
Random effects						
TCU & household	Yes		Yes		-	
Individual	Yes		-		-	
Household & spatial	-		-		Yes	
Fixed effects at ward level	-		Yes		-	

Statistically significant results are bolded
*OR = Odds Ratio
†CrI = Credible Intervals
§AR1 = First Order Autoregressive Process

Table 1.S2: Adjusted effect size estimates of the larviciding intervention on malaria prevalence in Dar es Salaam, 2004-2008 (N=64,537).

	Model (1)		Model (2)		Model (3)	
	OR*	**95% CrI†**	**OR***	**95% CrI†**	**OR***	**95% CrI†**
LARVICIDING INTERVENTION	**0.79**	**(0.66-0.94)**	**0.80**	**(0.66-0.97)**	**0.79**	**(0.67-0.93)**
Age						
Under five years of age	1.00	-	1.00	-	-	-
≥5 and <15 years of age	**0.82**	**(0.76-0.90)**	**0.83**	**(0.76-0.90)**	-	-
≥15 and <30 years of age	**0.67**	**(0.61-0.73)**	**0.67**	**(0.62-0.74)**	-	-
≥30 and <45 years of age	**0.60**	**(0.54-0.66)**	**0.60**	**(0.54-0.67)**	-	-
≥45 and <60 years of age	**0.55**	**(0.48-0.63)**	**0.55**	**(0.48-0.63)**	-	-
≥60 years of age	**0.47**	**(0.39-0.56)**	**0.47**	**(0.40-0.56)**	-	-
Male sex	**1.08**	**(1.01-1.15)**	**1.08**	**(1.02-1.15)**	-	-
Slept outside ward (previous 2 weeks)	0.90	(0.77-1.04)	0.88	(0.76-1.02)	-	-
Treated for malaria (previous round)	**0.65**	**(0.56-0.75)**	**0.65**	**(0.56-0.75)**	-	-
Took malaria drug (previous 2 weeks)	1.02	(0.89-1.16)	1.01	(0.89-1.15)	-	-
ITN used the night before	**0.93**	**(0.86-0.99)**	**0.92**	**(0.86-0.99)**	-	-
House has closed ceiling	0.93	(0.85-1.01)	0.94	(0.87-1.03)	**0.89**	**(0.81-0.96)**
House has window screens	**0.90**	**(0.82-0.98)**	**0.90**	**(0.82-0.98)**	**0.89**	**(0.81-0.97)**
Trend for time (AR1§)	Yes		Yes		Yes	
Semi-parametric smooth for rainfall	Yes		Yes		Yes	
Random effects						
TCU & household	Yes		Yes		-	
Individual	Yes		-		-	
Household & spatial	-		-		Yes	
Fixed effects at ward level	-		Yes		-	

Statistically significant results are bolded
*OR = Odds Ratio
†CrI = Credible Intervals
§AR1 = First Order Autoregressive Process

Table 1.S3: Investigation of potential spillover effects from larviciding to control areas and from control to larviciding areas in Dar es Salaam, 2004-2008 (N=64,537).

Variables§	OR*	95% CrI†
Larviciding intervention	**0.77**	**(0.65-0.92)**
Spillover from control to larviciding areas (100 m buffer)	1.10	(0.82-1.47)
Spillover from larviciding to control areas (100 m buffer)	0.71	(0.33-1.44)

Statistically significant results are bolded
*OR = Odds Ratio
†CrI = Credible Intervals
§ All models are adjusted for age, sex, sleeping outside of the ward (previous 2 weeks), being treated for malaria in a previous round, use of malaria drugs (previous 2 weeks), use of ITN, complete ceiling, window screen, precipitation, and time trend. Random effects at household and TCU levels are also included.

Table 1.S4: Sensitivity analyses of modeling assumptions and their impacts on the effect size estimate of the larviciding intervention.

Parameters§	Larviciding Intervention	
	OR*	95% CrI†
LAG FOR THE LARVICIDING INTERVENTION		
28 days lag	**0.81**	**(0.68-0.97)**
35 days lag	**0.79**	**(0.66-0.93)**
45 days lag	**0.81**	**(0.69-0.96)**
60 days lag	**0.84**	**(0.70-0.99)**
MODELING PROCESS FOR TIME TREND		
1st order autoregressive	**0.79**	**(0.66-0.93)**
1st order random walk	**0.79**	**(0.67-0.94)**
2nd order random walk	**0.81**	**(0.69-0.96)**
LAG FOR THE WEEKLY RAINFALL ESTIMATES		
7 weeks lag	**0.79**	**(0.66-0.94)**
8 weeks lag	**0.78**	**(0.66-0.93)**
9 weeks lag	**0.79**	**(0.67-0.94)**
7, 8, and 9 weeks lags	**0.78**	**(0.66-0.93)**
ADDING DIFFERENT COVARIATES		
Quintiles of socio-economic status (asset-based)	**0.79**	**(0.66-0.94)**
Occupation of household head	**0.79**	**(0.66-0.93)**
Education level of household head	**0.78**	**(0.66-0.93)**

Statistically significant results are bolded
§ All models are adjusted for age, sex, sleeping outside of the ward (previous 2 weeks), being treated for malaria in a previous round, use of malaria drugs (previous 2 weeks), use of ITN, complete ceiling, window screen, precipitation, and time trend. Random effects at household and TCU levels are also included.
*OR = Odds Ratio
†CrI = Credible Intervals

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PAPER #2: COST-EFFECTIVENESS OF LARVICIDING FOR URBAN MALARIA CONTROL IN TANZANIA

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ABSTRACT

Background

Larviciding for malaria control can contribute to an Integrated Vector Management (IVM) approach. This intervention is currently supported in settings where breeding habitats are 'few, fixed, and findable', such as urban areas of sub-Saharan Africa, but the knowledge base regarding the cost-effectiveness of larviciding is non-existent.

Methods

Program costs and effectiveness data were collected from the Dar es Salaam Urban Malaria Control Programme in Tanzania. Cost-effectiveness ratios (CER) were estimated from the provider and societal perspectives for standard indicators using different malaria transmission scenarios.

Results

CER for microbial larviciding were highly dependent on the assumed baseline malaria incidence rates. Using the societal perspective, net CER were estimated (in 2012 US dollars) at $43 (95% uncertainty intervals [UI]: $15-181) per disability-adjusted life year averted (DALY) when

malaria incidence was 902 infections per 1,000 individuals, increasing to $545 (95% UI: $337-1,558) per DALY at an incidence of 122 per 1,000. Larviciding was shown to be cost-effective in Tanzania for incidences as low as 40 infections per 1,000 people per year.

Conclusion

This is believed to be the first study to estimate the cost-effectiveness of larviciding for urban malaria control in sub-Saharan Africa. The results support the use of larviciding as a cost-effective intervention in urban areas and managers of national malaria control programme should consider this intervention as part of an IVM approach.

BACKGROUND

Integrated Vector Management (IVM), as endorsed by the World Health Organization (WHO) [1], emphasizes rational decision-making, intersectoral collaboration, and the combination of different tools for vector control. Strategies included in an IVM approach should be based on local eco-epidemiological conditions with the aim of improving '*the efficacy, cost effectiveness, ecological soundness and sustainability of interventions'*[2]. Currently, insecticide-treated nets (ITNs) and indoor residual spraying (IRS) are among the most widely used vector control methods in sub-Saharan Africa (SSA) [3]. The scaling-up of these two interventions during the last decade, coupled with improved access to early diagnosis and prompt treatment, has contributed to the important decline in malaria burden on this continent [4, 5]. Nevertheless, IRS and ITNs could be insufficient to achieve the long-term goal of malaria elimination in much of SSA [6, 7] and current gains might not be sustained '*without adapting to the changing threats to and opportunities for reducing transmission*' [3].

An additional strategy for malaria control, Larval Source Management (LSM), the management of potential mosquitoes larval habitats, has had historical successes [8-12] and was one of the primary methods for malaria control until the 1950s, when IRS with DDT became the preferred control method [13]. Environmental management and larviciding could nevertheless play a role when other vector control interventions have achieved their maximum practical impact and/or in the malaria pre-elimination and elimination phases [13]. A recent systematic review of LSM interventions has shown that, under selected circumstances in various Asian and African settings, LSM can decrease malaria burden [14]. LSM should only be considered in specific contexts, however, as this type of intervention is likely to be most effective in areas where larval habitats are '*few, fixed, and findable*' [15]. In SSA, these conditions are likely to be

found in settings of focal and low to moderate transmission, such as urban environments, desert fringes, high altitudes, and some densely populated rural areas [13]. Further, LSM could contribute to IVM when dominant vectors are biting and/or resting outdoors (exophagic and exophilic behaviour) and to help manage insecticide resistance [13]. The knowledge base regarding the cost-effectiveness of LSM interventions is scarce, however. Environmental management was the subject of only one cost-effectiveness study that was based on the analysis of a colonial-era integrated malaria control programme carried out in copper mining communities of former Northern Rhodesia (present day Zambia) [16]. It is believed that only one cost analysis of larviciding programmes has been performed to date [17, 18] and the cost-effectiveness of this type of intervention remains to be assessed. This adds to the paucity of data on the cost-effectiveness of vector control interventions in urban areas.

The aim of this paper is thus to estimate the cost-effectiveness of larviciding for malaria control in urban areas of SSA, drawing from the recent large-scale community-based larviciding program carried out by the *Urban Malaria Control Programme* (UMCP) in Dar es Salaam (United Republic of Tanzania) [19-24]. Cost-effectiveness ratios (CER) per malaria infection averted, malaria deaths prevented, and disability-adjusted life years (DALY) avoided are reported from both provider and societal perspectives for different transmission intensity scenarios and microbial larvicide formulations.

METHODOLOGY

Dar es Salaam Urban Malaria Control Program

This economic analysis is based on a large-scale larviciding intervention conducted in urban Dar es Salaam, Tanzania's largest city and economic capital. The dominant malaria vectors are *Anopheles gambiae s.s*. and *Anopheles funestus*. These vectors transmit *Plasmodium*

falciparum who is responsible for more than 90% of infections [25]. The principal types of breeding habitats encountered in Dar es Salaam are: drains, borrow pits, ponds, aquatic habitats associated with urban agriculture, and swamps [26]. Malaria transmission is year-round but exhibits seasonal variations related to the two rainy seasons: the short rains of October to December and the long rains of March to May.

The Urban Malaria Control Programme (UMCP) was launched in 2004 with the goal of developing a sustainable larviciding intervention as part of an integrated malaria strategy [21, 27, 28]. The UMCP targeted 15 urban wards, five in each of the three municipalities that composed Dar es Salaam (Temeke, Ilala, and Kinondoni), covering 56 km^2 of the city and encompassing a population of 610,000 residents (2002 census) [29]. Larviciding was operationalized through a vertically managed community-based delivery system [17]. Routine mosquito surveillance and control was delegated to modestly paid community members called Community-Owned Resource Person (CORP) [21, 27, 28]. Larviciding was initiated in March of 2006 in three of the 15 UMCP wards (one in each municipality), and subsequently scaled-up to nine wards in May of 2007, and to the entire study region in April of 2008.

Costing

Costing data for this study were extracted from the UMCP cost analysis described in Worrall [18] and Worrall and Fillinger [17]. Both studies adopted an '*ingredients approach*' [30] to analyse costs, which is consistent with methods used for costing large-scale ITN and IRS programmes. The cost analysis was informed by data from the first phase of larviciding, when the intervention was operational in three wards, and mapping and larval surveillance activities were being carried out in the remaining wards [17, 18]; thus operational costs from these three wards were extrapolated for the entire study area. All resources used and the opportunity costs of

existing inputs were taken into account. Specifically, the costs of the intervention include: community sensitization, training (including international consultants), field personnel, ward supervisors, larvicide purchase and distribution, transportation, materials, office space and furniture (including overheads), storage, and monitoring and evaluation (note that all research costs were excluded). Costs of capital items were spread over their estimated useful life and annualized using a 3% discount rate.

The UMCP used microbial larvicides for vector control manufactured by Valent BioSciences Corp. (Illinois, USA). The active ingredient of this product is a biological agent and is available in two formulations: 1) custom granule (CG) for hand application (*Bacillus sphaericus*; VectoLex®), and 2) water dispersible granule (WG) for liquid application (*Bacillus thuringiensis* var. *israelensis*; VectoBac®). Differences in international toxic units per milligrams of product between the two formulations result in higher costs for the CG formulation [17]. Although the UMCP made the programmatic decision to routinely apply CG, the impact on CERs of using the less expensive WG formulations will be explored.

For the purpose of this analysis, the larviciding intervention was presumed to be part of an ongoing programme and costs were, therefore, aggregated over 10 years (2004-2014) - 2004 being the pre-implementation phase when ward mapping, programme planning, and training occurred. Larviciding was operationalized starting in 2005. Other assumptions include that the intervention would not be scaled-up beyond UMCP wards and that the only increase in the number of persons protected would be due to population growth. To this end, ward-specific population counts from the 2002 and 2012 censuses were used and it was found that population growth averaged 1.62% over that period: from 610,000 in 2002 to 716,000 in 2012 [31, 32]. International technical consultants were assumed to be required for the first 5 years of the

programme, time after which it was considered that capacity building, technical support, and troubleshooting of the intervention would no longer require international expertise. Results are reported based on the economic costs of the intervention as it is considered more appropriate for comparisons of interventions' efficiency than using financial costs. All prices have been adjusted to 2012 US dollars (USD) using the US Gross Domestic Product (GDP) deflator [33] after being converted from local currency using average exchange rates for the year they were disbursed.

Effectiveness data

The main clinical outcome reported by the UMCP is the prevalence of malaria infection, as determined by Giemsa-stained thick smear microscopy. Initial results from the first phase of the larval control intervention, restricted to children under five years of age, (N=4,450), suggested that the odds of malaria infection were decreased by 72% [27]. Further, anopheline larval abundance has been shown to be reduced by 96% during this same time period [21]. Analyses including individuals of all ages and using data from all phases of the larviciding intervention's rollout (N=64,537) have shown that the odds of malaria infection were 21% lower for individuals living in larviciding wards (Odds Ratio=0.79; 95% Credible Intervals (CrI): 0.66-0.93) [28]. This logistic regression model was re-fitted in order to provide an effect size estimate on the relative risk scale. This yielded a prevalence ratio of 81% (95% CrI: 0.70-0.94). This effect size measure provides a conservative approximation of the rate ratio [34] and will be used to estimate the number of infections averted.

Health outcomes

CERs will be reported for the following health outcomes: malaria infections averted, malaria-associated deaths prevented, and disability-adjusted life years (DALY) avoided. One limitation of the UMCP data is that it collected information on prevalent cases, not incident ones.

In order to estimate these three health outcomes, however, one needs a measure of incidence [35]. A two-component mixture of continuous-time Markov Chains was used to calculate incidence rates from UMCP data in these analyses (available from Castro *et al*. [36]).

Number of deaths prevented was estimated by multiplying the number of infections averted by the proportion of malaria cases found to be symptomatic and the case fatality rate. Of all prevalent malaria cases recorded by the UMCP, only 17% reported either having had a fever in the last two weeks before the survey or were found to have a body temperature higher than 37.5° Celsius at the time of the interview. Further, a clear relationship between age of prevalent malaria cases and occurrence of fever was not observed. For this reason, it was decided to assume that the proportion of new infections that would contribute malaria morbidity would remain constant across age groups. Malaria case fatality rate in the city of Dar es Salaam was available for 2006 from official Ministry of Health statistics. The reported case fatality rate of 0.63% (among symptomatic cases presenting at health facilities) is about a third of the average for mainland Tanzania (1.82%) [37].

DALYs were calculated by combining malaria morbidity and mortality. Years of life lost due to disability were obtained by multiplying the number of cases prevented by the condition's disability weight and the average duration of that condition. The approach used by the 2010 update of the Global Burden of Disease (GBD) was adopted [38, 39] and, accordingly, age weighting and discounting of DALYs were not applied. Detailed description of the calculations can be found in Supplementary Appendix2.1.

Provider's resources savings

The provider's perspective takes the viewpoint of the Tanzanian Ministry of Health and Social Welfare. Costs savings per malaria infection averted were estimated by taking into

account 1) the proportion of symptomatic individuals that seek treatment at a health facility, 2) the proportion treated as outpatient, 3) the proportion diagnosed with microscopy, 4) the costs of diagnosing malaria using microscopy, 5) the cost of diagnosing malaria using a rapid diagnostic test (RDT), 6) the cost of treating an uncomplicated falciparum malaria with artemether-lumefantrine, 7) the cost of diagnostic and hospitalization of a complicated falciparum malaria case treated with intramuscular quinine dihydrochlorine, and 8) the proportion of symptomatic individuals seeking care through community health workers. Finally, any user fees for diagnosis and treatment that would be collected by health facilities were subtracted from costs savings.

After accounting for treatment-seeking behaviour, the provider's cost of treating one symptomatic case of malaria was estimated to be of $5.15 (17% of malaria infections were assumed to be symptomatic). This latter amount was used to aggregate costs savings over the 10-year duration of the larviciding programme and to discount savings occurring in the future at a 3% rate. Detailed information on the cost function used can be found in Supplementary Appendix 2.1.

Society's resources savings

It has been argued that the most relevant reference case in economic evaluations should reflect the societal perspective, where all costs and consequences of the intervention are aggregated without regards to whom they accrue [30, 40]. In Tanzania, it was estimated that 55% of all treatment costs of malaria in children under five years of age were borne by the household [41]. To estimate household costs in Dar es Salaam, the framework developed by Sicuri *et al*.[41] was generalized to individuals of all ages. Specifically, treatment-seeking behaviours, user fees, medicine costs, transportation costs, productivity losses due to clinical cases (or caring for sick children) of malaria, anemia, and neurological sequelae, and funeral costs were taken

into account. The indirect costs per malaria infection (asymptomatic and symptomatic) and per death were estimated at $1.39 and $40.39, respectively (a detailed description of calculations can be found in Supplementary Appendix2.1). These costs were added to the provider's costs savings to obtain the resources that would have been saved, from the societal perspective, for each infection averted.

The opportunity costs incurred by community members as a result of the larviciding intervention were not captured. Accounting for these costs would have negligible impact on the results of this economic evaluation, as it would only involve taking into account time to allow UMCP teams to access properties where breeding habitats could be found [17].

Cost-effectiveness scenarios

A central feature of any cost-effectiveness analysis is the definition of the alternative to the studied intervention. WHO recommends a state of transmission without any intervention as the alternative [35]. This might not be the most realistic scenario as larviciding should be used as part of an IVM approach [1], in conjunction with other appropriate vector control measures [13]. To circumvent this issue and to enable generalization of these results, CERs were calculated as a function of incidence and the detailed results are presented considering three different scenarios:

- Scenario #1: Uses the baseline incidence for the year 2005, when malaria transmission was highest. The estimated incidence for that year was of 902 infections per 1,000 people per year that would result in 153 clinical malaria episodes per 1,000 people per year (assuming that 17% of cases will be symptomatic).For urban areas, malaria case incidence rates in this range have been described as characteristics of low transmission settings [42, 43].

- Scenario #2:This scenario assumes moderate malaria transmission that corresponds to what was observed in 2006 in the UMCP, when other control interventions were being scaled up. Malaria incidence has been estimated at 227 infections per 1,000 people per year.
- Scenario #3**:** The last scenario corresponds to the situation in which other malaria control interventions have already been scaled-up and achieved impact. This scenario assumes an annual malaria infection incidence of 122 infections per 1,000 people per year and is the lowest incidence recorded during the UMCP in 2008.

Sensitivity analysis

One-way sensitivity analyses were used for parameters whose choice depends on methodological issues (e.g., larviciding formulation). Probabilistic analyses were performed to assess the impact of uncertainty in the effectiveness parameters, health outcomes, and costs. A Monte Carlo simulation model was built in R package v.2.15.1 [44] and parameters were re-sampled 100,000 times. The specific distributions from which the parameters were drawn are described in Supplementary Appendix 2.2. The measure of dispersion reported for the CERs are the 95% uncertainty interval (UI) - the 2.5% and 97.5% percentiles of the Monte Carlo simulations. Finally, the uncertainty surrounding the cost-effectiveness of larviciding was summarized using cost-effectiveness acceptability curves.

Ethical considerations

All UMCP data collection procedures were provided ethics approval from the Medical Research Coordination Committee of the National Institute for Medical Research, Ministry of Tanzania (Reference number NIMR/HQ/ R.8a/Vol. IX/279 &234). Similarly, the Harvard School of Public Health's Institutional Review Board also approved the research protocol

(Protocol # 20323-101). Informed consent was obtained from all study participants or, on behalf of children under 18 years of ages, from their legal guardians.

RESULTS

The economic costs of the 10-year UMCP larviciding programme were evaluated at a present value of $5,111,234 (Table 2.1). The average economic cost per person protected per year (PPPY) was of $0.87. This number is lower than the economic cost PPPY year of $1.05 estimated by Worrall and Fillinger [17] because population growth was factored-in and international consultants were only included for the first five years of the programme.

The first scenario assumed high urban malaria transmission and resulted in the most optimistic cost-effectiveness results with 1,178,999 malaria infections averted over the 10-year programme duration (Table 2.2). Larviciding would prevent 1,265 deaths and result in a total of 65,125 DALYs averted. It was evaluated that these cases would result in costs savings of $878,301 (at present value) for the provider (assuming that 17% of infections are symptomatic), and an additional $1,433,425 would be saved from the perspective of the society. The gross CER has been estimated at $4.3 per infection averted, $4,040 per death prevented, and $78 per DALY avoided. Taking into account costs savings, the cost of the programme per DALY avoided decreased to $65 from the provider's perspective and to $43 from the societal perspective.

When considering the second transmission scenario, the number of infections averted was much smaller (Table 2.2). Consequently, the present value of costs saved by averting cases from the provider's perspective was of $220,677 and gross and net CER from both the provider and societal perspectives were similar. The last scenario used a very low incidence rate and, as expected, the CER were the least cost-effective of all scenarios. It was estimated that larviciding

would avert 159,282 malaria infections. Again, gross CER and net CER from the provider and societal perspective were of the same order of magnitude.

Table 2.1: Projected economic cost per year and population covered by the UMCP larviciding intervention.

Year	Economic Costs*	Economic Costs (Discounted)	Population Covered
2004 (Y00)†	$147,882	$147,882	0
2005 (Y01)	$600,619	$583,125	637,406
2006 (Y02)	$600,619	$566,141	647,447
2007 (Y03)	$600,619	$549,652	657,880
2008 (Y04)	$600,619	$533,642	668,717
2009 (Y05)	$567,366	$489,415	679,973
2010 (Y06)	$567,366	$475,160	691,662
2011 (Y07)	$567,366	$461,320	703,797
2012 (Y08)	$567,366	$447,884	716,394
2013 (Y09)	$567,366	$434,839	729,469
2014 (Y10)	$567,366	$422,174	743,040
Total	$5,954,555	$5,111,234	6,875,784

Note: All prices are in 2012 US dollars.
*Economic costs for Y01-Y04 are higher because we assumed that international consultants were required for capacity building, planning, and trouble-shooting of the intervention.
†Pre-implementation year (Y00) has a 6-month duration.

Table 2.2: Number of cases averted, deaths prevented, disability-adjusted life years averted, and gross and net cost-effectiveness ratios for the larviciding intervention.

Scenarios	Total	Gross CER*	CER* Provider's Perspective	CER* Societal Perspective
SCENARIO #1 - INCIDENCE RATE OF 902 PER 1,000				
Infection averted	1,178,999	$4.3	$3.6	$2.4
Death prevented	1,265	$4,040	$3,345	$2,213
DALY averted	65,125	$78.5	$65.0	$43.0
SCENARIO #2 - INCIDENCE RATE OF 227 PER 1,000				
Infection averted	296,228	$17.3	$16.5	$15.3
Death prevented	318	$16,077	$15,383	$14,250
DALY averted	16,363	$312.4	$298.9	$276.9
SCENARIO #3 – INCIDENCE RATE OF 122 PER 1,000				
Infection averted	159,282	$32.1	$31.3	$30.1
Death prevented	171	$29,900	$29,206	$28,073
DALY averted	8,798	$580.9	$567.4	$545.4

Note: All prices are in 2012 US dollars.
*CER: Cost-Effectiveness Ratio

One-way sensitivity analyses – Larviciding formulations

If a water dispersible formulation was used, the present value of the 10-year larviciding programme's costs would be reduced to $4,076,908 (20% less than the costs associated with the custom granule formulation), and the average economic cost per person protected per year would be of $0.69. Assuming that the water dispersible formulation has the same efficacy as the custom granule used by the UMCP, the larviciding programme becomes more cost-effective (Table 2.3). In fact, net societal CERs ranged from $1 to $24 per malaria infection averted, and from $27 to $428 per DALY averted depending on the scenarios under considerations.

Probabilistic sensitivity analysis

The uncertainty surrounding parameters' estimates was explored through a probabilistic sensitivity analysis. CERs per infection averted, death prevented, and DALY avoided are presented with their 95% UI in Table 2.4. Uncertainty in parameters to calculate costs savings per malaria cases averted did not have an overwhelming influence on the CER, as demonstrated by the relatively high overlap between both gross and net CERs. Because of the relatively wide credible intervals around the prevalence ratios for the larviciding intervention (i.e., 95% CrI: 0.70-0.94) [28], there is about a 4-fold difference between the 2.5^{th} and 97.5^{th} percentiles of the simulated distributions for the gross CER. Net societal CER per additional DALY avoided had a 95% uncertainty interval of $15-181 for the scenario where transmission was highest, $165-822 for the second scenario, and $337-1,548 for the lowest transmission scenario.

Cost-effectiveness acceptability curves show the proportion of simulations that were cost-effective for a range of policy-makers' willingness to pay (Figure 2.1). For the scenario where transmission was highest, 95% of Monte Carlo simulations had a willingness to pay threshold under $154 for an additional DALY averted (societal perspective and the custom granule

formulation). This number increased to $652 and $1,225 for the second and third scenarios, respectively. To generalize these findings, net CERs were computed from the provider and societal perspectives for a range of incidence rates. Figure 2.2 shows that, except for very low incidences (i.e., <40 infections per 1,000 people per year), larviciding can be considered cost-effective.

Table 2.3: Impact ongross and net cost-effectiveness ratios of changing the formulation from custom granule to the less expensive water dispersible formulation.

Scenarios	Gross CER*	CER* Provider's Perspective	CER* Societal Perspective
SCENARIO #1 - INCIDENCE RATE OF 902 PER 1,000			
Infection averted	$3.5	$2.7	$1.5
Death prevented	$3,222	$2,528	$1,395
DALY averted	$62.6	$49.1	$27.1
SCENARIO #2 - INCIDENCE RATE OF 227 PER 1,000			
Infection averted	$13.8	$13.0	$11.8
Death prevented	$12,824	$12,130	$10,997
DALY averted	$249.2	$235.7	$213.7
SCENARIO #3 - INCIDENCE RATE OF 122 PER 1,000			
Infection averted	$25.6	$24.9	$23.6
Death prevented	$23,850	$23,155	$22,023
DALY averted	$463.4	$449.9	$427.9

Note: All prices are in 2012 US dollars.
*CER: Cost-Effectiveness Ratio

Table 2.4: Impact ofprobabilistic sensitivity analyses on gross and net cost-effectiveness ratios for the three malaria incidence scenarios.

Scenarios	Gross CER* [95% UI†]	CER* Provider Perspective [95% UI†]	CER* Societal Perspective [95% UI†]
SCENARIO #1 - INCIDENCE RATE OF 902 PER 1,000			
Infection averted	[$3-12]	[$2-11]	[$1-10]
Death prevented	[$2,593-11,110]	[$1,879-10,399]	[$793-9,346]
DALY averted	[$50-215]	[$36-201]	[$15-181]
SCENARIO #2 - INCIDENCE RATE OF 227 PER 1,000			
Infection averted	[$11-47]	[$10-11]	[$9-46]
Death prevented	[$10,321-44,217]	[$9,612-43,503]	[$8,543-42,438]
DALY averted	[$200-856]	[$186-842]	[$165-822]
SCENARIO #3 - INCIDENCE RATE OF 122 PER 1,000			
Infection averted	[$21-88]	[$20-87]	[$19-86]
Death prevented	[$19,195-82,232]	[$18,491-81,503]	[$17,419-80,444]
DALY averted	[$372-1,592]	[$358-1,578]	[$337-1,558]

Note: All prices are in 2012 US dollars.
*CER: Cost-Effectiveness Ratio
†95% UI: 95% Uncertainty Interval

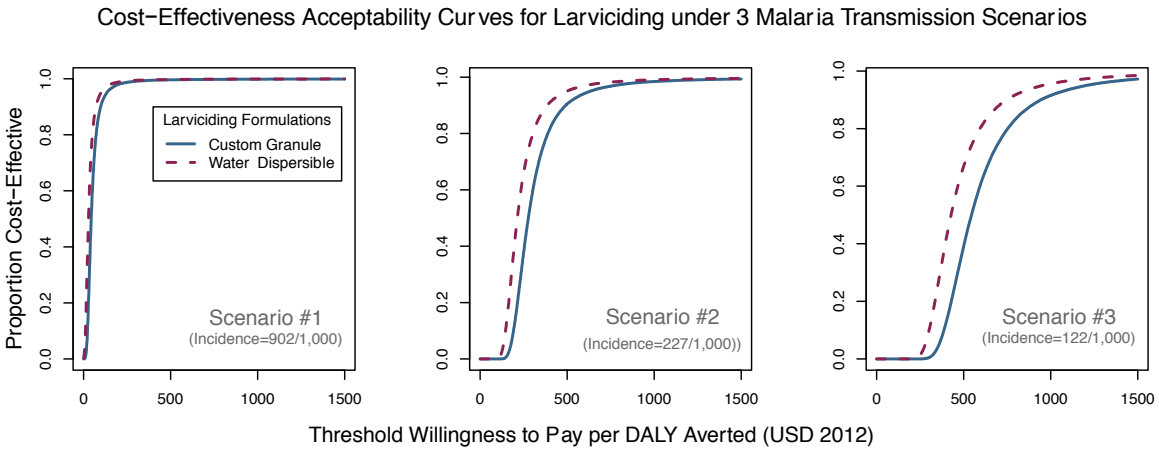

Figure 2.1: Cost-effectiveness acceptability curves (societal perspective) for larviciding with the custom granule and water dispersible formulations under the three malaria transmission scenarios.

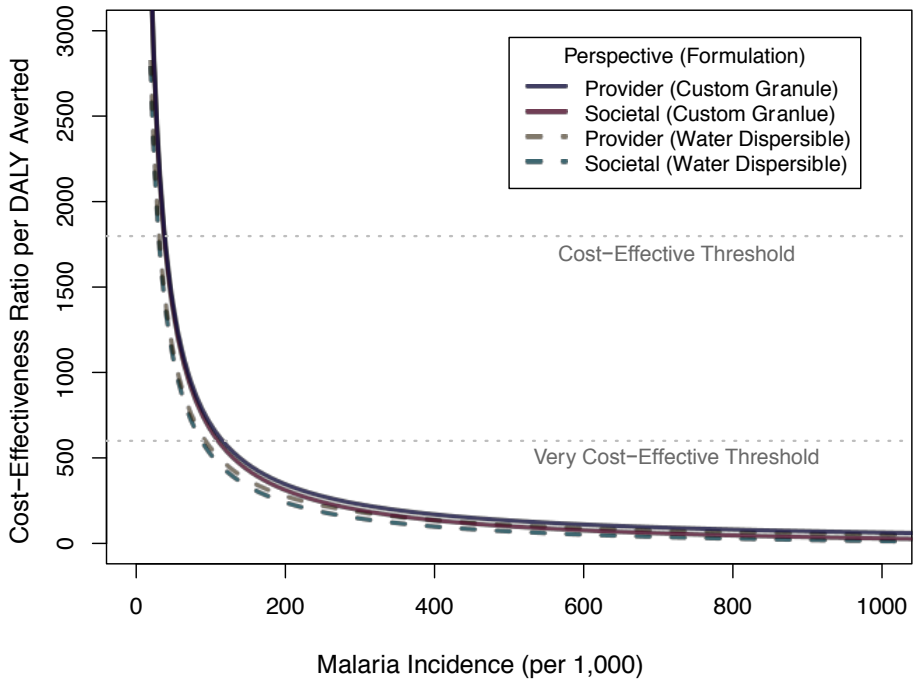

Figure 2.2: Net cost-effectiveness of larviciding (custom granule formulation) per disability-adjusted life years as a function of malaria incidence for the provider and societal perspectives.

The very cost-effective threshold is defined as a cost-effectiveness ratio below the per capita Gross Domestic Product (GDP) of Tanzania ($599 USD), and the cost-effective threshold to three times the per capita GDP.

DISCUSSION

This paper presents results from the first economic evaluation of a large-scale larviciding intervention for malaria control under programmatic conditions. The cost-effectiveness of larviciding has been shown in this study to be highly dependent on the assumed baseline malaria incidence. WHO proposed that interventions with a CER per DALY averted less than a country's per capita Gross Domestic Product (GDP) could be regarded as '*very cost-effective*' and those for which the cost-effectiveness is less than three times the country's per capita GDP as '*cost-effective*' [35, 45]. Given Tanzania's per capita GDP of $599 USD (2012), larviciding can be considered very cost-effective under a wide variety of transmission scenarios. Even low transmission settings with incidences above 40 infections per 1,000 people per year had CER that fell within the range of cost-effective interventions. With regards to the three malaria transmission scenarios, it was found that, even for the lowest malaria transmission scenario, 61% of Monte Carlo simulations fell below the very cost-effective threshold (societal perspective) and 98% of them below the cost-effective threshold.

These analyses also suggest that, if the same efficacy is assumed for both types of larviciding formulation, using a water dispersible larvicide is more cost-effective. Indeed, the provider CER for urban settings with the highest malaria transmission (Scenario #1) was estimated to be of $49 per DALY avoided (provider's viewpoint), $27 if the societal perspective was adopted. In practice, the use of both formulations will likely be required as they are designed for different aquatic habitats: water dispersible granule being suited for open and non-vegetated breeding habitats, whereas the custom granule formulation is designed for habitats with emergent vegetation [17]. Hence, depending on the relative abundance of each type of aquatic habitats, the CER for larviciding should fall within the CERs calculated for the custom granule and water

dispersible formulations.

Contextualizing these results is challenging because of inherent differences of cost-effectiveness studies of other malaria vector control interventions. A systematic review of economic evaluations of ITN and IRS programmes suggested that these interventions are highly cost-effective in rural areas with a median CER per additional DALY averted of $27 (range $8.15-110) and $143 (range $135-150) for ITN and IRS, respectively (in 2009 USD) [46]. Although this same review reported higher median financial costs per person protected per year for ITN of $2.20 and IRS of $6.70 (in 2009 USD) - as compared to $1.05 for the UMCP larviciding programme - the CERs estimated here are generally higher. A number of reasons can explain this differential and economic evaluations studies of ITN and IRS interventions conducted in SSA were systematically reviewed to address this point (see Supplementary Appendix2.3 for details on this systematic review).

First, protective efficacy for larviciding is lower than that of ITN and IRS [47, 48]. It was previously estimated that larviciding reduced the odds of malaria parasitaemia by 21% in the general population covered by UMCP activities [28]. The effectiveness estimate used in this economic evaluation can be considered conservative, however, since larviciding exhibited a greater protective effect for children under five years of age (i.e., Odds Ratio=0.61; 95% Credible Interval: 0.46-0.80) [28]. Although the evidence based on the effectiveness of ITN is fairly robust [47], a recent Cochrane review of IRS interventions concluded that '*the number of high quality trials are too few to quantify the size of effect*' [48]. Nevertheless, out of the seven IRS cost-effectiveness studies reviewed here, three of them assumed that the effect size of IRS was equal to that of ITN [49-51]. Thus, economic analyses of some of the IRS interventions could be considered imprecise.

Second, economic evaluation of ITN studies almost exclusively focus on the group of children at highest risk of malaria morbidity and mortality: children under five years of age. The ability to deliver ITN to the specific age group where malaria burden is highest decreases costs while maximizing health gains. Targeting larviciding, or to a lesser extent IRS, to children under five years of age is not in the realm of possibilities as these are population interventions. Finally, the baseline incidence rates used in this study comprised both asymptomatic and symptomatic infections whereas most other studies assumed that all cases would be symptomatic. In fact, the three malaria incidence scenarios entail that there would be between 21 (scenario #3) and 180 symptomatic cases (scenario #1) per 1,000 individuals per year. The median baseline malaria case incidence (symptomatic) used in the reviewed studies was of 900 and of 1,184 infections per year per 1,000 individuals for the ITN and IRS studies, respectively. Although these incidence rates fall into a realistic range for most endemic rural areas of SSA, malaria incidence is assumed to be much lower in urban areas. This last point is important because, although the costs of ITN and IRS programmes should remain relatively stable in urban areas, lower malaria incidence rates would reduce the number of DALY averted and increase CER of these interventions. The same can be said of malaria case fatality rates that are generally lower in urban areas where prompt access to diagnostic and early treatment services are generally easier. This partly explains why the CER per death averted estimated for larviciding in urban Dar es Salaam is higher than the one reported for ITN and IRS in rural areas [46]. Importantly, the reviewed studies were almost exclusively conducted in rural areas. The question of which malaria control intervention is most cost-effective in urban settings, therefore, remains an open one.

Four potential methodological limitations of this study need to be acknowledged. The

first concerns the generalizability of these results. This economic evaluation concerns a single larviciding programme in Dar es Salaam, where the costs were extrapolated from the first phase of larviciding, when only three out of the 15 wards where carrying-out the intervention [17]. If density of larval habitats in the other wards were higher or lower than that in these three wards, costs could have been under- or overestimated. Further, our results are likely to be generalizable only to other urban areas with similar malaria epidemiology. The estimated net CERs, that take into account costs savings from the provider and the societal perspectives, are unlikely to apply in settings where health systems characteristics, treatment seeking behaviors, and wages are drastically different. Second, health outcomes were not discounted in this economic evaluation, in accordance with the methodology adopted by the 2010 GBD update. Discounting DALYs at 3%, however, would have yield a net CER (society's perspective) of $82, $528, and $1,040 per DALY averted for the first, second, and third transmission scenario, respectively. This increase of the CER by a factor of two highlights the impact of social value choices in economic evaluation. Yet, even when discounting health outcomes, larviciding remains below the cost-effective threshold for all scenarios (and below the very-cost effective threshold for scenarios #1 and #2). Third, using other protective measures such as ITN, window screening, and closed ceilings are believed to have synergistic effects with the larviciding intervention [28]. Not taking these synergies into account could underestimate the population impact of larviciding and the cost-effectiveness of the intervention. Finally, health insurance coverage, which could affect CER for both the provider and societal perspectives, was not taken into account. Given that health coverage is relatively low in Dar es Salaam, with only 7.8% of women and 5% of men aged 15-49 years of age having any form of insurance [52], this omission is, however, unlikely to dramatically impact the results.

In conclusion, this economic evaluation of the Dar es Salaam UMCP larviciding programme has shown that, according to commonly used GDP thresholds, this intervention is very cost-effective in most transmission settings where malaria incidence is above 110-116 infections per 1,000 per year (above 40 infections per 1,000 to be deemed cost effective). This study also lends support for the Tanzanian National Malaria Control Programme strategic plan to scale-up larviciding interventions by 2020 to selected urban areas of the country [53]. Given limited health budgets, however, decision-makers should still prioritize scaling-up ITN and IRS in rural areas because larviciding interventions have been shown to be more costly when the density of breeding habitats is high and/or the population density is low [17, 18]. Once coverage of these interventions is satisfactory in highly endemic areas, larviciding could be part of an IVM approach for malaria control, if local conditions warrant its use. This is especially true if other interventions have achieved their maximum impact and/or if the National Malaria Control Programme of a specific country wishes to move forward from malaria control to the pre-elimination and elimination phases. Finally, this study also highlights the lack of cost-effectiveness analyses for malaria control in urban areas of SSA, and it remains unknown which combinations of interventions (e.g., ITN, IRS, LSM) are most cost-effective in such settings.

ABBREVIATIONS

CER=Cost-effectiveness Ratio; CORP=Community Owned Resource Persons; DALY=Disability Adjusted Life Year; GBD= Global Burden of Disease; GDP=Gross Domestic Product; ITN=Insecticide Treated Net; IRS=Indoor Residual Spraying; IVM=Integrated Vector Management; LSM=Larval Source Management; PPPY=per person protected per year; SSA=Sub Saharan Africa; UI=Uncertainty Interval;UMCP=Urban Malaria Control Programme.

COMPETING INTERESTS

None declared.

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AUTHORS' CONTRIBUTIONS

MCC developed the original research idea for this paper. MMG performed the literature review, abstracted costs data from the different sources, and conducted the cost-effectiveness analyses. MMG drafted the manuscript while MCC contributed intellectual content and edited the paper. The final version of the manuscript was seen and approved by all authors.

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SUPPLEMENTARY APPENDIX 2.1

DETAILS ON THE METHODOLOGY AND ASSUMPTIONS USED IN THE COST-EFFECTIVENESS ANALYSIS OF LARVICIDING FOR URBAN MALARIA CONTROL

In this section, the methodology and assumptions used to estimate the cost-effectiveness ratios of larviciding for urban malaria control in Tanzania are described. This supplemental material is organized into three sections. First, the data and assumptions used to calculate the number of disability-adjusted life years averted (DALY) are described. Second, the methodology used to estimate provider's resources savings that would accrue by preventing malaria infections is presented. Third, the methodology adopted to estimate society's resources savings is defined.

DISABILITY-ADJUSTED LIFE YEARS

Previous Global Burden of Disease (GBD) assessments used the judgment of a small group of health-care professionals to assign disability weights to 483 sequelae of diseases and injuries. In contrast, the GBD 2010 update mapped 1,160 sequelae into 220 distinct health states, and weights were elicited through a large-scale multi-country respondent survey [1]. The health states and disability weights derived from this latest iteration of the GBD were used to estimate years of life lost due to disability. The seven malaria-related health states, proportion of cases assigned to each state, and their respective disability weights were abstracted from the GBD 2010 study report [2], and are presented in Table 2.S1. The only exception is that the motor plus cognitive impairment state disease duration was estimated from the life expectancy at the average age of malaria death in Dar es Salaam (reliable information on the age distribution of neurological sequelae could not be found and the distribution of malaria deaths was used as the most plausible proxy).

Table 2.S1: Description of health states, proportion of cases falling into each state, and disability weight used to calculate number of life years lost to disability.

Health States	Proportion of cases	Duration	Disability Weight
Mild case of acute infectious disease episode	66.3%	21 days	0.005
Moderate case of acute infectious disease episode	33.2%	21 days	0.053
Severe case of acute infectious disease episode	0.5%	21 days	0.210
Mild anemia	15.47%	28 days	0.005
Moderate anemia	20.28%	28 days	0.058
Severe anemia	4.61%	28 days	0.164
Moderate motor plus cognitive impairments	0.00906%	48.3 years	0.221

The proportion of malaria cases that would lead to mild, moderate, and severe anemia was calculated independently using local information. Following the approach outlined in the GBD 2010 update [3], the mean hemoglobin shift caused by malaria infections is estimated at 8.36 g/L and this shift was applied to the population distribution of hemoglobin levels in Tanzania. Separate distributions for individuals aged 0-4 years and 5-14 years, for men aged 15+ years, and for women aged 15+ years were used (Table 2.S2). Information on hemoglobin distributions were obtained from the scientific literature for the city of Dar es Salaam for all age groups except for the 5-14 years old age group, which was based on data from coastal Tanzania. The hemoglobin shift was subtracted from the hemoglobin distributions described in Table 2.S2, and the increase in the prevalence of mild, moderate, and severe anemia was calculated using the appropriate age and sex-specific cut-off values for these anemia categories [3]. The average increase in prevalence across the different age and sex groups were combined using the distribution of malaria cases in these groups as weight (Table 2.S3). The duration of malaria-attributable anemia was estimated to be the same for the three severity classes of anemia. Previous studies suggested that it usually takes 4-5 weeks to achieve hematological recovery following malaria infection [4-6] and a disability duration of 28 days was therefore used for these three anemia sequelae.

Table 2.S2: Distribution of hemoglobin levels (g/L) used to calculate proportion of malaria cases that would lead to mild, moderate and severe anemia for different age and sex groups.

Population Groups	Hemoglobin (g/L)		References
	Mean	SD	
Children aged 0-4 years (both sexes)	106.4	15.4	[7]
Children aged 5-14 years (both sexes)	111.5	13.9	[8]
Female aged ≥15 years	112.0	18.0	[9]
Male aged ≥15 years	128.0	16.0	[9]

Note: Mild anemia was defined as a hemoglobin level below 120 g/L for all age groups (except for males aged ≥15 years were a cut-off of 130 g/L was used). For moderate anemia, a threshold of 110 g/L was used (120 g/L for males aged ≥15 years). Severe anemia was defined using a cut-off hemoglobin level of 80 g/L (90 g/L for males aged ≥15 years).

Table 2.S3: Age distributions of malaria cases and malaria deaths.

Age Groups	Proportion of Malaria Cases*	Proportion of Malaria Deaths†
0-4 years old	19.1%	51.4%
5-14 years old	30.9%	10.9%
15-29 years old	26.9%	8.4%
30-44 years old	14.2%	11.9%
45-59 years old	5.7%	5.3%
60+ years old	3.3%	12.0%

*Age distribution of prevalent malaria cases estimated from the UMCP data.
†Age distribution of malaria deaths estimated from the Dar es Salaam Demographic Surveillance Site through verbal autopsies (including unspecified acute febrile illness).

Years of life lost were calculated by multiplying the expected number of deaths at each age by the remaining life expectancy at age of death in Tanzania [10]. The age distribution of malaria deaths (Table 2.S3) was obtained from the Dar es Salaam Demographic Surveillance Site (DSS), conducted from 1994 to 2002 as part of the Adult Morbidity and Mortality Project (AMMP) [11], which, despite its name, collected information on individuals of all ages. Cause of death was ascertained through verbal autopsies. Because the cause of death was not specifically coded as malaria unless there was confirmatory evidence from another source (e.g. hospital

records) [12], malaria deaths were considered to be those with a cause of '*malaria*' or '*unspecified acute febrile illness*', following the approach used by the AMMP and others [13,14]. Social value choices, such as age weights, were not incorporated into DALYs and health outcomes were not discounted, in accordance with the approach adopted in the GBD's 2010 update [15].

PROVIDER'S RESOURCES SAVINGS

A decision tree was developed to quantify the costs savings that would follow averting malaria cases in Dar es Salaam from the provider's perspective (Figure 2.S1), which takes the viewpoint of the *Tanzanian Ministry of Health and Social Welfare*. Costs savings per malaria infection averted were estimated by taking into account 1) the proportion of symptomatic individuals that attended a health facility [P_{HF}], 2) the proportion treated as outpatient [P_{Out}], 3) the proportion diagnosed with microscopy [P_{Mic}], 4) the cost of diagnosing malaria using microscopy [CD_{Mic}], 5) the cost of diagnosing malaria using a rapid diagnostic test (RDT) [CD_{RDT}], 6) the cost of treating an uncomplicated falciparum malaria with artemether-lumefantrine (ALu) [CT_{Out}], 7) the cost of diagnostic and hospitalization of a complicated falciparum malaria case treated with intramuscular quinine dihydrochlorine [CDT_{In}], and 8) the proportion of symptomatic individuals seeking care through community health workers [P_{CHW}]. Finally, any user fees for diagnosis [UF_{Dx}] and treatment [UF_{Tx}] that would be collected by health facilities were subtracted from costs savings. Because children under five years of age are exempted from paying user fees, user fees were weighted by the probability of not having to pay them (using the age distribution of malaria cases described in Table 3). Costs savings per symptomatic malaria case averted were calculated using the formula below and parameter values are described in Table 2.S4.

$$\text{Provider's Cost}_{Symptomatic} = P_{HF}\left\langle P_{Out}\left\{(P_{Mic} * CD_{Mic}) + (1 \quad P_{Mic}) * CD_{RDT}) + CT_{Out}\right\} + \left[(1 \quad P_{Out}) * CDT_{In}\right] \quad UF_{Dx} \quad UF_{Tx}\right\rangle$$
$$+P_{CHW}\left\langle CD_{RDT} + CT_{Out} \quad UF_{Dx} \quad UF_{Tx}\right\rangle$$

The proportion of symptomatic cases attending a health facility and seeking care through community health workers was estimated using UMCP data regarding the number of individuals who had a fever in the previous two weeks and sought advice or treatment at a health facility. That proportion was standardized using the age-distribution of prevalent malaria cases and it was estimated that, in Dar es Salaam, 65.7% of individuals infected with malaria (symptomatic) would seek treatment at a health facility and 4.4% through community health workers.

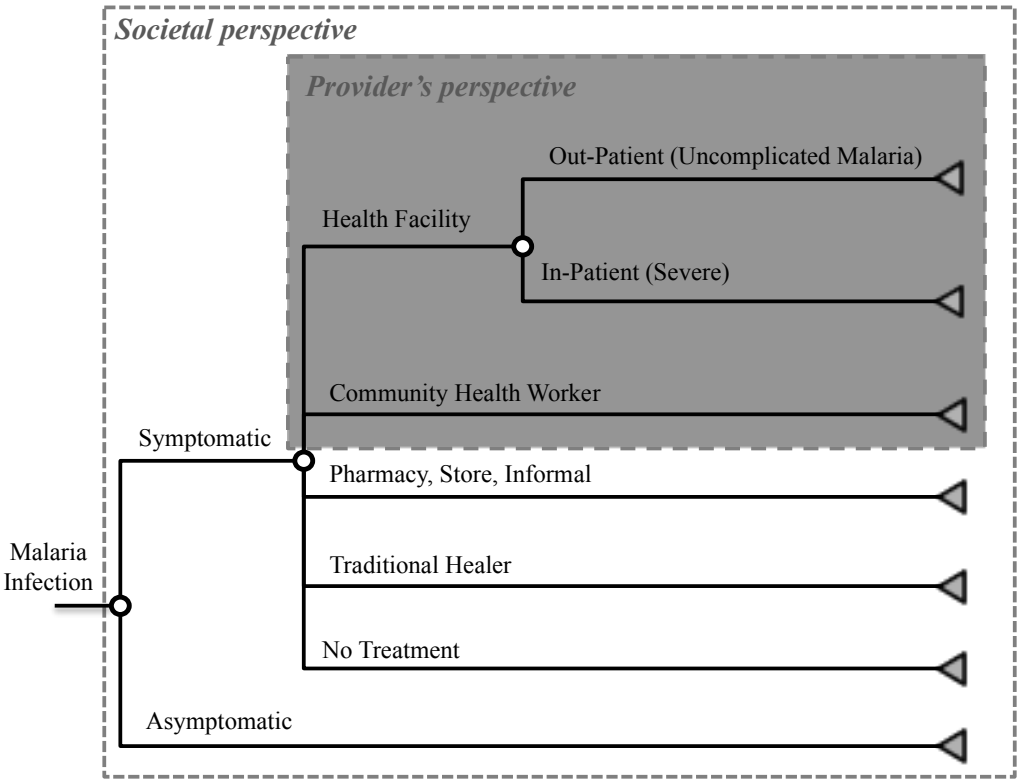

Figure 2.S1: Decision tree model to calculate cost savings.

Table 2.S4: Parameters and data sources used to calculate costs saved by averting one symptomatic malaria case.

Parameters	Value	Data Sources
P_{HF}	65.7%	UMCP data
P_{CHW}	4.4%	UMCP data
P_{Out}	91.7%	Ministry of Health data [16]
P_{Mic}	44%	Masanja *et al*. [17]
CD_{Mic}	\$0.59	Harchut *et al*. [18] (1)
CD_{RDT}	\$1.45	Harchut *et al*.[18](1)
CT_{Out}	\$1.85	Negotiated WHO/Coartem Price [19](2)
CTD_{In}	\$74.26	Lubell et al. [20] (3)
UF_{Dx}	\$0.26	Ministry of Health data(4)
UF_{Tx}	\$0.15	Ministry of Health data(4)

Note: All prices are in 2012 US dollars.
(1) These costs include overhead, labor costs, equipment, and general consumables.
(2) Drug price per tablet of 0.057 USD'09 with 20% adjustment for wastage, 10% for shipping, and 10% for CIF. We calculated a weighted average, using age as a proxy for weight, of the number of tablets required for an average ALu dose from the age distribution of cases in the UMCP data.
(3) Pooling data from all sites of this multi-center study. Costs include those for the antimalarial and other drugs, supportive treatment, diagnostic tests, treatment for adverse events and hotel costs for inpatient stay.
(4) The user fees are weighted by the probability that the patient is exempted from paying them (i.e., children under five years of age).

Once a malaria case present at the health facility, the proportion treated as outpatient and the number of hospitalizations need to be estimated. To this end, it was found from Tanzanian Ministry of Health data that 8.32% of all malaria cases presenting at health facilities were treated as in-patients [16]. The Tanzanian MoH's standard treatment guidelines states that '*where possible*, *laboratory investigations are mandatory*' [17]. Despite the fact that laboratory facilities are widely available in Dar es Salaam, a certain number of cases will be solely treated based on clinical symptoms (presumptive treatment). To produce consistent estimates of cost-effectiveness across interventions, all suspected malaria cases were assumed to be parasitologically confirmed either using RDT or microscopy, as per their National Malaria Control Program's guidelines. Specific data on the proportion of malaria diagnosis performed by RDT versus microscopy in Dar es Salaam could not be found. Instead, information from a study conducted in 2012 in two

rural districts of Tanzania was used. This study reported that, among patients with fever who had a clinical diagnosis, RDT were used 56% of the time [18]. Provider's costs per diagnosis were informed by an economic evaluation conducted in six health facilities of Dar es Salaam that found that cost per diagnostic test (costs include laboratory materials and labor expenses) was $1.44 for RDT and $0.59 for microscopy (2008 USD) [19].

Standard treatment guidelines for Tanzania recommend ALu as first line treatment for uncomplicated malaria and quinine dihydrochlorine injection for complicated malaria [17]. All uncomplicated malaria cases were assumed to be treated as outpatients with ALu. To calculate cost per ALu treatment, the negotiated Novartis/WHO price of $0.057 per tablet was used (2009 USD) [21]. Because the number of tablets required per treatment is a function of a patient's weight, average treatment costs were calculated based on the weight distribution, proxied by age (as described in the MoH's Standard Treatment Guidelines [17]), of prevalent malaria cases in the UMCP data. Further, drug costs were inflated by 20% to adjust for wastage, an additional 10% for local transport, and 10% was added for international transport to properly reflect the costs incurred by the MoH [19]. All in-patients were presumed to have complicated malaria and estimated costs for treating such cases were abstracted from a recent multi-center trial of quinine versus parenteral artesunate for severe malaria [22]. The cost of treating a severe malaria case with quinine was estimated at $63.50 (2009 USD). This includes drugs, fluids, laboratories, and hotel costs – the latter being obtained from WHO's *choosing interventions that are cost-effective* framework – but excluded lifetime health care costs associated with neurological sequelae.

Individuals seeking care through community health workers were assumed to be diagnosed with RDT and treated with ALu. Because of lack of specific cost data on community health workers, the cost estimates of RDT from health facilities were used and the cost of ALu

was presumed to remain the same. Using the cost function described above and accounting for treatment-seeking behavior, the provider's costs of treating one symptomatic case of malaria was estimated to be of $5.15 (17% of malaria infections are assumed to be symptomatic). The latter amount was used to aggregate costs savings over the 10-year duration of the larviciding program and to discount savings occurring in the future at a 3% rate.

SOCIETY'S RESOURCES SAVINGS

To estimate household costs in Dar es Salaam, the framework developed by Sicuri *et al*.[23] was generalized to individuals of all ages (Figure 1). Specifically, treatment-seeking behaviors, fees, medicine costs, transportation costs, productivity losses due to clinical cases of malaria (or caring for sick children), anemia, and neurological sequelae, and funeral costs were taken into account.

Household direct costs are described in Table 2.S5. Data from the UMCP was used to estimate the proportion of symptomatic malaria cases falling into five mutually exclusive treatment-seeking behaviors. For treatment in health facilities, user fees for diagnostic and treatment as well as transportation costs were taken into account. Because of the paucity of costs data regarding community health workers, societal costs were presumed to be the same as for those seeking treatment at health facilities, minus the transportation costs which is assumed to be null in the case of community health workers. For treatment in pharmacy/store, it was estimated that transportation costs would be negligible and that the only direct expenditure would be the cost of treatment with ALu. A small proportion of individuals sought care through traditional healers. Fees for such services were abstracted from the literature and it was premised that the same transportation costs reported by patients attending health facilities would apply for those reaching traditional healers. Individuals not seeking treatment were assumed to accrue no direct

costs. Funeral costs were estimated from insurance premiums [24] and self-reported expenditure on funerals among individuals aged 15-59 years of age in Tanzania [25].

Table 2.S5: Inputs and data sources to calculate household direct costs per symptomatic malaria episode.

Treatment Seeking	Household Direct Cost per Symptomatic Malaria Episode			
	Proportion[(1)]	Fee	Medicine Costs	Transportation Costs
Health Facility	65.70%	$0.26[(2)]	$0.15[(4)]	$0.29[(6)]
Community Health Worker	4.42%	$0.26[(2)]	$0.15[(4)]	-
Pharmacy/Store	3.95%	-	$0.77[(5)]	-
Traditional Healer	0.04%	$2.70[(3)]	-	$0.29[(6)]
No Treatment	25.90%	-	-	-

Note: All prices are in 2012 US dollars.
(1) UMCP data.
(2) Ministry of Health Data. User fee for diagnostic by community health worker is assumed to be equal to that of health facilities.
(3) Average between the fee reported by Sicuri et al. [23] and the one reported by Somi et al. [26].
(4) Based on the user fee for treatment in the health sector. User fee for treatment by community health worker is assumed to be equal to that of health facilities.
(5) Medicine costs for treating one malaria episode with artemether-lumefantrine. Cost estimate based on 798 private for-profit outlets in mainland Tanzania reported by Tougher et al. [27] and adjusted for the average weight (proxied by age) of malaria cases in Dar es Salaam.
(6) Average transportation cost of 259 patients from 6 health facilities of Dar es Salaam, as reported by Yukick et al. [22].

Household indirect costs were estimated by calculating productivity losses due to illness, anemia, and neurological sequelae. Changes in productivity were estimated using a human capital approach where market wage rates were used as a proxy for an individual's productive potential [28]. Time lost per symptomatic malaria episode has been estimated at 4.2 days in Tanzania [26]. Adult care-takers of sick children aged 0-9 years of age were presumed to also lose 4.2 days of productivity, and care-takers of children aged 10-14 to lose 1 day (25% of the time for younger children). Time lost in transportation or in medical facilities was not included to avoid double-counting, as affected individuals would already be out of economically productive activities due to malaria illness. The average monthly income in Dar es Salaam was abstracted from the 2006 Tanzanian Integrated Labour Force Survey (ILFS) database [29]. Taking into

account the probability of unemployment, the average income in Dar es Salaam was calculated per 5-year age groups and the overall average income was weighted by the age distribution of malaria cases. Further, it was premised that care-takers of sick children would be women above 15 years of age so that such productivity losses would be calculated using the average income of this gender group – income for women in Dar es Salaam are roughly 60% lower than that of men. Note that caretakers of sick individuals or individuals affected by malaria may be non-economically active students that would also experience a reduction in their amount of earned education. Because of methodological difficulties in precisely quantifying the accumulation of human capital in this population, this type of indirect costs was not considered in the present economic evaluation.

Iron deficiency anemia can lead to important cognitive deficits in children and has negative impacts on adult work capacity [30]. Malaria is an important contributor of iron deficiency anemia, even in asymptomatic individuals [31,32]. Productivity losses due to anemia are estimated to be of the order of 5% for blue-collar type work and can be as high as 17% for heavy manual labor [30]. Malaria infections cause a mean hemoglobin decrease of 8.4 g/L [3,33] and this shift was applied to the mean hemoglobin level of male and female aged 15 years of age. Distribution of hemoglobin levels for Dar es Salaam's adult population was abstracted from the literature (Table 2) and it was estimated that 16.9% of malaria cases would become anemic because of the infection. Productivity losses due to anemia were estimated by calculating average income per 5-year age groups, using data from Dar es Salaam in the 2006 ILFS [29], and assuming that income would be reduced by 5% due to anemia for the proportion of the population that became anemic as a result of malaria. Lost income was averaged using the age distribution of malaria cases as weights. The effect of malaria-attributable anemia on

productivity was assumed to last for 4 weeks, as informed by studies on the duration of post-malaria hematological recovery [4-6].

Severe malaria has been associated with long-term cognitive impairments [34-37]. The impacts of such persistent neurological sequelae on lifetime productivity are clear but precise effect size estimates are unavailable. The proportion of malaria infections resulting in neurological sequelae has been estimated to be 0.00906% [2], and the productivity of individuals with such sequelae was assumed to be reduced by 15% - an estimate that can be considered conservative. Individuals were further presumed to be economically productive between the ages of 15 to 64 years and the average yearly earnings of this age group was calculated using data from Dar es Salaam, as reported in the 2006 ILFS [29]. Yearly earnings were estimated at $946 USD in this population so that the productivity losses due to neurological sequelae would be of $142 USD per year for affected individuals. The present value of lifetime productivity losses (LPL) due to neurological sequelae was estimated using the following formulae and a 3% discount rate:

$$LPL = \begin{cases} E\{[1 \quad (1+r)^{(e_x \; 15)}]/r\} * (1+r)^{(15 \; Age_x)}; & \text{if } Age_x < 15 \text{ and } (e_x + Age_x) < 65 \\ E\{[1 \quad (1+r)^{(65 \; 15)}]/r\} * (1+r)^{(15 \; Age_x)}; & \text{if } Age_x < 15 \text{ and } (e_x + Age_x) \quad 65 \\ E\{[1 \quad (1+r)^{(e_x \; Age_x)}]/r\} * (1+r)^{(15 \; Age_x)}; & \text{if } Age_x \quad 15 \text{ and } (e_x + Age_x) < 65 \\ E\{[1 \quad (1+r)^{(65 \; Age_x)}]/r\}; & \text{if } Age_x \quad 15 \text{ and } (e_x + Age_x) \quad 65 \\ 0; & \text{if } Age_x \quad 65 \end{cases}$$

where E is the average yearly earnings, r is the discount rate (3%), e_x is the local life expectancy at age x, and Age_x is the age at which an individual develops neurological sequelae. The average lifetime productivity loss was then calculated using the age distribution of malaria deaths. Lifetime productivity loss due to premature mortality was not included in this analysis because

of extreme uncertainty in estimates of an individual's lifetime consumption of goods/services (education, health, etc.) that would need to be deducted from lifetime earnings.

Household direct and indirect costs were then combined assuming that only 17% of new malaria infections would be symptomatic and that asymptomatic infections would not lead to any costs, except through anemia-attributable productivity losses. The following formulas were used to calculate the average societal cost per malaria infection and per malaria death:

$$\text{Societal Cost}_{Infection} = P_{Symp}\left\{ \sum_{i=1}^{5} P_{TSBi} * (Fee_i + MedCost_i + Transport_i) + PL_{Ill} \right\} * + PL_{Hb} + (P_{NS} * LPL_{NS})$$

$$\text{Societal Cost}_{Death} = Cost_{Funeral}$$

where P_{Symp} is the proportion of infections that are symptomatic (17%); P_{TSBi} is the proportion of symptomatic individuals falling into each of the five treatment-seeking behaviors defined in Table 2.S5; Fee_i, $MedCost_i$, and $Transport_i$are the health fee, medicine costs, and transportation costs, respectively, incurred by individuals seeking care in each of these five categories (see Table 2.S5); PL_{Ill} is the productivity loss due to being sick or caring for sick children (note that PL_{Ill} is a weighted average of productivity losses by age group and is equal to $5.25); PL_{Hb} is the productivity loss associated with anemia ($0.20); P_{NS} is the proportion of all malaria infection leading to neurological sequelae (0.009%); LPL_{NS} is the present value of lifetime productivity losses due to neurological sequelae ($2,263);and $Cost_{Funeral}$ is the cost of a funeral ($40.4).

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SUPPLEMENTARY APPENDIX 2.2

Table 2.S6: Distributions and parameter values used for the probabilistic sensitivity analysis.

Parameters	Distribution*	Notes
EFFECTIVENESS		
Prevalence ratio for the intervention (log scale)	*Truncated Normal* (ln(0.81); 0.072)	1
DISABILITY-ADJUSTED LIFE YEARS		
Disability weight for infectious disease: mild	*Triangular* (min=0.002; max=0.011)	2
Disability weight for infectious disease: moderate	*Triangular* (min=0.033; max=0.081)	2
Disability weight for infectious disease: severe	*Triangular* (min=0.139; max=0.298)	2
Disability weight for anemia: mild	*Triangular* (min=0.002; max=0.011)	2
Disability weight for anemia: moderate	*Triangular* (min=0.038; max=0.086)	2
Disability weight for anemia: severe	*Triangular* (min=0.112; max=0.228)	2
Disability weight for cognitive impairments	*Triangular* (min=0.141; max=0.314)	2
Duration of a malaria episode (days)	*Uniform* (min=14, max=28)	3
Duration of anemia (days)	*Uniform* (min=21, max=35)	4
TREATMENT-SEEKING BEHAVIORS		
Proportion seeking care at/through health facility (PS_{HF}), community-health workers (PS_{TSB1}), pharmacy/store (PS_{TSB2}), traditional healers (PS_{TSB3}), and not seeking treatment (PS_{TSB4}).	PS_{HF} = *Triangular* (min=54%; max=81%) $PS_{TSBi} = P_{TSBi}+[P_{TSBi}*(P_{HF}-PS_{HF})/(1-P_{HF})]$	5
COSTS SAVINGS (PROVIDER)		
Proportion treated as out-patient (P_{Out})	*Triangular* (min=72%; max=95%)	6
Proportion diagnosed using microscopy (P_{Mic})	*Triangular* (min=33%; max=55%)	7
Costs of diagnostic with microscopy (CD_{Mic})	*Triangular* (min=0.45$; max=0.75$)	7
Cost of diagnostic with RDT (CD_{RDT})	*Triangular* (min=0.52$; max=4.94$)	8
Outpatient's cost of treatment (CT_{Out})	*Triangular* (min=1.26$; max=5.22$)	9
Inpatient's cost of diagnostic and treatment (CTD_{In})	*Triangular* (min=58.38$; max=90.51$)	10
COSTS SAVINGS (SOCIETY)		
Fee for traditional healer	*Triangular* (min=0.21; max=5.19)	11
Cost of artemether-lumefantrine at pharmacy/store	*Triangular* (min=0.51; max=1.03)	12
Transportation costs to health facility/healer	*Triangular* (min=0.20; max=0.42)	13
Number of days lost to malaria episode (N) and to care for children aged 10-14 years of age (N_{10-14})	N = *Triangular* (min=2; max=5) N_{10-14}=N**Uniform* (min=20%; max=30%)	14
Proportion of earnings lost to anemia	*Uniform* (min=2.5%; max=7.4%)	15
Proportion of earnings lost to neurological sequelae	*Triangular* (min=10%; max=20%)	16
Funeral costs	*Triangular* (min=30.53$; max=50.26$)	17

Note: All prices are in 2012 US dollars.
*The modes of the triangular distributions correspond to the values used to calculate the cost-effectiveness ratios.

Notes:

1- Adapted from Maheu-Giroux and Castro [1]. Because it is biologically impossible for larviciding to cause an increase in malaria incidence, the normal distribution was truncated for values above the null.

2- The 95% confidence intervals of the disability weights reported in the 2010 GBD study were used as minimum and maximum values of the triangular distribution [2].

3- For the duration of malaria episodes, the same distribution as the one reported in the GBD 2010 study was used [3].

4- The post-malaria recovery period reported in the literature [4-6] was used and ±1 week was added to that quantity.

5- Lowest and highest age-specific proportions of individual attending health facilities in the UMCP data. The other 4 treatment-seeking behaviors were rescaled such that the sum of these proportions would still be equal to 1. PS_{TSBi} refers to the re-sampled proportion whereas P_{TSBi} refers to the values described in Table 5.

6- Minimum for severe malaria is reported in Reyburn *et al*. [7]. An upper bound of 95% for this distribution was assumed.

7- Minimum and maximum values of the triangular distributions were calculated as ±25% the mode of the distribution.

8- Minimum is obtained by considering only the price of test (excluding labor), as reported by Harchut *et al*. [8]. Maximum value is taken from White *et al*. [9].

9- Minimum value is the negotiated WHO/Novartis price, excluding adjustments for wastage and transport. Maximum value corresponds to the price reported in the AFRO essential drug price indicator.

10- Minimum and maximum values as reported by Lubell *et al*. [10].

11- Minimum is reported by Somi *et al*. [11] and maximum by Sicuri *et al*.[12].

12- Minimum and maximum values correspond to the interquartile range reported by Tougher *et al*. [13].

13- Minimum and maximum values correspond to the 95% confidence interval reported by Yukich *et al*. [14].

14- Values for this triangular distribution are taken from the review of Chima *et al*. [15]. For children aged 10-14 years of aged, it was assumed that it would correspond to 20-30% of an adult illness time.

15- Minimum value taken by reducing by 50% the estimate of 5% loss in earning. Maximum value corresponds to a situation where 20% of workers in Dar es Salaam are involved in manual work where lost in earnings is estimated at 17% [16].

16- A uniform distribution was used to acknowledge the fact that prior information on this parameter is uncertain. The minimum and maximum values correspond to the authors' evaluation of a plausible conservative range.

17- Minimum value reported by Ngalula *et al*. [17] and maximum value by Dercon *et al*. [18].

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SUPPLEMENTARY APPENDIX2.3

SYSTEMATIC REVIEW OF COST-EFFECTIVENESS ANALYSES OF INSECTICE-TREATED BEDNETS AND INDOOR RESIDUAL SPRAYING FOR MALARIA CONTROL IN AFRICA

In order to contextualize the results of this economic evaluation of larviciding for malaria control, cost-effectiveness analyses of indoor residual spraying (IRS) and insecticide-treated bendets (ITN) for malaria control in SSA were systematically reviewed. This review will help examine the methodological issues and assumptions upon which these economic evaluations are based.

METHODOLOGY

PubMed was queried using the terms described below (Table 2.S7). No time restriction was imposed. The search retrieved 402 publications that were evaluated based on either title alone (n=253) or title and abstract (n=149). The eligibility and exclusion criteria are described in Table 2.S8. A total of 12 articles for IRS and 24 for ITN were selected based on their title and abstract but 5 IRS and 6 ITN studies were excluded after reading the paper (Table 2.S9). Finally, one IRS study was identified through other means and included in the review. Hence, a total of 7 IRS and 18 ITN cost-effectiveness studies were included in the final review.

Table 2.S7: PubMed search query information for the systematic review

PubMed Search:
(malaria OR falciparum) AND (cost OR cost-effectiveness) AND ((ITN OR bed net* OR bednet* OR net OR long-lasting insecticide-treated net* OR LLIN) OR ((insecticide OR residual house spraying OR indoor residual spraying OR IRS))) AND (Africa)

Table 2.S8: Eligibility and exclusion criteria for the systematic review.

Eligibility Criteria	-Study conducted in Africa. -Study reports cost-effectiveness of IRS or ITN. -Malaria cases, malaria deaths, or DALYs are the health outcomes.
Exclusion Criteria	-Study not relevant to malaria. -Literature review. -Letter to the Editor. -Studies conducted on packages of interventions where we cannot distinguish between IRS, ITN, or any combinations of interventions. -Study is published in a language other than English, French, or Portuguese.

Table 2.S9: Studies retrieved, selected, and included in the systematic review.

Articles Retrieved (IRS and ITN combined)	402
Articles selected based on title and abstract	IRS = 12 ITN = 24
Final number of articles included in the review	IRS = 7 ITN = 18

RESULTS

A summary of the reviewed cost-effectiveness studies of IRS is present in Table 2.S10. Cost-effectiveness studies of ITN is presented in Table 2.S11.

Table 2.S10: Summary of cost-effectiveness analyses of insecticide residual spraying interventions conducted in sub-Saharan Africa.

Country	Year of Program	Currency	Age Group	Perspective	Cost PPY	Effect Size	Incidence per 1,000	CER / Infection	CER / Death	CER / DALY	Ref
Low and Middle Income Countries	NA	USD 2001	NA	Provider	NA	50% reduction in incidence; 17% reduction in child mortality	NA	NA	NA	Once a year: Malathion =$12; DDT =$9; Deltamethrin =$10; λ-cyhalothrin =$10; Twice a year: Malathion =$24; DDT =$17; Deltamethrin =$18; λ-cyhalothrin =$19	[1]
South Africa and Mozambique	SA =1997-1999; MZ =1999-2001	USD 2005	<5	Provider	SA =$3.27 and MZ =$3.90	5.5 child deaths averted per 1,000 child-years	NA	NA	SA =$4,357; MZ =$3,933	SA =$132; MZ =$119	[2]
SSA	Hypothetical 10 years program	Int 2000	<5	Provider	NA	50% reduction in incidence; 20% reduction in case fatality	Incidence: Afr-D= 1,436; Afr-E= 1,184. Mortality: Afr-D= 7; Afr-E = 8.	NA	NA	Afr-D =$32; Afr-E =$41	[3]
Kenya	1999-2000	~USD 2000	0-99	Provider	$0.88	RR=0.25 (0.24-0.27)	NA	$9	NA	NA	[4]

Table 2.S10 (Continued): Summary of cost-effectiveness analyses of insecticide residual spraying interventions conducted in sub-Saharan Africa.

Country	Year of Program	Currency	Age Group	Perspective	Cost PPY	Effect Size	Incidence per 1,000	CER / Infection	CER / Death	CER / DALY	Ref
SSA (model)	NA	USD 1995	<1	Provider & Community	Once yearly ($5.76-10.18); Twice yearly ($11.53-20.36)	52% decrease in all cause mortality	1,500	NA	NA	Once yearly ($16-29); Twice yearly ($32-58)	[5]
Mozambique	0	USD 2000	2-15 (parasitaemia) & 0-99 (clinical case)	Provider	$4.82	11,857 malaria cases averted	NA	$29.43	0	NA	[6]
Model Area in Africa	1978	~USD 1975	0-99	Gross CER	$2	40% reduction in crude death rate (adult); 50% reduction in infant mortality	NA	NA	$250 (all); $600 (infants)	NA	[7]

Table 2.S11: Summary of cost-effectiveness analyses for insecticide-treated bednet interventions conducted in sub-Saharan Africa.

Country	Year of Program	Currency	Age Group	Perspective	Cost PPY	Effect Size	Incidence per 1,000	CER / Infection	CER / Death	CER / DALY	Ref
Low and Middle Income Countries	Hypothetical Program	USD 2001	<5	Provider	NA	5.5 child deaths averted per 1,000 child-years	NA	NA	NA	Permet-rhin =$17 Deltamet-hrin =$11	[1]
Eritrea (ER); Togo (TG); Malawi (MW); Senegal (SG); Tanzania (TZ);	ER=2001-2005; TG=2004; MW=1999-2005; SG=2000-2005; TZ=2002-2005	USD 2005	<5	Provider	Cost per ITN: ER=$3.98; TG=$3.32; MW=$3.36; SG=$8.05; TZ=$4.80	50% reduction in incidence; 20% reduction in case fatality	NA	NA	Including re-treatment: ER=$438; TG=$1,174; MW=$1,105; SG=$2,199; TZ=$788.	Including re-treatment: ER=$13; TG=$36; MW=$33; SG=$67; TZ=$24.	[2]
SSA	Hypothetical 10 years program	INT 2000	<5	Provider	NA	RR=0.25 (0.24-0.27)	Incidence: Afr-D=1,436; Afr-E=1,184. Mortality: Afr-D=7; Afr-E=8.	NA	NA	Afr-D =$29 Afr-E =$41	[3]
Kenya	1999-2000	~USD 2000	0-99	Provider	$2.02-2.34	19% decrease in all cause mortality; 46% decrease in malaria-related morbidity	NA	$29	NA	NA	[4]

Table 2.S11 (Continued): Summary of cost-effectiveness analyses for insecticide-treated bednet interventions conducted in sub-Saharan Africa.

Country	Year of Program	Currency	Age Group	Perspective	Cost PPY	Effect Size	Incidence per 1,000	CER / Infection	CER / Death	CER / DALY	Ref
SSA (model)	NA	USD 1995	<5	Provider & Community	Not mentioned	0.69 (ITN vs IRS)	1500	NA	NA	Bednet only $19-85; Bednet & insecticide $25-96	[5]
South Africa (KwaZulu -Natal)	1998-1999 (Comparison ITN vs IRS)	USD 1999	All	Provider	7.62	HR for infant mortality of 0.78	253 (174.5 /0.69)	16	$1,696	NA	[8]
DRC	2005-2006 (Comparison ITN vs diagnosis, treatment, IPTp, ANC services)	USD 2005	Pregn-ant women	Provider	NA	Reduction in all-cause mortality of 17% among U5	Used an infant mortality rate of 95/1,000	NA	$411.13	$17.22	[9]
Togo	2004-2005	USD 2004	<5	Provider	$5.95 (per LLIN distributed)	Reduction in incidence of 50% and 5.5 deaths averted per 1,000	1,209	4.4	$856	$22.1	[10]
United Republic of Tanzania	2004-2006	USD 2006	<5	Provider	$7.57 (per ITN delivered)	PE=27%	Incidence of malaria outpatient in U5 is 723/1,000	NA	$873	NA	[11]
United Republic of Tanzania	1996-2000	USD 2000	<5	Provider	$13.38 per treated-net year	NA (73 deaths averted)	Infant mortality =73; Child mortality =15	NA	$1,559	$57	[12]

Table 2.S11 (Continued): Summary of cost-effectiveness analyses for insecticide-treated bednet interventions conducted in sub-Saharan Africa.

Country	Year of Program	Currency	Age Group	Perspective	Cost PPY	Effect Size	Incidence per 1,000	CER / Infection	CER / Death	CER / DALY	Ref
Kenya	1997-1999	USD 1996	<5	Provider & Community	$1.40 ($1.90 per ITN)	Reduction in incidence of 46%; reduction in all cause mortality of 19%	NA	NA	$1,214	$49	[13]
Sub-Saharan Africa	Not mentioned	USD 1995	1-119 months	Provider	3.79	Not mentioned	U5 =1,500; 5-10 =555	NA	NA	No rebound =$44	[14]
Guinea	Not mentioned	USD 1994	<5	Provider	3	50% reduction in incidence; 35% reduction in all-cause mortality	Mortality =14	NA	NA	$43	[15]
The Gambia	1990-1995	USD 1990	The cohort of childre n born in 1990 and followe d for 5 years	Provider	NA	Estimated from 10 villages	1-6 mo =200; 6-12 mo =800; 1-5 years =1,000	NA	$711	NA	[16]
The Gambia	1991-1992	USD 1992	<10	Provider & Community	NA	U5 mortality reduced by 17%	440	NA	$471	$31.5	[17]

Table 2.S11 (Continued): Summary of cost-effectiveness analyses for insecticide-treated bednet interventions conducted in sub-Saharan Africa.

Country	Year of Program	Currency	Age Group	Perspective	Cost PPY	Effect Size	Incidence per 1,000	CER / Infection	CER / Death	CER / DALY	Ref
Ghana	1993-1994	USD 1994	<5	Provider & Community	$1.2 per child-year ($2.4 per bednet)	All-cause mortality reduced by 25% in U5.	NA	NA	$2,003	$73.5	[18]
West Africa	5 years of follow-up	~USD 1996	Cohort of new-born	Provider	NA	60% decrease in mortality in the 1-4 years old; 45% decrease in clinical episodes	NA	NA	NA	100% compliance = $18.88; 50% compliance = $38.04	[19]
The Gambia	1989-1990	USD 1990	1-4 years of age	Provider & Community	$5.65 per child-year	0	NA	NA	$187.53	$7.9	[20]

ANC = antenatal care; DRC = Democratic Republic of the Congo; INT = international dollar; IPTp = intermittent treatment for malaria in pregnancy; ITN = insecticide treated nets; IRS = indoor residual spraying; LLIN = long-lasting insecticide-treated nets; NA = not applicable; U5 = under five years of age; USD = United States dollar.

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PAPER #3 : DO MALARIA VECTOR CONTROL MEASURES IMPACT DISEASE-RELATED BEHAVIOUR AND KNOWLEDGE? EVIDENCE FROM A LARGE-SCALE LARVICIDING INTERVENTION IN TANZANIA

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ABSTRACT

Background

Recent efforts of accelerated malaria control towards the long-term goal of elimination had significant impacts in reducing malaria transmission. While these efforts need to be sustained over time, a scenario of low transmission could bring about changes in individual disease risk perception, hindering adherence to protective measures, and affecting disease-related knowledge. The goal of this study was to investigate the potential impact of a successful malaria vector control intervention on bednet usage and malaria-related knowledge.

Methods

Dar es Salaam's Urban Malaria Control Program was launched in 2004 with the aim of developing a sustainable larviciding intervention. Larviciding was scaled-up using a stepped-wedge design. Cross-sectional and longitudinal data were collected using a randomized cluster sampling design (2004-2008). Prevalence ratios (PR) for the effect of the larviciding intervention

on bed net usage (N=64,537) and household heads' knowledge of malaria symptoms and transmission (N=11,254) were obtained from random effects regression models.

Results

The probability that individuals targeted by larviciding had used a bednet was 5% time less than that of the non-intervention areas (PR=0.95; 95% credible intervals (CrI): 0.94-0.97) and the magnitude of this effect increased with time. Larviciding also led to a decline in household heads' knowledge of malaria symptoms (PR=0.88; 95% CrI: 0.83-0.92) but no evidence of effect on knowledge of malaria transmission was found.

Conclusion

Successful control interventions could bring about further challenges to sustaining gains in reducing malaria transmission if not accompanied by strategies to avoid changes in individual knowledge and behaviour. This study points to two major research gaps. First, there is an urgent need to gather more evidence on the extent to which countries that have achieved significant decline in malaria transmission are also observing changes in individual behaviour and knowledge. Second, multidisciplinary assessments that combine quantitative and qualitative data, utilizing theories of health behaviour and theories of knowledge, are needed to optimize efforts of national malaria control programmes, and ultimately contribute to sustained reduction in malaria transmission.

BACKGROUND

The last decade witnessed a rapid scale-up of effective malaria control interventions supported by the mobilization of important programmes and initiatives [1]. The increased coverage of packages of interventions of proven efficacy is believed to have led to important declines in malaria transmission and disease burden, particularly after 2005, in some areas of sub-Saharan Africa [2-4]. Globally, it is estimated that malaria incidence has declined by 17% and that malaria mortality rates have been reduced by 26% since 2000 [5]. The persistent shrinking of the malaria map and shift from moderate/high to low malaria endemicity in some countries has important consequences on population-level immunity[6], and raises questions for programme managers and policy-makers regarding sustainability of the achievements to avoid resurgence, as observed in the past [7], and to pursue malaria elimination [8,9]. In fact, out of the 99 malaria-endemic countries, 34 have now set or are realistically considering elimination targets [10].

The Global Malaria Eradication Program (1955-1969) taught us that maintaining momentum when malaria transmission is declining is of prime importance to programmatic success [11]. One of the cardinal requirements for moving beyond control to elimination is to sustain high rates of effective coverage of control measures within a low transmission environment [12]. Reducing malaria to low transmission levels, however, could negatively impact disease risk perception by local communities, policy makers, and international funders [13-15]. Few studies thoroughly investigated the impacts of malaria control on individual health behaviour and disease-related knowledge. Qualitative evidence suggests that bednet usage could decrease following a reduction in mosquito nuisance and malaria transmission [13,16,17]. Further, lack of experience with episodes of malaria illness and inaccurate home diagnosis have

been suggested as contributing factors to delays in appropriate treatment-seeking behaviour [18,19].

This paperaddresses the issue of potential behaviour change following successful malaria control efforts. Specifically, the potential impact of a vector control strategy on malaria-related behaviour and knowledge is assessed using data from the Urban Malaria Control Programme (UMCP) in Dar es Salaam (United Republic of Tanzania) [20]. This programmewas chosen because after three years of larval control the odds of individuals living in areas treated with larvicide being infected with malaria were 21% lower than those who lived in untreated areas [21]. This study's hypothesis is that as mosquito density and malaria transmission are reduced in Dar es Salaam, three changes could happen. First, as fewer infections are observed, people do not perceive malaria as a major risk for their health (or that of their family), and therefore the use of protective measures is relaxed. Although this change was not observed in a recent qualitative study in Zanzibar, it was stressed as a real possibility in low transmission areas [22]. Second, as people witness fewer episodes of malaria in their immediate social network, their ability to recognize symptoms of the disease is reduced. Third, as the perception of malaria as a major health threat decreases, overall knowledge about disease transmission is progressively reduced as well. However, given the fact that the UMCP larval control activities were done on a weekly basis, and considering that the population was aware of the work of larval control personnel, there is a chance that the link between mosquitoes and malaria is not compromised by reduced transmission. Thus, this paper examines the effects of the larval control strategy in Dar es Salaam on: i) reported bednet usage; ii) knowledge of malaria symptoms; and, iii) knowledge that mosquitoes transmit malaria.

METHODS

Study site

Dar es Salaam is the largest city of the United Republic of Tanzania with an estimated population of 2.7 million in 2005[23]. The smallest administrative units is the ten-cell unit (TCU), which is usually comprised of ten to 20 houses, but may contains as many as 100 [24]. Malaria transmission in Dar es Salaam is year-round [25] and incidence of malaria often peak after the rainy seasons.

Data collection

The UMCP was launched in 2004 with the goal of developing a sustainable community-based larviciding intervention. From 2004 to 2008, a total of six randomized cluster-sampled household surveys were conducted in the targeted area [21]. For the first survey round, ten TCUs per ward were randomly drawn and all households in the selected TCUs were eligible to participate. From the second survey round onwards, TCUs selected in the first round were followed up longitudinally, and cross-sectional data were collected from ten additional TCUs. Upon obtaining informed consent, the location of each household was georeferenced and a detailed questionnaire was administered. Information collected included: i) house characteristics; ii) head of household; iii) use of protective measures; and, iv) individual characteristics of household members. An asset index was constructed by performing a principal component analysis of the household's possessions and used as a proxy of socio-economic status (SES). A total of 48,525 individuals contributed information to the study and 9,379 of these were interviewed more than once. Including follow-up data, the total sample size is 64,537 data points, of which 11,254 are from household heads.

The larviciding intervention was rolled-out sequentially: it started in March 2006 in three wards, scaled up to nine wards in May 2007, and to all intervention areas in April 2008. More details about the UMCP design and data collection can be found elsewhere [20,21,26].

Statistical analyses

The three main outcomes of this study are: i) reported bednet usage the night before the survey (any type of bednet); ii) household head's knowledge of at least five malaria symptoms; and, iii) household head's knowledge that mosquitoes transmit malaria. The larviciding intervention was lagged by five weeks, as described by Maheu-Giroux and Castro [21].

Random effect models where used to take into account clustering of individuals at the household and TCU levels in the regression models (Model 1). As the larviciding intervention was not randomized [21,26], the possibility that ward characteristics are correlated with the intervention cannot be eliminated. Therefore, sensitivity of the resultswas assessed by including ward fixed effects in the statistical models (Model 2). Finally, the possibility that the changes in preventive behaviours and malaria knowledge were not constant through time after initiation of larviciding activities was examined (Model 3). Since the outcomes are not rare events, reporting odds ratios overstates the relative risk association. Model-adjusted prevalence ratios (PR) were therefore calculated directly from logistic regressions using marginal standardization [27,28]. A Bayesian framework was chosen because it offered the flexibility to consider fixed effects and cluster-level random effects, and straightforward computations of the prevalence ratios (PR) and their credible intervals (CrI).

Covariates included in the final multivariate models were selected based on careful consideration of the following issues: i) subject-matter knowledge about confounding; ii) variable exhibiting sufficient variation; and, iii) extent of potential measurement errors.

Covariates included in the model when the outcome is bednet usage were: age, gender, use of insect repellent, use of sprays, use of coil, living in a house with window screens, SES quintiles, weekly rainfall lagged by two weeks (including a quadratic term), and having been surveyed in a previous survey round. Since all models included both follow-up and cross-sectional data, controls for follow-up individuals were added in order to account for any potential Hawthorne effect[29], or the fact that individuals interviewed multiple times adapt their response to questions based on what is expected to be correct. As for the models where the outcome is either knowledge of malaria symptoms or knowledge of malaria transmission, variables controlled for were: age, gender, having been surveyed in a previous survey round, and SES quintiles. Effect modification of the intervention by age, the household's head gender, and SES (dichotomized as richer *vs* poorer than the median) was investigated using the model that provided the best fit as indicated by the deviance information criterion. Details on model specifications, prior distributions, model fitting and convergence, and sensitivity analyses can be found in Supplementary Appendix3.1.

Ethical considerations

Ethical approval was granted by the Medical Research Coordination Committee of the National Institute for Medical Research, Ministry of Tanzania (Reference #NIMR/HQ/R.8a/Vol. IX/279&234), and by the Harvard School of Public Health Institutional Review Board (Protocol #20323-101). Upon informing the study participants on the goal, specific objectives, risk and benefits of the study, written informed consent was obtained. For children younger than 18 years of age, the parent or guardian provided signed informed consent on their behalf.

Table 3.1: Characteristics of study participants stratified by larviciding phase and intervention status.

Variables	Baseline	First phase		Second phase		Third phase
	Control	Control	Larviciding	Control	Larviciding	Larviciding
Individual-level characteristics (n)	**26,338**	**13,818**	**3,096**	**4,749**	**7,366**	**9,170**
Male sex	35.2%	35.5%	36.6%	36.3%	38.2%	39.4%
Age						
Younger than 5 years of age	15.4%	13.3%	13.3%	13.2%	11.5%	10.0%
Between 5 and 14 years of age	27.6%	27.9%	29.1%	28.4%	29.6%	31.2%
Between 15 and 29 years of age	28.5%	29.5%	29.3%	28.2%	28.9%	29.1%
Between 30 and 44 years of age	16.4%	17.3%	16.1%	18.4%	18.8%	18.4%
Between 45 and 59 years of age	7.2%	7.2%	7.7%	7.6%	7.1%	7.3%
Aged 60 years or above	4.9%	4.8%	4.5%	4.1%	4.1%	4.0%
Missing	0.1%	0.1%	0%	0%	0%	0%
Reported use of mosquito repellent	1.3%	4.2%	3.7%	2.5%	3.1%	3.3%
Reported use of coil	5.7%	8.4%	5.9%	5.9%	7.3%	5.8%
Interviewed during the wet season	41.1%	47.5%	51.4%	51.8%	30.9%	38.3%
Previously surveyed participant (follow-up)	16.9%	31.0%	30.4%	32.4%	31.3%	27.5%

Table 3.1 (Continued): Characteristics of study participants stratified by larviciding phase and intervention status.

Variables	Baseline	First phase		Second phase		Third phase
	Control	Control	Larviciding	Control	Larviciding	Larviciding
Head of household and house characteristics (N)	**5,127**	**2,505**	**522**	**726**	**1,099**	**1,275**
Male sex	64.2%	71.6%	71.6%	70.8%	73.3%	74.7%
Age						
Younger than 30 years of age	8.2%	2.4%	2.9%	3.0%	1.7%	1.6%
Between 30 and 49 years of age	48.1%	47.3%	43.9%	47.2%	50.8%	48.9%
Between 50 and 64 years of age	31.1%	37.0%	42.3%	39.5%	36.6%	38.4%
Aged 65 years or above	11.7%	13.1%	10.9%	9.9%	10.5%	10.6%
Missing	0.9%	0.2%	0%	0.3%	0.5%	0.5%
Occupation of the household head						
Business/Government/Formal sector	59.3%	66.3%	65.7%	58.3%	69.5%	77.3%
Farmer/Fisherman	2.2%	1.2%	1.5%	1.1%	0.9%	0.6%
Informal sector	19.2%	20.0%	18.4%	25.3%	17.0%	12.0%
Retired/No job/Domestic	17.9%	11.5%	13.8%	13.8%	11.7%	9.2%
Missing	1.4%	1.0%	0.6%	1.5%	0.8%	0.9%
Socio-economic Status						
Lowest quintile	31.9%	18.5%	21.5%	5.1%	9.1%	7.0%
Second quintile	27.6%	24.2%	16.5%	19.6%	16.3%	14.8%
Third quintile	13.9%	18.2%	19.2%	20.9%	15.0%	19.2%
Fourth quintile	11.6%	21.5%	20.5%	26.9%	31.2%	28.3%
Highest quintile	15.0%	17.5%	22.4%	27.5%	28.4%	30.7%
Education level of household head						
Illiterate	6.2%	6.9%	4.2%	4.0%	2.9%	1.2%
Primary	58.9%	43.5%	48.5%	37.5%	32.7%	35.0%
Secondary	29.2%	44.2%	39.1%	55.9%	59.4%	59.8%
Tertiary	3.6%	4.5%	7.1%	1.9%	4.3%	3.4%
Other	0.3%	0%	0.4%	0%	0.1%	0%
Missing	1.8%	0.9%	0.8%	0.7%	0.6%	0.6%
House has window screens	23.7%	24.2%	45.6%	22.2%	30.3%	39.7%
House has whole ceiling	25.1%	29.5%	36.0%	44.5%	41.7%	34.8%

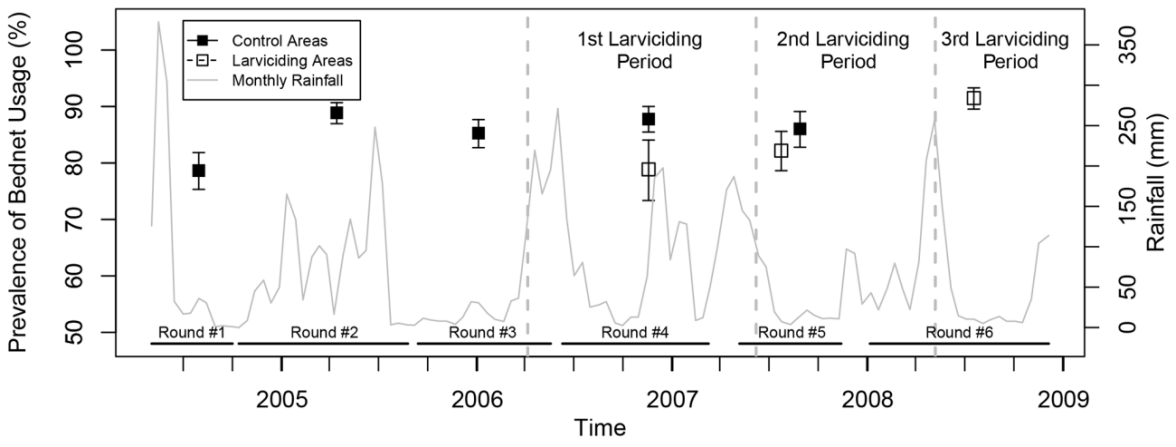

Figure 3.1: Prevalence of bed net usage stratified by survey round and larviciding status. Confidence intervals are based on 9,999 bootstrap replicates at the TCU levels. (The time frame of larviciding phases and survey rounds do not overlap perfectly. Thus, due to small sample size and the geographically limited extent of data collection (only one ward), results for 697 data points in the larviciding area in survey round 3, and 744 data points in control area in survey round 6 are not shown).

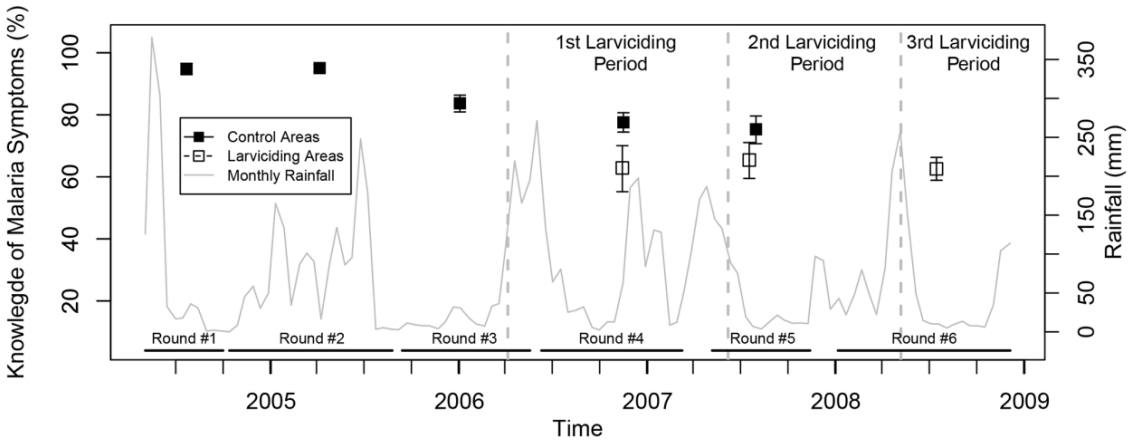

Figure 3.2: Proportion of household heads knowing at least five symptoms of malaria, stratified by survey round and larviciding status.

Confidence intervals are based on 9,999 bootstrap replicates at the TCU levels. (Prevalence estimates based on small sample size and geographically limited extent of data collection (only one ward) are not represented).

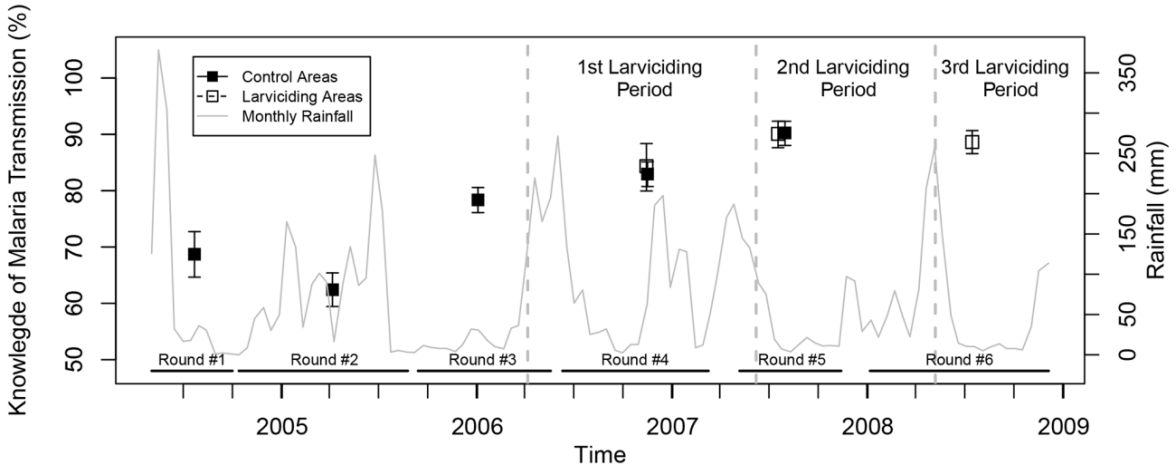

Figure 3.3: Proportion of household heads that know that mosquitoes transmit malaria, stratified by survey round and larviciding status.

Confidence intervals are based on 9,999 bootstrap replicates at the TCU levels. (Prevalence estimates based on small sample size and geographically limited extent of data collection are not represented).

RESULTS

Characteristics of study participants, stratified by larviciding phase and intervention status, are presented in Table 3.1. Given the survey design, the proportion of individuals surveyed during the wet season exhibited marked differences; a larger proportion of interviews for the larviciding areas of the first larviciding phase and of the non-intervention areas of the second larviciding phase were performed during the wet season. The proportion of household head between 50 and 64 years of age increased with time (as a result of aging and the fact that older household heads enrolled with time), and SES and house-proofing conditions also exhibited increasing trends with time.

Reported use of bednet increased steadily in the non-intervention areas from 78.7% in mid-2004 to 86.0% in 2007, but exhibited yearly variation related to precipitation (Figure 3.1), and was lower in larviciding areas as compared to non-intervention ones. With regard to knowledge of malaria symptoms by the household head, a continuous decline was observed throughout the study period in non-intervention wards from 94.8 to 75.3% (Figure 3.2), and in larviciding wards from 62.9 to 62.6%. The proportion of household heads with knowledge that mosquitoes transmit malaria rose steadily during the study period in the non-intervention group from 68.7 to 90.2% (Figure 3.3), and non-intervention and larviciding areas did not appear to differ much.

Univariate regression models suggested that the probability of using a bednet the night before the survey for individuals residing in larviciding areas was 6% lower (95% CrI: 4-7%) than for individuals living in non-intervention areas (Table 3.2). This result was not affected when adjusting for additional covariates and when including fixed effects at the ward level. When examining if the intervention only had an immediate effect or one that changes with time,

the decline in bednet usage observed in the larviciding wards was found to be accentuating with time (Table 3.2) so that, after three years of larviciding, the probability of using a net for individuals living in the intervention wards was 10% lower (PR=0.90, 95% CrI: 0.84-0.95) than for individuals in non-intervention wards.

The impact of the larviciding intervention on knowledge of malaria symptoms was also shown to be statistically significant (Table 3.3). Here, adding fixed effects at the ward level slightly changed the PR for the intervention from 0.91 (95% CrI: 0.87-0.95) to 0.88 (95% CrI: 0.83-0.92). The PR were unaffected when adjusting for potential confounders. Further, time since initiation of larviciding activities had no effect on knowledge of malaria symptoms.

No evidence supporting a change in knowledge of malaria transmission as a result of the larviciding intervention was found (Table 3.4). Results were not affected by adding fixed effects at the ward levels or by adjusting for potential confounders. When allowing for a change of the effect of the intervention with time, the results suggested that household heads living in larviciding areas were less likely to recognize mosquitoesas vector of malaria as time since initiation of larviciding activities increased. Indeed, the model predicts that three years after initiation of the larval control intervention, the probability that household heads residing in larviciding areas recognized mosquitoes as vector of malaria was 10% lower (PR=0.90; 95% CrI: 0.75-1.04) than for those living in non-intervention areas. This result did not reach statistical significance, however.

Finally, neither being under five years old, living in a household headed by a male, nor being below the median SES was found to be modifying the effect of the larviciding intervention on reported bednet usage (Table 3.5). For both the knowledge of malaria symptoms and malaria transmission outcomes, the product term between the larviciding intervention and gender of the

household head was not statistically significant, indicating that this variable is not an effect modifier. Being below the median SES asset-based index, however, significantly modified the effect of the larviciding intervention on malaria knowledge. In fact, the PR for the larviciding intervention for heads of household above the median SES was 0.89 (95% CrI: 0.84-0.94) as compared 0.84 (95% CrI: 0.78-0.90) for those living below the median SES. Even though the product term between SES and the larviciding intervention reached statistical significance for knowledge of malaria transmission, the CrI of the SES stratum-specific PRcross the null.

Table 3.2: Effect size estimates of the larviciding intervention on reported bed net usage the night before the survey.

Outcome: Bed net usage (N=64,537)	**Model 1**		**Model 2**		**Model 3**	
	PR*	**95% CrI†**	**PR***	**95% CrI†**	**PR***	**95% CrI†**
Univariate						
Larviciding intervention	**0.94**	**(0.93-0.96)**	**0.94**	**(0.93-0.96)**	**0.95**	**(0.93-0.96)**
Time since initiation of larviciding (years)	-	-	-	-	**0.98**	**(0.96-0.99)**
Multivariable‡						
Larviciding intervention	**0.96**	**(0.94-0.97)**	**0.95**	**(0.94-0.97)**	**0.96**	**(0.94-0.97)**
Time since initiation of larviciding (years)	-	-	-	-	**0.98**	**(0.97-0.99)**
Trend for time (AR1§)	*Yes*		*Yes*		*Yes*	
Random effects (Household and TCU)	*Yes*		*Yes*		*Yes*	
Fixed effects at ward level			*Yes*		*Yes*	

Statistically significant results are bolded.
To account for the fact that the coefficients of the ward fixed effects exhibited slow convergence, the number of iterations used for inference was doubled to 120,000 for Model (2) and (3).
*PR: Prevalence ratio
†CrI: Credible interval
§AR1: First-order autoregressive
‡Control variables include: age, gender, dummy for being a follow-up observation, use of insect repellent, use of sprays, use of coil, living in a house with window screens, socio-economic status, and weekly rainfall lagged by two weeks (with quadratic term).

Table 3.3: Effect size estimates of the larviciding intervention on knowledge of at least five malaria symptoms.

Outcome: Symptoms knowledge (N=11,254)	**Model 1**		**Model 2**		**Model 3**	
	PR*	**95% CrI†**	**PR***	**95% CrI†**	**PR***	**95% CrI†**
Univariate						
Larviciding intervention	**0.91**	**(0.87-0.95)**	**0.88**	**(0.83-0.92)**	**0.87**	**(0.82-0.92)**
Time since initiation of larviciding (years)	-	-	-	-	1.03	(0.99-1.07)
Multivariable‡						
Larviciding intervention	**0.91**	**(0.87-0.95)**	**0.88**	**(0.83-0.92)**	**0.87**	**(0.82-0.92)**
Time since initiation of larviciding (years)	-	-	-	-	1.01	(0.98-1.05)
Trend for time (AR1§)	*Yes*		*Yes*		*Yes*	
Random effects (TCU)	*Yes*		*Yes*		*Yes*	
Fixed effects at ward level			*Yes*		*Yes*	

Statistically significant results are bolded.
*PR: Prevalence ratio
†CrI: Credible interval
§AR1: First-order autoregressive
‡Control variables include: age, gender, dummy for being a follow-up observation, and socio-economic status.

Table 3.4:Effect size estimates of the larviciding intervention on knowledge of malaria transmission.

Outcome: Knowledge of malaria transmission (N=11,254)	**Model 1**		**Model 2**		**Model 3**	
	PR*	**95% CrI†**	**PR***	**95% CrI†**	**PR***	**95% CrI†**
Univariate						
Larviciding intervention	1.01	(0.96-1.05)	1.00	(0.95-1.05)	1.01	(0.95-1.06)
Time since initiation of larviciding (years)	-	-	-	-	0.97	(0.92-1.02)
Multivariable‡						
Larviciding intervention	1.01	(0.96-1.05)	1.00	(0.95-1.05)	1.02	(0.97-1.07)
Time since initiation of larviciding (years)	-	-	-	-	0.96	(0.92-1.01)
Trend for time (AR1§)	*Yes*		*Yes*		*Yes*	
Random effects (TCU)	*Yes*		*Yes*		*Yes*	
Fixed effects at ward level			*Yes*		*Yes*	

Statistically significant results are bolded.
*PR: Prevalence ratio
†CrI: Credible interval
§AR1: First-order autoregressive
‡Control variables include: age, gender, dummy for being a follow-up observation, and socio-economic status.

Table 3.5: Effect modification of the larviciding intervention by age, gender, and socio-economic status on bed net usage, knowledge of malaria symptoms, and knowledge of malaria transmission.

Effect modification of the larviciding intervention by age, gender, and socio-economic status (Prevalence ratios and 95% credible intervals)

Bed net usage (N=64,537) †

	Aged ≥5 years	<5 years‡
Control	1.00	**1.02 (1.01-1.03)**
Larviciding	**0.95 (0.94-0.97)**	1.00 (0.99-1.01)
Within Strata Effect	**0.95 (0.94-0.97)**	**0.95 (0.93-0.97)**

	Female head	Male head	Rich	Poor
Control	1.00	1.00 (0.99-1.01)	1.00	**0.98 (0.97-0.99)**
Larviciding	**0.95 (0.94-0.97)**	1.00 (0.99-1.01)	**0.95 (0.93-0.96)**	1.01 (0.99-1.03)
Within Strata Effect	**0.95 (0.94-0.97)**	**0.96 (0.94-0.97)**	**0.95 (0.93-0.96)**	**0.97 (0.95-0.99)**

Knowledge of malaria symptoms (N=11,254) ‡

	Female head	Male head	Rich	Poor
Control	1.00	1.01 (0.99-1.03)	1.00	**0.95 (0.92-0.97)**
Larviciding	**0.86 (0.80-0.91)**	1.02 (0.98-1.06)	**0.89 (0.84-0.94)**	**0.95 (0.91-0.99)**
Within Strata Effect	**0.86 (0.80-0.91)**	**0.88 (0.83-0.93)**	**0.89 (0.84-0.94)**	**0.84 (0.78-0.90)**

Knowledge of malaria transmission (N=11,254) ‡

	Female head	Male head	Rich	Poor
Control	1.00	1.06 (1.04-1.09)	1.00	0.90 (0.88-0.92)
Larviciding	0.98 (0.92-1.04)	1.04 (0.99-1.08)	1.05 (0.99-1.10)	**0.89 (0.83-0.95)**
Within Strata Effect	0.98 (0.92-1.04)	1.02 (0.96-1.07)	1.05 (0.99-1.10)	0.94 (0.88-1.00)

Statistically significant results are bolded.
To account for the fact that the coefficients of the ward fixed effects exhibited slow convergence for the 'Bed net Usage' models, the number of iterations used for inference was doubled to 120,000.
† Models for the bed net usage outcome are adjusted for: age, gender, dummy for being a follow-up observation, use of insect repellent, use of sprays, use of coil, living in a house with window screens, socio-economic status, and weekly rainfall lagged by two weeks (with quadratic term). Models also include: a semiparametric time trend, random effects at household and TCU levels, and fixed effects at the ward level (as in Model 2).
‡ Models for the knowledge of malaria symptoms and malaria transmission outcomes are adjusted for: age, gender, dummy for being a follow-up observation, and socio-economic status. Models also include: a semiparametric time trend, random effects at TCU level, and fixed effects at the ward level (as in Model 2).

DISCUSSION

These results showed that individuals targeted by the larviciding intervention in Dar es Salaam were significantly less likely to have used a bednet the night before the survey. The magnitude of this effect increased with time such that, three years after the initiation of larviciding activities, individuals in intervention areas were 10% less likely to use their bednet as compared to individuals living in non-intervention areas. There was also a decline in household heads' knowledge of malaria symptoms and this effect was more pronounced for individuals of low SES. No differences between larviciding and non-intervention areas, with respect to knowledge of malaria transmission, were found.

With regard to bednets, several studies have suggested that their use is a function of night-time temperature, perceived malaria risk and density of nuisance biting insects [30-32]. Thus, the significant reduction in the probability of using a bednet in UMCP intervention areas could result from two factors. First, the UMCP made a programmatic decision to control larval stages of nuisance biting insects such as *Culex quinquefasciatus* (a mosquito involved in the transmission of lymphatic filariasis, but not malaria), as an effort to gain community support. A significant reduction in nuisance biting rates could deter individuals from using bednets if personal protection against mosquito bites is not perceived as being necessary anymore. Nevertheless, data from the first phase of the UMCP intervention suggest that routine larviciding was not successful in suppressing nuisance biting, and culicine mosquitoes were still responsible for more than 100 bites per exposed person per night in the intervention wards [20]. The impact of controlling nuisancebiting insects will be context specific, however, depending on the relative abundance of different species of mosquitoes. Second, the reduction in the prevalence of malaria infection from 20.8% in 2004 to 1.7% in 2008 following larval control [21,26] can potentially

change the individual perception of malaria risk. In this case, the disease may not be perceived as a threat to health anymore, leading to varied behaviour changes, including reduced adoption of personal protective measures, such as bednet use. The reported results tend to support this hypothesis.

Despite the significant reduction in the probability of using a bednet following the larviciding intervention, the proportion of individuals using a net in non-intervention areas increased throughout the study period.In October 2004the Tanzania National Voucher Scheme was launched. The aim of this programme was to provide every pregnant woman with a printed voucher valued at TZS2,750 (USD2.75 in 2004) to purchase a discounted-price bed net[33]. In October 2006, a second voucher was introduced targeting mothers and caretakers of infants aged nine months at the time of measles vaccination [34] and , in January 2007, the value of the voucher was increased to TZS3,250 [35]. The subsequent introduction and improvements of these financial incentives could thus have resulted in higher bed net ownership and usage.

A decline in the knowledge of malaria symptoms, particularly in areas under the UMCP larval control intervention, is also worrisome. Caregivers' inability to recognize malaria symptoms has been cited as an impeding factor for early treatment of severe malaria in Tanzania [19]. With lower transmission intensities, population-level immunity is expected to decrease and the clinical spectrum of severe malaria may change with cerebral malaria accounting for a higher proportion of cases[6]. Therefore, early and proper recognition of symptoms is crucial to reduce malaria morbidity and mortality [36]. Of particular concern is the finding that SES is modifying the relationship between larviciding and knowledge of malaria symptoms. Given that out-of-pocket expenditure for malaria treatment usually consumes a larger proportion of low SES

households' budget [37], inappropriate or delayed treatment could potentially be exacerbated in these disadvantaged households by their inability to recognize malaria symptoms.

If knowledge is formed based on experience, one could hypothesize that as malaria transmission goes down, and fewer cases are observed, personal experience with malaria episodes also reduces, and thus the ability of individuals to properly identify disease symptoms may be compromised. That would be maximized if malaria was not perceived as a major threat. While intuitively it is reasonable to assume that these changes would increase over time (assuming that transmission remains fairly low or declines even further), this study's results do not support that. In addition, the available data do not allow assessing the mechanisms through which knowledge of malaria symptoms is changed.

Regarding knowledge that mosquitoes transmit malaria, there is no evidence of changes following the UMCP larval control. Two factors could explain this result. First, community sensitization and participation are a central component of an integrated vector management strategy as endorsed by the World Health Organization [38]. In Dar es Salaam, each TCU has a leader and the UMCP worked closely with them to foster support for the larviciding activity, and to guarantee unrestricted access to breeding habitats, many located on private properties. Therefore, the population living in the UMCP area was aware of the presence and the purpose of larval control teams. Second, larval control personnel conducted their work wearing a UMCP T-shirt, displaying the name of the project and the life cycle of the mosquito. Thus, the weekly presence of the larval control teams may have acted as a regular reminder of the importance of mosquitoes for malaria transmission. These two factors could potentially overcome the expected decline in knowledge in scenarios of low malaria transmission.

The strengths of this study include its large geographic and temporal extents, availability of reliable baseline information, control of many potential confounders, reporting of effect size estimates on the risk ratio scale, a large sample size, and detailed use of robustness checks and sensitivity analyses. The study has some limitations. First, the order of the rollout of the intervention was not randomly allocated. If ward-level characteristics are correlated with the intervention, the reported effect size estimates could be biased. Nevertheless, including fixed effects at the ward level, which control for ward-level time-invariant confounders, did not affect the reported effect size estimates. Second, information on knowledge of malaria symptoms and transmission was only collected from household heads. Intra-household decisions about health expenditure and treatment-seeking behaviour follow a complex process that involves trade-offs and bargaining among household members. This paper's inferences are thus based on the assumption that the household head's level of malariaknowledge is representative of that of other household members involved in this decision making process. The fact that gender was not found to be an effect modifier tends to support this assumption.

This study's findings need to be discussed in light of the current efforts of intensified malaria control with the goal of eradication. In countries considering elimination, and in areas where transmission has been reduced to very low levels for a few years, acquired immunity is low and thus sustaining gains of malaria control becomes crucial to prevent outbreaks and resurgence of the disease [11], such as that occurred in Sri Lanka during the late 1960s [7]. If knowledge and behaviour change follows successful interventions that reduce malaria transmission to low levels, then sustainability of control efforts and gains may be at risk. A potential strategy to address these issues, currently largely neglected by national malaria control

programmes, is the implementation of a comprehensive behavioural change communication process, which addresses gaps in knowledge and problems in disease risk perception.

Conclusions

This study points to two major research gaps. First, there is an urgent need to conduct more studies, similar to this one, to assess the extent to which countries that have achieved significant decline in malaria transmission are also observing changes in individual behaviour and knowledge. Second, multidisciplinary assessments that combine quantitative and qualitative data, utilizing theories of health behaviour and theories of knowledge, are needed to inform and optimize efforts of national malaria control programmes, and ultimately contribute to sustained reductions in malaria transmission.

COMPETING INTERESTS

The authors have declared that they have no competing interests.

AUTHORS' CONTRIBUTIONS

MCC developed the original research idea of the paper, designed the UMCP household survey and supervised data collection with inputs from UMCP collaborators, advised on data analysis and interpretation, and edited the manuscript. MMG performed the data analyses, interpreted the results, and wrote the manuscript.

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SUPPLEMENTARY APPENDIX 3.1:

BACKGROUND

In this supplementary appendix, we provide detailed information on the statistical analyses we performed. We have organized this supplement in four sections. First we describe in greater details the three model specifications used in the manuscript. Second, the different prior distributions for the models' parameters and hyperparameters are defined. Third, we described how the models were fitted and the type of convergence diagnostic performed. Lastly, we describe some of the sensitivity analyses we performed to assess the robustness of our findings.

MODEL SPECIFICATIONS

We assumed that our binary outcomes followed a Bernoulli distribution, $Y_i \sim Bernoulli(p_i)$, where p_i is the probability of an individual having the outcome, which is itself a function of covariates modelled with a *logit* link. We present three models with increasing levels of complexity, as described below.

Model 1: TCU and household random effects model

$$\text{logit}(p_{itjk}) = \quad + \quad (\text{Intervention}_{\text{it}}) + \quad X_{it} + f(\text{Time}) + \quad _{\text{j}} + \quad _{k} + \quad _{itjk}$$

$$\mu_j \sim N(0,\sigma_\mu^2), \upsilon_{\text{k}} \sim N(0,\sigma_k^2), \text{and } \varepsilon_{\text{itj k}} \sim N(0,\sigma^2)$$

where p_{itjk} is the probability of individual i at time t living in TCU j and, if applicable, household k, to have the outcome of interest (i.e., used a bednet, know malaria symptoms, and know how malaria is transmitted); β is the coefficient of the larviciding intervention; δ is a vector of coefficients for control variables in X; μ_j is a TCU-level random effect; and υ_k is an household random effect. Note that the household level random intercept is included only when the

outcome is bednet usage (individual level variable) as information on knowledge of malaria symptoms and transmission was recorded for household heads only. Finally, the time trend was accounted for with *f(.)*, a semi-parametric smooth function where a spline penalty follows a first order autoregressive process [1].

Model 2: TCU and household random effects model with ward fixed effects

$$\text{logit}(p_{itjk}) = \quad + \quad (\text{Intervention}_{it}) + \quad X_{it} + \quad \text{Ward}_{it} + f(\text{Time}) + \quad _{j} + \quad _{k} + \quad _{itjk}$$

$$\mu_j \sim N(0,\sigma_\mu^2), \upsilon_k \sim N(0,\sigma_k^2), \text{and } \varepsilon_{itjk} \sim N(0,\sigma^2)$$

where p_{itjk} is the probability of individual *i* at time *t* living in TCU *j* and, if applicable, household *k* to have the outcome of interest; ω is a vector of coefficients for the ward fixed effects; and β, δ_d, *f(.)*, μ_j, and υ_k are similar to those described in Model 1.

Model 3: TCU and household random effects model with ward fixed effects and allowing for change in slope as a function of time since initiation of intervention

$$\begin{aligned}\text{logit}(p_{itjk}) = \quad & + \quad (\text{Intervention}_{it}) + \quad (\text{Time Since Intervention}_{it}) + \\ & X_{it} + \quad \text{Ward}_{it} + f(\text{Time}) + \quad _{j} + \quad _{k} + \quad _{itjk}\end{aligned}$$

$$\mu_j \sim N(0,\sigma_\mu^2), \upsilon_k \sim N(0,\sigma_k^2), \text{and } \varepsilon_{itjk} \sim N(0,\sigma^2)$$

where p_{itjk} is the probability of individual *i* at time *t* living in TCU *j* and, if applicable, household *k* to have the outcome of interest; β is the coefficient for the level shift in the outcome due to the intervention; γ is the coefficient for the change in slope as a function of time (in years) since the initiation of the larviciding activities; and ω, δ_d, *f(.)*, μ_j, and υ_k are similar to those described in Models 1 and 2.

PRIOR DISTRIBUTIONS

Priors for the regression parameters were assumed to have non-informative Gaussian (mean = 0, precision= 0.001) distributions. Priors for the standard deviations of the random effects at the TCU and household levels were assumed to follow non-informative Uniform (0, 100) distributions. The hyperparameters for the first order autoregressive semi-parametric smooth were given a Gamma (shape = 1, scale = $1e^{-5}$) prior for the precision parameter, as proposed by Natário and Knorr-Held [2], and a Gaussian (mean = 0, precision = 0.40) prior for the first lag correlation parameter, which was defined on the logit scale. In order to improve mixing of the MCMC chains and faster convergence, hierarchical centering and parameter expansion were used [3,4].

MODEL FITTING

The Bayesian models were fitted using Markov Chain Monte Carlo (MCMC) simulations. All analyses were performed using the R statistical software [5]. Estimation of the marginal posterior distribution of the parameters of interest was performed using JAGS [6,7]. An adaptive phase of 5,000 iterations and a minimum of 65,000 iterations from the Metropolis-Hasting algorithm were used for inferences (5,000 iterations used as burn-in). Convergence and stationarity were assessed through visual inspection of trace plots, the Raftery-Lewis statistic [8], and the Heidelberger and Welch's diagnostic [9]. The 'rjags' and 'CODA' libraries were used as an interface to run JAGS directly from R [10] and perform convergence diagnosis [11], respectively. Observations with missing data for age (n=44) were retained in the analysis using the missing indicator method [12].

SENSITIVITY ANALYSES

The robustness of our results to model specification was also investigated. Specifically, we examined the sensitivity of the choice of penalty type for the time trend (1st order

autoregressive versus 1st and 2nd order random walks), different covariates adjustments (SES versus educational level and occupation), potential spillover effects (contamination of our intervention wards from non-intervention areas), and presence of spatially structured effects using Conditionally Auto-Regressive models [13]. Results from these sensitivity analyses demonstrated that our reported effect size estimates were robust to our modelling assumptions and only the three main models described above will be reported in this paper.

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