Impact of odour-baited mosquito traps for malaria control:

design and evaluation of a trial using solar-powered mosquito trapping systems in western Kenya

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To the peoples of Africa

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Chapter 1

General introduction

Background

Malaria is a multifaceted disease caused by protozoan parasites belonging to the genus *Plasmodium.* The parasite is transmitted to humans by bites of an infected *Anopheles* mosquito. Only mosquito species of the genus *Anopheles* can transmit human *Plasmodia*. In 2015 over three billion people were to a certain extent exposed to the risk of malaria transmission and about 20% of the world population (1.2 billion) lives in parts of the world with a high risk of infection (WHO, 2015b). Estimates from 2015 state that worldwide, 214 million malaria cases occurred leading to 438,000 deaths (Figure 1.1). However, the number of malaria related deaths is controversial, with some authors suggesting that the actual number of casualties is approximately twice as high (Murray *et al.*, 2012).

Although a decline in malaria cases and deaths has been observed since 2000, the group that is most affected remains to be found in Sub-Saharan Africa [SSA] (90%), in particular children below the age of five years (WHO, 2015b). At least in 109 nations or territories malaria is prevalent, and it is the fifth cause of death from infectious disease worldwide (RBM, 2013). Besides, the burden of malaria is not only expressed and felt in health parameters. The economic burden caused due to malaria morbidity and mortality is estimated at US$ 12 billion per year absorbing up to 40% of the health expenditure in SSA countries (RBM, 2013; Sachs *et al.*, 2002).

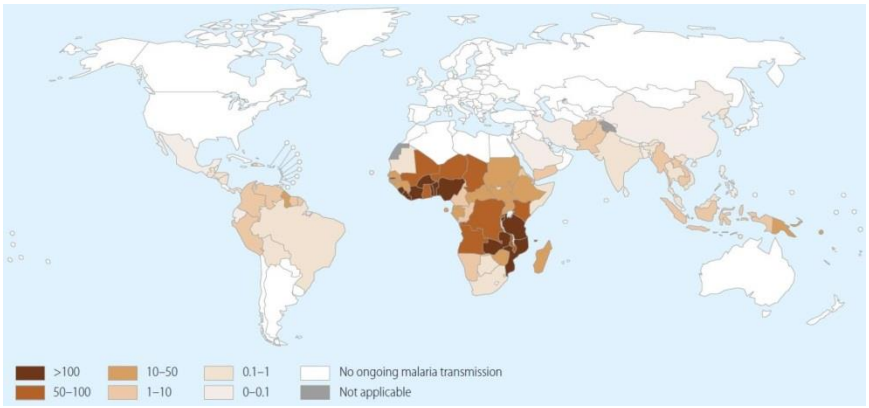

Figure 1.1: Confirmed malaria cases per 1000 people. Source: World Health Organisation, *Malaria Report* 2015

Life cycle

Malaria is caused by infection with parasites of the genus *Plasmodium.* There are currently five known species of *Plasmodium* that affect humans*: P. falciparum, P. malariae, P. ovale, P. vivax* and *P. knowlesi* (White *et al.*, 2014). The main route of malaria transmission is from human to human through the bite of a female anopheline mosquito. Mosquito females rely on blood meals to develop offspring. The parasites

reproduce in the mosquito to become infective for humans (Figure 1.2). When an infectious female bites a human, the parasites find their way to the liver where they reproduce asexually and develop into merozoites. Mature merozoites, having erupted from the liver cells, invade red blood cells to reproduce again and invade other red blood cells (Leggat, 2003). A vital process besides these phases is the differentiation of merozoites into gametocytes; if a female *Anopheles* consumes a blood meal ingesting the gametocytes, the cycle starts all over again (Leggat, 2003; Sherman, 1998).

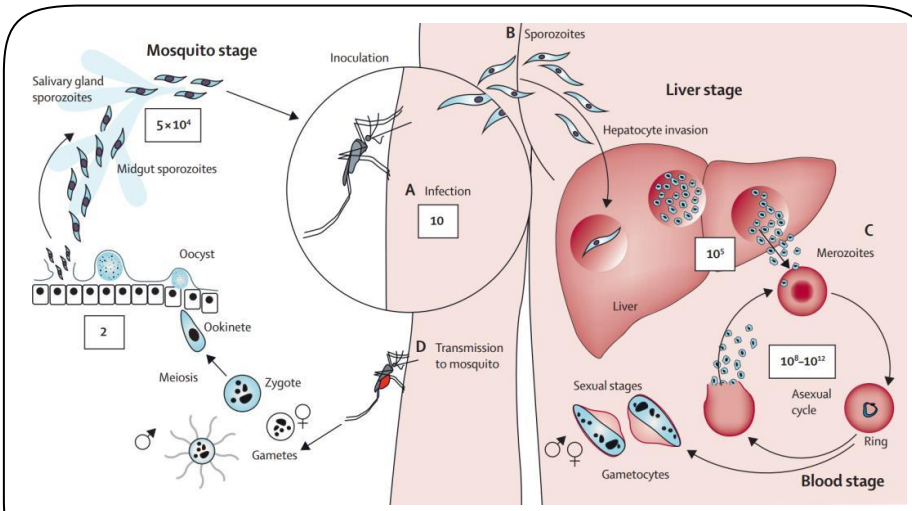

Figure 1.2: Life cycle of the *Plasmodium* parasite in humans and malaria mosquitoes. Source: Malaria, The Lancet 2014, Nicholas J White, Sasithon Pukrittayakamee.

Over 400 *Anopheles* species are known, whereas approximately 60 are capable of transmitting *Plasmodium*. The majority of malaria in SSA is spread by mosquitoes belonging to the *An. gambiae* complex , and to a lesser extent *An. funestus* (Sinka *et al.*, 2012). In particular *An. gambiae sensu stricto* and *An. arabiensis* are major contributors to transmission. *An. funestus and An. gambiae* are principally endophagic (indoor biting) and have their resting place indoors (endophilic), whereas *An. arabiensis* is described as opportunistic, exophagic and exophilic (Figure 1.3).

From past to present

In 1880, malaria parasites were first identified using a microscope followed by the discovery of mosquitoes as the parasite-transmitting vector (Capanna, 2006), and after the discovery of the transmission cycle by Ronald Ross scientists had more insight in interrupting the transmission and how to control malaria (Hay *et al.*, 2004). An extensive variety of efforts followed to get rid of the disease during the 19th and

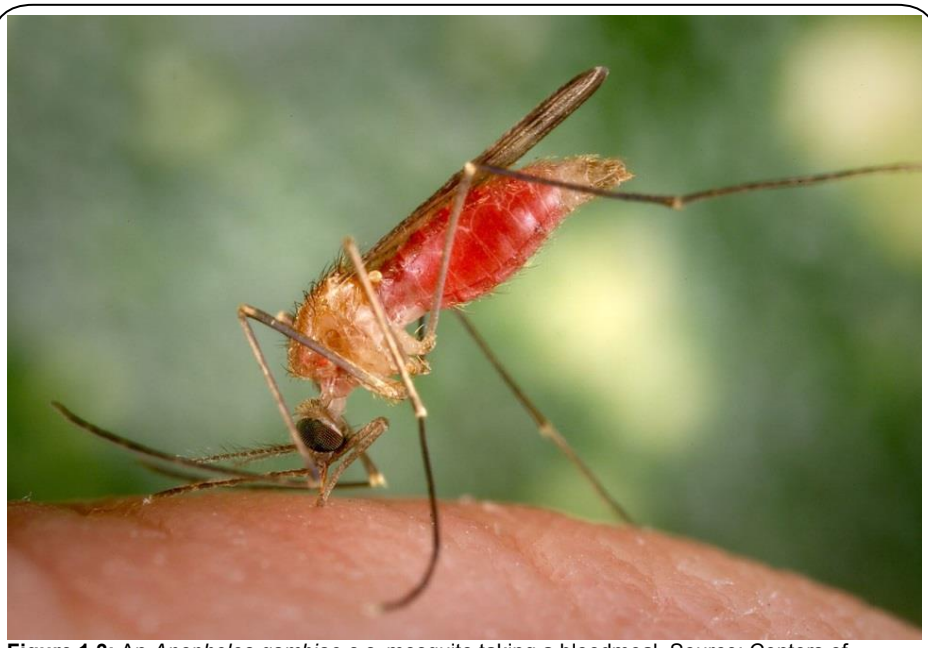

Figure 1.3: An *Anopheles gambiae s.s.* mosquito taking a bloodmeal. Source: Centers of Disease Control, United States of America

20th century. Mainly as a result of improved housing, the development of social settings and altered agricultural methods, a major reduction of malaria was achieved. Following the discovery of dichlorodiphenyltrichloroethane [DDT] in 1940, synthetic insecticides became the main instrument in the fight against malaria and in 1955 the World Health Organization [WHO] initiated GMEP (global malaria eradication programme). Insecticides opened the door to large-scale malaria control, with great short-term results. Although many parts of the world were engaged in deploying this method, the process of eradication stagnated. Due to the multifaceted and obstinate nature of the disease, WHO ceased the GMEP in 1969 (Hay *et al.*, 2004). Malaria was eliminated from many areas, mainly in temperate zones, and regarded to be a minor health issue in many formerly-endemic areas; the disease, however, was not controlled in tropical zones and even found its way back in some controlled areas as further efforts against malaria were disregarded. In the following decades malaria developed to be one of the most important threats to public health in SSA countries (Murray *et al.*, 2012).

In 1998 a new world wide initiative was called into life with the Roll Back Malaria Partnership Global Malaria Action Plan [RBM GMAP]. This global framework for coordinated action against malaria aims to create agreement among key actors in malaria control, harmonizes action and assembles means to combat malaria in endemic areas. Initiators WHO, UNICEF, the World Bank and UNDP had set an

ambitious goal by stating that malaria related deaths would be near zero by 2015 (RBM, 2013). The focus shifted again toward malaria elimination, and numerous efforts were made to develop and implement effective methods to prevent, diagnose and cure malaria. Principally due to intensified use of long-lasting insecticidal nets [LLINs] and indoor residual spraying [IRS] of insecticides in houses, large reductions in malaria morbidity and mortality were observed between 2000 and 2013: 30% less malaria deaths and 50% less malaria infections in children and adolescents (Murray *et al.*, 2012; WHO, 2015b). Not only did vector control contribute to the decline in malaria, effective case management insured that malaria was treated promptly. Rapid diagnosis tests [RDTs] and artemisinin-based combination therapy [ACT] has been made widely available and affordable.

However, with the present tools and interventions the goal of malaria eradication has to overcome several challenges. Current knowledge on the endgame of malaria emphasizes the heterogeneous character of the disease stressing the complexities and dynamics of transmission, ecology and environment (Alonso *et al.*, 2011c; Feachem *et al.*, 2010; White *et al.*, 2014). Every region has its own set of these factors, making an one fits all strategy unlikely to succeed (Mendis *et al.*, 2009). Finally, we arrived in an age where the effective methods to control malaria are threatened. Current vector control is under pressure as malaria mosquitoes become resistant against insecticides used (Ranson *et al.*, 2011). Moreover, worrying numbers of reports about mosquito species biting outdoors and during the day make bed nets and IRS less effective (Russell *et al.*, 2013; Sougoufara *et al.*, 2014). Likewise, case management is becoming less effective as malaria parasites develop resistance against ACTs (Dondorp *et al.*, 2010).

Because of these challenges it is recognized that upscaling of present-day tools with the existing understanding will not be sufficient to eradicate malaria; it is addressed that research on developing tools, innovative interventions, and strategies to interrupt transmission needs to be pursued in order to attain the goals set by RBM (Alonso *et al.*, 2011c; Snow, 2015; Tanner *et al.*, 2015).

Malaria control

Insecticide treated nets

Insecticide-treated bed nets, impregnated with a pyrethroid derivative, mostly permethrin, have proven to be effective over the past decades. Numerous studies in different settings focussing on different health outcomes have found significant effects of LLINs on malaria morbidity and mortality. A systematic review in 2009 by the Cochrane collaboration reviewed over 20 large scale studies examining the impact of

LLINs on several health outcomes (Lengeler, 2009). However, several studies conducted in 1990s found that the decrease in child mortality attributed to the use of bed nets appeared significantly lower in study sites with a high malaria transmission (Binka *et al.*, 1996; D'Alessandro *et al.*, 1995; Fraser-Hurt *et al.*, 1999; Habluetzel *et al.*, 1997; Nevill *et al.*, 1996). During a large scale bed net trial in Asembo, Kenya, it became clear that it is possible to reduce morbidity and save the life of one on every four children by implementing LLINs (Phillips-Howard *et al.*, 2003; ter Kuile *et al.*, 2003). Nonetheless, results are heavily compromised if re-treatment of the nets is not regularly performed. And a decline of the positive effect of LLINs on morbidity and mortality is found after the first year in a number of studies (Binka *et al.*, 1996; D'Alessandro *et al.*, 1995; Habluetzel *et al.*, 1997; Nevill *et al.*, 1996; Phillips-Howard *et al.*, 2003). Additionally, a limitation of LLINs to control malaria is that people are not protected against malaria transmission when vectors are exophagic, biting outdoors. The most prominent vectors in SSA traditionally prefer to bite indoors (Pates *et al.*, 2005). However due to the impact of permethrin indoors, mosquitoes tend to become more exophagic over time (Geissbuhler *et al.*, 2007). In relation to this it is found that LLINs can have a community wide effect, which in turn reduces the chance of transmission outdoors (Binka *et al.*, 1996; W. A. Hawley *et al.*, 2003; Howard *et al.*, 2000).

Indoor residual spraying

Indoor residual spraying is the procedure of applying insecticides on the inside of residencies or other roofed constructions to kill, reduce the life span or repel mosquitos. It is obtainable in multiple formulations, and sprayed on walls and resting places of mosquitoes. It kills mosquitoes depending on the insecticide, but the repellent effect of IRS keeping the vector outside is the primary transmission interrupting process (RBM, 2013). IRS has an extensive history as effective intervention method against malaria. Strong evidence exists of the effectiveness of IRS in reducing malaria incidence (Murphy, 2003; Pluess *et al.*, 2010). It has been a foremost contributor to the elimination of malaria in the United States, parts of Russia and numerous areas in Europe and Asia. Moreover, IRS has contributed to controlling malaria in SSA. However, in areas of perennial transmission IRS alone or in combination with other strategies is not effective and sustainable over time (Pinder *et al.*, 2015). The large scale project on IRS conducted in Garki, Nigeria, is the best example. This study showed a significant decline in prevalence of the disease, but only during the wet season, and effects were not sustainable (Gramiccia & Molineaux 1980). In another study with stable malaria IRS had a protective effect on the incidence of young children, however, no difference was found between the control and intervention concerning all age prevalence (Curtis *et al.*, 1998). In a similar transmission situation, the prevalence of malaria was lowered with 50% after spraying, this was nonetheless not sustainable enough to last (Sharp *et al.*, 2007). In

case of unstable malaria, IRS had more profound effects in two large scale studies: prevalence and incidence had dropped to a fraction of the original state (Misra *et al.*, 1999; Rowland *et al.*, 2000). Additionally, a review by the Cochrane collaboration concluded that proof of IRS improving health outcomes is limited regarding long-term observational data.

Case management

Subsequent to preventing malaria through vector control, diagnosing and treating infections is the most important approach to control malaria. And if performed systematically at a large scale, case management with artemisinin combination therapy [ACT] is capable of reducing the transmission intensity and child mortality (Thwing *et al.*, 2011). In situations with higher transmission intensity, though, the influence of early diagnosis and treatment of infected individuals on transmission is restricted. Since in areas where people are exposed to many infective bites, some immunity is developed and infected individuals are often asymptomatic (WHO, 2015a). Consequently, case management principally saves and cures lives and is not an instrument to interrupt transmission. In western countries, early diagnosis and treatment with appropriate drugs almost always results in recovery. However, in low and middle income countries early diagnosis and access to health care are not as widely available as in the higher income countries. An additional concern of case management and effective treatment in these developing settings, as mentioned before, is the resistance of the parasite against drugs (Dondorp *et al.*, 2010). Large scale misuse and bad compliance make medicines ineffective. A proper diagnosis should be administered, the right drugs prescribed and taken in the precise dose for the right period (Amexo *et al.*, 2004; Gwer *et al.*, 2007).

Alternative control measures

Besides the three conventional fields of controlling malaria as described by RBM and WHO, there are several novel methods being developed. The vanguard of new controlling interventions exists out of vaccines making the parasite innocuous within the infected individual (Penny *et al.*, 2015), control of mosquito larvae (larval source management) and the genetic modification of anopheline mosquitoes (Elden, 2011; Takken *et al.*, 2009).

Since the 1970s researchers have extensively been looking for an effective vaccination against malaria infection. Unlike most other infectious diseases, immunity is minimal after contact with the pathogen. It takes many infections before the immune system starts to accumulate resistance against malaria. To-date only one vaccine has proven effectiveness and is currently being investigated in Sub Saharan Africa with further trials (Tinto *et al.*, 2015). Where present vector control strategies are recognized not to be effective when vectors bite outdoors and before dusk, interventions that do target these characteristics can make a major contribution

towards eradication. Mosquito larval control as well as the genetic modification of mosquitoes aim to reduce the number of infective bites. The first method attempts to put pressure on the mosquito population by finding ways to interrupt the development of larvae (Fillinger *et al.*, 2011). The latter focusses on manipulating the genome of mosquitoes to disable its capabilities to carry the parasite; or to sterilise male mosquitoes to disrupt reproduction (Sinkins *et al.*, 2006). However, when released in nature the survival of modified strains is posing a great challenge (Alphey, 2014).

Odour-baited traps

Another development and possible alternative method to reduce malaria - and the subject of this thesis - is the use of odour-baited mosquito traps [OBT] to mass trap malaria vectors. Unlike any other intervention it attempts to target the olfactory pathway: the sense on which the vector relies to track down potential blood meals (Takken *et al.*, 1999; Zwiebel *et al.*, 2004). OBTs are already, and for many years, successfully deployed for the control of tsetse flies, the principle vectors of human and animal trypanosomiasis (Vale *et al.*, 1988).

For malaria mosquitoes, research has focussed on the mechanism and elements that are mediating the host-seeking process of the mosquito. During the past decennia it became clear that mosquitoes are attracted to a combination of body odour and carbon dioxide (Andreasen *et al.*, 2004; Takken, 1996). Synthetic lures trying to mimic a host have been tested and studies demonstrate that malaria mosquitoes are attracted to synthetic odour (Okumu *et al.*, 2010b; Verhulst *et al.*, 2011a). Based on these findings a trapping mechanism was developed to attract and kill malaria mosquitoes (Hiscox *et al.*, 2014). The research on malaria mosquito trapping has intensified over the past five years reporting on the relative attractiveness and possible health impact (Njiru *et al.*, 2006; Okumu *et al.*, 2010c). However, there has never been a large scale epidemiological study attempting to find the relationship between deploying odour-baited mosquito traps, vector densities and malaria incidence and prevalence. The OBT could have great implications for malaria control for it is not susceptible to any form of insecticide or drug resistance, and could complement the existing intervention methods by reducing vector densities in areas of high or low malaria transmission. Moreover, it could unlike IRS and LLINs also target mosquitoes during daylight and outdoors providing a community effect rather than only an individual effect.

Malaria epidemiology

The spread of malaria depends on the lifecycle of the *Plasmodium* parasite in humans and malaria vectors, and on the behaviour and environment of these hosts (Greenwood, 1997). Interventions to control or eliminate malaria are concentrating on the disruption of the transmission to ultimately reduce the incidence, prevalence and

mortality of malaria (WHO, 2015b). A decline in the local malaria incidence begins if the average number of new cases occurring from an infected individual (the R_0) is less than one. Likewise if the number of infectious bites of mosquitoes (entomologic inoculation rate) becomes less than one per human, malaria will shrink. Starting from these concepts, malaria epidemiology is constructed and complex versions of epidemiological models allow for thorough understanding how to interrupt transmission (Reiner *et al.*, 2013). These models and theories form the basis for evaluation of the impact of malaria interventions. Current vector control interventions focus on prevention of the interaction of host-seeking mosquitoes with humans by using repellent insecticides or LLINs (Hemingway, 2014). Direct results of these interventions are fewer infective bites and less offspring. However, the actual effect of vector control measures on malaria transmission may vary due to a large number of variables in a specific setting. For example, whether there is other mosquito control or whether the primary vector bites indoors or outdoors, or if there is a preference to bite humans or also other animals (Chitnis *et al.*, 2012). The availability of humans to mosquitoes may depend on the distance from breeding sites or the accessibility of houses, but also on human social economic status and human behaviour like outdoor occupation (Griffin *et al.*, 2010).

Heterogeneity in human populations may also influence the evaluation of trials to effective drugs against malaria infection or chemoprophylaxis to prevent infection. Different levels of immunity and varying demographic backgrounds can be important predictor variables (Crompton *et al.*, 2014). The number of new cases over a certain period (incidence) or the percentage of people testing positive in a cross section of the population (prevalence) as well as different transmission parameters are often used for evaluation. Trials evaluating the effect of such vector or parasite interventions on the malaria epidemiology rely on the proper monitoring of these outcomes. An appropriate health and demographic surveillance (HDSS) designed to sensibly collect the data of interest is of vital importance to achieve a valid result (Alonso *et al.*, 2011a). Ultimately, if the epidemiology at a local scale is well understood, and data relating to malaria infection and the intervention applied is carefully collected, predictions based on mathematical models may further explore the effectiveness and implications of such interventions (Chitnis *et al.*, 2010; Griffin *et al.*, 2010).

This thesis

Presently it is recognized by the Roll Back Malaria programme that malaria eradication is the goal. In order to attain this, several challenges have to be dealt with. Current instruments to control malaria like IRS, LLINs and case management are

unlikely to achieve this goal alone. Current strategies and interventions have to be improved and new developments initiated. Leading groups and institutions working on malaria control repeatedly emphasize this, identify the challenges encountered and spearhead solutions to overcome them.

The aim of this PhD dissertation is to develop and conduct an epidemiological study to assess the impact of mass trapping of mosquitoes by means of odour-baited traps on malaria vectors, malaria incidence and prevalence. The study was conducted on Rusinga Island, an area with approximately 25,000 inhabitants in Lake Victoria, Kenya.

Objectives of the thesis

- To describe a detailed protocol about the SolarMal project so that similar studies may be aided with the methods and implementation
- To develop an appropriate statistical design to analyse the intervention trial
- To develop new outcome measures that consider the spatial effects of interventions against pathogens over time and through space
- To describe the design, implementation and results of a novel and effective health and demographic surveillance system based on a digital data platform to monitor the progress of a large scale intervention
- To present the collection methods and results of variables associated with the relationship between malaria and OBTs for future modelling purposes
- To elucidate risk factors for malaria at the study site
- To use a geostatistical model to emphasize the importance of considering the geographical heterogeneous nature of malaria risk factors when introducing a malaria control intervention
- To demonstrate that OBTs contribute to a reduction in malaria vectors and therewith biting
- To study if there is a substantial reduction in malaria incidence in intervened areas and island wide
- To study if there is a significant reduction in malaria prevalence in intervened areas

Chapter 2 introduces the study protocol of the intervention trial. It is an overview chapter that includes all different disciplines and research plans of the project. Timelines, brief research strategies, methods of data collection and structures to evaluate the data are described.

The third chapter describes the methods of data collection and introduces a new time efficient and cost effective data management platform and organization tool. Health and demographic surveillance systems (HDSS) are often installed on sites in low and

middle income countries to monitor specific health interventions in a research population. Logistics and organisation of data collection, quality and management have always been a time and cost consuming effort. Here a complete digitized system relying on computer tablets to collect data in the field and advanced available free software to manage the data server is presented.

In Chapter 4 the experimental design of the SolarMal trial is described. The implications of a stepped-wedge cluster-randomized trial to evaluate a pathogen is described and two new outcome measures are suggested. By modelling possible randomisation procedures and different sizes of intervention effectiveness, an appropriate statistical design is chosen for analysing the SolarMal project.

Chapter 5 describes the findings of the HDSS. In order to conduct a proper trial relying on data collection by HDSS, the data collected should be able to reflect the demographic dynamics as well as possible. This chapter reports detailed figures on demographic parameters and household characteristics.

The heterogeneous nature of malaria is present at all geographic levels. Risk factors are not equally distributed, and therefore effects of interventions will not have similar effects in different settings. Chapter 6 performs a malaria risk factor analysis by using two models, a standard linear regression model and a geographic weighted regression model that accounts for geographic variation of risk factors. It is concluded that malaria and risk factors for malaria are highly heterogeneous distributed, even on a micro epidemiological scale. Recommendations are made to aid guidance of malaria intervention deployment and future field implementation of OBTs.

The 7th chapter describes the outcome of the SolarMal project following the study protocol of Chapter 2 and using the proposed analysis of Chapter 4. It is concluded that OBTs have a significant effect on malaria vector densities and malaria prevalence, comparable to the effect of bed nets on some malaria vectors and malaria prevalence.

The final chapter discusses the results and methods of this thesis. Weak and strong aspects are put forward in the light of recommendations for future research.

Chapter 2

Mass mosquito trapping for malaria control in western Kenya: study protocol for a stepped wedge cluster-randomised trial

Alexandra Hiscox*, Tobias Homan*, Collins K. Mweresa, Nicolas Maire, Aurelio Di Pasquale, Daniel Masiga, Prisca A. Oria, Jane Alaii, Cees Leeuwis, Wolfgang R. Mukabana, Willem Takken, Thomas A. Smith

** Both authors contributed equally to this work*

Publication under review

Abstract

Background: Increasing levels of insecticide and drug resistance, as well as outdoor, residual transmission of malaria threaten the efficacy of existing tools used for control of this disease. The development of odour-baited mosquito traps has led to the possibility of controlling malaria through mass trapping of malaria vectors. Through daily removal trapping it is anticipated that vector populations could be suppressed to a level where continued transmission of malaria will no longer be possible. **Methods:** A stepped wedge cluster-randomised trial design was used for the implementation of mass-mosquito trapping on Rusinga Island, western Kenya (The SolarMal Project). Over the course of two years (2013 – 2015) all households on the island were provided with a solar-powered mosquito trapping system. A continuous health and demographic surveillance system combined with parasitological surveys three times a year, successive rounds of mosquito monitoring and regular sociological studies allow measurement of intervention outcomes before, during and at completion of the rollout of traps. Data collection will continue after achieving mass coverage with traps in order to estimate the longer term effectiveness of this novel intervention. Solar energy was also exploited to provide electric light and mobile phone charging for each household and the impacts of these immediate tangible benefits upon acceptability of, and adherence to the use of the intervention are being measured. **Discussion:** This study will be the first to evaluate whether the principle of solar-powered mass-mosquito trapping could be an effective tool for the elimination of malaria. If proven to be effective this novel approach to malaria control would be a valuable addition to the existing strategies of long-lasting insecticide-treated nets and case management. Sociological studies provide a knowledge base for understanding usage of this novel tool.

Key words: Vector control, mass trapping, anopheline mosquitoes, odour-baited trap, transmission, clinical malaria, stepped wedge cluster-randomised trial

Significant reductions in malaria infections and mortality since the year 2000 are associated with increased coverage of vector control interventions such as long-lasting insecticidal nets [LLINs] and indoor residual spraying [IRS], as well as improved availability and access to preventive therapies, diagnosis and treatment (Bhatt *et al.*, 2015). However, the development and spread of insecticide resistance, drug resistance and the occurrence of residual malaria transmission outdoors and in the early evening threatens the long term sustainability of current tools for malaria control. This necessitates the development of new alternatives, particularly as many regions move towards malaria elimination (Alonso *et al.*, 2011c; Tanner *et al.*, 2015). In 2013 an estimated 538,000 people lost their lives due to malaria with 90% of those deaths occurring in the WHO African Region (World Health Organization, 2015); a region where millions of dollars of malaria-associated economic losses are suffered every year (Sachs *et al.*, 2002). With the addition of new tools for malaria control that could reduce household spending on malaria-associated expenses, millions of people could escape the cycle of poverty and disease. Estimates show that for each dollar spent to control malaria, up to 60 USD worth of benefits could be gained for the overall well-being of a society in the sub-Saharan Africa region (WHO, 2015).

Studies to characterise the components of human odour which are attractive to host-seeking *Anopheles gambiae s.s.* have led to the identification of a large number of compounds (Mukabana *et al.*, 2012b; Okumu *et al.*, 2010b; Verhulst *et al.*, 2011b) which, at appropriate concentrations, can be combined to create synthetic mosquito lures that mimic a human host (Menger *et al.*, 2014b; Okumu *et al.*, 2010b). These lures can remain attractive to mosquitoes even after a year of use (Mweresa *et al.*, 2015). Synthetic lures can be placed in counter flow trapping systems and used to lure and capture host-seeking mosquitoes both inside and outside houses (Hiscox *et al.*, 2014; Jawara *et al.*, 2009; Matowo *et al.*, 2013). By capturing mosquitoes outdoors, rates of mosquito house entry can be lowered by between 33% and 80% under semi-field conditions (Hiscox *et al.*, 2014; Menger *et al.*, 2014b) and by 50% in the field (Menger *et al.*, 2015). It is anticipated that above a certain threshold level of trap coverage, traps could be used to effectively reduce *Anopheles gambiae* s.l. and *Anopheles funestus* populations enough to lower the entomological inoculation rate to a level at which malaria transmission cannot be sustained (Okumu *et al.*, 2010a). The principle of mass-trapping for the control of tsetse flies has already been demonstrated in several African countries (Keating *et al.*, 2015; Rayaisse *et al.*, 2010) and we expect that this principle can also be applied to malaria vectors.

The Asembo Bay area of western Kenya was one of the first regions in sub-Saharan Africa to receive insecticide-treated bed nets [ITNs] as part of a trial in the mid-1990s (Hawley *et al.*, 2003; Phillips-Howard *et al.*, 2003; ter Kuile *et al.*, 2003), but despite increasing population coverage of ITNs since 2000, as well as provision of

Artemether-Lumefantrine, intermittent IRS and presumptive treatment in pregnancy, malaria remains prevalent in western Kenya (Idris *et al.*, 2014; Zhou *et al.*, 2011). The history of sustained vector control interventions as well as extensive prior understanding of malaria and malaria interventions in the Lake Victoria region of Kenya mean that this setting is ideal for a study investigating the efficacy of odour-baited traps combined with long-lasting insecticidal nets [LLINs] and case management for malaria control.

In this rural region of Kenya few residential buildings are connected to the main electrical grid and most households light their homes using kerosene tin lamps. The requirement of an energy supply to power the electrical fan inside the odour-baited trap prompted the decision to integrate the mosquito trapping systems into a solar-home system, henceforth referred to as a solar-powered mosquito trapping system [SMoTS]. SMoTS include two electrical [LED] lights and a mobile phone charging port in addition to the odour-baited mosquito trap. These additional, immediate, private benefits of the system were expected to increase usability and improve adherence to the public health intervention that requires the sustained participation of residents (Oria *et al.*, 2014).

Here we describe the study design and methods used by the SolarMal project to test this intervention on Rusinga Island, western Kenya. The SolarMal project is the first trial to measure the efficacy of this novel approach to malaria vector control. A stepped wedge cluster-randomised approach is applied to the intervention rollout so that the intervention coverage gradually increased from no coverage to coverage of all eligible households over the course of 24 months.

Study Objectives

Primary Objective

- To determine whether augmentation of the Kenyan national malaria control (LLINs + case management) by mass-trapping of malaria vectors will lead to elimination of malaria from Rusinga Island, western Kenya.

Secondary Objectives

Medical (all outcome measures include contemporaneous comparison of intervened with non-intervened areas, as well as before-and-after measures of intervened areas compared with baseline):

- To measure the effect of mass-mosquito trapping on clinical malaria incidence, measured as fever + positive rapid diagnostic test [RDT] result.

- To determine the impact of mass-mosquito trapping on malaria prevalence measured by RDT.
- To calculate differences in both measured and reported all-cause fevers following the introduction of odour-baited traps.

Entomological (all outcome measures include contemporaneous comparison of intervened with non-intervened areas, as well as before-and-after measures of intervened areas compared with baseline):

- To assess whether the mass-trapping of mosquitoes reduces the population density of malaria vectors on Rusinga Island.
- To determine whether the mass-distribution of odour-baited mosquito traps leads to changes in mosquito species composition.
- To record changes in entomological inoculation rate associated with implementation of the intervention.
- To compare mosquito densities and species composition indoors and outdoors.

Sociological:

- To determine the behavioural, socio-cultural and organisational factors that influence the effective and sustainable use of SMoTS
- To foster learning relevant to adapting the implementation and sustainability strategy as an integral component of the intervention.
- To understand how the introduction and use of SMoTS affects and/or is affected by the use of other malaria control interventions.

Methods/ Design

Study area and participant eligibility

The study is underway on Rusinga Island, western Kenya; an island that is located approximately 75 km southwest of the city of Kisumu and has a surface area of around 44 km^2. Research activities are conducted through the Thomas Odhiambo Campus of the International Centre of Insect Physiology and Ecology [*icipe*] in Mbita Point, located a couple of kilometres from Rusinga Island. In a population census conducted by the project in May 2012 the total population of the island was 23,337 people, living in 4,062 households. The majority of the population belongs to the Luo ethnic group and *Dholuo* is the main language spoken by residents. Many families in this area are polygamous and a household (locally referred to as a homestead or *dala*) may comprise of more than one house. The primary occupations of people are fishing in Lake Victoria and small-scale farming. The climate is tropical with a long rainy season typically occurring from February to May with a shorter rainy season

from October to November. Malaria is typically endemic in this region and transmission occurs throughout the year (Beier *et al.*, 1994; Zhou *et al.*, 2011).

All households and residents of Rusinga Island are eligible for inclusion in the study with recruitment commencing in June 2012 and continuing until November 2015. The assignment of households to clusters and metaclusters (see section on study design below) was completed in May 2013 and any household constructed before this point was eligible to receive an odour-baited trapping system. Households constructed after this time were eligible to participate in the health and demographic surveillance, parasitological, entomological and sociological studies, but were no longer recruited to the intervention arm of the study as this could have led to a higher density coverage of traps in areas receiving the intervention towards the end of the rollout.

In order for the results of the intervention to be generalizable across whole societies, all residents of the island are eligible for participation regardless of age, gender, ethnicity, health status or whether they are natives of the island. For overall participation in the study and recruitment to health and demographic surveillance [HDSS] as well as malaria testing by RDT, individual written consent is provided by adults aged 18 years and older and for mature minors. For persons aged 13-17 years individual assent is provided alongside written consent of an adult. For persons under 13 years of age written parental consent is provided before recruitment to the study. All consent forms are in either English or *DhoLuo* and are signed by the recruiter and a witness. Informed verbal consent is provided by individuals or heads of household before participation in sociological and entomological studies respectively. Participation in the study is voluntary and all participants are free to withdraw at any time without giving a reason for their withdrawal.

Enumeration of the population and recruitment of participants is ongoing throughout the study period (i.e. from May 2012 until November 2015). Three rounds of HDSS take place during each year of the study, recording births and deaths as well as in and out migration across both arms of the study. A unique identification number is assigned to every individual, house and household recruited to the study during the HDSS.

The population of Rusinga is sensitised about project activities and findings in a number of ways throughout the course of the study. An initial community launch day was held on the island in August 2012 with the aim of informing community members about the project using song, dance, sketches and speeches. In order to ensure good communication between the project scientific staff and the study participants, a community advisory board [CAB] was established, including representatives of key groups of stakeholders. The CAB meets formally four times each year to receive

updates on project progress and plans from scientific staff and in turn to provide feedback from the community and to discuss project plans. Informal meetings between the CAB and project staff are also held whenever the need arises. In May 2013 a public balloting event was held where the sequence of the rollout was selected with the participation of community members (Oria *et al.*, 2014). Thereafter, weekly community training workshops were held to train each cluster of approximately 50 households in the maintenance of SMoTS.

Intervention – solar-powered mosquito trapping systems (SMoTS)

The odour-baited traps (Suna traps) that are used during this intervention were developed in collaboration between Wageningen University and Research Centre (the Netherlands), the International Centre of Insect Physiology and Ecology [icipe] and Biogents AG (Germany) (Hiscox *et al.*, 2014) (Figure 2.1). The traps are baited with a blend of five organic attractants that mimic a human odour and lure mosquitoes towards the trap (Menger *et al.*, 2014b). The blend of five chemicals is supplemented with a carbon dioxide mimic (Turner *et al.*, 2011) in order to increase the attraction of malaria vectors to the trap. The odour baits are produced at the field site in Kenya by impregnating strips of nylon with each attractant at the appropriate concentration (Mukabana *et al.*, 2012a). Baits are prepared in batches and stored at -20°C to prevent the organic chemicals from volatising before they are used. Semi-field studies have shown that baits remain attractive to *An. gambiae* even after weekly use over 52 weeks (Mweresa *et al.*, 2015). During the course of the study odour baits are replaced in each intervened household by project field staff at three-monthly intervals. Previous studies have shown that a host-seeking mosquito can detect human or animal odours at distances of 50 metres or more (Gillies *et al.*, 1968; Gillies *et al.*, 1970) and we expect that the odour-baited Suna trap has a similar radius of attraction. Traps were suspended outside houses, beside the primary sleeping area with the fan section at 30 cm above the ground, a position that has previously been shown to result in the highest mosquito catch rates (Hiscox *et al.*, 2014). As described in the background section above, the requirement of electrical power for the trap means that each SMoTS comprises of an odour-baited mosquito trap, solar panel, battery, two LED lights, one mobile phone charging port and the associated electrical wiring.

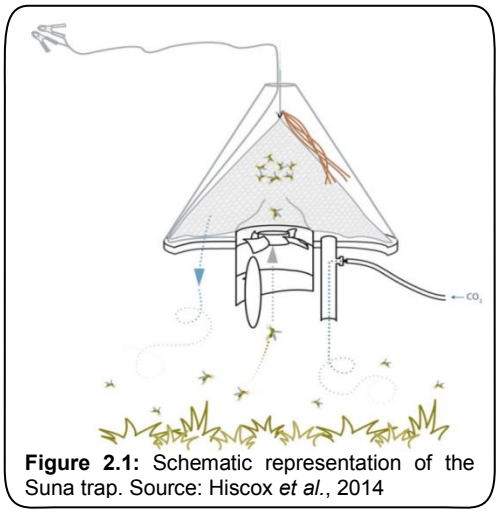

Figure 2.1: Schematic representation of the Suna trap. Source: Hiscox *et al.*, 2014

During the course of the study each eligible household on Rusinga Island was offered one SMoTS. If a household comprised of more than one residential structure (house), the project staff requested household members to reach a consensus agreement on which house the SMoTS should be installed on. If no consensus was reached, the SMoTS was not installed.

Two weeks prior to SMoTS installation in any given cluster, residents of the cluster were invited to attend a community training workshop held at a local community centre, such as a church or school building. During each training workshop study participants were reminded of the aims of the study and took part in question-and-answer sessions about malaria transmission and prevention. Demonstration SMoTS were used to show participants how the system operates and how to empty the trap of mosquitoes and clean it on a weekly basis (Oria *et al.*, 2015). Contact information for project-employed technicians was provided so that any technical faults in the systems could be reported and resolved promptly.

Study Design

The SolarMal trial uses a stepped wedge cluster-randomised trial [SWCRT] design (Hemming *et al.*, 2015) where the intervention is allocated to geographically defined clusters in a randomised order until full coverage is achieved. This trial design is appropriate for a vector control intervention such as an odour-baited trap that is expected to have an impact which extends to an area beyond the house on which it is installed (spill-over effect). Replication of the intervention in multiple clusters while maintaining contemporaneous control areas can be achieved with a cluster-randomised trial [CRT] design, typically aiming to reduce infection at the individual level by targeting a whole community/area with the intervention. The stepped wedge design provides the opportunity of attaining area-wide coverage and group randomisation by the gradual crossover of all clusters to the intervention arm. In this way the effect of the intervention can be measured when used at relatively small scale, up to mass-coverage.

Randomising the intervention allocation

Clusters of households were constructed by means of a travelling salesman algorithm whereby the shortest distance from one household to another is continually chosen, creating a cluster after every 50 or 51 households (Figure 2.2). The number of houses per cluster is expected to be large enough for measurement of the maximal intervention effect at the centre of the cluster, avoiding spill-over from surrounding non-intervened areas. The degree of protection among people living in households at the edges of clusters may be affected by mosquitoes from surrounding non-intervened areas; alternatively, intervened households located at cluster edges may

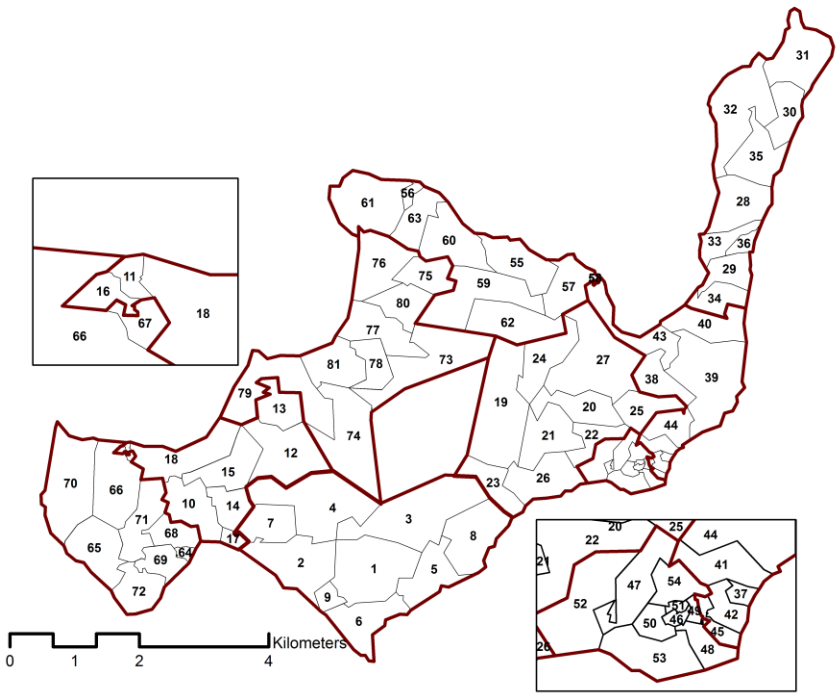

Figure 2.2: Rusinga Island with 81 project clusters, each containing 50-51 households, numbered consecutively in the order in which the SMoTS were installed. Metaclusters, each containing nine clusters, are outlined in bold red lines. Insets show close-up views of geographically smaller clusters in the northwest and southeast of the island.

exert an effect on mosquitoes in neighbouring areas which are yet to receive the intervention, as was observed during the early bed net studies (Hawley *et al.*, 2003).Computer simulations of possible rollout scenarios were made on basis of a human susceptible-infected-susceptible transmission model (Silkey *et al.* under review). A hierarchical design was selected and adopted as the rollout strategy for SolarMal. The design groups the 81 clusters of 50 or 51 households into nine larger areas, each referred to as a metacluster. Within every metacluster the intervention was subsequently introduced to each of nine clusters in a random order. Once the intervention had been applied to all clusters in one metacluster the rollout moved randomly to the next metacluster; all clusters eventually received the intervention according to this SWCRT design. During a community rollout ballot held in May 2013, nine possible rollout sequences were presented for blind selection, one starting in each of the nine metaclusters. After placing a printed map of each sequence in a sealed, unmarked envelope and placing the nine envelopes in to a box, one member of the community was chosen at random to draw an envelope and open it to reveal

the order of the rollout which would be followed (Oria *et al.*, 2014). The selected SWCRT sequence is illustrated in Figure 2.2.

Demographic surveillance

During successive rounds of health and demographic surveillance (see Figure 2.3 for schedule), records of the complete population of the island were maintained by door to door visits, collecting data using a tablet computer installed with data collection and management software (Homan *et al.*, 2015). Data is uploaded to the local server on a daily basis creating a near real time demographic database that subsequently serves other parts of the project. A team of fieldworkers collect data simultaneously in all nine metaclusters on a daily basis. Over the course of three months all households and individuals are visited by fieldworkers to update demographic information. By conducting successive rounds of surveillance, data was available for each of the 81 clusters throughout the baseline and rollout period, thus providing information about both arms of the intervention for before-and-after and contemporaneous measures of intervention effect. The last survey before the start of the intervention rollout served as a baseline record of the population and took place from January-June 2013. The location of all houses was recorded using a GPS built in to the tablet computers.

Measurement of malaria incidence and prevalence

Clinical malaria incidence is recorded during the routine HDSS surveillance of all individuals (three rounds of surveillance each year, see Figure 2.3). During household visits residents are asked to report any fever in the previous two weeks, two days and at the time of the visit. If fever is reported to have occurred within two weeks of the visit, body temperature is measured using an in-ear thermometer (Braun™ IRT 3020). If the measured in-ear temperature is greater than 37.4°C the individual is tested for malaria using an RDT (*SD BIOLINE*™ Malaria Ag P.f/Pan *HRP-II*/pLDH). Any person with a positive RDT is provided with an appropriate dose of Artemether –Lumefantrine or referred to a local health clinic in the case of pregnancy, child under six months of age or severe symptoms. By collecting clinical malaria data continuously, information is available for baseline and throughout the course of the rollout for all 81 of the clusters.

In addition to the detection of malaria-associated fever within the HDSS, cross sectional malaria prevalence surveys are carried out in a randomly selected 10% of the study population three times per year (Figure 2.3). All selected individuals are tested for malaria using an RDT and a dry blood spot is also collected from each person as well as a measure of in-ear temperature. Validation of RDTs is performed using high-resolution melting PCR [HRM-PCR] (Kipanga *et al.*, 2014) on a random sample of 200 dry blood spots from each round of surveillance. As for the HDSS and clinical malaria monitoring process, this data collection method allows for

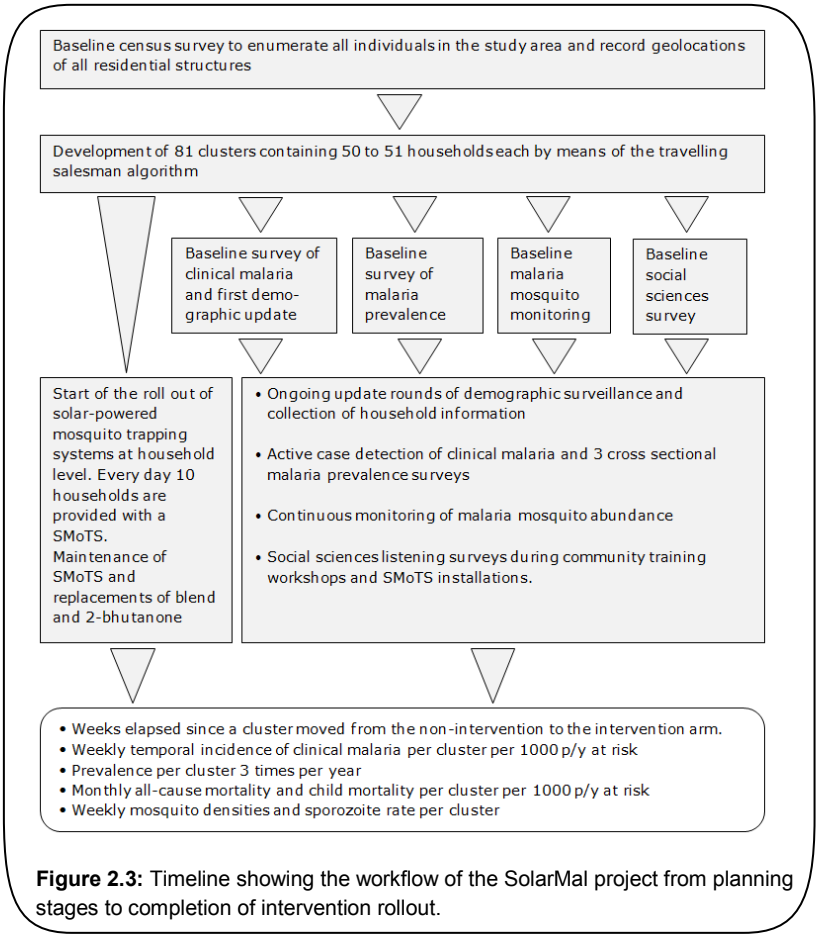

Figure 2.3: Timeline showing the workflow of the SolarMal project from planning stages to completion of intervention rollout.

measurement of malaria prevalence in all 81 clusters of the SWCRT at regular intervals throughout the course of the project.

Entomological data collection and evaluation

Monitoring of mosquitoes began in September 2012 and will continue until December 2015 (see Figure 2.3). Sampling of mosquitoes at houses is performed using Mosquito Magnet-X® traps (American Biophysics corporation, North Kingstown, RI), baited with the same blend of five chemicals that are used for the intervention (Menger *et al.*, 2014b) and carbon dioxide produced by yeast and molasses fermentation (Mweresa *et al.*, 2014). For each round of sampling 80 households are randomly selected with replacement from the active database maintained by the HDSS. In common with data collection in other arms of the project, random selection of households for entomological monitoring enables measurement of entomological outcomes across the island throughout the duration of the SWCRT. Working four

nights a week, ten houses are sampled every night with traps set at dusk (between 17:00h and 18:00h) and collected after dawn (between 07:00h and 08:00h). Each house is sampled once inside the house and once outside, with the inside/outside order randomised. The complete round of sampling takes four weeks to complete, following which there is a two week period without sampling to make preparations for the next round. When a house has already been installed with a SMoTS, the Suna trap is disconnected during the two nights when the MM-X trap is used instead.

After collection of traps, mosquitoes are knocked down using a -20°C freezer and identified to species group on the basis of morphology (Gillies *et al.*, 1987). Specimens are separated and pooled by collection date, house of collection, inside/outside location, morphologically identified species group, sex and abdominal status. Pooled mosquitoes are stored in 80% ethanol for subsequent molecular analysis: PCR for identification of *An. gambiae* s.l. complex and *An. funestus* s.l. complex (Koekemoer *et al.*, 2002; Scott *et al.*, 1993), and HRM-PCR for detection of *Plasmodium* DNA and blood meal analysis (Kipanga *et al.*, 2014).

Household and environmental data

Information was collected on variables that could have a direct or indirect effect on the association between the intervention and malaria infection or entomological outcomes. Every third health and demographic surveillance round incorporated a digital questionnaire for the collection of information about houses and households. Information about the construction materials used to build each house and the number of rooms was recorded, as well as the presence/absence of eaves and whether there were preventative measures taken against mosquitoes, such as LLINs and IRS. Indicators of socio-economic status were also included in these update rounds; as was information on land and house ownership, occupation and highest level of education of the head of household. Additionally, high resolution satellite images were obtained to provide data on possible confounding environmental variables including the normalized difference vegetation index, and a water accumulation index [TWI].

Social sciences

A mixture of quantitative and qualitative approaches to social science data collection were used. Prior to the commencement of the intervention rollout a structured questionnaire was carried out with one adult male and one adult female in each of 204 randomly selected households (5% of all households). The questionnaire was repeated with a new random selection of 5% of households after completion of the rollout (see Figure 2.3).

In addition to the structured questionnaires, listening surveys were conducted during each community training workshop to record trends in questions asked by community members over the course of the rollout. Listening surveys were performed during the installation of SMoTS in order to gauge initial reactions to the intervention. Data is also collected informally during other project community events such as an event held to launch the project on the island and the rollout ballot, among others. Throughout the course of the study, focus group discussions with specific stakeholders not only provided a useful tool for gathering information on community knowledge, attitudes and perceptions, but also helped the project to build links with the community.

Throughout the duration of the study, community members are able to contact a project community liaison officer and the solar technicians by phone in order to report technical faults in the SMoTS. A detailed record of phone calls is maintained by an on-site project manager and these records are used to schedule maintenance activities as well as to understand how well the systems are performing over time. Intermittent spot checks carried out once a week in randomly selected households during the evening allow the field staff to monitor the performance of systems during the hours of darkness. During the final phase of the project (December 2014 – December 2015), interviews with key stakeholders and focus group discussions will be used to develop and finalise a sustainability plan for the maintenance of SMoTS beyond 2015.

Data entry and management

The collection and management of data was fully digitalised, with all data entered by means of a tablet computer. Open Data Kit [ODK] (Hartung *et al.,* 2010) is used to build and conduct questionnaires. Data are uploaded to a secure local server on a daily basis. Demographic data are stored and then transferred to OpenHDS, a data management platform (Asangansi *et al.*, 2013; Homan *et al.*, 2015). New information is automatically incorporated into the demographic core database. This data management platform allows for data cleaning immediately after upload to the server. To prevent duplication of ID codes in the system, the OpenHDS software generates a new unique ID for each individual, house and household as required. There are several built- in methods to prevent errors in data entry. Mostly, answers need to be logical and are listed as multiple choice in the electronic questionnaires. For instance, a male cannot be recorded as having a pregnancy, and the age of a new-born cannot be more than one year.

A system, SU2, to ensure quality post-hoc was deployed in 2013 (SU2). The programme, which automatically runs every night, provides the data manager with a report on operational statistics and inconsistencies in data collected the previous day. The SU2 software tracks which individuals and houses are visited on a daily basis

and produces an up-to-date geodatabase of locations to visit for uploading to the tablet computer. Maps based on this information guide fieldworkers in navigating through their assigned area and recognising which houses and individuals still need to be visited during a round of surveillance.

Power and sample size rationale

There is some controversy about power calculations for SWCRTs (Hussey *et al.*, 2007), and the power of our design depended on the correlation between observations on the same individuals at sequential HDSS visits. We could not determine the level of correlation from the single baseline enumeration visit. A lower bound for the minimum detectable effect size is therefore that of a single visit per person, occurring halfway through the rollout. Using previously published formulae, this approach could have anticipated to have had 80% power to detect approximately 52% reduction in clinical incidence (Hemming *et al.*, 2011). Conversely, a parallel CRT with six repeated visits and independent outcomes for each visit would have power to detect an approximately 23% reduction in clinical incidence, corresponding to an upper bound to the anticipated minimum detectable effect size. Analogous calculations for prevalence (Hemming *et al.*, 2011), using a baseline malaria prevalence of 23.9% (RDT prevalence rate during the baseline survey for this project) and sample size of around 1,860 persons (10% of the population that was initially enumerated for this project) suggest that a single prevalence survey should have had 80% power to detect a 27% reduction in prevalence. Six repeated surveys carried out, might have power to detect effects as small as an 11% reduction in prevalence, assuming that correlations between repeated observations were small.

Analytical plan

The datasets included for the analysis comprise results of the HDSS, clinical malaria surveys, cross sectional malaria prevalence surveys and monitoring of mosquito densities. Malaria fever incidence is the primary outcome of the trial. Data is included up to the end of the next month after full intervention coverage was attained. For analyses of parasitological as well as entomological outcomes, intervention status is classified week by week on an intention to treat basis. The whole study cluster is classified as intervened or non-intervened based on whether installation was complete in that cluster by the end of the week. Clusters are excluded from analysis during weeks in which some, but not all, of the households are provided with the intervention (i.e. during the week in which installations took place in that cluster). For malaria prevalence and incidence numbers and proportions of positive RDT tests are summarised by week and arm of the trial. For mosquito densities, rates of anophelines collected per trapping night are presented by week and arm of the trial.

Following the SWCRT design described by Silkey *et al.* (under review) an analytical plan was constructed. The primary analysis of the impact of the trial on malaria incidence, prevalence and vector densities follows two measures of effect: a contemporaneous comparison comparing the outcomes in intervened clusters with the not yet intervened clusters and a comparison of the final results in intervened areas with the baseline status. Generalized linear mixed models [GLMM] with a binomial distribution will be deployed to carry out significance testing against the null hypothesis of no effect using a likelihood ratio test. For mosquito densities a GLMM will be used with a Poisson distribution. For analysis of medical and entomological data random effects will be used to allow for spatial effects as well as effects of round of surveillance. Final models will consider possible confounding effects on the relationship between the intervention effect and measured outcomes.

Ethical approval

Ethical approval was obtained from the Kenyan Medical Research Institute [KEMRI]; non-SSC Protocol No. 350. All participants were provided with written and oral information regarding the project aims, the ongoing demographic surveillance, the implementation of the intervention, and the collection and use of blood samples, mosquito sampling and social sciences activities. Adults, mature minors and caregivers of children provided written informed consent in English or in the local language agreeing to participation in the SolarMal project.

Discussion

The long term sustainability of malaria control achieved through the use of LLINs and case management with drugs is threatened by the development of insecticide and drug resistance. The SolarMal project has been designed to test for the first time whether mass-trapping of mosquitoes can form a viable option for malaria control on Rusinga Island in Kenya, in addition to the already established LLIN + curative strategy of the Kenyan National Malaria Control Programme. The study takes place in an area where LLIN coverage is high and drugs for case management are available and accessible.

The primary outcomes of the study will provide information about the efficacy of mass-mosquito trapping on clinical malaria incidence, *Plasmodium* parasite prevalence, mosquito densities, EIR and sociological outcomes. A SWCRT design allows for before-and-after as well as contemporaneous measures of intervention effect; and clustering of the intervention permits measurement of a possible spill-over effect of traps in to neighbouring non-intervened areas. Through gradual scale-up of intervention coverage over two years, with baseline measurements before the commencement of the rollout and at least seven months of follow-up after completion of the rollout, an understanding of the time taken to achieve an impact through mass-

trapping will also be gained. By gathering data on multiple outcomes it will be possible to attribute an effect on malaria to the intervention. Likewise, if the intervention is ineffective it will be possible to offer explanations for this outcome. Understanding the mechanism behind a successful intervention will be vitally important in optimising the system for future scale-up and, in the instance of no observed effect, understanding this result will also allow improvements to the approach which could lead to success in the future.

In addition to the anticipated impact on malaria, members of the study population are expected to immediately benefit through the electrical lighting and mobile phone charging facilities provided with the SMoTS. Electrical lighting is expected to reduce a reliance on kerosene that is typically used to light houses in this region. As the fumes emitted by burning kerosene are known to negatively affect the respiratory system (Lam *et al.*, 2012), replacement of kerosene lamps by electric lights is likely to remove this health hazard. As well as removing health risks attributed to inhalation of kerosene fumes, the risk of fire and burns (Peck *et al.*, 2008) is also reduced by providing electric indoor lighting. With a reduced expenditure on kerosene and mobile phone charging the intervention should lead to financial savings and improved socioeconomic status which in turn may lead to other health improvements.

In order to ensure that risks to the population are minimised, the continued use of LLINs by all age groups is recommended at all community meetings and training sessions. Participation in the intervention does not affect the use of existing health facilities. The creation of a CAB has facilitated regular exchanges of information between scientists, project field staff and the Rusinga Island community and it is expected that some members of this board will remain actively involved in the maintenance of the SMoTS beyond the follow-up period of the study. By the completion of the rollout in mid-2015 the community were beginning to form groups to save money for the purpose of maintaining SMoTS beyond the research period. The provision of electrical lighting and mobile phone charging provides an incentive for users to keep the systems running and links with Kenyan solar-home system providers are being made to ensure continuous provision of replacement components at prices which are affordable for low-income households. By working closely with the Kenyan Ministries of Health and Energy the SolarMal project has formed a strong basis for continuing and expanding the use of SMoTS on Rusinga Island and elsewhere in the region.

If the intervention is proven to be an effective tool for malaria control, researchers will work together with industry and policy makers to develop cost-effective, long-lasting and readily available malaria mosquito trapping systems for use in at-risk areas. It is anticipated that a scale-up of systems would follow a public-private model with

investment from governments and NGOs as well as financial contributions by end-users. Scale up would initially be focussed in the East African region with exploratory studies in the Americas and Southeast Asia.

Authors' contributions

WRM and WT conceived the concept for the study, TH, NM, ADP and TS designed the HDSS system, AH, CM and WT designed and conducted the entomological monitoring, PAO, JA and CL designed and conducted the social sciences research, all authors were involved in the overall study design and execution and in writing the analytical plan. AH, TH and TS drafted the manuscript. All authors read and approved the final manuscript before submission.

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Chapter 3

Innovative Tools and OpenHDS for Health and Demographic Surveillance on Rusinga Island, Kenya

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Abstract

Background: Health in low and middle income countries is on one hand characterized by a high burden associated with preventable communicable diseases and on the other hand considered to be under-documented due to improper basic health and demographic record-keeping. Health and Demographic Surveillance Systems have provided researchers, policy makers and governments with data about local population dynamics and health related information. In order for an HDSS to deliver high quality data, effective organization of data collection and management are vital. HDSSs impose a challenging logistical process typically characterized by door to door visits, poor navigational guidance, conducting interviews recorded on paper, error prone data entry, an extensive staff and marginal data quality management possibilities. **Methods:** A large trial investigating the effect of odour-baited mosquito traps on malaria vector populations and malaria transmission on Rusinga Island, western Kenya, has deployed an HDSS. By means of computer tablets in combination with Open Data Kit and OpenHDS data collection and management software, experiences with time efficiency, cost effectiveness and high data quality are illustrated. Step by step, a complete organization of the data management infrastructure is described, ranging from routine work in the field to the organization of the centralized data server. **Results and discussion:** Adopting innovative technological advancements has enabled the collection of demographic and malaria data quickly and effectively, with minimal margin for errors. Real-time data quality controls integrated within the system can lead to financial savings and a time efficient work flow. **Conclusion:** This novel method of HDSS implementation demonstrates the feasibility of integrating electronic tools in large-scale health interventions.

Key words: Health and Demographic Surveillance System; Mobile data collection; Data management platform; Malaria; Kenya

Background

Health and demographic surveillance systems [HDSS] are used to provide a framework for prospective collection of demographic and public health data within a community. Such systems, originally called population laboratories, have been in operation since the 20th century, and constitute the basis of population-based research in areas where national or local authorities lack a proper registration system to monitor the most important demographic events (Kesler & Levin, 1970). In order for population and health researchers to acquire longitudinal data on communities, systematically constructed systems have undergone several developments (Garenne & Koumans, 1997); where originally the focus remained on surveying demographic data (demographic surveillance systems, DSS), principally due to efforts of the INDEPTH network (International Network of field sites with continuous Demographic Evaluation of Populations and Their Health in developing countries), health indicators became a routine part of science-driven surveillance systems, retitling the concept as HDSS (health and demographic surveillance system) (INDEPTH, 2002). Despite these developments, public health systems in developing countries often lack adequate infrastructure to monitor demographic and health information; rural areas in particular experience challenges with the collection of reliable health-related data. The World Health Organization [WHO] states that vast rural areas in Sub-Saharan Africa are a reservoir for a variety of predominantly preventable communicable diseases such as HIV/AIDS, tuberculosis and malaria (WHO; World Health Statistics 2014) .The absence of well-operating national or local demographic and health surveillance systems hampers evidence-based research into these diseases. Over the past decades there are numerous examples of scientific institutions deploying community-based HDSSs in order to provide policy makers and governments with recommendations on health planning and intervention methods. A classic example is the Garki project in Nigeria where, during the 1970s, field experiments were conducted to understand the effects of Indoor Residual Spraying [IRS] and Mass Drug Administration [MDA] on malaria and entomological outcomes (Gramiccia & Molineaux, 1980). Another, more recent, malaria control study which used HDSS to capture prospective data was the Asembo Bay Cohort Project, which ultimately showed a large protective effect of Long Lasting Insecticidial Nets [LLIN] against malaria infection.

Nowadays, community-based HDSSs are established at an increasing number of sites to investigate a range of different health indicators and diseases. The main goal of the INDEPTH network is to harmonize the data of HDSSs from different sites in developing countries to achieve a valid comparison of information and accordingly get more insight into health related trends (Sankoh *et al.*, 2011).

There are currently 43 INDEPTH associated centres that run one or more HDSSs for scientific purposes (Sankoh *et al.*, 2012). At all these HDSS sites, the field and data management operations pose logistical challenges. Interviews in most sites are essentially paper based which makes conducting questionnaires time consuming and error prone. Visiting households and individuals can be time consuming, as keeping track of where fieldworkers navigate and which community members have been visited can only be done manually. Likewise, transferring data from paper into a digital form is a lengthy process with a lot of room for error. Not only the content of data can be entered incorrectly, but assigning new data to the right entity or ID is an error-prone process with small typos leading to unrecognizable and ultimately squandered data (Gyapong *et al.*, 2013; Kahn *et al.*, 2012; Kouanda *et al.*, 2013; Scott *et al.*, 2012). Finally, accumulating and managing data relies heavily on obsolete database software with limited data quality assurance structures.

The past decade has borne witness to major developments in mobile computer technology as well as software applications. Advanced computer tablets and improved data collection and management software have become accessible and affordable to the wider public. In high and middle income countries there are numerous examples of ways to utilize the available technologies to improve health (Bloomfield *et al*., 2014; Martínez-Pérez *et al*., 2013). Although there have been several pilot studies which experimented with a telephone-based technology to collect health and demographic data, in the lower income countries these technologies remain mainly underused because of logistical and organizational constraints (Asangansi *et al.*, 2010; Schobel *et al.,* 2014).In some low- income countries, mobile computer technology and advanced data collection and management software has been tested. In Akpabuyo Nigeria, the use of computer tablets with practical collection software and a comprehensive data management system has been tested (Asangansi *et al*., 2013). The study showed that it is possible to save a great deal of time compared to the paper-based and analogue data collection and management. Not only time could be saved, costs could also be decreased considerably and data quality increased. Another study in Malawi investigated how the use of computer technology and software could best be organized to create a feasible system of health data collection and management (Matavire & Manda, 2014). A governmental initiative in Kenya in 2006 marked a first step towards a digitalized health management (Odhiambo-Otieno, 2005).

In 2012 an HDSS was initiated on Rusinga Island, western Kenya, to facilitate a large malaria control trial, the SolarMal project (Hiscox *et al*., 2012).This paper describes the computer-based HDSS developed for this project. It is shown that community-based health research served by HDSSs may be of higher quality, more cost-effective and more time efficient than currently deployed surveillance systems.

Methods

Study location and population

Rusinga Island with approximately 25,000 inhabitants is located in Lake Victoria, western Kenya (0°21′ S and 0°26 south, 34°13′ and 34°07’ east). The island is administratively part of Homa Bay County in western Kenya (Figure 3.1) and is connected to the mainland with a causeway. The land surface area of Rusinga Island is approximately 44 km^2 with an elevation between 1100 m and 1300 m above sea level. Average daily temperatures lie between 16 and 34 degrees Celsius with temperatures higher during the dry seasons which occur between June-October and late December-February. The SolarMal project, including HDSS activities, operates through the International Centre of Insect Physiology and Ecology [*icipe*] at the village of Mbita Point just across the causeway, on the mainland. The population of Rusinga Island belongs to the Luo ethnic community and, besides the national language of Swahili, DhoLuo is primarily spoken. Fishing and farming are the principal occupations. There are several health facilities in the area; one public health centre, three government-run dispensaries and three private clinics. A district hospital is found at Mbita Point. Malaria transmission occurs throughout the year, with peaks in transmission at the end of the rainy seasons where parasite prevalence is around 30% (WHO Country Profile 2013: Kenya, Malaria). Furthermore, schistosomiasis, filariasis, HIV, and tuberculosis are endemic on Rusinga (Central Bureau of Statistics MoPaND. Kenya Demographic and Health Survey 2003).

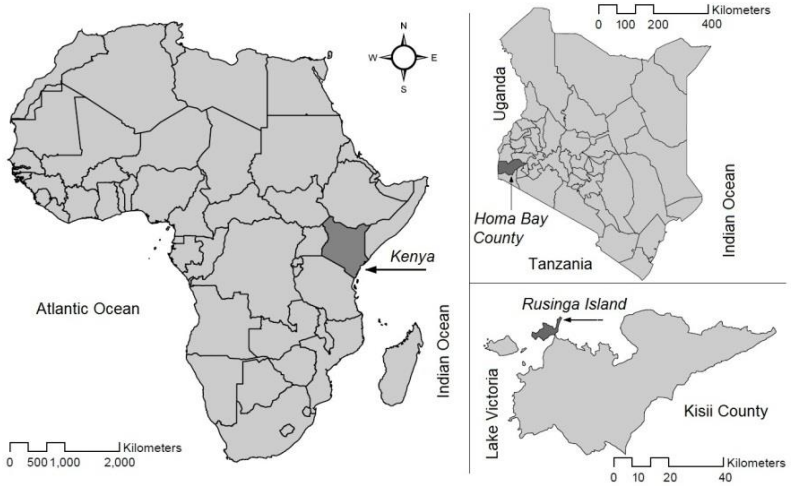

Figure 3.1: Study site: Africa with Kenya highlighted dark grey; in the right upper corner Kenya with Homa Bay County highlighted; Homa Bay County with Rusinga Island tinted in dark grey.

Data collection system

The HDSS team consists of 10 fieldworkers [FWs], one fieldworker manager [FWM], a database manager and a system developer. Fieldworkers who spoke DhoLuo fluently and had a prior basic knowledge of computing were trained to use mobile tablet computer devices (Samsung Galaxy Tab 2, 10.1). A pilot study was conducted to test the usability of the computer tablets, as well as digital questionnaires, prior to the initial HDSS census. The HDSS uses the Open Health and Demographic Surveillance [OpenHDS] data system (Asangansi *et al*., 2013), a software platform that is based on a centralized database. This database is linked to a web application for data management, linked to a tablet computer-based mobile component which allows digitalization of data at the point of capture, and wireless synchronization to the central data store based on the Open Data Kit [ODK] platform (Asangansi *et al.*, 2013; Hartung *et al*., 2010) (Figure 3.2). ODK is a free, open-source application intended to facilitate mobile data collection services. ODK consists of two software components for data collection, transfer and storage, and various tools exist for the

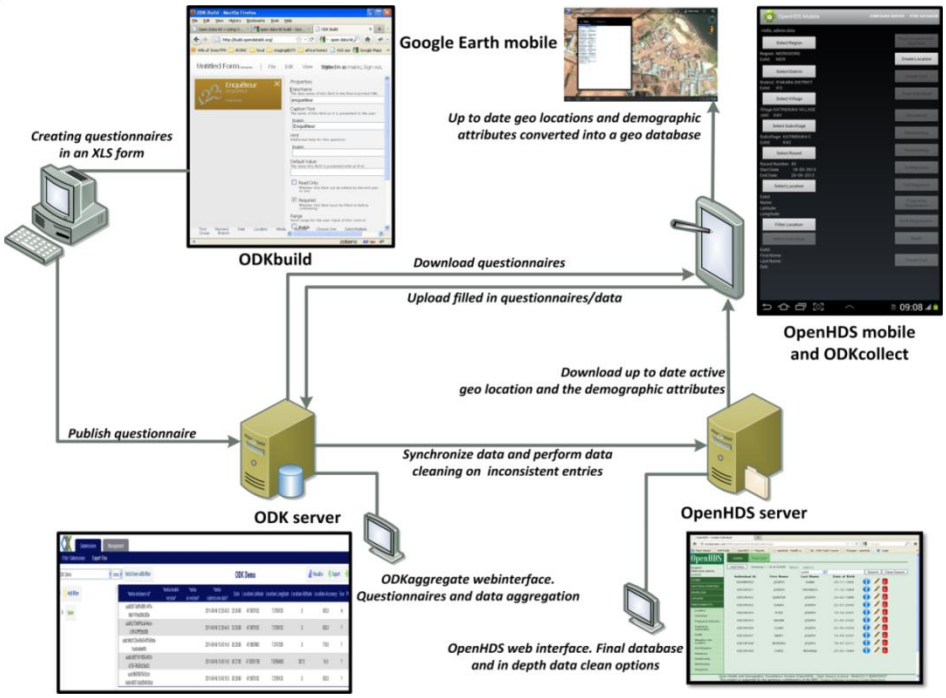

Figure 3.2: Data pathways using the ODK and OpenHDS platform: electronic questionnaires are created uploaded to the computer tablets by the ODK server. Wireless synchronization of digitalized data collected at the point of capture is transferred to the central data store based on the ODK server. Cleaned data is transferred to the OpenHDS server that in turn synchronizes the up to date database to the computer tablets.

authoring of the electronic questionnaires used in the data collection process. ODK-Collect is used to render electronic questionnaire forms on mobile devices running the Android operation system, which includes forms to report core vital events as well as customized forms. ODK-Aggregate is a web application that supports data transfer and storage at a local server or a "cloud" server.

In addition to ODK-Collect, the OpenHDS mobile data collection application is installed on the tablets. This application contains a database which is pre-populated with data on the administrative location hierarchy in the study area (district, villages, neighbourhoods), and any information previously collected on individuals, houses and households in the area. This allows selection of the individual or house using the software during a visit to a household, and makes it possible to simply amend or add new information associated with the individual or house that has been selected. The differentiation made between houses and households follows the local culture, where the term *dhala* is used for a group that is socially and financially dependent or formed of related family members sharing the same facilities and recognizing one member as head of the household. A house is always defined as a single residential structure. The XLS-Form application is used for authoring questionnaire forms for ODK in the X-Form format. This allows integration of all possible structures of questions into the questionnaire: open answers, multiple choice answers, as well as posing constraints and requirements to answer outcomes. Questionnaires are published to ODK-Aggregate, and then downloaded to the tablets using ODK-Collect. This includes both questionnaires for capturing core vital events (births, deaths, in- and out-migrations) and study-specific questionnaires (parasitology, malaria incidence etc.). Electronic forms which are completed in the field using OpenHDS mobile are stored in ODK-Collect and synchronized over a Wi-Fi connection at the field station to the central database through ODK-Aggregate server (Figure 3.2). After subsequent automated customized data checks, cleaned data is then submitted to the definite OpenHDS database. At the end of each update round, clean data is synchronized to the tablets to ensure that the most up to date information is taken back to the field for consecutive follow up surveys.

Data collection rounds

The SolarMal project was initiated in January 2012 and will run through December 2015. The population census survey took place from June to September 2012, enumerating households, houses and individuals on the island. During the census survey, fieldworkers were assisted by individuals of the local community that are enrolled in a malaria programme, the Rusinga Malaria Project. The fieldworkers of the HDSS were familiarized with the population and geography of the island. In subsequent rounds of data collection, regular communication with the Rusinga Malaria Programme members and village elders enabled fieldworkers to find newly created households. All houses were mapped using the Global Positioning System

Table 3.1: An individual health questionnaire administered to everyone enrolled in the study. In the right column an example of an individual's answer in bold.

Question	Answer possibility
Individual ID	*ABCDE100*
Fieldworker ID	TO01
Illness over past 2 weeks	**Yes**; No
If illness reported: what symptoms?	1) Diarrhoea, **2) Fever**, 3) Vomiting, 4) Rash, 5) Bowel ache, **6) Head ache**, 7) Cough/sore throat, **8) Joint pain**, 9) Dizziness, 10) Other (manually specify)
Fever over the last 2 days?	Yes; **No**
Current fever?	**Yes**, No
Under malaria treatment now?	Yes; **No**
If illness or fever reported: take temperature measurement	37.6
If temperature 37.4 °C or above: RDT test	1) Negative, **2) *P. falciparum***, 3) Other *Plasmodium*, 4) Mixed malaria infection, 5) respondent refused to take test
Do you suffer respiratory symptoms?	**Yes**, No
If respiratory symptoms are experienced: Did you seek medical attention?	**Yes**, No
If medical attention: what medical attention was sought?	1) Doctor, 2) Nurse, 3) Community health worker, **4) Traditional healer**, 5) Other (manually specify)
Do you use any drug for the fever?	**Yes**, No
If using drugs against fever: which drugs?	1) Anti malarials, 2) Antibiotics, **3) Pain killers**, 4) Other (manually specify)

function on the tablet, recording latitude and longitude with an accuracy of five to 15 meters. Households are given a unique code consisting of two letters, relating to the name of the village where it is located, followed by a two digit number. Houses within a multi-house household have one extra letter, and all individuals are assigned a unique code comprising of five letters and two digits. Individuals were asked to provide their full name, sex, date of birth, main occupation and their relationship to the head of household. Subsequent analyses of individual data were performed using unique individual ID codes in order to ensure the anonymity of personal data.

To ensure that FWs are adding data to the correct corresponding house and individual in the field in subsequent follow up surveys, each house was provided with a door sticker showing its unique ID (Figure 3.3). The unique ID is also expressed as a barcode which is scanned with the tablet on arrival at the house and recorded in the data base. Once scanned, the barcode is validated against existing barcodes in the mobile application of OpenHDS and the application allows questionnaires to be filled in and stored. Each household is visited three times a year to collect and update demographic and malaria-related data. Members of the HDSS team visit all residential structures in nine geographic areas on the island simultaneously taking approximately three months to cover their area. At all households observed pregnancies, new births, deaths and migrations which have occurred since the previous visit, are recorded and updated. Digital questionnaires concerning demographic information are consistent with the HDSS questionnaire format of the INDEPTH network (Table 3.1). Moreover, the standardized questionnaire formats are widely used in East Africa and Kenya and therefore apply well to our research site.

Figure 3.3: Project sticker with barcode on the doorpost of a house: barcode scanning, integrated into the mobile data collection, allows quick identification of locations and study population to add or amend health and demographic information.

Figure 3.4: Navigating assigned houses: converting the near-real time demographic database into a geo-database displayed with Google Maps Mobile assists fieldworkers with tracking every house.

Upon arrival at a household the barcode is scanned and a digital log, which includes the interview date and time, is automatically created. After recording deaths and births, migrations into or out of the household are documented. There is a differentiation between migrations within the island and from elsewhere. Individuals moving within the island maintain their individual ID which becomes associated with the new household. These individuals found in the system by filtering on

their previous village and their name, subsequently selecting and migrating him or her. Moving out of Rusinga puts the individual in an inactive state in the database; people moving into Rusinga are provided with a new unique ID code if not previously enumerated, and all personal information is collected, as in the census survey. These individuals are found in the system by filtering on their previous village and their name and subsequently associating the individual ID with the new household ID through the completion of a migration form. If it is known that the individual in question does not plan to be a resident of the island no questionnaire is filled out. If it is known that an absent person is definitely coming back, no out migration is documented. To distinguish between temporary and permanent migration we use six months as a threshold. General information about the house construction, composition of household members and the presence and use of bed nets (as a malaria preventive tool) is collected for every house which is newly added to the database and for existing houses once per year.

Use of geographical information

On basis of the geographical coordinates of houses and demographic as well as malaria-related data gathered during the census of July 2012, the study design for the sequence of the rollout of the SolarMal intervention was developed and has been described elsewhere (Silkey *et al.,* Personal Communications). Briefly, the island is divided into 81 clusters each containing 50 or 51 households, with nine clusters making up one metacluster. Metaclusters form the geographical basis for the HDSS follow up surveys. The fieldworkers are each assigned one of the metaclusters in which to visit every house and individual once during an interval of three months. One fieldworker is deployed to an area conditional on relative progress in the surveillance. For navigational purposes, the demographic database is converted into a geographic database (KML file), allowing us to plot houses to be visited in the Google Earth mobile (Version 7.1.3. 1255) application integrated in the tablet (constructed with ESRI 2011. ArcGIS Desktop: Release 09. Redlands, CA: Environmental Systems Research Institute). Using the GPS function, FWs can track themselves on the map navigating in real time from one house to another (Figure 3.4). Furthermore, the geographic database also includes all server data enabling the FWs to select any house on the Google Earth map, consequently displaying the personal information of people living there.

Data quality and management

Data quality is initially controlled by designing questionnaires which permit answers to fall within an acceptable range. For example, using input constraints a date can only be entered as a date format, only women can deliver a child, a body temperature must lie within 35 to 42 degrees Celsius. After questionnaires have been entered in the field, the data is transferred to the ODK-Aggregate server. Unique IDs for

individuals, houses and households are automatically generated per FW to ensure that no duplicate values are entered in the system. Questionnaires which were not fully completed are not accepted for upload to the server. Data is then transferred from ODK-Aggregate to the OpenHDS server using the Mirth Connect data integration platform. All events entered during field visits are checked for inconsistencies during this step. Faulty records are filtered for further checking, and an error report is sent to the data manager by email. Births or deaths registered with an event date long in the past, multiple new-borns or separate deaths with the same date of event will be double checked with the FW or with the head of household. In addition, doubtful migrations are double checked, for instance if a child of three years old was found to be migrated because of marriage or work. Once in the OpenHDS server, the data manager has access to information about all individuals who have ever been active in the database, as well as their event history. A range of options to detect residual inconsistencies and perform data cleaning are available. An error often found in HDSSs is that individuals or households were duplicated during the census round under a slightly different name with different unique IDs at geographical border areas of FWs. An option to merge individuals and their past events provides a practical solution to this problem. In addition to this real time data quality control a web-based monitoring system was introduced that allows the data manager and FWM to extract a weekly snapshot of certain fieldwork related matters in the database (SU2 Web based monitoring). The web interface displays information about where FWs have been in the past week, as well as which household visits are yet to take place. Subsequently, the geographical database converted to KML files are uploaded to tablets at the beginning of every follow up round. The tool automatically removes individuals and houses which have already been visited during a given round of surveillance from the visit plan, publishing a file with remaining houses to be visited that can be uploaded to the computer tablets. Furthermore, the tool can be used to produce graphs of how many individual and houses were visited and how many forms were filled in during the previous week, allowing the performance of fieldworkers to be tracked. The tool gives the opportunity to see where FWs have been, how long they have taken to conduct the work delivered, as well as which forms have been filled in and how often. This information gives the FWM a quick insight into every FW's performance, so that inconsistencies can be addressed promptly and systematically. Additionally, on a weekly basis the tool generates 20 houses on basis of the houses already visited, to be revisited by the FWM. During re-visits, the usual procedure of demographic questionnaires is conducted and discrepancies between the results obtained by the FWM and FW are discussed with the FW in question.

Finally, all data of the HDSS, as well as entomological, parasitological, geographical and sociological data are fed into a MySQL relational database ready to be analysed. All data are linked through the unique individual, house or household IDs, making

extraction of spatial and temporal data a mere case of entering the desired query in to MySQL. Nightly backups of the databases are automatically copied to a network-attached storage system. The local server is a highly secured drive located at the field station *icipe*.

Ethical clearance

Ethical approval was obtained from the Kenyan Medical Research Institute (KEMRI); non-SSC Protocol No. 350. All participants are provided with information regarding the project outline, the ongoing HDSS procedures, the implementation of the intervention, and the collection and use of blood samples. Adults, mature minors and caregivers of children provided written informed consent in the local language agreeing to participation in the SolarMal project.

Results and Discussion

Resource allocation

We describe a data collection and management platform which advances the electronic systems employed in HDSSs in developing countries a step further mainly by integrating mobile-device based data collection with a centralized real-time data system. This integration is one of the important improved aspects within the described HDSS, resulting in organizational and scientific advantages. HDSS sites often rely on paper-based conducting of questionnaires before the data is entered in to a digital database (Derra *et al.*, 2012; Gyapong *et al.*, 2013; Kahn *et al.*, 2012; Pison *et al.*, 2014; Scott *et al.*, 2012). The Android operating system is used on powerful tablet computers, allowing us to develop or deploy the desired software. In combination with the freely available mobile data collection software, ODK-Collect and OpenHDS mobile, collecting data on paper is set to become obsolete. This not only saves time because data can be entered by merely navigating through the digitalized form, also the process of double-entry of paper questionnaires in to a digital format is no longer necessary. Fewer field workers and staff are required to perform the same job as before. Besides the cost-effectiveness on the basis of reduced staffing, the use of stationery is reduced to a minimum amount. Fieldworkers are provided with computer tablets, tablet protection covers and a paper notebook for occasional notes. Stationary in the office is reduced to a flip board to manage discussions, and some paper notebooks and pencils. All data collection and management is fully digital. Thus where traditional paper based HDSSs would approximately use one A4 for updates on household information and one A4 for individual health information, a digitalized data collection with 25,000 people and 8,000 houses would save over 30,000 A4 papers per survey. In the last five years there are sites where HDSSs have migrated from paper-based to some sort of digitalized entering system (Kouanda *et al.*, 2013;

Odhiambo FO, 2012; Sacoor *et al.*, 2013; Sifuna *et al.*, 2014; Wanyua et al., 2013). However, none of these sites have linked data collection software in the field directly to a real-time database. At the moment of writing, there is at least one other collection system using computer technology to integrate collection, management and database utilities; the LINKS system is in some ways similar to the system described in this paper (Pavluck *et al.*, 2014). LINKS also uses the ODK platform to collect data and is deployed at several sites in Africa. It is an easy implementable, cost reducing and efficient platform; however, the concept of a near real time database and its advantages is not exploited. Furthermore, there are examples of health data collection systems where PDAs and telephones are used, which is considerably more efficient than the paper based surveillances. However, they show major limitations in terms of user-friendliness and scalability (Anantraman *et al.*, 2002; DeRenzi *et al.*, 2011). This is mostly caused by the obsolescence and limited compatibility of software and hardware used.

Time and organizational efficiency

Making use of the latest openly available technology, data collection in the field enables researchers and field workers to be time efficient, resulting in cost reductions and organizational efficacy. At most INDEPTH affiliated HDSS sites the Household Registration System [HRS] is used for managing demographic and health-related data, either by digitalizing filled in paper forms or direct digital entry in the field (Derra *et al.*, 2012; Gyapong *et al.*, 2013; Kouanda *et al.*, 2013; Odhiambo *et al*., 2012; Wanyua *et al*., 2013). There are also examples of HDSS sites where a different data management system is developed relying on paper or non-paper based data collection (Kahn *et al.*, 2012; Sacoor *et al.*, 2013; Scott *et al.*, 2012). The data collection system described in this paper has several advantages compared to the HRS in terms of organizational efficiency (Phillips *et al.*, 2000). Firstly, traditional cleaning of data accumulating to an entity like an individual or household is largely removed. As the OpenHDS mobile application is a copy of the aggregated longitudinal database, in the application interface, adding data is only possible after selecting an existing entity. The constant uploading of collected data to the OpenHDS server and the synchronization of the database to the tablets makes reliable continuity of the data achievable.

Secondly, the entire process of creating an electronic questionnaire, up to viewing the collected data in a server, is a manageable, time efficient task for any scientist once basic training has been provided. The XLS-Form authoring tool allows also non-computer scientists to create a questionnaire with the option to apply the preferred constraints. Concepts in questionnaires such as skip logic, input constraints, structured data model and an entry concept from the start, which the HRSs lack (Phillips *et al.*, 2000), have in our project let to only few forms of mistakes and errors

that were relatively easy to detect. In a sample of our data we detected some incorrectly entered dates of birth and names, however in the following visit this personal data is always checked and corrected appropriately. The number of corrected mistakes in demographic data after one data collection round was never more than one percent. Simply uploading the XLS- form within ODK-Collect on the computer tablet allows one to conduct the questionnaires in OpenHDS mobile. All questionnaires related to the core demographic data collection are standardized and configured to OpenHDS mobile.

Thirdly, translating the real time database into a geographical database is a convenient way to assist FWs in real-time navigating their area of data collection. Demographic or disease-related data can be linked to a house location with its coordinate using the free Google Earth software. Tapping a house location on the device shows all the available household information. This combination of real time GPS navigation and fixed visiting points in space enables the FW to invest a minimal amount of effort in locating households at the study site. In this way fieldworkers of the HDSS manage to visit an average of approximately 15 houses and 40 people per day. The visiting of houses without a digital navigation platform can leave room for suboptimal walking routes.

Finally, after data collection has finished and data content has been cleaned, records can immediately be used to guide other parts of the project that rely on data collection structure of OpenHDS. Also, where the analysis of data in current HDSSs can only commence after it is manually entered and cleaned, this system allows one to have a dataset ready for analysis shortly after collection. Data cleaning is performed on a daily basis and, with roughly 500 data entries per day the data manager usually finishes routine cleaning in less than two hours. Manually entering great amounts of questionnaires and post-hoc cleaning of entered data can take many more hours even if every single questionnaire is digitally entered and cleaned in one minute.

One aspect of this particular HDSS is the facilitation of healthy team cohesion. The SolarMal project is a multidisciplinary project with multiple researchers collecting data on sociological, entomological and parasitological outcomes integrated with a HDSS. The complete project data and storage is linked to the OpenHDS infrastructure, there are twice-monthly meetings with all project staff to discuss data-related issues and all research areas make use of the data gathered through the HDSS in planning and carrying out data collection activities and subsequently analysing the data.

Data quality assurance

Organizational efficiency and data quality assurance go hand in hand, commencing from the OpenHDS platform where all data is centrally stored. Having the ODK-

Aggregate and the OpenHDS server opens up the possibility for the data manager to check and clean the contents of data in a consistent way on a daily basis. This near-real-time quality assurance is conducted on the level of the ODK-Aggregate by means of a customized list of queries looking for inconsistencies that are easily detectable, like double visited individuals. The more in-depth data cleaning is then possible at the level of the OpenHDS. The platform offers a range of tools to check, research and amend all aspects of the demography in a population. Another large advantage of this system is the automatic generation of unique IDs. Automating the assignment of IDs avoids duplication of individuals or multiple individuals with the same ID. All data collected in the project are related to one of these three levels of unique IDs, in this way it is safeguarded that data collected is attributed to the right person or house. Furthermore, by means of the KML file, the FW knows which house is visited. Selecting the house ID in the OpenHDS mobile application directly gives access to editing and attaching new data to the individuals living there. Demographic and other questionnaires can easily be filled in and attached to the right unique ID, thus reducing confusing data accumulation drastically. In addition, all houses are provided with a door sticker with a unique bar code and the house and household ID. Scanning the barcode confirms the physical presence of the FW at the house, so that the data entered truly correspond to the house that is visited and it is not possible for a FW to enter data remotely. Lastly, a web-based monitoring of the database to monitor the performance of FWs is under development. This monitoring allows the FWs and data manager to follow the performance of every FW. Monitoring of fieldworkers to increase data quality is not a new concept (Asangansi *et al*., 2013; Schobel *et al*., 2014). However, a near-real-time database that automatically displays FW performance is a convenience never described. Tracking the route walked by FWs, and observing the number of individuals and questionnaires filled in are currently the most prominent and helpful tools to detect fieldworker inconsistencies. More importantly, simple analysis of this data can shed light on interviewer bias, which can directly be discussed with the FW in question.

Challenges and future research

Despite the advancement of and improved accessibility of information technology, the development and implementation of the described infrastructure in low and middle income countries will meet obstacles and limitations. Primarily, the requirement of electricity and a computer server near the field work site are vital. Likewise, this operation only becomes truly feasible with a trained data manager who has advanced I.T. skills. During this pioneering phase, having access to or collaborating with a software developer is also necessary. So, although on one hand cost and time savings are made in the long term, setting up the initial facilities requires a significant financial investment and demands a well-designed strategic plan for the context of the HDSS. Another complementary investment is the training of staff involved in the

HDSS in how to handle the hardware and the software. Digitalization of the HDSS process from an existing paper-based system can lead to a drastic reduction of personnel, which facilitates the operational procedures of the HDSS. Furthermore, there are many HDSS currently using paper based systems that desire to migrate to a fully digitalized HDSS. This transition can introduce a whole set of unforeseen difficulties that rely on complex logistical issues which necessitate more data and software professionals (Wilcox *et al.*, 2012).

One of the biggest issues experienced throughout the past HDSSs, is dealing with migration of the population under study. Where the OpenHDS system allows this problem to be handled much more promptly than paper-based or obsolete household registration systems, it is still a challenge to make sure that internal migrations between households are correctly processed. Individuals can always be immigrated again, but the reintroduction relies on the name given by the person in question. We experienced that sometimes other names are given or the original name was incorrectly provided.

Conclusion

In regions that lack adequate organization to monitor demographic and health information little is known about population dynamics and the epidemiology of disease. It is these areas where health is often heavily compromised and where collection of specific health-related data can greatly improve our understanding of health issues. The HDSS within the SolarMal project provides an example of a user-friendly infrastructure for field data collection in evidence-based research in low and middle income countries by making use of the currently available technologies. Whereas most HDSSs still work with paper based or obsolete digital systems, this paper describes a totally digitalized platform that allows fieldworkers and field managers to quickly and systematically keep clean data, make fewer mistakes with data collection and make use of a structured data model and entry concept from the start. Stakeholders such as government health officers, local administrators and scientists have easy access to real time data storage on a secure central database which enables them to conduct near-real-time quality assurance. Besides, remote progress monitoring allow scientists to quickly detect inconsistencies. Most importantly, this system could radically increase cost-effectiveness by saving time and money on stationery, data clerks, organizational costs and manual logistics.

Authors' contribution

AdP is the software developer that helped with improving and advising on the data management platform as well as providing expert comments on the manuscript. KO is

the local database manager applying the OpenHDS and ODK platform in the field. IK is the fieldworker manager, organising the field activities and linking this to the data management platform. AH, CM, WM and WT are part of the overall program management and have directly worked a lot on embedding and integrating the data management platform into the SolarMal project. NM has supervised the complete implementation of the platform and provided expert comments on the manuscript. All authors read and approved the final manuscript.

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Chapter 4

Design of trials for interrupting the transmission of endemic pathogens

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Publication under review

Abstract

Background: Many interventions against infectious diseases have geographically diffuse effects. This leads to contamination between arms in cluster-randomised trials. Pathogen elimination is the goal of many intervention programs against infectious agents, but contamination means that standard CRT designs and analyses do not provide inferences about the interventions' potential to interrupt pathogen transmission at maximum scale-up. **Methods:** A generic model of disease transmission was used to simulate infections in stepped wedge cluster-randomized trials of a transmission-reducing intervention, where the intervention has spatially diffuse effect. Simulations of such trials were then used to examine the potential of such designs for providing generalizable causal inferences about the impact of such interventions, including measurements of the contamination effect. The simulations were applied to the geography of Rusinga Island, Lake Victoria, Kenya, the site of the SolarMal trial of the use of odour-baited mosquito traps to eliminate *Plasmodium falciparum* malaria. These were used to compare variants in the proposed SWCRT designs for the SolarMal trial. **Results:** Measures of contamination effects were found to provide measures that could be assessed in the simulated trials. Assuming the spatial contamination inspired by analyses of trials of insecticide-treated nets against malaria. When applied to the geography of the SolarMal trial these measures were found to be robust to different variants of SWCRT design. Analyses of the likely extent of contamination effects supported the choice of cluster size for the trial. **Conclusion:** The SWCRT is an appropriate design for trials to assess the feasibility of local elimination of a pathogen. Estimates of the effects of incomplete coverage can be made by analysing the extent of contamination between arms in such trials, and also support inferences about causality. The SolarMal example illustrates how generic transmission models incorporating spatial smoothing can be used to simulate such trials for purposes of power calculation and optimization of cluster size and randomization strategies. The approach is applicable to a range of infectious diseases transmitted via environmental reservoirs or via arthropod vectors.

Introduction

Pathogen elimination is the goal of many intervention programs against infectious agents such as mass chemotherapy, vaccine programs, behaviour change to reduce contacts, and vector control. The objective of interrupting transmission in whole populations impacts the choice of trial study designs. Typical before-and-after comparisons of populations have no replication and no contemporaneous control, and therefore an effective sample size of one. If transmission continues post-intervention it is impossible to know whether this was the result of bad luck. If transmission is successfully interrupted with a before-and-after design, it is unclear whether the intensity of intervention was appropriate, a massive overkill, or whether the disappearance of the pathogen was fortuitous. In such studies, it is not possible to distinguish changes in transmission resulting from the intervention from stochastic fluctuations in transmission levels or, in the case where pathogens are endemic, from environmental variation.

Randomization is critical if a study is to provide robust evidence of causality (Cartwright, 2010). Where assignment at the individual level is impossible, cluster-randomized trials [CRT] are often the best way to derive causal inferences about infrastructural or behavioural interventions. Clustering may be needed due to the nature of the intervention or where effects at the community level are anticipated which would be averaged across the whole population in an individual-level randomized trial (Hussey *et al.*, 2007; Mdege *et al.*, 2012; Zhan *et al.*, 2014). CRTs are therefore the usual approach to achieve replication and contemporaneous controls in trials of infectious disease interventions, which typically provide both individual protection to the immediate recipients and also induce community effects by reducing onward transmission. Cluster size is critical in such trials: if the clusters are too small then the effect of the interventions will be propagated beyond the cluster edge via the community effect throughout the whole population, biasing the difference between the trials arms towards zero; if the clusters are too large, and hence few in number, there are insufficient degrees of freedom to distinguish the intervention effect from residual stochastic variation among clusters. Only with a sufficient number of adequately-sized clusters is it possible to improve the inference from a standard before-and-after CRT.

Unfortunately, standard parallel CRT designs cannot provide a rigorous test of whether local elimination of a pathogen is feasible. This requires scale-up to universal coverage over the whole area, which cannot be achieved if there are untreated control clusters. For this purpose we propose the use of stepped wedge cluster randomized trials [SWCRT], in which the intervention is introduced one cluster at a time until the whole area is covered. SWCRT elegantly combine the elements of group randomization, replication, contemporaneous controls, and complete coverage.

Population-based trials of infectious disease interventions do not directly estimate the efficacy of an intervention in reducing the rate of transmission that would be observed in a laboratory setting. This is both because interventions are generally not applied perfectly, and also because what is measured (the effectiveness) is generally the cumulative effects of recurrent transmission events, conditional on the pattern of contacts. Different effectiveness measures can be estimated in CRTs (and SWCRTs), either by comparing clusters before intervention with those that have already been intervened, or by comparing the whole study area with a non-intervention area (or possibly the same area, pre-intervention) (Halloran *et al*., 2010; Halloran *et al.*, 1991). With an appropriate cluster size, it is also possible to estimate the range and gradient of the intervention effect across cluster boundaries. The latter is exemplified by an analysis of CRTs of insecticide treated nets [ITNs] (Binka *et al.*, 1998; Hawley *et al.*,2003; Howard *et al.*, 2000) for the control of malaria. These analyses confirm that if the central area of the intervention clusters is far enough away from the intervention boundaries, an estimate of the locally maximum intervention effect can be made, unaffected by contamination from control clusters. These studies also provide information about the effects of imperfect coverage that can be used to parameterize process models for predicting the impact of sub-optimal deployment in other settings.

With SWCRT designs, while the individual cluster size may be approximately constant in terms of either area or population, the boundaries between the arms are constantly changing, and hence the size of congruent intervention areas, increases during the course of the study. Eventually the entire population receives the intervention, so the maximal intervention population is obtained (Wolbers *et al.*, 2012). Thus, the overall size of such a trial is likely to be very large, with the costs of intervention deployment large in relation to those of data collection. An adequate sample size in terms of the total number of individuals enrolled or volume of data is a given (as seen in our application example, the Solar Power for Malaria Control trial [SolarMal]) and so these trials are likely to be powered to allow analysis of the temporal pattern of effectiveness. In this spirit, we evaluate designs under the assumption of one large overall sample size, as per section 1, so that the assessment of power is a comparison of power and time dependent measures of effectiveness among designs rather than a calculation intended for estimation of absolute sample size needed to detect a given size of signal.

Empirical power and sample size calculations for CRT and SWCRT designs have been proposed (Reich *et al.*, 2012; Wolbers *et al.*, 2012), but these do not directly address the issue of community effects, either as contaminating the control arm of the study or as potential target for measurement. Our approach, to address the impact of community effects directly, is compatible with that of Halloran, *et al.* (Halloran, 2012),

where each household in our simulation is a mini-community with its own population, and its own location relative to other mini-communities on the landscape.

In this paper, simulations of SWCRTs are used to consider how these designs might be analysed to provide generalizable causal inferences about an intervention, giving particular consideration to the impact of variations in the cluster size relative to the extent of community effects. We use a generic model of disease transmission for the simulations, so that the results are broadly applicable to a range of infections transmitted either directly, via environmental reservoirs, or via arthropod vectors. Two new measures of effectiveness, inspired by analyses of CRTs of ITNs as protection against malaria infection, are proposed and their merits for inferring causality from the data produced in a SWCRT design are considered. The new measures are applied as an example to the design of a trial of the use of odour-baited mosquito traps [OBTs] to reduce mosquito population size, reduce biting intensity, and eliminate *P. falciparum* malaria from Rusinga Island, Lake Victoria, Kenya (SolarMal) (Hiscox *et al*., 2012).

Methods

Simulation model of infection

The core of all simulations presented in this paper is a simple individually-based susceptible-infected-susceptible model of infection transmission. The model does not aim to reproduce the within-host dynamics of any particular pathogen, since each infection is recorded only at one point in time, and each individual is available to be infected again at the next time step. The model aims to capture the force of infection at each time step before, during, and after the intervention is introduced across the study area. Once the behaviour of the model is confirmed, the theoretical impacts and interactions of the pathogen's initial incidence, the extent of the community effect, and the efficacy of the proposed intervention are explored via simulations of three study design schemes for assigning sequences to clusters of uniform physical size. For this discrete time model, incidence is defined as the proportion of individuals with disease recorded at the specified time step. Empirical power estimates and confidence interval widths of model predictions are used to evaluate the proposed experimental designs, in terms of both optimal design structure and most informative measures of effectiveness. From these general results, a preferred design structure is selected for the SolarMal trial (Hiscox *et al*., 2012).

Discrete-time stochastic simulations of disease transmission are implemented using a one week time step and a population of simulated individuals indexed with i, where $N(t)$ is the cumulative number of individuals having received the intervention for the

first time at time step t. The total number of individuals in the simulation is then $N(T)$, where T is the last time step of the intervention. Simulated individuals are allocated to random point locations in a defined geometry. To initialize the simulation to a stable state, infections are independently assigned to each individual with a probability equal to a specified incidence, $\overline{y_0}$ for each week of the initial ten weeks of the simulation. For subsequent time points, $t > 10$, new infections were generated via a two-state autoregressive [AR] process with distributed lag, such that, for each individual i at time step t the incidence is:

$$y(i,t) \sim \text{Bernoulli}\ (E[y(i,t)) \quad (1a)$$

$$E\,[y(i,t)] = 1 - \exp\,(-\beta_0 \overline{y_r}\,(i,t)) \quad (1b)$$

where β_0 , the transmission parameter, is the expected number of infectious contacts received by each host per time step; $\overline{y_r}(i,t)$ is the infectious reservoir for each simulated individual at time step t defined as the percentage of infected members in its neighbourhood:

$$\overline{y_r}(i,t) = \sum_{\tau=6}^{10} w_\tau \frac{\sum_j y(j,t-\tau) I_r(i,j)}{\sum_j I_r(i,j)} \quad (2)$$

and $I_r(i,j)$ is an indicator variable taking the value 1 if hosts i and j are located a distance less than r from each other, and is otherwise 0. These weights w_τ (which sum to 1) specify a kernel defining the lag times varying between 6-10 time units (weeks). To achieve an approximately stable endemic state with strictly positive transmission, the parameter β_0 is assigned a value based on the mean infectious reservoir across the whole study population at time 0,

$$\overline{y_r}(0)\beta_0 = -\frac{ln(1-\overline{y_r}(0))}{\overline{y_r}(0)} \quad (3)$$

leading to a susceptible-infected-susceptible model of infection dynamics with the generation-time distributed according to the lag. The generation-time, and spatial averaging of the infectious reservoir $\overline{y_r}(i,t)$ over each neighbourhood is intended to approximate the spatial and temporal pattern of *P. falciparum* transmission. It is intended to approximate to proportionality the data that might be generated in a trial in which the outcome is incidence of clinical disease, which in turn is assumed to vary proportionately to the force of infection. A latent period equivalent to six weekly time steps is simulated in order to capture the delay between the infection process and clinical disease and the approximate generation time of the infection (this is a very simple approximation to the generation time of *Plasmodium falciparum* malaria). The

direct effect of the intervention is to reduce the force of infection in the intervention clusters, by the protective efficacy against infection, so that the individual and time-specific transmission is modelled as

$$y(i,t) \sim \text{Bernoulli}\ (E[y(i,t)) \quad (4a)$$

$$E\,[y(i,t)] = (1 - \exp(-\beta_0 \overline{y_r}\,(i,t)(1 - C_r(i,t)E_s)) \quad (4b)$$

where $\overline{y_r}(i,t,)$ is defined as before and captures the state of the reservoir for each individual at each time step, E_s is the efficacy of the proposed intervention in protecting users from any single infection event (i.e. the proportionate reduction in the probability that infection occurs); and $C_r(i,t)$ is the percentage of each individual's neighborhood that has received the intervention at time t. $1 - C_r(i,t)E_s$ thus represents the proportion of transmission that withstands the effect of the intervention.

Since the simulation does not aim to capture effects of changing immune status in the course of the trial, *i.e.*, the transmission parameter β is held constant at β_0 E_s can capture effects achieved by reducing the infectious reservoir with chemotherapy, vaccines, isolation of infectious cases, or reducing the vectorial capacity for vector borne diseases.

Simulated trial designs for random geographies with uniform initial incidence

To evaluate the impact of various initialization parameters, ten island landscapes were simulated. For each landscape, 1000 households were allocated to random point locations in a square grid of dimension $9\ \text{km} \times 9\ \text{km}$ Four-thousand individuals were randomly assigned across these households, with each household constrained to have at least one member. Once the locations of these households were assigned, the neighbours of each inhabitant was calculated as all those individuals within a community radius r, the maximum physical extent of the postulated community effect. The landscape description was completed by dividing the grid into 81 equal-area (but not equal population) clusters and calculating a median location of all households within each cluster.

Three possible CRT designs were simulated for each landscape: the *random*, the *oil drop*, and the *hierarchical* designs, represented schematically in Figure 4.1. For the first design, the order in which clusters are selected to receive the intervention was completely random, *i.e.*, the intervention sequences for the random design are single permutations of the cluster numbering. For the second design, a cluster was initially selected at random from among the 81 possible clusters; clusters were then chosen at increasing median cluster distance from the initial cluster, forming a single intervention zone that increased in size until the grid was completely covered.

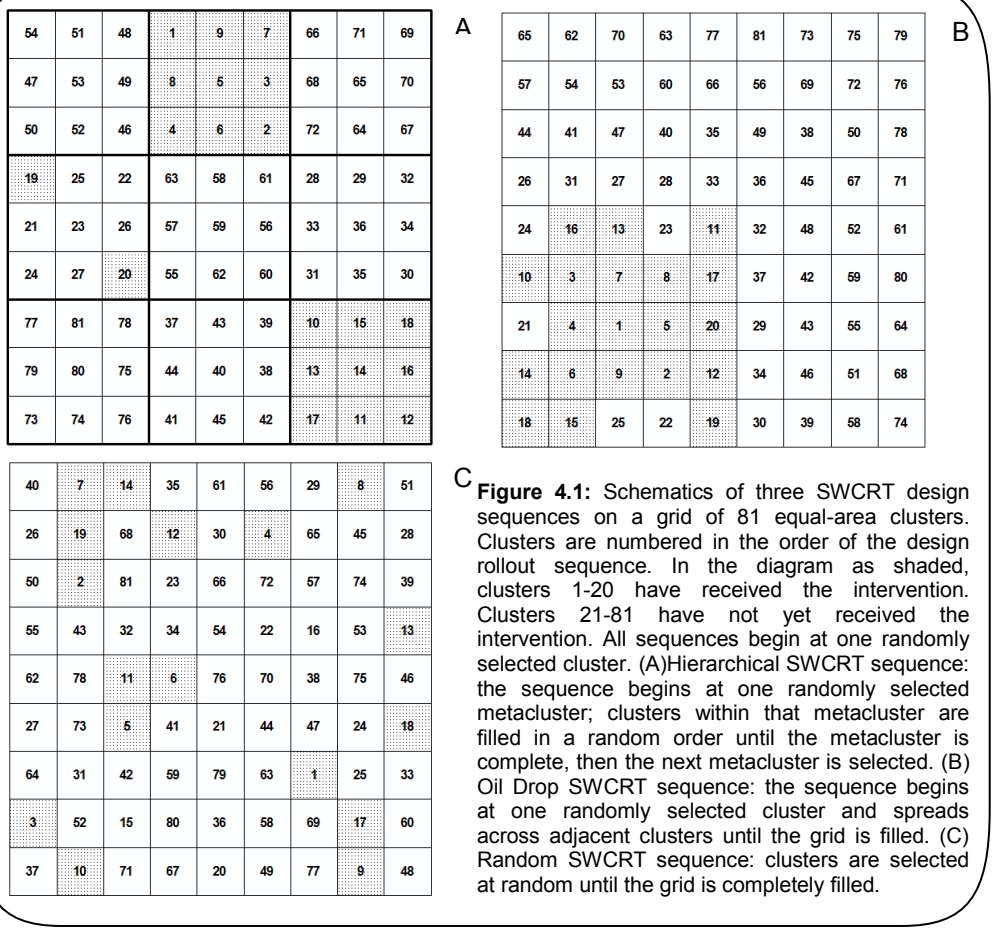

Figure 4.1: Schematics of three SWCRT design sequences on a grid of 81 equal-area clusters. Clusters are numbered in the order of the design rollout sequence. In the diagram as shaded, clusters 1-20 have received the intervention. Clusters 21-81 have not yet received the intervention. All sequences begin at one randomly selected cluster. (A)Hierarchical SWCRT sequence: the sequence begins at one randomly selected metacluster; clusters within that metacluster are filled in a random order until the metacluster is complete, then the next metacluster is selected. (B) Oil Drop SWCRT sequence: the sequence begins at one randomly selected cluster and spreads across adjacent clusters until the grid is filled. (C) Random SWCRT sequence: clusters are selected at random until the grid is completely filled.

The third, hierarchical, design is a compromise between the random and the oil drop, motivated by the desire to retain comparators remote from the intervention while maintaining sufficient randomness not to bias experimental outcomes. For the hierarchical design, the grid was divided into nine equal-size meta-clusters, which were further subdivided into nine equal-size clusters. Hierarchical sequences were generated with the following algorithm: one cluster of the 81 was selected at random; all clusters within the same meta-cluster as the initial cluster were then selected at random until all had received the intervention and the meta-cluster was full. The next cluster was then chosen at random from the remaining 72 clusters. The procedure was repeated until all clusters in all meta-clusters on the grid had received the intervention. The relative randomness of these design structures can be stated in terms of the number of suitable sequences that could be generated for each design. A total of 81! possible sequences exist for the random design 81 possible sequences

exist for the oil drop design, and $(9)! \times (9)!$ possible sequences exist for the hierarchical design.

The simulated intervention was introduced to all households within a single cluster during each time step. The duration of the intervention introduction across the study was 81 time steps (weeks), $T = 81$. The total number of individuals in the study was $N(T)$, so that at each time t, some number $\mathrm{N(t)}$ of individuals moved to the intervention arm, which had total size at time t of $\sum_{\tau=1}^{t}(N\tau)$. The non-intervention arm was divided into those who have neighbours with the intervention and were thus susceptible to first order community effects, and a pure comparator group who were neither recipients of the intervention nor neighbours of any recipients of the intervention. The total number of individuals in these three groups, and the numbers of clinical cases occurring within each group, (intervened, non-intervened but nearby, non-intervened but remote) were tallied during the initialization period and at all subsequent time steps, as per Figure 4.2 in the supplementary information.

Eighty simulations were run for each of 100 randomly generated cluster allocation sequences corresponding to the random, oil drop, and hierarchical designs for 45 parameterizations comprised of five levels of initial pathogen incidence (10%, 20%, 30%, 50%, and 80%), three levels of neighbourhood radius (0.5, 1.0, and 1.5 km), and three levels of intervention efficacy (0%, 30%, and 80%) across ten randomly generated landscapes, where each landscape was a set of 1000 randomly distributed households across the island, with a total population of 4000 inhabitants.

Simulated trials for non-uniform population densities and initial incidence

If there are underlying spatial trends in the disease, correlated with the spatial pattern of the roll-out, this makes it difficult to interpret the results of a SWCRT. To evaluate the performance of the different designs in such situations, simulations were run assuming spatial heterogeneity in initial incidence, with a smooth spatial pattern in initial incidence described by bivariate probit distributions $N(\mu_1, \mu_2, \begin{bmatrix} 1 & \rho \\ \rho & 1 \end{bmatrix})$ and with the maximum incidence at a random location on the $9\ \mathrm{km} \times 9\ \mathrm{km}$ grid. These spatial distributions of infection were simulated with a range of different spatial patterns of the roll-out of the intervention.

Similarly, heterogeneity in host population density might also affect the efficiency of different designs. To evaluate this, simulations were run assuming a population concentrated at the grid edges, a distribution *e.g.* typical of many islands. Half of the households initially assigned to the 21 most central grid squares were reallocated to randomly sampled locations (and clusters) further from the centre than this, thereby depleting the population in the core region. For these simulations, 700 randomization

sequences corresponding to the three design structures were evaluated at one level of initial incidence of 20%, two levels of efficacy (30%, and 80%), one level of community radius (1 km) and a total population, $N(T)$, of 4000 individuals. Eight hundred simulations were carried out for each randomization sequence.

Intervention effectiveness measures

Following Halloran, Longini, and Struchiner (Halloran, Longini & Struchiner, 2010), a series of effectiveness measures $\hat{e}_1(\mathrm{t})$, $\hat{e}_2(\mathrm{t})$, ... $\hat{e}_6(\mathrm{t})$, were computed from the results of the simulated trials. These include estimates of direct, indirect, and overall effects, and two novel measures, $\hat{e}_5(\mathrm{t})$ and $\hat{e}_6(\mathrm{t})$, that distinguish non-intervened individuals according to whether they are considered to be close to, or remote from the intervention at time *t*. These measures, on which we propose to base inferences about intervention effects are given in Table 4.1. To calculate these measures at each time step the population was classified into intervened, remote from the interventions, and neighbouring the intervention, but not yet intervened categories (see Supplementary Information Figure 4.1). Three of the effectiveness measures, $\hat{e}_1(\mathrm{t})$,$\hat{e}_2(\mathrm{t})$, and $\hat{e}_3(\mathrm{t})$, involve comparisons with the baseline mean outcome at each time step, which is the incidence at the time step before the first introduction of the intervention to the island computed as:

$$\overline{Y}_b = \frac{\sum_{\tau=-b}^{\tau=-1}\sum_i y(i,\tau)}{bN(T)} \tag{5}$$

where b is the number of time steps included in the baseline, $y(i,t)$ is the observed value of the outcome, (*i.e.*, presenting with the disease or not), and $N(T)$ is the total population at risk $\hat{e}_4(\mathrm{t})$, $\hat{e}_5(\mathrm{t})$ and $\hat{e}_6(\mathrm{t})$ are contemporaneous measures of effect that depend on the randomized assignments of clusters, and so are particularly relevant for causal inference. The standard contemporaneous direct effectiveness measure $\hat{e}_4(t)$, directly compares the clinical case rate in the intervened and non-intervened populations at each time step. We propose a new direct effectiveness measure, $\hat{e}_5(\mathrm{t})$ in Table 4.1, which restricts the contemporaneous comparator group to those hosts located remotely from the intervention. While $\hat{e}_5(t)$ estimates the direct effect of the intervention, as the trial proceeds this becomes the cumulated effect of many transmission events (so it is not an estimate of the efficacy E_s used in the generation of the simulated trials). We also define a new indirect effectiveness measure, $\hat{e}_6(t)$, applying the same contemporaneous comparator group as $\hat{e}_5(t)$ in order to measure the influence of the intervention in the non-intervened group (*i.e.*, the community effect). As before, *remote* is strictly defined as all members of the non-intervened group who have no neighbours in the opposite arm of the trial at a given time step; where neighbour status is determined from the given community radius, r, beyond which the spill-over effect of the intervention is anticipated to be negligible.

Table 4.1: Intervention effectiveness measures as adapted from Halloran, Longini, and Struchiner (2010).

Measure #	Intervention group	Mean outcome intervention group	Comparator group	Time-dependent effectiveness measure
Baseline comparison groups				
1	Intervention	$\frac{\sum_i y(i,t)I(i,t)}{N(t)}$	Baseline	$\hat{e}_1(t) = 1 - \frac{\sum_i y(i,t)I(i,t)}{\overline{Y}_b N(T)}$
2	Naive	$\frac{\sum_i y(i,t)(1-I(i,t))}{N(T)-N(t)}$	Baseline	$\hat{e}_2(t) = 1 - \frac{\sum_i y(i,t)(1-I(i,t))}{\overline{Y}_b(N(T)-N(t))}$
3	Trial population	$\frac{\sum_i y(i,t)}{N(T)}$	Baseline	$\hat{e}_3(t) = 1 - \frac{\sum_i y(i,t)}{\overline{Y}_b N(T)}$
Contemporaneous comparison groups				
4	Intervened	$\frac{\sum_i y(i,t)I(i,t)}{N(t)}$	Naive	$\hat{e}_4(t) = 1 - \frac{(N(T)-N(t))\sum_i y(i,t)I(i,t)}{N(t)\sum_i y(i,t)(1-I(i,t))}$
5	Intervened	$\frac{\sum_i y(i,t)I(i,t)}{N(t)}$	Naïve remote from intervention	$\hat{e}_5(t) = 1 - \frac{\sum_i y(i,t)I(i,t)\sum_i(1-I^*(i,t))}{N(t)\sum_i y(i,t)(1-I^*(i,t))}$
6	Naïve close to intervention	$\frac{\sum_i y(i,t)(1-I(i,t))I^*(i,t)}{\sum_i(1-I(i,t))I^*(i,t)}$	Naïve remote from intervention	$\hat{e}_5(t) = 1 - \frac{\sum_i y(i,t)(1-I(i,t))I^*(i,t)\sum_i(1-I^*(i,t))}{\sum_i y(i,t)(1-I(i,t))I^*(i,t)\sum_i y(i,t)(1-I^*(i,t))}$

$y(i,t)$:outcome measured for individual *i* at time *t*; $\overline{Y}_b$: mean outcome at baseline; $N(t)$: total individuals in intervened clusters at time t; $I(i,t)$: indicator taking value 1 if individual *i* is in an intervened cluster at time *t*, 0 otherwise; $I^*(i,t)$: indicator taking value 1 if individual *i* is intervened or less than distance *r* from the nearest intervened cluster at time *t*, 0 otherwise, so that $(1-I(i,t))I^*(i,t)$ indicates those individuals in the naïve close to intervention category. Following Halloran, effectiveness measures $\hat{e}_1$, $\hat{e}_2$, $\hat{e}_4$ are direct measurements of intervention effectiveness, of which only $\hat{e}_4$ is contemporaneous. $\hat{e}_3$ is the overall measure of effectiveness for a before and after study $\hat{e}_5$ and $\hat{e}_6$ are novel contemporaneous measurements that separate the direct and indirect effects during intervention roll-out, avoiding the bias caused by contamination of the comparator group.

In practice, the community radius must be defined on the basis of observations from previous trials, or the biology of the pathogen. Randomness in the infection process cannot be separated from sampling variation. To enable comparison among effectiveness measures for the purpose of these simulations the population at risk was equivalent to the total simulated population $N(T)$, fixed at a value of 4000, and the data from all simulated individuals contributed to the effectiveness calculations. We further considered a range of r values, where community membership for each individual is defined at each time step, $I^*(i,t)$ is an indicator, taking the value 1 if $x(i,t) \leq r$ and 0 if $x(i,t) > r$.

Each of these six time-specific effectiveness estimates, evaluated at each time step during the simulation is of the form: $\hat{e}(t) = 1 - \frac{Y_1(t)}{Y_0(t)}$ where $Y_0(t)$ and $Y_1(t)$ are risks or rates in the comparator and intervention group respectively. Corresponding to each of these measures, cumulative effectiveness measures can be computed as: $\hat{E}(t) = 1 - \sum_{\tau=0}^{\tau=t} Y_1(\tau) / \sum_{\tau=0}^{\tau=t} Y_0(\tau)$ where both the numerator and denominator are summed over all time points up to t. An overall value for each effectiveness measure is obtained by cumulating up to the end of the trial.

Confidence intervals

In a real trial $\sum_{\tau=0}^{\tau=t} Y_1(\tau)$ *and* $\sum_{\tau=0}^{\tau=t} Y_1(\tau)$ are estimated from proportions of tested individuals positive for the infection or disease. Estimates of the ratio of these two proportions, and hence of the cumulated, or overall effectiveness, $\hat{E}(t) = 1 - \sum_{\tau=0}^{\tau=t} Y_1(\tau) / \sum_{\tau=0}^{\tau=t} Y_0(\tau)$ (see above), can thus be made using logistic regression models, with random effect terms to allow for temporal variation, cluster differences in incidence, and if necessary for re-testing of the same individuals at repeated time-points. Approximate model-based confidence intervals for the ratio of the two proportions and hence for the effectiveness, can then be made using the delta method (Oehlert, 1992).

For comparison of simulated trials, the distribution of effectiveness measures and their confidence intervals were calculated by carrying out 1,000 independent simulations of each trial and analysing the empirical distributions of the outcomes.

Power, design and sequence evaluation

A characteristic of the SWCRT design is that, as the membership of the populations shifts from non-intervened to intervened at each time step, so does the power of the chosen effectiveness measure. Point estimates were made from the simulations for each of the six effectiveness measures, and the power of each design was estimated for each time step. In each case the same radius, r, was used for defining neighbors in the calculation of effectiveness measures $\hat{e}_5(t)$ and $\hat{e}_6(t)$ as was used in

generating the simulations(in an actual field trial, the effects of using different radii to define neighbours will be analysed in order to estimate the best fitting r). Empirical two-sided 90% confidence intervals of direct comparisons with baseline $\hat{e}_1(t)$, $\hat{e}_2(t)$, and indirect comparison with baseline $\hat{e}_3(t)$, and contemporaneous $\hat{e}_4(\mathrm{t})$ $\hat{e}_5(\mathrm{t})$ and $\hat{e}_6(\mathrm{t})$ effectiveness measures were drawn at each time step across all simulations. Results for the randomly generated sequences corresponding to the three different types of designs are ranked inversely by confidence interval half-width.

We derived the power estimates by comparing simulation results run under the null ($H_o : E_s$ =0) and two alternative hypotheses ($H_o : E_s = 0.30$ and $H_o : E_s = 0.80$). Specifically, the 95% quantile of the empirical null distribution was taken as an estimate of the critical value corresponding to a type I error of ten percent ($\alpha = 10\%$). This value directly corresponds to $\beta_{critical}$ under the alternative hypothesis. In addition to the overall power of a design structure, the value of β for each effectiveness measure and time step was calculated as the area-under-the-curve to the left of $\beta_{critical}$ under the alternative (empirical) distribution. The power for each effectiveness measure at each time step was then calculated as 1- β.

All simulations were carried out at the High Performance Computing Core at the University of Basel in R version 3.02.

Simulated trial design for the SolarMal trial

A baseline health and demographic surveillance survey [HDSS] was carried out from May - July 2012 on Rusinga Island. Four thousand-sixty-two households with a total membership of 23,337 inhabitants were enumerated. Approximately 22% of the residents were diagnosed via rapid diagnostic tests as infected with *P. falciparum*.

The cluster size for the trial was matched to the logistical limit of the number of households that could receive the intervention within a week (*i.e.*, 50). Thus, in contrast to the simulations of regular grids, in the application the clusters were of approximately equal population but not equal geographic size. A minimal spanning tree algorithm (Hahsler *et al.*, 2007), used to solve the classical travelling salesman problem, provided an optimal one-way path among households across Rusinga. The 4062 households along the path defined by the minimal spanning tree were then counted off along the path into 81 clusters; 12 of which are randomly selected to be assigned a total of 51 households, the remainder having 50 households assigned. A large number of randomizations, each consisting of an ordering of the 81 clusters thus defined, were randomly generated, corresponding to either hierarchical, oil drop or random SWCRT designs. For the hierarchical designs, contiguous sets of nine clusters were amalgamated into single meta-clusters (see Supplementary Information Figure 4.2). A trial, involving roll-out of one cluster per week, and based on each

randomization was simulated, with each of the 23,337 individuals on the island modelled as a single stochastic element. At each time step, individuals were identified within one of three groups: intervened, non-intervened but within the community radius of at least one intervened individual, or non-intervened beyond the community radius of any intervened individual, and each of the effectiveness measures listed in Table 4.1 was computed.

To classify individuals into these groups, pairwise great-circle distances among all households were calculated, and used as a basis for identifying all the neighbours within the community radius, r, for each individual within each household. A value of 1 km for r was used, based on the approximate scale of the effects in the trials of ITNs (Binka *et al.*, 1998; Hawley *et al.*, 2003). The percentage of infections $I_r(i,j)$ averaged across the individuals neighbourhood were fed into the calculation for the infective reservoir at each time step. Likewise, intervention coverage rates $C_r(i,t)$ for the neighborhood of each house were calculated for each time step and fed into the effectiveness calculation (Equation (4)).

Analysis of effectiveness for the simulated trial design for SolarMal and sequence selection

Point estimates and empirical 95% confidence intervals of the six direct and indirect effectiveness measures were drawn for each time step from a set of 1000 independent replications of the simulated trial. The duration of utility of a given effectiveness measure is also of interest and is defined as the number of weeks from the start of introduction of the OBTs until the CI-width of an effectiveness measure increased to 10%. A further ranking was made in order of total area under the CI-width versus time step curve until from the 18th to 65th week of the 81-week rollout (complete coverage). For this ranking procedure, confidence interval [CI] widths from the first and last two months were discarded as either the treatment or comparison groups were tending to zero and the effectiveness measures began to fluctuate wildly. Among those sequences with good statistical properties, additional sociological constraints were applied to select a group of sequences acceptable to a community stakeholder council; in particular, the intervention schedule should be constrained so that entire villages, receive the intervention within six months.

Results

Model confirmation and explanation of the interrelationship between effectiveness measures

Comparison of the average incidence in the intervention arm with that in the non-intervention arm in illustrative simulations (Figure 4.2) clearly indicate that the transmission simulator can capture the main features that we would expect of a trial that succeeds in interrupting, or near-interrupting transmission of a pathogen. There was considerable variation in the incidence in the control arm in the first part of the intervention period (following time step 40). Only a very small number of individuals were initially included in the intervention arm. The decrease in incidence in the

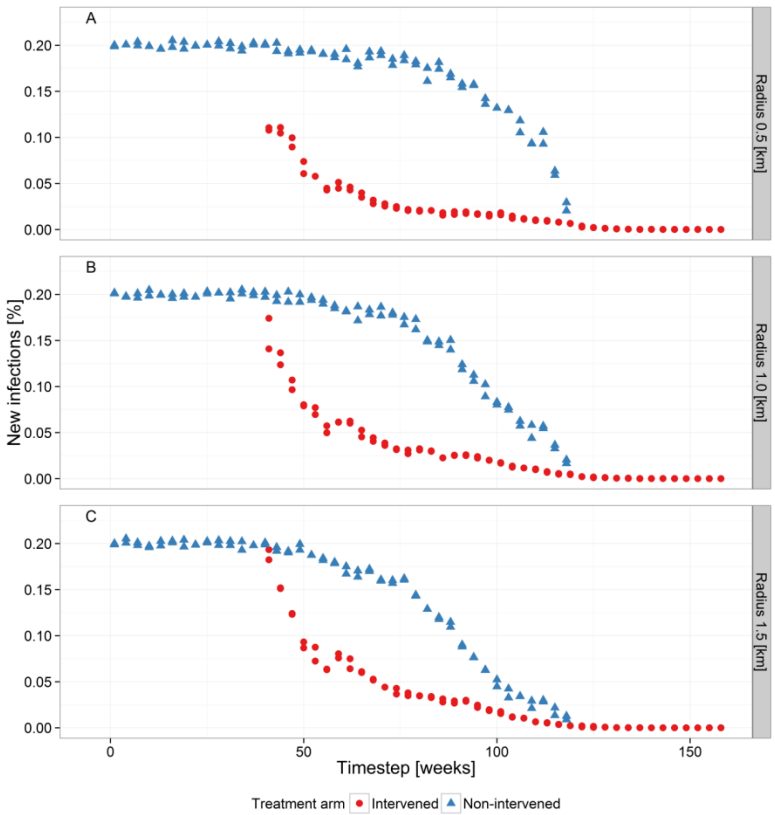

Figure 4.2: Example single random SWCRT sequence runs of the transmission simulator. Incidence of clinical events in intervened (red) and non-intervened (blue) populations as modelled by the transmission simulator for three levels of community radius, (A) 0.5 km, (B) 1.0 km, (C) 1.5 km. The cluster width is held constant at 1 km, corresponding to an area of 1km². The transmission model input efficacy is 80%. During the first 40 time steps of each simulation the incidence of clinical events is an ARMA (auto-regressive moving average) process that oscillates around the initial incidence value of 20%. The intervention commences at time step 41 and from time steps 41 to 121, the incidence of the pathogen decreases sharply in both arms due to the direct effect of the intervention and the community effect. The community effect has more impact at greater radii.

intervention arm was then rapid, and only after about 20 further time points was an effect on the non-intervention arm evident. As the intervention was rolled-out further, the infection was almost eliminated from the intervention arm, while the incidence in the control arm became highly variable between time points, presumably as a result of the reduced sample size in this arm. Incidence in the intervention arm continued to decrease, even once 100% coverage was achieved, eventually reaching zero. This reflected the delay in the system resulting from the assumed generation time of the infection, together with the fact that the final extinction event was stochastic.

The effectiveness measures, computed time-specifically from a single theoretical random design simulation in which $\overline{y}(0) = 0.2, E_s = 0.8$, and $r = 1\mathrm{km}$ are shown in Figure 4.3. During the initial ten time steps after the intervention introduction, the direct effectiveness measures $\hat{e}_1(t)$, $\hat{e}_4(t)$ and $\hat{e}_5(t)$ were much lower than the efficacy in preventing infection since many of the infections at the start of the implementation were received before the hosts joined the intervention arm. These infections were initially pre-patent, that is, pre-symptomatic). Once the pre-patent period was exceeded, the direct effectiveness estimates rapidly reached and then exceeded the efficacy against infection, reflecting the cumulative effect on multiple generations of parasites.

The indirect baseline $\hat{e}_2(t)$ and direct contemporaneous $\hat{e}_4(t)$ effectiveness measures diverged quickly at the beginning of the simulation and converged at the end the simulation run. The baseline measure $\hat{e}_2(t)$ was initially much lower than the direct effectiveness, and first climbed steeply towards the end of the simulation, when most residual non-intervention areas were close to the intervened clusters. Reflecting the fact that the non-intervention zones were relatively infrequent at the start (when there was a low indirect effect) but were frequent at the end (when there were few infections to avert), the addition of the indirect effect into the effectiveness calculation made little difference, so that when direct and indirect effects (computed by comparison with baseline) were added together, the effectiveness profile was similar to that for the direct effect alone. Proposed contemporaneous indirect $\hat{e}_6(t)$ effectiveness measure initially climbed quickly (within the first two months of rollout) to its maximum value and then oscillated due to sample size fluctuations as new clusters were brought into the intervention arm.

The overall effect $\hat{e}_3(t)$, computed by comparison with baseline, was dominated by the effect of scale-up of the intervention and therefore increased approximately linearly with time. Cumulation of the numerators and denominators of the effectiveness estimates led to smoother curves than those in Figure 4.3, each of them tending towards a clear value at the end of the intervention. Cumulation did not change the inferences to be made by examining each measure independently.

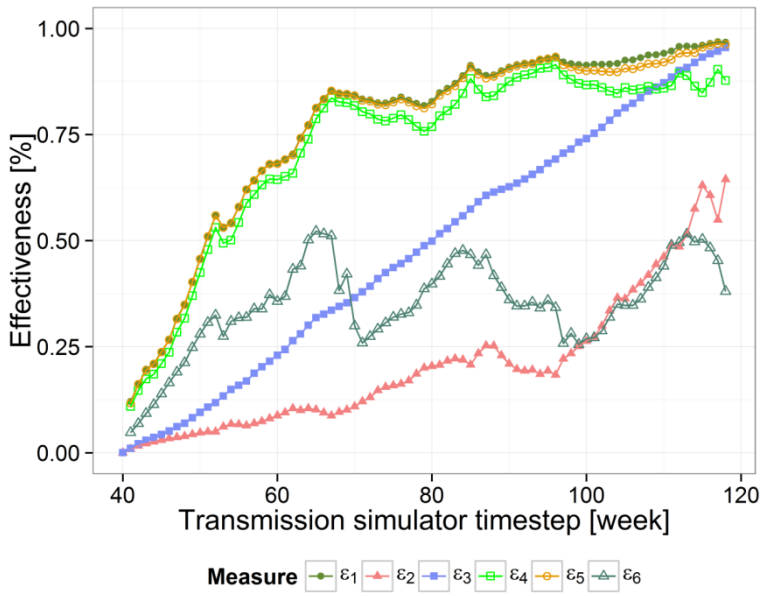

Figure 4.3: The relationship between the six effectiveness measures from Table 4.1 during a single random SWCRT sequence run of the transmission simulator. $\hat{e}_1(t)$ (filled green circle) is a direct comparison between outcomes in the intervened group versus the status at baseline, $\hat{e}_2(t)$ (filled pink triangle) is a direct comparison between outcomes in the non-intervened group versus the status at baseline, and $\hat{e}_3(t)$ (filled blue square) is an overall comparison of the entire study area versus baseline. $\hat{e}_4(t)$ (bright green square) is a direct comparison between the intervened and all non-intervened, $\hat{e}_5(t)$ (gold circle) is a direct comparison between the intervened and those remote from the intervention, $\hat{e}_6(t)$ (dark green triangle) is a direct comparison between non-intervened populations close to and remote from the intervention.

Results from design and landscape simulations

In the simulated trials, regardless of initial parameterization or landscape (uniform or random hotspot, random geography or central depletion geography), the simulated interventions in all cases had a cumulative impact of eliminating the pathogen by the end of the roll-out. Details of the effectiveness measures and power computed from the simulations are given in the Supplementary Tables. In all cases, the efficacy estimates and power of comparisons against baseline measures is high because the sample size of the comparator group is the largest possible - *i.e.* the entire study population.

For all design structures and radii of effect, r, values of initial incidence, ϵ_5 are higher than the other measures of contemporaneous effectiveness (i.e., the gold line is always above the light green and dark green lines in Figure 4.4). This is because ϵ_5

compares intervened individuals with only those naive individuals remote from any contamination effects, and for whom therefore the intervention effects are minimal. In contrast, the comparator group for ϵ_4, the conventional CRT effectiveness measure, contains individuals influenced by the spatial effect of the intervention and so measures an effect diluted by contamination. ϵ_6, measures the magnitude of this contamination effect, and so increases in the cases where ϵ_4 and ϵ_5 diverge. Similar trajectories of these measures over the time were observed for each of the three designs, but the effectiveness increased much more steeply over time when the initial incidence was low, and increased only gradually with $\overline{y_0}$ = 80%.

The optimal cluster size is one in which the direct and contamination effects are clearly separable, so an appropriate cluster size achieves high values of ϵ_6 and large differences between ϵ_4, and ϵ_5. In our simulations this corresponds most closely to clusters of width equal to the radius of the contamination, r. With clusters larger than this (i.e. the analyses with r=0.5 km, equivalent to half the cluster width) ϵ_6, remains low, because there is relatively little contamination effect. With small clusters relative to the radius(i.e. the analyses with r=1.5 km) the estimated direct effect of the intervention ϵ_4, corresponding to the conventional result, is much lower than ϵ_5 in most of the simulations (Figure 4.4), because the effect of the intervention spreads out across the whole surface.

Particular interest lies in the statistical power of the contemporaneous comparisons during the roll-out, where the results are not easy to predict heuristically, because the relative power of the measures is constantly varying. Analyses considering a single time point at time step 60 (Table 4.2), indicate that among the contemporaneous measures, the one employing the remote comparator, $\hat{e}_5(t)$, is generally of higher power than the direct comparison of intervened and non-intervened naïve clusters $\hat{e}_4(t)$ (Table 4.2 At r equal to the cluster width, $\hat{e}_4(t)$ is the most powerful out-come, followed by $\hat{e}_5(t)$, then $\hat{e}_6(t)$.

At higher r (corresponding to a greater degree of spatial smoothing of the intervention effects), $\hat{e}_4(t)$ generally has lowest power. In general, power decreases with increasing baseline incidence, $\overline{y_r}0$ and correlates positively with intervention efficacy. While the power of outcome $\hat{e}_6(t)$ does not show a clear relationship with the design type, the power of $\hat{e}_4(t)$ and $\hat{e}_5(t)$ is generally somewhat higher with the oil-drop design, followed by the hierarchical, and then the random order, though the differences are small.

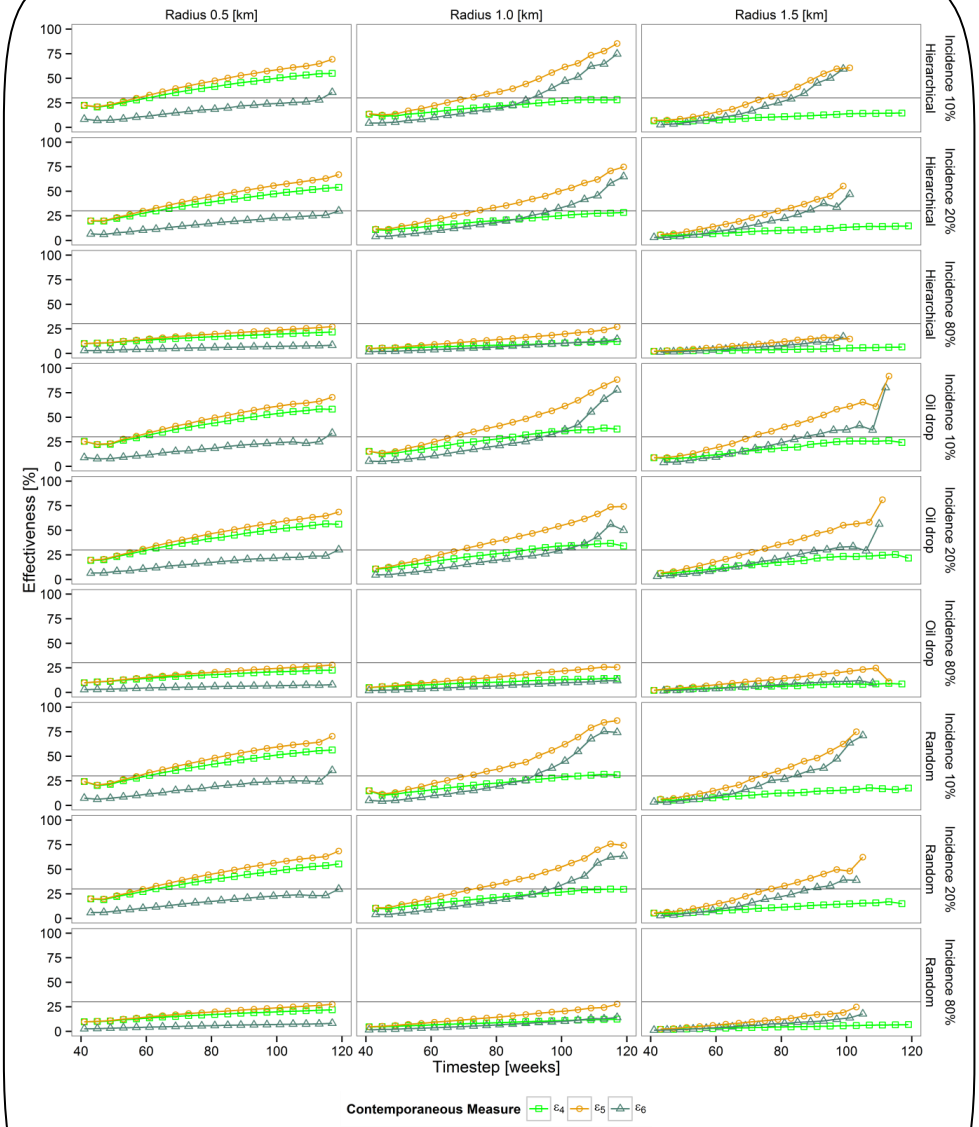

Figure 4.4: The three contemporaneous effectiveness measures over time: ϵ_4 (bright green square), ϵ_5 (gold circle), ϵ_6 (dark green triangle). The horizontal lines correspond to the simulated efficacy E_s equal to 30%

	r	$\overline{y_r}(0)$	$\hat{e}_4(t)$	$\hat{e}_5(t)$	$\hat{e}_6(t)$
Hierarchical	0.5	0.10	0.99	0.90	0.51
		0.20	0.99	0.90	0.52
		0.50	0.98	0.83	0.41
		0.80	0.85	0.59	0.18
	1	0.10	0.83	0.82	0.67
		0.20	0.87	0.74	0.56
		0.50	0.81	0.64	0.45
		0.80	0.53	0.45	0.29
	1.5	0.10	0.58	0.95	0.91
		0.20	0.59	0.86	0.78
		0.50	0.50	0.62	0.51
		0.80	0.28	0.45	0.37
Oildrop	r	$\overline{y_r}(0)$	$\hat{e}_4(t)$	$\hat{e}_5(t)$	$\hat{e}_6(t)$
	0.5	0.10	0.99	0.93	0.53
		0.20	0.99	0.94	0.54
		0.50	0.98	0.88	0.41
		0.80	0.86	0.64	0.18
	1	0.10	0.91	0.84	0.64
		0.20	0.93	0.82	0.59
		0.50	0.88	0.74	0.48
		0.80	0.60	0.52	0.28
	1.5	0.10	0.75	0.84	0.63
		0.20	0.77	0.82	0.61
		0.50	0.69	0.76	0.51
		0.80	0.41	0.52	0.31
Random	r	$\overline{y_r}(0)$	$\hat{e}_4(t)$	$\hat{e}_5(t)$	$\hat{e}_6(t)$
	0.5	0.10	0.98	0.89	0.52
		0.20	0.99	0.90	0.52
		0.50	0.97	0.83	0.40
		0.80	0.84	0.58	0.18
	1	0.10	0.80	0.80	0.66
		0.20	0.84	0.73	0.58
		0.50	0.79	0.63	0.45
		0.80	0.50	0.44	0.29
	1.5	0.10	0.54	0.94	0.88
		0.20	0.54	0.79	0.74
		0.50	0.45	0.56	0.48
		0.80	0.25	0.41	0.36

Table 4.2: Power of three contemporaneous effectiveness measures at week 60, midway through the intervention rollout, type *I* error = 10 % and efficacy E_s of 30%.

The power of both $\hat{e}_5(t)$ and $\hat{e}_6(t)$ both increase throughout the roll-out in most of the settings shown in Figure 4.5 and Figure 4.6, though in some cases there is a loss of power towards the end, when the comparator groups become small. The primary drivers of a measure's power are thus the efficacy, the initial incidence and community study radius, regardless of design, with results becoming less consistent at community radii of greater than half the cluster diameter.

Results of simulations for the SolarMal project

All three study design structures were simulated across the SolarMal landscape, with similar relationships seen among the designs simulated across the theoretical grid. The overall evaluation with the project team of both operational and statistical considerations led us to conclude that the best design for the SolarMal project would be the hierarchical SWCRT. The logistics of the SolarMal project were such that one meta-cluster, comprising nine clusters, could be completed on average every three months

Hierarchical sequences were ranked inversely on the basis of the maximum confidence interval width for $\hat{e}_5(t)$ between simulation time steps 60 and 100. Approximately 1/3 of the hierarchical sequences examined met this minimal criteria.

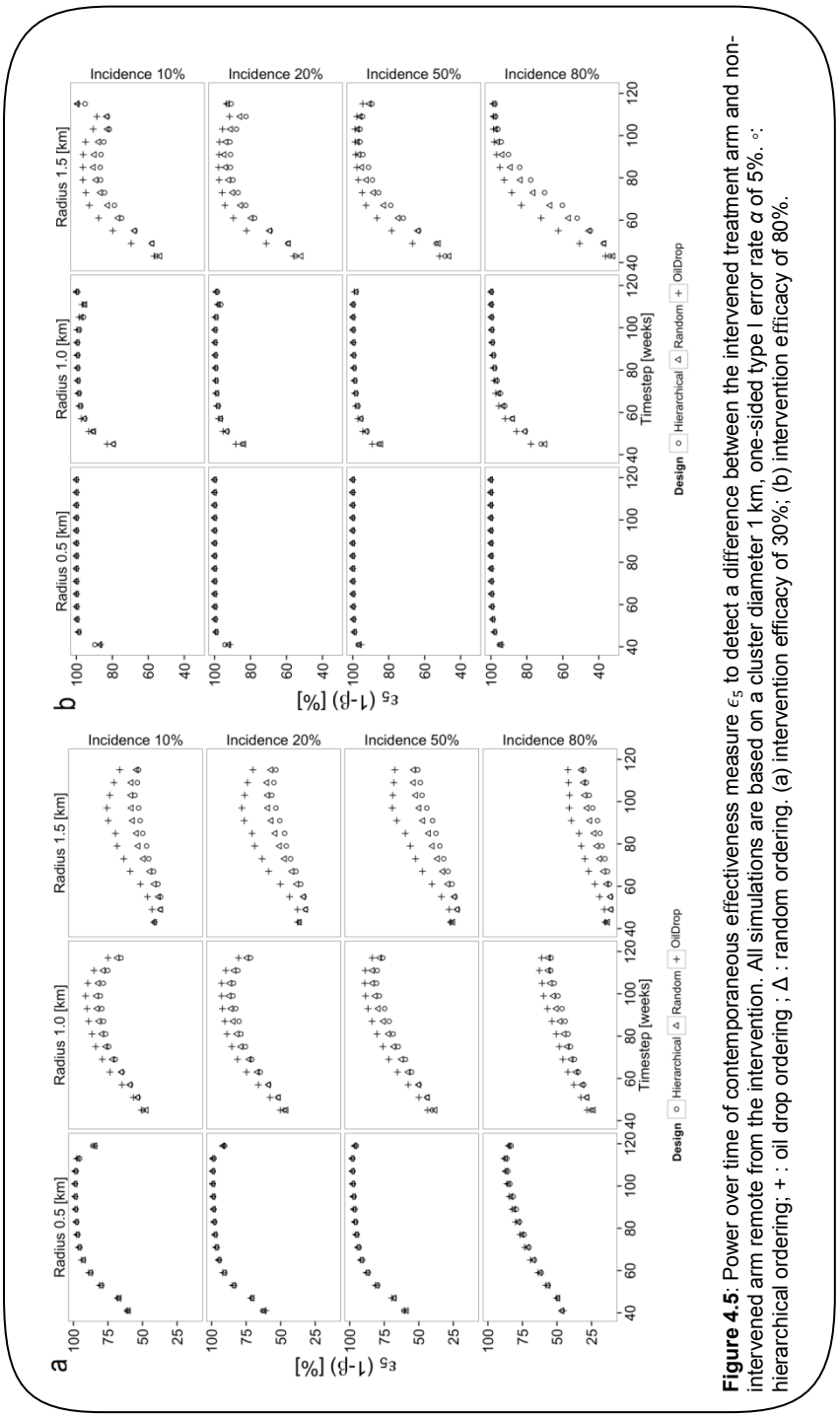

Figure 4.5: Power over time of contemporaneous effectiveness measure ϵ_5 to detect a difference between the intervened treatment arm and non-intervened arm remote from the intervention. All simulations are based on a cluster diameter 1 km, one-sided type I error rate α of 5%. ○: hierarchical ordering; + : oil drop ordering ; Δ : random ordering. (a) intervention efficacy of 30%; (b) intervention efficacy of 80%.

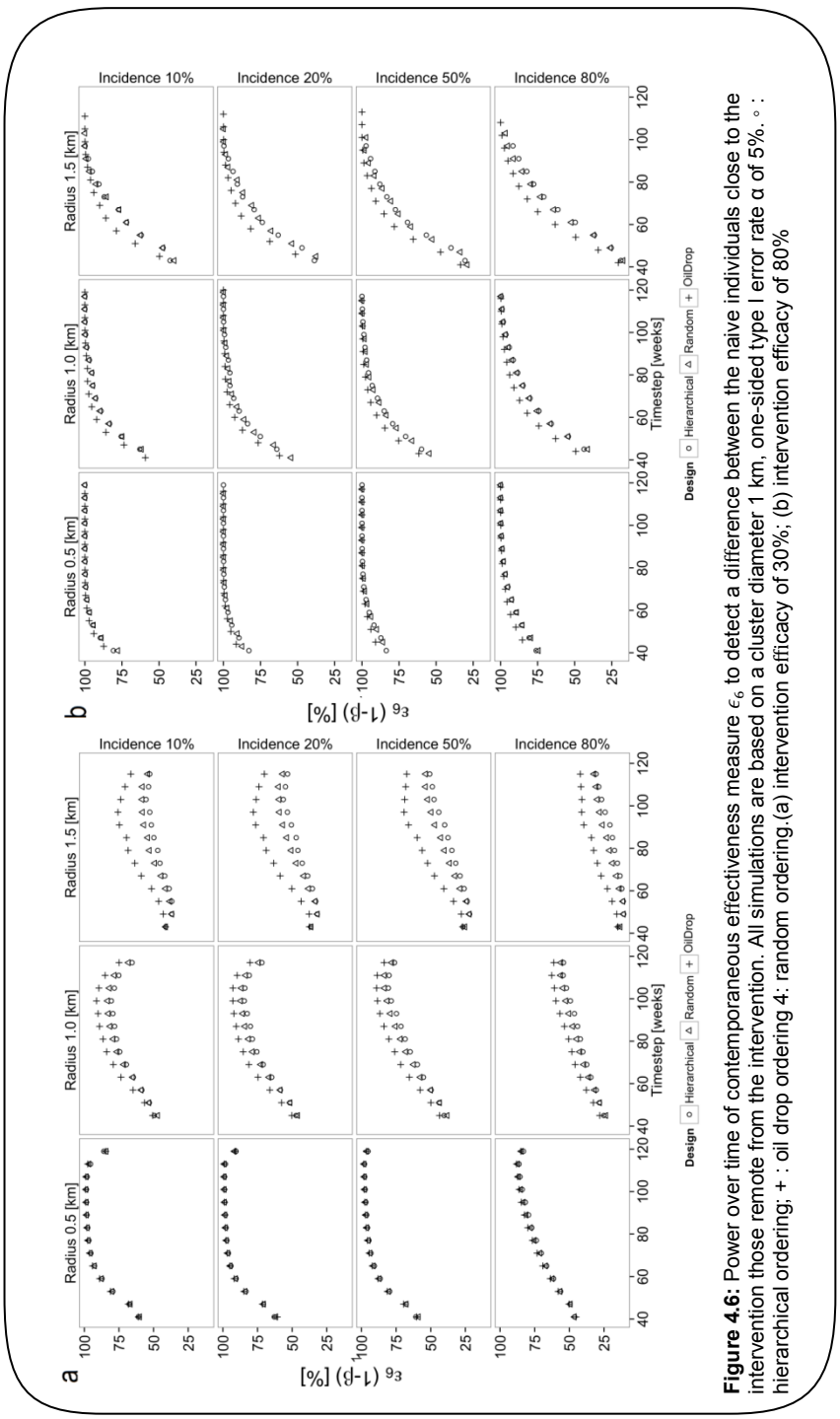

Figure 4.6: Power over time of contemporaneous effectiveness measure ϵ_6 to detect a difference between the naive individuals close to the intervention those remote from the intervention. All simulations are based on a cluster diameter 1 km, one-sided type I error rate α of 5%. ∘ : hierarchical ordering; + : oil drop ordering 4: random ordering.(a) intervention efficacy of 30%; (b) intervention efficacy of 80%

A further sociological constraint, that members within a single village receive the intervention within a six month time frame was considerably more restrictive. From a total of 10,000 sequences evaluated, 55 met this requirement; Furthermore, each meta-cluster was to have equal chances of being selected first for the intervention lottery; this restraint reduced the final set of acceptable sequences to 27. Examination of the CI-width-vs-time graphs showed wide variation among sequences that can be directly related to the geography of Rusinga. Certain geographic features reappear consistently in the effectiveness graphs as the design is rolled out. For example, when meta-cluster VIII, located at the base of the peninsula in the north east corner of the island, appears in the last half of a randomization sequence, the precision of the estimated effectiveness rapidly decreases, see Figure 4.7. One should expect similar geographic signatures to be found in future geographically informed trial designs.

Discussion

CRTs are widely used to evaluate interventions against infectious agents (such as hygiene or vector control measures) because of well-known ethical and logistic limitations of individually randomized RCTs in evaluating health interventions that are applied at the level of the population or group (Hussey *et al.*, 2007). The present study proposes two extensions to the usual CRT design.

Firstly, we propose that the collection of outcome data should include zones where contamination is likely to occur. Contamination between intervention and control arms is generally seen as something to avoid in CRTs, leading to attempts to separate the study arms with buffer zones (Hayes & Moulton, 2009). However CRTs with buffer zones provide information only about the effects of a fixed level of coverage and of a single cluster geometry. It can be difficult to exclude the possibility that contamination substantially biases estimates of effect, since this bias, in the general case, cannot be estimated from the trial data. Rather than struggling to avoid the impact of such unknown community effects, we propose that explicit measurement of the treatment effectiveness in the boundary zones between intervention and control areas should be used to estimate these effects in space and time. Zones of imperfect coverage are needed if inferences are to be made about the radius of effect, the relative magnitudes of individual and community level effects, or the temporal dynamics of spill-over effects.

Secondly, we note that local elimination of a pathogen is a single all-or-nothing outcome at the level of whole area, so an empirical refutation of its feasibility requires scale-up to universal coverage and cannot be achieved if there are untreated control

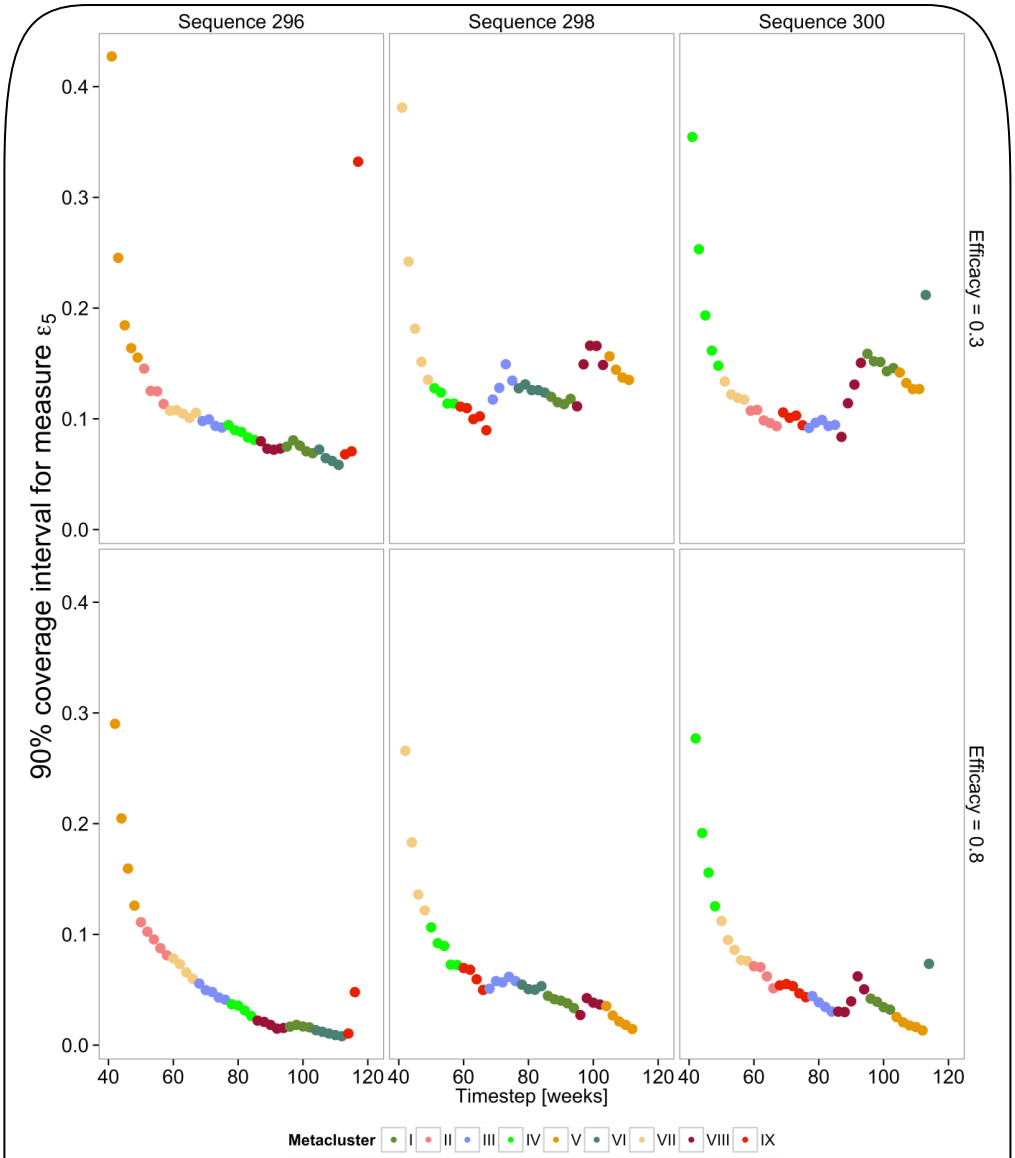

Figure 4.7: Sequence Selection. Three hierarchical sequences applied across Rusinga Island for two levels of intervention efficacy, 30% and 80%. Results are colour coded by the meta-cluster membership. Reading from the left the meta-cluster sequences are [V, II, VII, III, IV, VIII, I, VI, IX], [V, IV, IX, III, VI, I, VIII, V, II], and [IV, VII, II, IX, III, VIII, I, V, VI]. Coverage intervals widen upon introduction of the intervention to meta-cluster VIII, located at the base of the peninsula in the north east of the island, in the right two sequences. Coverage intervals were off the scale for the last meta-cluster of sequence 298. Of the three cluster sequences presented, only sequence 296 met the criteria for entry into the pool for the SolarMal randomization sequence selection lottery (coverage intervals of the primary effectiveness measure,ϵ_5, less than 10% from time points 60 to 100 and no single village roll-out greater than six months' duration).

clusters. If elimination proves not to be achievable, it is important to be able to estimate how near was the attempt to success. Conversely, elimination may be achievable at some coverage less than the maximum that can be reached, in which case there is a need to identify this coverage, and to understand what would be needed elsewhere. This specific requirement to consider the impact of maximal coverage over a wide area provides a strong rationale for adopting SWCRT designs for addressing the feasibility of pathogen elimination, additional to the questions of power, bias and efficiency usually considered in the debate between proponents of parallel designs and of SWCRTs (Hemming *et al.*, 2013; Hemming *et al.*, 2015; Kotz *et al.*, 2012a, 2012b, 2013).

It is often difficult to gain acceptance for CRTs in operational settings because program managers generally aim for complete coverage (Hemming *et al.*, 2013) and hence tend to evaluate programs using simple before and after designs. SWCRT designs are under-exploited because program implementers often do not appreciate the importance of randomization, which is critical for inferring causality. They have more immediate concerns in getting programs off the ground, and only appreciate the need for inference about the effects of the intervention after the event (Pearson *et al.*, 2010). The SolarMal trial is one situation where this is not the case, and provided an opportunity to implement a widespread intervention trial with careful attention to design.

The evaluation of the distances over which community effects operate in the ITN trials (Binka *et al.*, 1998; Howard *et al.*, 2000) provides a basis for evaluating the sizes for estimated community radii for the SolarMal trial, since we assume that community effects of OBTs and of ITNs result from the same phenomena of mosquito dispersion while foraging for food (nectar and blood) and oviposition sites. In a larger malaria control trial in Asembo, close to the SolarMal site, effects were found for distances up to 900 m from cluster boundaries (Hawley *et al.*, 2003), while on the Kenyan coast significant effects persisted for distances up to 1.5 km (Howard *et al.*, 2000). Our simulations suggest the precision of the effectiveness measures is robust to variations in community radius above 1 km and that clusters with radii greater 1 km should be used in such trials. Rusinga Island is, however, large enough for only about nine clusters of this size, and nine clusters would not provide a sufficient degree of replication for a standard CRT.

The use of a stepped wedge means that much smaller individual clusters can be used than in a conventional parallel design of CRT, since as the intervention is rolled out, adjoining clusters are assigned to the intervention, and the radius of intervened areas grows. This also motivated us to consider the oil-drop design, in which the intervention spreads out across the whole area from a single randomly chosen point.

While this approach is unbiased over repeated sampling, correlation between the geographical pattern in disease incidence and the roll-out pattern is likely to make such a design difficult to interpret. Conversely, for the SolarMal trial a completely random order of assignment of the 81 clusters would have led to intervened areas that are too fragmented for much of the period of scale-up (and also violated the community's desire to limit asynchronicity of introduction within a village). The hierarchical SWCRT with nine metaclusters each divided into nine clusters, represents a compromise that may increase the information obtainable from analyses of the spatial effects of the OBTs across cluster-boundaries, while reducing the risk of a strong correlation between baseline disease incidence and roll-out pattern.

Further analysis is needed to determine how to optimize such designs given this trade-off between the benefits of independent allocation of clusters and optimal geometry of the intervened areas. It is not obvious how to assess the implications for causal inference of the dependent assignment of clusters in the hierarchical and oil-drop designs. Since the geometry of the intervened areas is time-dependent, the seasonality of the disease is also relevant, and although our limited analysis did not find substantial effects of spatial heterogeneity in population density or disease transmission on the precision of the effectiveness measures, these remain factors that should be considered. For the SolarMal study, we did not aspire to achieve optimality and a number of possible designs and sequences were simulated. Various metrics of the power of each effectiveness measure to estimate the spatial effect of the intervention on clinical malaria incidence were assessed, and a set of the preferred sequences of the hierarchical design was presented to community representatives as alternatives, and the one to be implemented was drawn by lot.

The new effectiveness measures that we propose for quantification of both individual and community level effects at different levels of proximity to the intervention will form the basis of statistical models of the effects of varying coverage in space and time. An extension of such empirical time- space- models will be to include time-weighted lags in the effects of coverage, akin to the modelling of SWCRT proposed by Hussey and Hughes (Hussey *et al.*, 2007). This will allow generalized prediction of the likely impact of different patterns of coverage of OBTs in space and time. The broad principles of the analysis will be similar for different outcomes: densities of host-seeking mosquitoes (as measured by sentinel OBTs), parasite positivity (by rapid diagnostic test), malaria fever incidence, and all-cause mortality. Another extension of this work would be to develop analytical formulae for interval estimation of the novel outcome measures, and to assess their nominal coverage against intervals obtained 5as in this paper) from repeated simulations, however in practice, the model-based confidence intervals described above, or sampling-based approaches such as bootstrapping or Bayesian Markov chain Monte Carlo provide alternatives to the

development of such bespoke methods. Sampling-based approaches are especially attractive since they can easily be applied to extended models incorporating lags and covariates. A program in R that can be used to simulate trials with different values of $\overline{y}(0)$, E_s, r, and $N(T)$ appears in the supplementary material. This program could be adapted both to consider further effects of spatial and temporal heterogeneity in risk, and also for the design of other trials with different geographies.

Conclusion

Contamination between arms in CRTs can be a source of information about the effects of incomplete coverage, and can provide supporting evidence for causal inference. It follows that trials should be designed with such analyses in mind, and contamination should not be seen simply as a problem to be avoided. Where scale-up to complete coverage is required, as in assessments of the feasibility of local elimination of a pathogen, the SWCRT is an appropriate design. This leads to temporal changes in which zones are affected by contamination. The SolarMal example illustrates how generic transmission models incorporating spatial smoothing can be used to simulate such trials for purposes of power calculation and optimization of cluster size and randomization strategies. The approach is applicable to a range of infectious diseases transmitted via environmental reservoirs or via arthropod vectors.

Author's contributions

The manuscript was drafted by MS and TS. Computations were carried out by MS, TH, NM and TS. All authors contributed to the development and implementation of the trial design, to revisions of the manuscript and approved the final version.

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Chapter 5

Profile: The Rusinga Health and Demographic Surveillance System, Western Kenya

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Abstract

The health and demographic surveillance system on Rusinga Island, Western Kenya, was initiated in 2012 to facilitate a malaria intervention trial: The SolarMal project. The project aims to eliminate malaria from Rusinga Island using the nationwide adopted strategy for malaria control (insecticide-treated bed nets and case management) augmented with mass trapping of anopheline mosquitoes. The main purpose of the health and demographic surveillance is to measure the effectiveness of the trial on clinical malaria incidence, and to monitor demographic, environmental and malaria-related data variables. By the end of 2014, the 44 km² island had a population of approximately 25,000 individuals living in 8746 residential structures. Three times per year all individuals are followed up and surveyed for clinical malaria. Following each round of surveillance a randomly selected cross section of the population is subject to a rapid diagnostic test to measure malaria. Additionally, extensive monitoring of malaria vectors is performed. Data collection and management is conducted using the OpenHDS platform, with tablet computers and applications with advanced software connected to a centralised database. Besides the general demographic information, other health related data is collected that can be used to facilitate a range of other studies within and outside the current project. Access to the core dataset can be obtained through the INDEPTH Network or the corresponding author.

Why was the HDSS set up?

A malaria intervention study based on removal trapping of anopheline mosquitoes in addition to the Roll Back Malaria [RBM] control strategy (RBM, 2013) was initiated on Rusinga Island, Western Kenya in 2012. Mosquito traps baited with a synthetic lure that mimics human odour are placed at the household level to reduce mosquito population density and, as a consequence, lower the intensity of malaria transmission (Hiscox *et al*., 2012). Traps are powered by solar energy, which is also used to provide electric light and mobile phone charging points for the household members. The combination of solar energy with malaria control led to the project being named SolarMal. A health and demographic surveillance system [HDSS] was established to facilitate continued monitoring of demographic, and particularly malaria-related, variables. In addition, the complex roll-out logistics of the SolarMal intervention required accurate and up-to-date information about the population and their housing. Although the main objective of the HDSS is to measure the effectiveness of the vector control intervention on health and population outcomes, the collected demographic and malaria specific data may be used for validation of epidemiological models as well as entomological and parasitological research. The most prominent objectives facilitated by the HDSS are:

(i) Longitudinal monitoring of demographic dynamics to provide a robust framework for research.
(ii) Studying the epidemiology of malaria,
(iii) Analysing the effect of the SolarMal intervention on malaria prevalence, transmission and mosquito abundance.
(iv) Measuring the interaction between the intervention and existing approaches to malaria control, and environmental and socio-economic variables.

The SolarMal HDSS collects demographic information, malaria related variables and other information on factors that are likely to influence malaria epidemiology and malaria mosquito ecology. The HDSS provides different disciplines within the project with an up-to-date population database. The entomological and parasitological experimental designs, as well as the logistics for rolling out the intervention, rely on the continued updating of the study population (WT, personal communication.). An important component of SolarMal is the inclusion of sociological studies and the population database enables social scientists to conduct targeted sociological research. Since 2012 an extensive baseline survey and 8 subsequent follow up rounds have been conducted. The roll out of the intervention traps started in June 2013 and was completed in May 2015, at that point covering all households on the island.

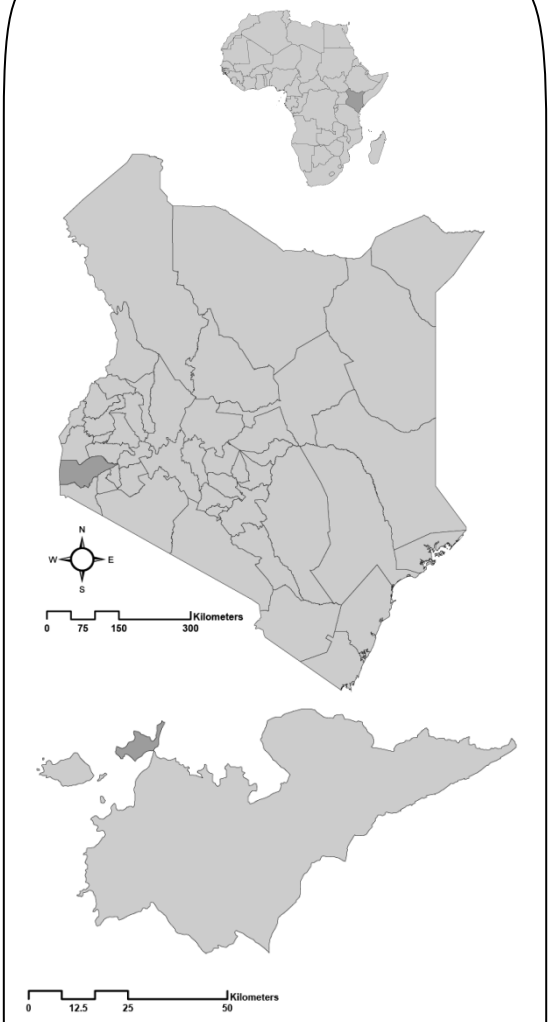

Figure 5.1: The upper Figure shows Africa with Kenya highlighted dark grey in the middle, Kenya with Homa Bay County highlighted; lower Figure depicts Homa Bay County with Rusinga Island in dark grey.

Where is the HDSS area?

Homa Bay County is located in Western Kenya at Lake Victoria, within the former province of Nyanza, exposed to the south of the Winam Gulf. Rusinga Island is situated between latitudes 0°21′ and 0°26 South, and longitudes 34°13′ and 34°07’ East (Figure 5.1). A causeway connects the island with the mainland. Rusinga Island stretches over 44 sq. km with an elevation between 1100 m and 1300 m above sea level. Mean daily temperatures vary from 16 to 34 degrees Celsius with higher temperatures in the dry seasons that occur between June-October and late December-February. Seasonality in precipitation is experienced as one long rainy season ranging from March into May (average of 198 mm per month in the period 2012-2014) and a short rainy season from October to early December (average of 132 mm per month). The local administration comprises of two chiefs, each governing one part of the island; Rusinga East and Rusinga West.

The local authority divided the island into eight subzones containing a total of 36 villages and about 10 beach communities (Figure 5.2). For the purpose of the SolarMal trial and to measure the impact of the intervention most effectively, the island was divided into nine metaclusters each consisting of nine clusters. Each cluster comprises of 50 or 51 households. The HDSS operates from the International Centre of Insect Physiology and Ecology [*icipe*] at the village of Mbita Point at the mainland side of the causeway.

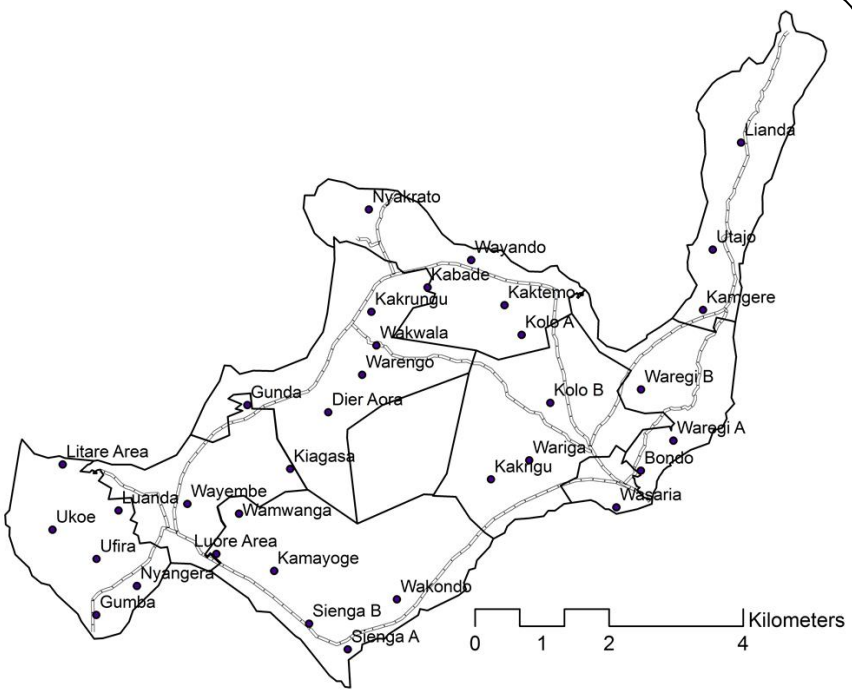

Figure 5.2: Rusinga Island with an uninhabited hill in the middle. Boundaries of meta-clusters (thick black lines); villages (indicated with dots); roads (dashed lines).

Who is covered by the HDSS and how often have they been followed up?

The population of Rusinga Island belongs to the Luo ethnic group and DhoLuo is the main spoken language. The national languages (English and Swahili) are also used. Fishing and farming are the principal occupations, with people typically harvesting millet, sorghum and maize and fishing tilapia and Nile perch. Christianity is the predominant religion (84%) in this area; the Muslim community (12%) forms a minority.

Most houses on the island are made of mud or cement walls with iron sheet roofs. Connection to the electrical grid is rare and there is little to no supply of piped potable water. There are several health facilities on the island; one governmental health centre, one government clinic, two private clinics and one drug dispensary. Non-governmental organisations have established a further two clinics. A district hospital is found at Mbita point village. All members of the population are visited three times a year. By August 2015, each location had been visited eight times, including the baseline enumeration. With the baseline conducted in 2012, and the latest update round completed in mid-2015, currently eight rounds of surveillance have been

carried out in the course of the first two complete years of health and demographic surveillance. During this period, a total of 33,283 people were registered in the database, with residences divided over 8746 houses, and belonging to 5457 households. The actual number of people living on Rusinga island mid-2015 was 24,643.

The leading causes of death in this area are HIV/AIDS related, with an HIV prevalence of 26% (Ministry of Health Kenya: HIV estimates, 2014). Malaria is hyper-endemic and existent in this region throughout the year, with peaks in transmission at the end and just after the rainy seasons, where *Plasmodium* parasite prevalence of around 30% is reported (WHO Country Profile 2014: Kenya, Malaria). The population is characterised by a seasonal influx of labourers searching for jobs in the fishing industry. Temporary in and out migrations are distinguished from permanent migration within the Rusinga HDSS. Households are recorded following the Luo description of a *dhala*: any set of houses that share a head of household and/or are economically dependent.

The age distribution of Rusinga has a typical East-African profile. Baseline studies (2012) and 2 years of data collection (2013 and 2014) demonstrate that approximately 40% of the population is under the age of 25 and almost 90% of the population is under the age of 45 (Figure 5.3). All consenting individuals living on the island are subject to the HDSS to monitor demographic and malaria-related variables. The HDSS, local population and the intervention programme are strongly connected by means of a community advisory board [CAB] which, together with project staff, regularly evaluates the progress of the project and matters encountered during fieldwork.

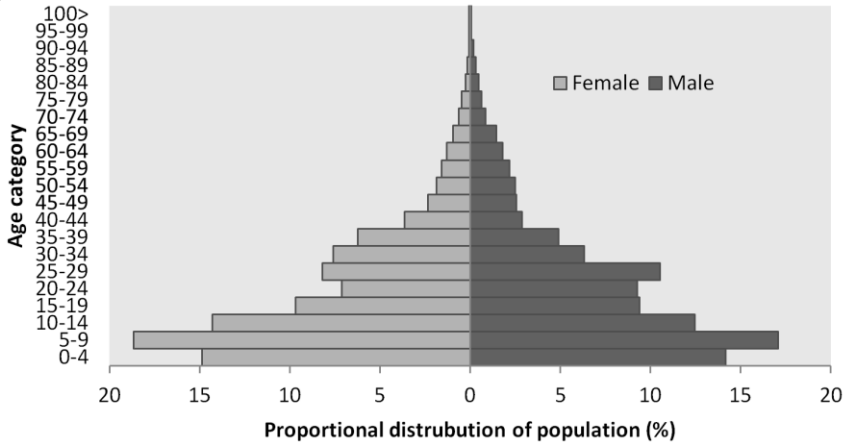

Figure 5.3: Population pyramid of Rusinga Island with the percent of people illustrated per age category.

Table 5.1: Content of questionnaires administered during the census and each follow up survey.

Visit form: scanning bar code on house to confirm follow up visit and set date of interview
Household (*): new household ID, number of houses in the household, name and ID of household head ID and name
House (*): new house ID, longitude and latitude, household head ID and name, photo of the house, number of individuals
Individual (*) : new individual ID, names, date of birth, sex, level of education, occupation, relation to the household head
Household characteristics (**): ownership of dwelling, # of rooms, # of bedrooms, location of kitchen, source of electricity, source of light, agricultural land ownership, wall construction, floor construction, roof construction, whether eaves are screened, whether IRS has been applied during the past year, bed nets reported, bed nets observed, # of bed nets, when were bed nets obtained, condition of bed nets, other mosquito control methods used by household members
Death registration: individual ID, name, date of death, outcome of verbal autopsy, verbal autopsy performed by, cause of death, place of death
Pregnancy observation: mother ID, # of months pregnant, attended health facility during pregnancy, received tt-injection(RBM, 2013), other medicines, estimated date of birth, woman's first pregnancy
Pregnancy outcome: delivery outcome, name of child, date of birth of child, sex, creation of new individual ID, house ID, household ID, link to parents ID
Migration-Out: individual ID, house ID, household ID, date of migration, within Rusinga, to which village/zone, out of Rusinga, reason for migration
Migration-In: previously registered by SolarMal, village/zone, new individual ID, names, date of birth, sex, highest level of education, primary occupation, relationship to the household, house ID, household ID, date of migration, reason of migration, moved from
Individual health: individual ID, any illness during the past 2 weeks, current fever reported, under malaria treatment at the time of the visit, temperature (if indicated illness), RDT(2012) result (tested if > 37.3 ° C), any respiratory symptoms, medical attention, what medical attention, drugs against fever, which drugs

What has been measured and how have the HDSS databases been constructed?

The baseline enumeration was carried out from June to September 2012, recording all households, houses and individuals on the island. All households were provided with an odour-baited malaria mosquito trap to attract and kill mosquitoes using a stepped-wedge cluster randomized trial design. The hypothesis is that mass trapping

of malaria vectors leads to reduced malaria transmission, incidence and prevalence. All structures with residents were mapped using the Global Positioning System [GPS] function on a tablet computer Households, houses and individuals are assigned unique identification codes. All inhabitants were requested to provide their full name, sex, date of birth, main occupation and their relation to parents and the head of household. During the census round, fieldworkers [FWs] were assisted in locating all houses and individuals by a local community based organisation, the Rusinga Malaria Project [RMP], which has been involved in malaria control practices on the island for over a decade. From January 2013, collection and updating of demographic and malaria and health related data started. The HDSS operates by house-to-house interviews, visiting on average 120 houses per day equally distributed across the nine metaclusters. Interviews take approximately 30 min. depending on the size of the household. Each HDSS round is completed in approximately three months. During household visits, observed pregnancies, new births, deaths and migrations which have occurred since the previous visit are recorded and updated (Table 5.1).

Clinical malaria is recorded during HDSS rounds based on fever recalls and a conditional RDT, and at the end of each round the team performs blood collections on a random sample of the population. Digital questionnaires on demography are consistent with the HDSS questionnaire format of the principal HDSS association globally; INDEPTH network (Sankoh *et al.*, 2005; Sankoh *et al.*, 2012). These standardised questionnaire formats are widely used in East Africa, including Kenya, and therefore apply well to our study site. The HDSS uses tablet computers and the OpenHDS system, which allows for rapid centralization of the data without a need for processing paper forms. This reduces data management overhead and allows for rigorous and timely quality control. A detailed description of this system can be found elsewhere (Homan *et al.*, 2015). The HDSS team consists of 10 FWs, a fieldworker manager [FWM] and a data manager. The local team has access to a senior software manager. A server running the OpenHDS software is hosted at the *icipe* field station in Mbita. OpenHDS, a software platform that is based on a centralised database, a web application for data management , is linked to a tablet computer-based mobile component which allows digitisation of data at the point of
capture, and wireless synchronization to the central data store based on the Open Data Kit [ODK] platform (Asangansi *et al.*, 2013; Hartung *et al.*, 2010). Samsung Galaxy Tab 2 tablet computers were used from the start for data collection, and upgraded after years to the successor Galaxy Tab 3. Data entry errors are minimised through basic range checks and the integration of different questionnaires through system-wide IDs in a guided workflow. The ODK and OpenHDS platforms allow the FWM and data manager to use a range of data cleaning options, many of which are guided by reports generated automatically on a nightly basis. This process enables

scientists to use the clean data for analysis with minimal delay. Furthermore, to monitor the performance of FWs a web-based tool was developed that monitors progress of the work FWs conduct over time, allowing the project to optimize the quality and effectiveness of data collection. Finally the data of all sub-disciplines of SolarMal are connected to each other by one of the three levels of unique codes and kept in a MySQL relational database. Calculation of demographic rates and further quality assurance is conducted using the iShare2 software (http://www.indepth-ishare.org).

Key findings

The demographic data collected during the census survey in 2012 up until May 2015 is the basis for Table 5.2. Reported demographic figures are calculated for the complete years of 2013 and 2014. To place the reported rates in context, the same measurements calculated by other HDSSs operating close to Rusinga in the years 2007 and 2010 are also reported in Table 5.2. Kaneko et al. (Kaneko *et al*., 2012) published demographic information on the basis of the Mbita HDSS covering Rusinga and neighbouring areas in 2011. An HDSS at Kisian and surrounding areas operated by the KEMRI/CDC some 150 km North-East of Rusinga reported rates for 2007 (Odhiambo FO, 2012). In calculating person-time at risk we defined residents as those who stayed in the HDSS area 60 days (two months) or longer. Registered individuals who stayed less than 60 days during a year were removed for the calculation of total person-years. Table 5.2 shows the key demographic indicators of the Rusinga HDSS for the years 2013 and 2014. The total population that was registered in the database by the end of 2013 was 29,206 and the total contributed person-years in 2013 was 24,350. The total number of individuals enumerated by the end of 2014 was 33,283.

By December 2014 the HDSS had registered a total of 8746 residential structures divided over 5457 households. The sex ratio is skewed towards females with 91 men for every 100 women.

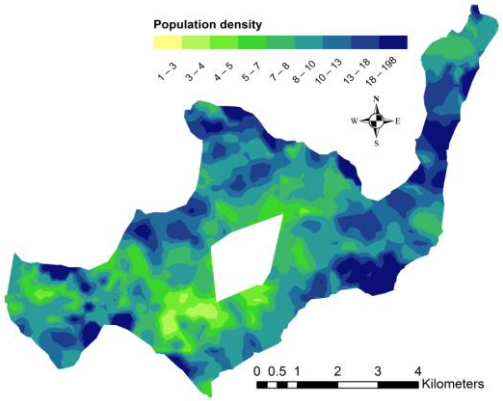

Figure 5.4: Distribution of population density on Rusinga Island for the year 2013.

Table 5.2: Key demographic indicators over the years 2013 and 2014 on Rusinga Island

Indicator	Unit	Rusinga 2013	Rusinga 2014	Mbita 2010	KEMRI 2007
Total population visited	*Total number of individuals enumerated*	29,206	33,283	-	-
Total houses visited	*Total number of houses enumerated*	8141	8746	-	-
Total households visited	*Total number of households enumerated*	4948	5457	-	-
Male : Female ratio	*Proportions of sexes*	91	91	91.2	90.1
Population density	*Average number of people per km²*	553	577	-	-
Total fertility rate	*Average number of live children per woman*	2.1	2.1	3.7	5.3
Crude birth rate	*Births per 1000 person years*	18.7	18.5	29.7	36.8
Crude death rate	*Deaths per 1000 person years*	6.3	5.8	9.1	15.9
Life expectancy at birth (Male)	*Expected years to live at birth*	66.9	68	57.5	46.5
Life expectancy at birth (Female)	*Expected years to live at birth*	68.8	68.6	61.0	46.5
Infant mortality ratio (<1 year)	*Infant deaths per 1000 live births*	17	11	14.1	76
Child mortality rate (1-4 years)	*Child deaths per 1000 person years*	7.4	6.8	-	16.5
Child mortality ratio (1-4 years)	*Deaths between age 1 and 5 per 1000 children*	29	27	-	58.8
Under-five mortality rate	*Under-five deaths per 1000 person years*	9.7	7.5	-	29.5
Under-five mortality ratio	*Under-five deaths per 1000 live births*	45	37	91.5	167.0
Crude in-migration rate (external)	*In-migrations per 1000 person years*	(*)	127.9	64.1	115
Crude out-migration rate (external)	*Out-migrations per 1000 person years*	164.6	148.9	86.2	111
Malaria prevalence	*Percentage of population with a positive RDT*	27.1	28.1	-	-
Malaria mosquito abundance	*Average number of mosquitoes per trap night*	0.30	0.21		

Rusinga HDSS demographic indicators compared with indicators reported during the Mbita HDSS in 2010 and the KEMRI HDSS in 2007.
(*)No in-migration rates reported for 2013. Catch-up enumerations in the first months of 2013 enumerated households which were missed in the baseline survey, and could therefore not reliably be distinguished from in-migration events

The average population density was 553 (2013) and 577 (2014) person-years per square kilometre calculated on basis of 44 km² of landmass. However, as shown in Figure 5.4, the population is not evenly distributed and there are densely populated fishing beaches and a large village in the southeast; the hill in the centre of the island is uninhabited. The total fertility rate [TFR] is calculated as the average number of children that would be born per woman if all women lived to the end of their childbearing years (15-49 years) yielding a TFR 2.1 for both years.

The crude birth rate [CBR] and death rate [CDR] are presented as the number of live births or deaths per 1000 residents. We found a CBR of 18.7 (2013) and 18.5 (2014), and CDRs of 6.3 and 5.8 were determined for 2013 and 2014. Compared with the HDSS of KEMRI/CDC at Kisian, both the Mbita and the Rusinga HDSS report a lower CDR. The life expectancy [LE] at birth for females and males is calculated as the total number of person-years lived in all age intervals of the static population divided by the number of alive individuals at the start of every 5year age interval. For males in 2014 the LE at birth was 68 years, for females the LE at birth was 68.6 years.

The infant mortality ratio was 17 in 2013 and 11 in 2014 (number of infant deaths, <1 year, per 1000 live births). This relatively large difference may be explained by the protective effect of the malaria vector intervention. The child mortality ratios in consecutive years were remained 27 (number of deaths between 1-4 years per 1000 children) and the under-five mortality ratios are presented as the number of deaths in that age category per 1000 live births was 45 and 37.

Calculation of all mortality rates as well as the CDR yield lower rates and ratios than the KEMRI/CDC HDSS. Our findings are comparable with the results of the Mbita HDSS (Kaneko *et al*., 2012). Unlike the Mbita and the Rusinga HDSSs, the KEMRI HDSS worked together with at least two health clinics in recording deaths, which most likely resulted in a more sensitive death registration system. In addition, it is common in Luo culture, to return to the place of birth at the time of death. As there are many working immigrants residing on Rusinga Island, this could explain the lower number of recorded deaths taking place on the island. The in-migration and out-migration rates are also calculated using person-years. The analysis of the migration rates for the year 2014 show a crude in-migration rate of 12.9 per 1000 person years and a crude out-migration rate of 148.9 (Odhiambo *et al*., 2012). Table 5.3 summarises characteristics of 6640 inhabited houses of which information about the house was collected. These results are comparable to other HDSSs in Western Kenya, such as Asembo and Gem (Odhiambo *et al*., 2012) and around Mbita (Kaneko *et al*., 2012; Wanyua *et al*., 2013). On Rusinga a typical house is made from mud walls, a roof of iron sheeting with a cement floor. Most houses have bed nets, but are not protected against mosquitoes flying into the house through the open eaves (Lindsay *et al.*, 1988). Only a fraction of the population has access to the electrical grid and the main

Table 5.3: Summary of house information collected over the year 2013

Indicator	No.	%	Indicator	No.	%
I) Ownership of house			*VIII) Wall structure*		
Owner	4955	74.6	Wood and mud	4327	65.2
Rent	1327	20	Bricks and/or blocks	1161	17.5
Other	358	5.4	Mud and cement	489	7.4
II) Number of rooms			Iron and sheet	565	8.5
1	1725	26	Other	98	1.4
2	2090	31.5	*IX) Floor structure*		
3	2142	32.3	Carpet	3694	55.6
4	417	6.3	Cement	2480	37.3
5	152	2.3	Earth, dung or sand	442	6.7
>5	114	2	Other	24	0.4
III) Location of kitchen			*X) Roof structure*		
Outside the house	2217	33.4	Iron sheets	6559	98.8
Main living area indoors	1413	21.3	Thatch	52	0.8
Separate kitchen building	1271	19.1	Asbestos	25	0.4
Separate room in the house	209	3.1	Other	4	0.1
In another house	1065	16	*XI) Screened eaves*		
Daytime outside; night inside	465	7	Yes	441	6.6
IV) Source of electricity			No	6199	93.4
None	6137	92.4	*XII) IRS sprayed 12 months prior to visit*		
Connected to power grid	162	2.4	Yes	2709	40.8
Generator	58	0.9	No	3604	54.3
Battery	65	1	Unknown	327	4.9
Solar power	218	3.3	*XIII) Bed nets reported*		
V) Source of light			Yes	6215	93.6
Kerosene powered	6356	93	No	425	6.4
Candle light	16	0.2	*XIV) Bed nets observed*		
Electric light	392	5.7	Yes	4830	72.7
None/other	64	0.9	No	1810	27.3
VI) Level of education of head household			*XVI) Condition of nets*		
Pre school	76	1.1	Undamaged or new	3929	59.2
Primary	4078	61.4	At least one breach	2301	34.7
Secondary	1814	27.3	Unknown	410	6.2
Higher	459	6.9	*XVII) Other mosquito control*		
Non-standard	174	2.6	Burning a mosquito coil	125	1.8
Unknown	39	0.06	None	6257	94.3
VII) Land for farming			Other	261	3.9
Yes	1480	22.3	**Total**	6640	100
No	5160	77.7			

sources of indoor light were kerosene lamps at the time when the SolarMal intervention was rolled out.
Finally, the average the island-wide malaria prevalence and the average number of malaria mosquitoes caught per trapping night for the rainy seasons in 2013 and 2014 are reported in Table 5.2. The malaria prevalence is established on basis of a cross sectional survey of 10 percent randomly selected people tested with a RDT. Malaria mosquito abundance is established on basis of three surveys of mosquito monitoring at 80 randomly selected households. Ignoring intervention arms, malaria prevalence did not differ much island wide between both years with 27.1% and 28.1% prevalence, respectively. However, we found a significant difference in malaria mosquito abundance with an average of 0.30 mosquitoes per trapping night in 2013 versus 0.21 in 2014.

Future analysis plan

The HDSS data are a valuable resource when studying the parasitological, entomological and sociological (Oria *et al.*, 2015) aspects of the malaria interventions. For example, the spatial and temporal distribution of malaria, and its vectors, in combination with environmental data, will be used to measure the effect of the introduction of odour-baited traps in combination with pre-existing widespread use of LLINs and case management. Other topics being studied are the emergence of malaria hot spots, models of the interaction between vector presences, and the spatial analysis of malaria. Data from the HDSS and the trial are used to parameterise mathematical models of malaria. However, this HDSS provides a platform not only to study and analyse malaria related outcomes within the SolarMal project, but also for other public health related research on Rusinga Island. From 2016 we establish prolonged monitoring of the intervention, and we strive to introduce eave screening to enhance the possible effect of odour-baited traps on malaria transmission. Furthermore, we will introduce verbal autopsy and various other standardised types of health related data. Knowledge, resources and objectives will be combined to equip the Rusinga HDSS with a broader scope of health-related subjects after the SolarMal project comes to an end.

What are the main strengths and weaknesses of the Rusinga HDSS?

A major strength of this HDSS is the innovative process for data collection in the field (OpenHDS and ODK) using tablet computers which simplifies the management of system-wide unique identifiers for individuals and houses and their linking to health- or intervention-related data. Point-of-capture digitization and the client-server architecture of the data management system saves time and money in terms of entering, accumulating, managing and processing data compared to its predecessor Household Registration System 2 (Phillips *et al.*, 2000). Data quality is of great importance in a HDSS, and due to a digital data collection organization rather than a

paper based system, the error rate of the collected data in the Rusinga HDSS is well below 1% according the quality metrics of iShare2. A weakness of the pioneering system in this phase is that support of a skilled software developer and data manager is required. Other applications with web interfaces that make this HDSS distinct are the real-time monitoring of demographic and health related events, keeping track of the performance of FWs and the use of geographical information systems to assist in precise navigation, and spatial research and analysis. Data can thus immediately be processed and used to facilitate all scientific disciplines in the project. Another strength of the Rusinga HDSS is the fact that it closely works together with the interest groups in the study area. By communicating with community health workers, and delegates from different segments on the island, a sustaining cooperation and interaction has been created. In the future it would be possible to expand the system to capture information on other health outcomes. A priority and an important improvement for the near future is the integration of verbal autopsies as part of the demographic surveillance.

Acknowledgements
Firstly we want to thank the population of Rusinga Island, for cooperating with us and for embracing the project. We are also very grateful to the International Centre of Insect Physiology and Ecology for enabling us to implement and manage all our scientific activities from the Thomas Odhiambo Campus in Mbita. Besides we want to acknowledge INDEPTH network for their overarching views and input.

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Key messages

- The Rusinga HDSS covers an island in Lake Victoria, Kenya. Living conditions and health indicators on Rusinga suggest to be better compared to HDSSs nearby.
- The Rusinga HDSS facilitates in-depth studies into the transmission of malaria. A trans-disciplinary intervention trial aiming for the elimination of malaria transmission is the core driver behind this surveillance.
- The HDSS uses the OpenHDS system which provides a cost-effective way to collect, store and manage data, as well as to safeguard quality assurance.
- The HDSS provide a robust foundation to conduct not only malaria research; future collaboration with local and international institutes will enable researchers to combine resources and interests.

Chapter 6

Spatially variable risk factors for malaria in a geographically heterogeneous landscape, western Kenya: an explorative study

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Abstract

Background: Large reductions in malaria transmission and mortality have been achieved over the last decade. Despite these gains considerable residual, spatially heterogeneous, transmission remains. To reduce transmission in these foci, researchers need to consider the local demographical, environmental and social context, and design an appropriate set of interventions. Exploring spatially variable risk factors for malaria can give insight into which human and environmental characteristics play important roles in sustaining malaria transmission. **Methods**: On Rusinga Island malaria infection was tested by rapid diagnostic tests in 3,632 individuals from 790 households. Demographic and environmental data was collected. Analyses were performed on 81 project clusters. A standard linear regression model was fitted containing multiple variables to determine how much of the spatial variation in malaria prevalence could be explained by the demographic and environmental data. Subsequently, a geographically-weighted regression was performed assuming non-stationarity of risk factors. **Results**: Scan statistics revealed two clusters which had significantly elevated numbers of malaria cases compared to the background prevalence across the rest of the study area. A multivariable linear model including environmental and household factors revealed that higher socioeconomic status, outdoor occupation and population density were associated with increased malaria risk. The local GWR model improved the model fit considerably and the relationship of malaria with risk factors was found to vary spatially over the island. **Discussion**: Identification of risk factors for malaria that vary geographically can provide insight into the local epidemiology of malaria. Examining spatially variable relationships can be a helpful tool in exploring which set of targeted interventions could locally be implemented. Supplementary malaria control may be directed at areas, which are identified as at risk.

Keywords: Malaria, spatial heterogeneity, geographically weighted regression, spatially variable risk factors, Kenya

Background

Across sub-Saharan Africa, malaria remains one of the leading causes of morbidity and mortality with up to 200 million symptomatic cases every year (World Health Organization, 2015). In Kenya, 75% of the population is at risk of malaria infection, but due to intensified control efforts the number of malaria cases has decreased two fold in one decade to well under five million annually. Interventions which have contributed to the decline of malaria transmission and mortality are the use of insecticide-treated nets [ITNs], long-lasting insecticidal nets [LLINs], indoor residual spraying [IRS] and treatment of patients with artemisinin-based combination therapy [ACT] (Murray *et al.*, 2012; Okiro *et al.*, 2010). The goal of WHO and Roll Back Malaria [RBM] is to continue the efforts to fight malaria until local elimination and eventually eradication is achieved (Alonso *et al.*, 2011c; RBM, 2013; Tanner *et al.*, 2008).

Since large successes have been realized and many areas have moved into a pre-elimination phase, the epidemiology of malaria is changing (Cotter *et al.*, 2013). Although malaria transmission has always been geographically heterogeneous, under pressure of current interventions the spatial heterogeneity of malaria becomes more pronounced, typically characterized by areas or clusters of households that persistently have higher proportions of infected individuals compared with the population average. In order to aid the malaria elimination phase, a better understanding of the epidemiology of malaria, considering geographical heterogeneity, is needed (Snow, 2015). Heterogeneity in malaria transmission is not a new phenomenon (Greenwood, 1989), but because of improved research methods and the enhanced capacity of information technology, recent studies have more frequently shed light on the smaller-scale geographical heterogeneity of malaria (Clark *et al.*, 2008; Ernst *et al.*, 2006; Wanjala *et al.*, 2011). Studies suggest that factors associated with the spatial clustering of malaria include: house structure, human behaviour, environmental, geographical and demographical variables (Bi *et al.*, 2013; Bousema *et al.*, 2011; Mosha *et al.*, 2014; Srivastava *et al.*, 2009; Toty *et al.*, 2010). Many studies have investigated clustering and the spatial heterogeneity of malaria risk (Bejon *et al.*, 2014; Brooker *et al.*, 2004; Kreuels *et al.*, 2008; Smith *et al.*, 2004) but fewer studies have investigated ways in which relationships of factors influencing this heterogeneity vary over space. Lessons can be learnt from studies that investigated the geographically varying nature of factors on agricultural (Feuillet *et al.*, 2014) and environmental (Luo *et al.*, 2009; Rodrigues *et al.*, 2014) outcomes. Relatively few studies have addressed the questions of causes of spatial heterogeneity in health outcomes (Comber *et al.*, 2011; Gilbert *et al.*, 2011) like malaria (Ehlkes *et al.*, 2014; Giardina *et al.*, 2014; Grillet *et al.*, 2010; Haque *et al.*, 2012).

In the present study, it is explored whether risk factors for malaria also vary over space. Household and environmental risk factors contributing to malaria prevalence were studied by means of a frequentist non-spatial risk model and clusters of elevated malaria risk were identified through scan statistics. The final aim of this study was to investigate the spatial heterogeneity in relationships between malaria prevalence and associated risk factors by Geographically Weighted Regression [GWR]. The added value of using this geostatistical model is explored, and the advantage compared to a standard linear regression model is evaluated.
The study is embedded as part of a baseline study in a large malaria vector control trial [SolarMal] on Rusinga Island, western Kenya (Hiscox *et al*., 2012). The SolarMal trial aims to reduce malaria transmission on Rusinga Island by mass trapping of malaria vectors with odour-baited traps [OBTs], which contain a blend of organic volatiles that mimic a human odour (Menger *et al.*, 2014a). Through daily removal trapping the project aims to reduce malaria vector populations and eventually decrease malaria transmission. The analysis of spatial heterogeneity of risk factors for malaria can give a better understanding of malaria epidemiology and can be of value for programme managers who want explore targeting interventions to specific geographical locations.

Methods

Study site and population

Rusinga Island is located in Lake Victoria off the shore of western Kenya (between 0°20′51.53” - 0°26’33.73” south, and 34°13′43.19” - 34°07’23.78” east). The island is located in Mbita sub-county, under the administration of Homa Bay County in western Kenya (Figure 6.1) and is connected to Mbita Point on the mainland by a causeway. Rusinga Island has a land surface of nearly 44 km^2 with most of the residential areas situated between 1,100 and 1,200 metres above sea level around the lakeshore of the island. This region experiences a bimodal pattern of rainfall, with the longer rains usually starting in March and ending in June and a shorter rainy season from November to December. Average temperatures range from 20 to 29° C in the rainy season and from 25 to 34° C in the dry season. On Rusinga Island, the population is traditionally part of the Luo tribe. The principal occupation is fishing and labour associated with fishing, otherwise many of the inhabitants are involved in rain-fed subsistence agriculture. Malaria transmission occurs throughout the year, with peaks in transmission late in the rainy seasons when parasite prevalence is approximately 30% across the population (WHO, 2015b)

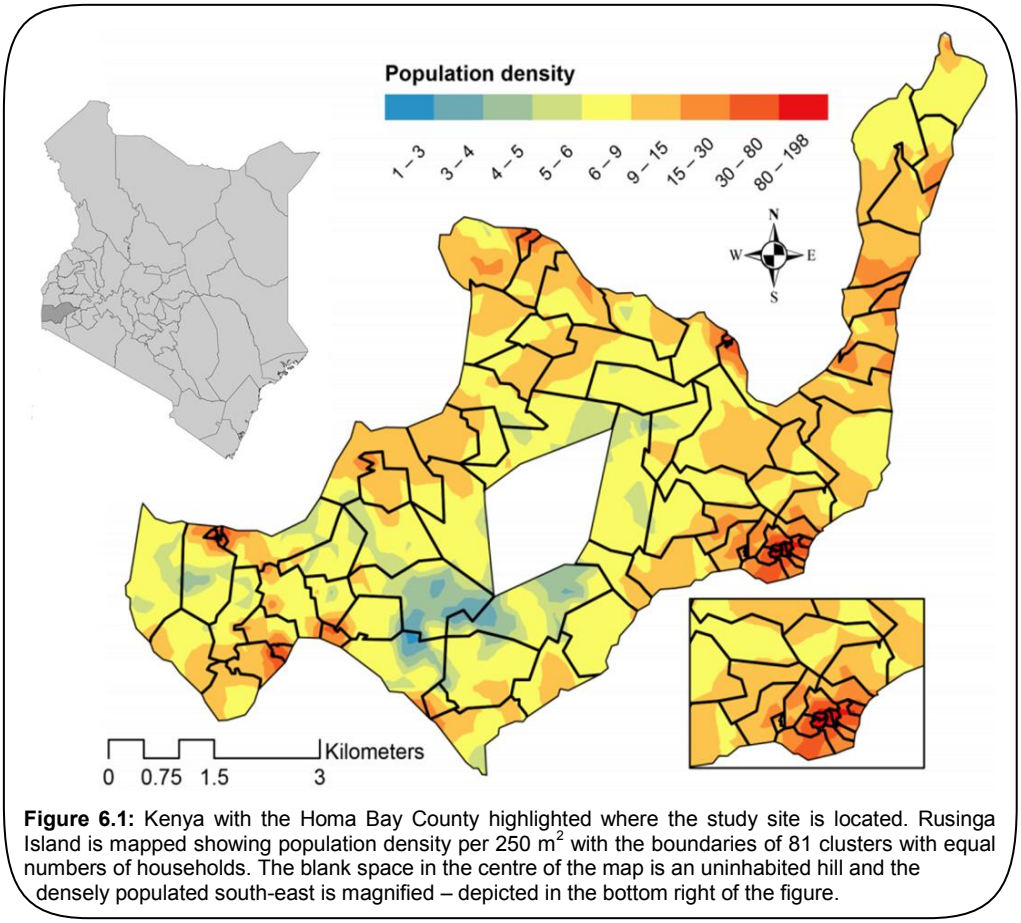

Figure 6.1: Kenya with the Homa Bay County highlighted where the study site is located. Rusinga Island is mapped showing population density per 250 m^2 with the boundaries of 81 clusters with equal numbers of households. The blank space in the centre of the map is an uninhabited hill and the densely populated south-east is magnified – depicted in the bottom right of the figure.

Plasmodium falciparum is the most prevalent species of malaria in western Kenya accounting for 98% of the cases and the malaria transmitting vectors are *Anopheles funestus* and to a lesser extent *Anopheles gambiae s.s.* and *Anopheles arabiensis* (Bayoh *et al.*, 2010; Olanga *et al.*, 2015).

Field set up

The SolarMal project is based at the Thomas Odhiambo Campus of the International Centre of Insect Physiology and Ecology (TOC-icipe) in the village of Mbita Point, one kilometre from the causeway which connects the island to the mainland. Meteorological data such as daily temperature and precipitation were obtained from the Suba meteorological field station at Rusinga Island (0°24′19.28" south and 34°08'51.94" east). A health and demographic surveillance system [HDSS] was set up to visit every individual living on Rusinga Island three times per year. A census enumeration survey, conducted from May to July 2012 recorded 23,337 individuals

residing in 6,954 residential structures (henceforth termed houses) divided into 4,063 economically independent households. During the census HDSS round, the coordinates of all residential structures, as well as public buildings, were recorded. Fieldworkers were equipped with mobile tablet computer devices (Samsung Galaxy Tab 2, 10.1) with in inbuilt global positioning system [GPS] receiver for the data collection. All individuals were asked to provide their full name, sex, date of birth, main occupation and their relationship to the head of household. An individual was considered eligible for participation in the study when he or she intended to live for at least six months on the island. Data collection and handling was conducted using general structured questionnaires in the OpenHDS data collection and management platform. Data were transferred on a daily basis to a secured local server enabling researchers to work with a completely digital near real time database. Clean data were deposited in a MySQL database. During baseline studies one HDSS update survey was conducted from January to June 2013. For the rollout of the intervention the island was divided into 81 geographically contiguous clusters with 50 to 51 households per cluster. The households were allocated to clusters according to a travelling salesman algorithm by which the shortest imaginary route connecting every household on the island was identified. A new cluster was created after every 50 – 51 households (Day, 1988) (Figure 6.1). 81 clusters is a sufficient number of units to carry out regression while a sample from approximately 50 households provides enough statistical power to estimate the true value for a cluster.

Malaria surveillance

During the baseline period before rollout of the intervention commenced, two parasitological prevalence surveys were conducted in a cross section of the study population. Households were randomly selected for inclusion in each prevalence survey to the point where 10% of the population was included. All members of selected households were informed in advance of the date and time of the survey and were invited to assemble at a public place such as a church or a school near their home for malaria testing. In total, residents of 790 randomly selected households were sampled, covering 1,223 houses. The first survey examined 1,822 individuals (7.8% of the total island population) and was carried out during the start of the short rainy season starting from September and finishing in November 2012. A second prevalence survey examined 1,810 individuals (7.7% of the total population) and was conducted from February to April 2013. Individual body temperature was measured by means of a Braun™ IRT 3020 ear thermometer. A drop of blood was obtained through a finger prick and directly tested for antigens of malaria parasites using an *SD BIOLINE*™ Malaria Ag P.f/Pan [*HRP-II*/pLDH] Rapid Diagnostic Test [*RDT]. The SD Bioline* RDT kit results distinguish between infection with *Plasmodium falciparum* and other *Plasmodium* species. However, tests results with more than one

positive reading or indicating multiple species of *Plasmodium* were pooled. If the individual tested positive for malaria antigens, an appropriate dose of Coartem® (Artemether/lumefantrine) was provided free of charge.

Household information

Besides the demographic information, Table 6.1 lists variables recorded concerning the house structure and existing malaria prevention behaviour and whether they were derived from the level of the individual or the household. An index of socioeconomic status [SES] was constructed by means of a principal component analysis producing tertiles of socioeconomic status on basis of six variables, (Vyas *et al.*, 2006) as used in the Kenyan national malaria indicator survey (KNBS, 2012). The variables used were: whether the dwelling was owned or rented, whether agricultural land was owned, highest education level of the head of household, location of the kitchen, the wall structure and the floor cover. Every individual was categorized in to one of the

Table 6.1: Variables considered for the global regression model of malaria prevalence.

Variable	Description for GWR per project cluster
Sex	% males
Age1	% of children under 5 years old
Age2	% of children between 5 and 15 years old
Age3	% of people above the age of 15
Occupation	% outdoor occupation
People per sleeping room	Mean people per sleeping room
People per house	Mean people per house
Screened eaves	% houses with open eaves
Condition of bed nets	% bed nets without damages
House sprayed last 12 months	% sprayed houses in last 12 months
Nets per person	Mean number of nets per person
Socio economic status1	% of people with highest SES*
Socio economic status2	% of people with lowest SES
House ownership	% of houses owned
Population density	Mean population density
Mosquito exposure	Mean malaria mosquito catches per house
NDVI	Mean NDVI **
TWI	Mean TWI ***
Distance to lake	Mean distance to the lake
Elevation from lake	Mean elevation from lake
Distance to clinic	Mean distance to nearest health clinic

***SES = socio economic status, **NDVI = normalized difference vegetation index, ***TWI = topographic wetness index**

three SES classes: high, intermediate and low. Data were transformed into continuous variables with means calculated per cluster. Means of variables per cluster were constructed either on basis of individual level data or household level data (Table 6.1). Sex was expressed as the proportion of males per cluster; age was

divided into three dummy variables, the proportion of children under five years old, between five and 15 years and above 15 years; occupation was categorized as the proportion of people in a cluster having an outdoor occupation; house ownership is the proportion of houses that are owner-occupied rather than rented; for SES the two lowest categories were pooled so a dummy variable remained for high SES and not a high SES, the percentage of people having the highest and the lowest socio-economic status; eaves as the percentage of houses with open eaves; and condition of nets is the proportion of people sleeping under an intact net.

Entomological monitoring

Monitoring of mosquitoes took place across five consecutive rounds from September 2012 until June 2013, selecting 80 households per round. Each time by means of a simple random sample, with replacement, of all households on the island. Mosquitoes were collected inside and outside selected households using odour-baited MM-X traps (American Biophysics Corporation, RI, USA) (Menger *et al.*, 2014b). Data from the first, second, fourth and fifth rounds of surveillance (September to November 2012 and March to June 2013) were pooled as they corresponded temporally with the two baseline malaria prevalence surveys. In total entomological data from 353 households were included in this study. The total number of female anophelines caught inside and outside each household was pooled as a single observation for that particular household.

Geographical variables

A multispectral QuickBird image, taken on 17/03/2010 with a spatial resolution of 2.4 m, was obtained through DigitalGlobe®. Initially, the image was used for geo-referencing of residential and public structures and infrastructure. The image was geo-referenced, radio-metrically corrected, corrected for sensor and platform-induced distortions, and was ready for orthorectification. Orthorectification was performed using a Digital Elevation Model [DEM]. The DEM used was an ASTER GDEM 2, the geographical coordinate system was referenced to the 1984 World Geodetic System [WGS84]. Several geographic variables were derived for each household using the image and DEM: elevation relative to lake, distance to lake, distance to nearest clinic, population density, the Normalized Difference Vegetation Index [NDVI] and the Topographic Wetness Index [TWI]. The NDVI is a commonly used indication of greenness and is calculated based on the values of the red and near infrared spectral bands within a radius of 250 metres. The TWI defines the wetness of an area and combines the upstream area with the local slope expressed as the number of cells 'upstream' of cells measuring 30x30m (900 m^2). Population density measures were calculated within a radius of 250 metres. All the geographical variables per household were averaged per project cluster for data analysis and the analysis was at cluster-

level. Geographic data and variables were pre-processed, compiled and displayed using ArcGIS (ArcGIS 10.2.1, ESRI Inc., Redlands, CA, USA).

Statistical analysis

For this analysis the measurements of both prevalence surveys were pooled and the mean malaria prevalence per project cluster on basis of individual RDT outcomes was analysed and mapped with smoothing using the areal interpolation technique. Areal interpolation is a kriging-based interpolation method that considers involvement of polygons of different shapes (Hawley & Mollering, 2005). A Gaussian distribution for data averaged over polygons was used to produce semivariograms. Semivariograms were then used to investigate the degree of spatial variation; the model function was chosen which captured the most empirical data points within its confidence intervals.

Unlike the regression analyses that are based on continuous household or individual data of project clusters (Table 6.1), the detection of potential 'hot spots' of malaria cases were analysed with a binomial distribution on an individual level, with the outcome variable malaria positive or negative. Kuldorff spatial scan statistic analyses were performed (SaTScan, v9.1.1) (Jung *et al.*, 2007; Kulldorff *et al.*, 1995) using a circular window that gradually scans the map of the island, quantifying the number of observed and expected observations within the window for every house. Within each circle, values in a radius around each household were compared to the expected values and a likelihood ratio test was subsequently performed. P-values were obtained by 999 Monte Carlo replications and when p-values were ≤ 0.05, houses in this circle were considered to be part of a significant hot spot of elevated malaria prevalence. The maximum scan window was set at 1.5 km and a maximum of 50% of the population was allowed in one possible hot spot.

Stationary epidemiological risk models assume that observations are geographically independent. These 'global' models assume that malaria and the coefficients of predictor variables apply to the whole island (Lopez *et al.*, 2006). Outcomes can be biased because the models do not account for spatial dependence considering that the relationship of risk factors for malaria can vary over space, such as demographical and environmental features. (Anselin, 1995). In order to gain an enhanced insight in to variation in malaria outcomes, incorporating potential spatial dependence of predictor and dependent variables is vital where disease patterns are spatially heterogeneous. Moreover, to effectively capture spatially variable associations between risk factors and malaria outcomes, regression coefficients may vary locally as well. To include these considerations of spatial non-stationarity a geographically weighted regression [GWR] model was deployed (Brunsdon *et al.*, 1996). A log transformation was performed to normalize the slightly positively skewed malaria prevalence data on cluster level.

To explore which predictor variables to include in the GWR model, a global multivariable regression (stationary model) was initially performed. In adopting the best model for explaining log transformed risk several other model features other than the best goodness-of-fit or statistical significance of predictors were looked at. Next, the assumption of normally distributed residuals of the estimated outcome (tested by the Jarque-Bera test) was tested as the model prediction function relies on normally distributed unexplained variance. The predictor variables that were included cannot have any multicollinearity in order to prevent duplication of capturing any predictive effect (indicated by a Variance Inflation Factor of <7.5). Moreover, regression residuals need to be randomly distributed to make sure that observed relationships are not inflated because the observed minus the predicted values are not independent from each other (Anselin, 2002). Regression residuals were examined for residual spatial autocorrelation [RSA]. Furthermore, a test to detect heteroscedasticity was carried out to get an idea of heterogeneity in the relationship between the predictor and dependent variables (Breusch-Pagan statistic). The model that satisfied all these requirements and had the highest R^2 was selected for further analysis in a GWR model. The model did not control for possible correlated observations.

In relationships between dependent and independent variables the GWR produces local linear regression models. The coefficients in a standard linear regression model are assumed to be the same at every location, whereas regression coefficients of a GWR model are attached to each individual location, in this case the location of a central point of a cluster (Fotheringham *et al.*, 1998). Coordinates of project clusters were determined by taking the centroids of the polygon features. The GWR regression model is thus:

$$y_i = \beta_0 + \sum_{k=1}^{p-1} \beta_k x_{ki} + \varepsilon_i \quad (1)$$

where every observation *i* has its own set of coordinates, y_i is the cluster prevalence and x_{ki} is the value for a covariate *k* for observation *i*, β_0 is the intercept, β_k is the coefficient estimate for a covariate *k*, and ε_i is the random error for observation *i*, and *p* is the number of regression coefficients to be estimated. Estimations of predictor variables were obtained using subsets of data in a radius around observed geographical data points. Weights were applied to the subsets of observations, with a Gaussian decaying influence as distance increases. The radius determining the distance at which neighbouring data points influence the local models is known as the kernel bandwidth. For this analysis an adaptive kernel function (bi-square) was chosen instead of using a fixed radius; it considers a number of neighbouring data points leading to weights:

$$W_{ij} = \begin{cases} \left[1 - \left(\frac{d_{ij}}{d_{iN}}\right)^2\right]^2 \\ 0 \end{cases} \quad (2)$$

where W_{ij} is the weight of data at location *j* estimated for location *i*, d_{ij} is the distance between locations *i* and *j*, d_{iN} is the distance to the spatial neighbours of location *i* and *N* is the number of neighbours considered W_{ij} takes zero for locations that are farther away from location i than the kernel bandwidth set. The optimal bandwidth and the associated weighting function were obtained by choosing the lowest score of the corrected Akaike information criterion [AIC*c*]. It seeks parsimony, finding a balance between model fit and amount of parameters in the model. The AIC*c* was obtained by reducing the estimation error of our dependent outcome to a minimum and is:

$$\mathrm{AIC}c = 2n \log e\,(\hat{\sigma}) + n \log e(2\pi) + \left\{\frac{n+tr(S)}{n-2-tr(S)}\right\} \quad (3)$$

where $\hat{\sigma}$ is the estimated standard deviation of the error, and *tr*(*S*) is the trace of the matrix of covariates.

A set of local goodness-of-fit statistics was derived by plotting the local R^2 per cluster. Furthermore, local coefficients and p-values belonging to predictor variables yielded were plotted to explore the geographically varying relationships with malaria prevalence. A semivariogram of regression residuals is constructed to explore the spatial structure of the model. To examine the final GWR model for possible spatial autocorrelation in the residuals [RSA], a Moran's I test was performed on the residuals between observed and predicted values of malaria prevalence. Finally the model predictions were validated by means of exhaustive cross validation. Many different samples of training and a validation sets were considered to validate predictions in every cluster.

Special attention is given to the issue of local multicollinearity because GWR outcomes can be heavily biased, and local coefficients can become inflated if different predictor variables have similar geographical patterns (Wheeler, 2007). Local multicollinearity is assessed by the condition number. This number increases if predictor variables show similar patterns, and when this number is above 30, the model is assumed to be unstable and unreliable.

Statistical analysis and model building were performed using R software (RStudio, Inc.© version 0.98.1102 package *spgwr*) , GWR4© (Newcastle University, England, UK) and ArcGIS (10.2.1, ESRI Inc., Redlands, CA, USA).

Ethical clearance

Ethical approval was obtained from the Kenyan Medical Research Institute [KEMRI]; non-SSC Protocol No. 350. All participants were provided with written and oral information regarding the project aims, the ongoing demographic and entomological surveillance activities, the implementation of the intervention, and the collection and use of blood samples. Adults, mature minors and caregivers of children provided written informed consent in the local language agreeing to participation in the SolarMal project activities.

Results

Possible hot spots of elevated malaria risk were identified by plotting the malaria prevalence per project cluster and smoothed with the areal interpolation technique (Figure 6.2A). The island-wide malaria prevalence was 24% and the prevalence per cluster varied between 9% and 75%. Subsequently a SatScan analysis was conducted revealing two significant hot spots of malaria; one in the west and one in the central north of the island (see Figure 6.2B). The primary hot spot of malaria is located in the central north of the island; the observed number of cases here was significantly higher than predicted from island-wide values (Table 6.2). The risk of malaria in this hot spot is almost three times higher than for areas outside this hot spot (RR = 2.65, LLratio = 42.509, p-value = <0.0001). Furthermore, a secondary hot spot of malaria was identified in the west of the island with more than twice the risk for malaria infection (RR = 2.12, LLratio = 20.399, p-value = 0.001).

Global linear regression

The multivariable global linear regression [GLR] model explains 26.8% (R^2) of the total variation between project clusters in malaria prevalence. The model and statistics on model assumptions are summarized in Table 6.3. The null-hypothesis of no residual spatial autocorrelation [RSA] in the model is maintained with the Moran's I statistic not being significant, showing that the regression residuals are randomly distributed and not missing key explanatory variable. The Breusch-Pagan statistic examines whether the relationship of predictor variables with malaria prevalence is similar around the island; heteroscedasticity is clearly present (with a p-value of 0.03). Furthermore, the residuals of the outcome variable are approximately normally distributed indicating no deviation from the distributional assumptions of the model. Because heteroscedasticity is significantly present in the GLR model, the robust p-value and standard errors were used to assess the relationships of the predictor variables with malaria prevalence. Outdoor occupation is the strongest significant predictor in the model with a coefficient of 0.57 (and a p-value of <0.0001).

Table 6.2: Summary results of hot spots detected by SatScan

Cluster	Relative Risk	LLratio	P-value	Number of individuals	Expected infected individuals	Infected individuals
1	2.65	42.51	<0.0001	298	29	69
2	2.12	20.40	0.001	212	23	46

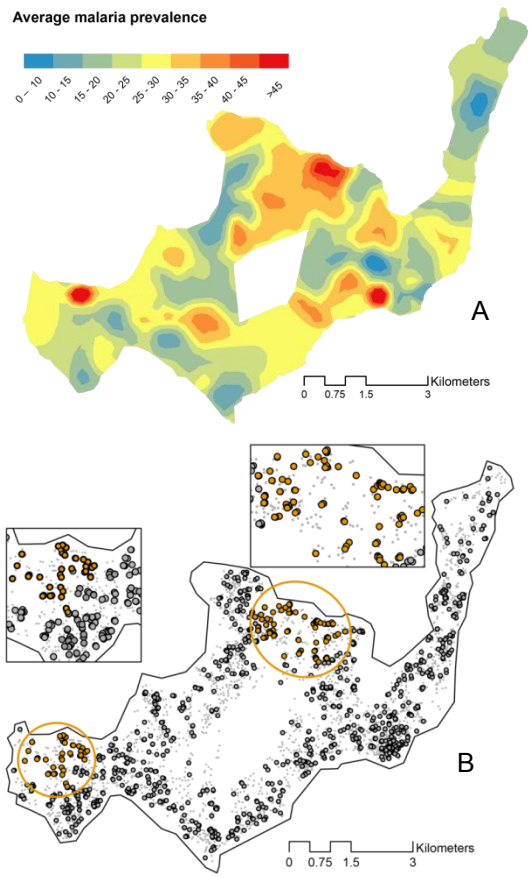

Figure 6.2: A) Mean malaria prevalence per cluster on the basis of sampled individuals across Rusinga Island using Aerial interpolation. B) Map of Rusinga Island showing two clusters of households (orange dots) with significantly elevated levels of malaria prevalence. The primary cluster is located at the central north of the island; a secondary cluster is covering an area to the west. Figure 6.2A would suggest another cluster of malaria in the south-east, however prevalence in this area is not significantly greater than in neighbouring areas. The grey dots (Figure 6.2B) with black outlines are the sampled houses in the prevalence surveys; the paler grey dots indicate all houses on the island.

Furthermore, belonging to a household with a high SES is positively associated with malaria prevalence with a significant coefficient of 0.24 (and a p-value of 0.02). A third significant predictor variable is population density, although the coefficient was only -0.004 (p-value of 0.001). All predictor variables in the final global model were tested for multicollinearity, and all are well below the threshold of 7.5 (Table 6.3).

6

Geographically weighted regression model

The predictor variables of the GLR model (outdoor occupation, SES and population density) were incorporated into a geographically weighted regression model. To determine the number of neighbouring clusters for local regression the bandwidth with the lowest AICc was chosen. The bi-square adaptive kernel function looks at an adaptive number neighbours and the influence of these neighbours decays following a Gaussian distribution so that closer observations have most weight. So local regression for clusters that have few data points adjacent, will include clusters farther away. Comparing the global and the local model shows that the GWR model performs better than the GLR model with an AIC (a measure to compare model quality) value of -43.8 versus -40.2 (Table 6.4).Moreover, the GWR model fits considerably better taking into account non-stationarity. The capability of the GWR model to predict malaria prevalence on basis

Table 6.3: Summary results for best non-spatial linear regression model for malaria prevalence

Variable	Coefficient	Std error	P-value	Robust Std error	Robust P-value	VIF**
Intercept	-0.827	0.059	<0.0001	0.061	<0.0001	-
Outdoor occupation	0.566	0.195	0.005	0.200	0.006	1.16
*Highest SES**	0.240	0.098	0.017	0.101	0.020	1.55
Population density	-0.004	0.001	<0.0001	0.001	0.001	1.38
Statistic	**Value**					
Joint Wald Statistic	18.75; p = 0.001					
Moran's I	0.45; p = 0.21					
Breusch-Pagan statistic	8.86; p = 0.03					
Jarque-Bera statistic	4.05; p = 0.13					

*SES = socio economic status, **VIF = variance inflation factor

of the selected predictors is best expressed by looking at the R^2, improving the model fit from 27% to 69%. Other indications that show a better fitting and predicting model are the residual sum of squares and the -2 Log Likelihood, both statistics are less than half compared to the local model. Exploring the spatial structure of the model residuals with an anisotropic averaged semivariogram shows that the distance up to which RSA occurs (the range) is 2.7 kilometres (Figure 6.3). The sill has a value of 0.825, indicating that the variance of residuals between households beyond the value of the RSA range is fairly high. Within the range the variance starts from 0.61 (the nugget), demonstrating that the degree of RSA is not pronounced.

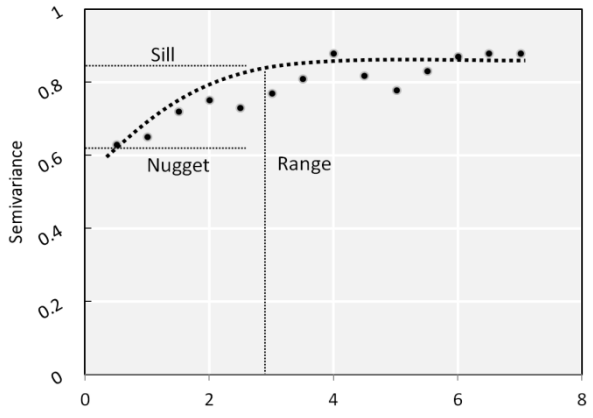

Figure 6.3: Semivariogram of the residuals of the final GWR model, with the dotted line showing the fitted value. The semivariance is shown on the y-axis. The semivariance of the residuals between households starts at 0.61 (nugget) demonstrating some spatial autocorrelation on distances up to 2.7 kilometres (range). Beyond this threshold the semivariance is high and stabilizes at 0.825 (sill) indicating minimal RSA.

Spatial autocorrelation in the residuals of the final GWR model was then assessed by a Moran's I test and this actually directed to some RSA. Nevertheless this yielded a p-value of 0.25, thus the null hypothesis of no significant RSA was maintained. R^2 values per cluster vary between 32% and 87 % with a mean of 63% (Figure 6.4A).

Table 6.4: Comparison between global regression and GWR model.

Variable	GLR	GWR
AIC	-40.86	-43.18
Moran's I	0.45; p = 0.21	0.23; p = 0.25
R^2	0.268	0.694
Residual sum of squares	2.53	0.985
-2 Log Likelihood	-50.86	-127.26

Model fit is compared with AIC, explanatory power of the models is compared by R^2 and the Moran's I of residuals indicates the degree of spatial autocorrelation.

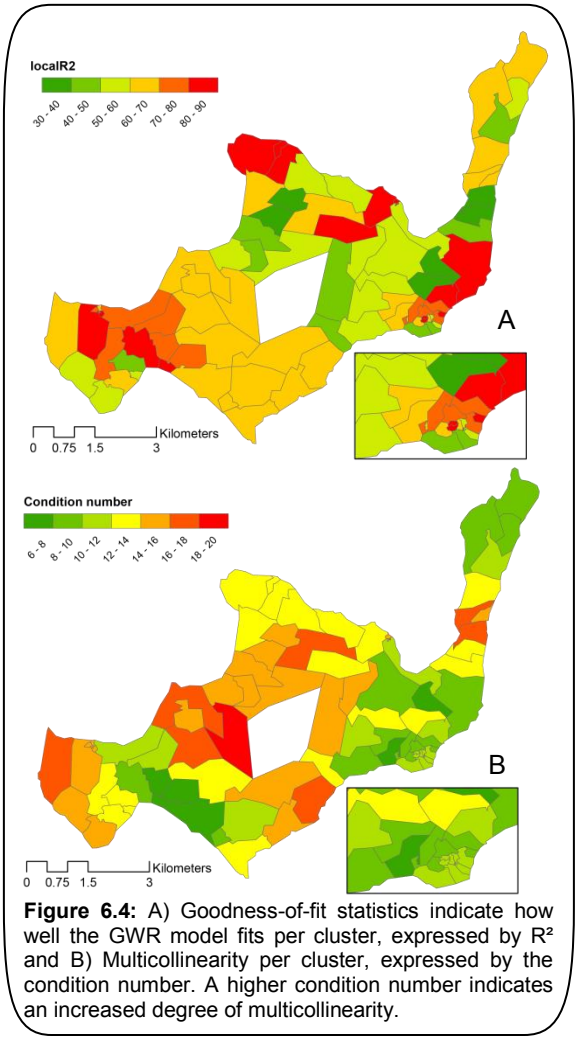

Figure 6.4: A) Goodness-of-fit statistics indicate how well the GWR model fits per cluster, expressed by R^2 and B) Multicollinearity per cluster, expressed by the condition number. A higher condition number indicates an increased degree of multicollinearity.

The local multi-collinearity assessed by the condition number yields values between 6.7 and 19.2 with a mean of 12.9, indicating that the model is marginally affected by multi-collinearity (Figure 6.4A).

Cross validation of the predicted malaria values with the measured values yielded predictions for 74 of 81 project clusters that were statistically significant.

Geographically varying effects of outdoor occupation, SES and population density in the GWR model are illustrated in Figure 6.5. Regression coefficients were back-transformed after the initial log transformation of malaria prevalence in the model, and reported as exponent-iated coefficients.

This is interpreted for the highest SES category as the relative malaria risk compared to being in a lower SES category or having another occupation. The same interpretation applies to the outdoor occupation variable. For average population density the interpretation of the coefficient is best expressed as the increase in malaria risk for every one person increase in the average number of individuals per 250m^2. Population density, outdoor occupation and

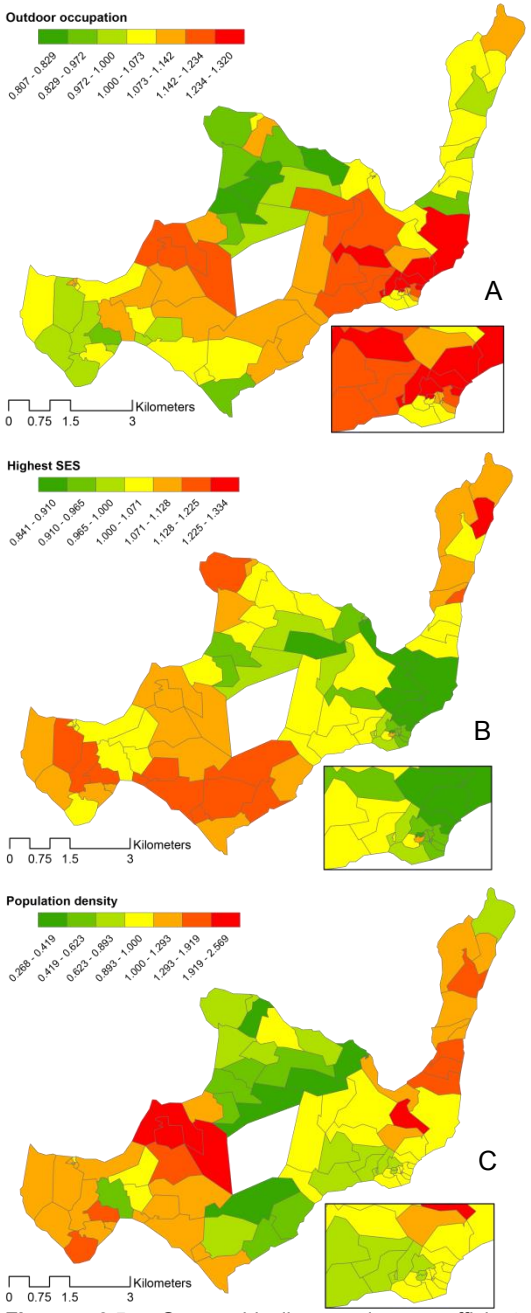

Figure 6.5: Geographically varying coefficients expressed as the relative risk per cluster for predictor variables of prevalence in the GWR model. A) Outdoor occupation, B) Highest SES, C) Population density

highest SES differ in having a positive or negative association with malaria prevalence. Coefficients of each variable can have a positive or negative association and the direction of the association varies depending on the local value of those explanatory variables. Coefficients that are equal to one indicate a similar malaria risk for the risk factor categories, whereas coefficients risks above one demonstrate an increased risk for malaria. The coefficients of malaria for population density varied between 0.268 and 2.569 indicating that the association between malaria and population density could be positive or negative depending on the area of the island. The variation in coefficients of malaria for those in the highest SES group ranged between 0.841 and 1.334, also indicative of a negative association in some areas of the island but a positive association in other areas. Outdoor occupation also had a spatially variable association with malaria, with exponentiated coefficients ranging between 0.807 and 1.320. P-values of regression coefficients of all three explanatory variables also vary over space (Figure 6.6), indicating that the statistically significant relationships were not equally strong everywhere on the island.

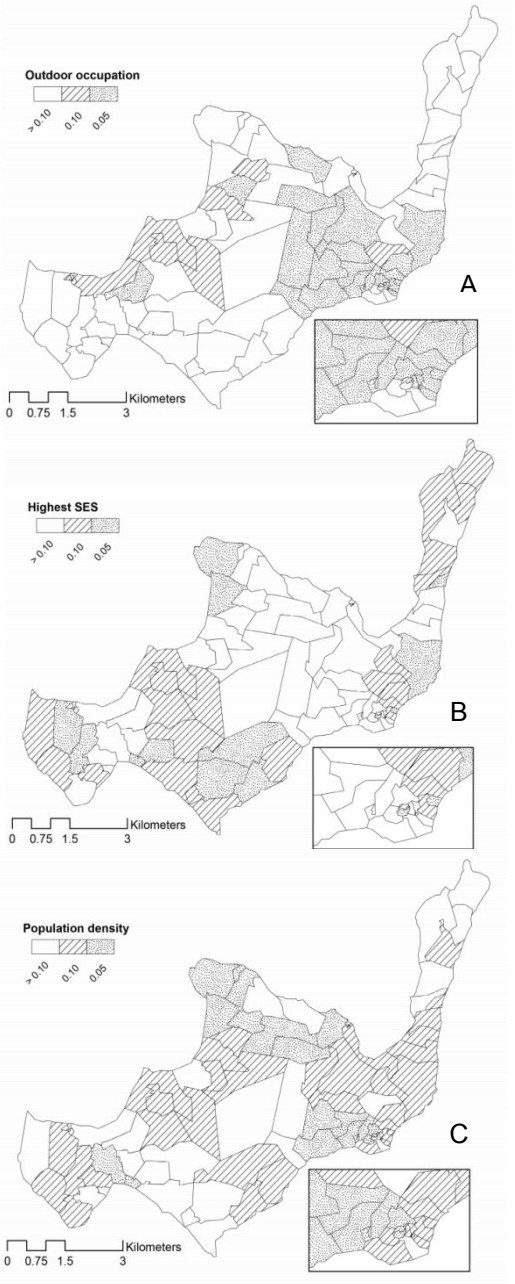

Figure 6.6: Geographically varying values of significance per cluster for predictor variables of malaria prevalence in the final GWR model. A) Outdoor occupation, B) Highest SES, C) Population density

Discussion

Over the past decade large reductions in malaria have been achieved, yet the current distribution of malaria is still spatially heterogeneous (Cotter *et al.*, 2013; Noor *et al.*, 2014). Considerable research is currently being conducted to find tools for malaria control that are able to target residual malaria transmission, in order to reach the goals set by the RBM initiative to eliminate malaria where possible, or reduce it to a minimum (Killeen, 2014; Owens, 2015). Established interventions such as LLINs, IRS and case management have proven to be effective but this one size fits all strategy is not appropriate when moving into the elimination phase (Snow, 2015). These existing methods will need to be complemented by novel tools, which may entail interventions targeting local geography, demography and societal context (Alonso *et al.*, 2011c). Exploring locally varying relationships of risk factors for malaria may aid in exploring and eventually targeting appropriate interventions. Traditional descriptions and models report on the progressively heterogeneous nature of malaria transmission, but analyses reporting on risk factors for malaria and disease usually ignore spatial heterogeneity of the underlying risk factors of disease (Pullan *et al.*,

2012).

In exploring spatially varying relationships of risk factors for malaria, factors that are directly related to malaria risk as well as proxy factors were used. Socioeconomic status, screened eaves and condition of bed nets are examples of factors directly influencing malaria risk, whereas distance to nearest clinic and environmental variables as TWI and NDVI can have an indirect effect because of access to anti-malarials or proximity to possible breeding sites for malaria vectors. The GLR model explained 27% of the spatial variance in malaria prevalence, however GWR analysis greatly improved model fit to 69%. A better fit by the GWR model is confirmed by a reduction in the residual sum of squares as well as an increased likelihood when comparing the global and the local model (Table 6.4). Local estimations of model fit did vary somewhat over the island (Figure 6.4A), and whilst there are several areas where the model does not fit more than 50%, in all study clusters an improved fit using the GWR was observed compared with the global model.

Outdoor occupation and activity at night have previously been associated with higher risk for malaria (Dunn *et al.*, 2011; Monroe *et al.*, 2015). In the case of Rusinga Island, many people are involved in fishing and labour related to fishing, and these activities are generally performed in shifts during the night. It is known that in between shifts, fishermen spend their time around fishing beaches close to their home with little or no protection against biting malaria mosquitoes. It is during the night that *Anopheles gambiae s.l.* and *An. funestus* mosquitoes exhibit their peak host-seeking behaviour, biting mostly indoors but also outdoors (Govella *et al.*, 2012), thus people who are active at night are expected to be at increased risk for receiving infective mosquito bites. Spatial heterogeneity of outdoor occupation in the south-east of the island is characterized by a large area where having an outdoor occupation leads to increased risk of malaria. This is the area of Rusinga with the highest proportion of fishermen. Malaria infections could be acquired there, subsequently fuelling the malaria reservoir and infection risk for others in these areas, a concept that has been proposed previously (Prosper *et al.*, 2012). Study clusters that include fishing beaches almost all appear to have higher risk because of outdoor occupations. For example the small cluster in the north and the smaller clusters west of the island, which fall within a malaria hot spot (Figure 6.2B). In the northern part of the island there are also clusters with a reduced risk of malaria for outdoor occupation; these clusters lie in one of the malaria hot spots. The effect is not as large and is also less significant, but possibly an explanation here can be that in this area farming, also an outdoor occupation, is the dominant occupation, usually performed during the day when mosquitoes are less active. Nevertheless working outside at dawn and dusk becomes increasingly more important as a predictor of malaria risk as the mosquito vectors are recurrently reported to bite after sunrise and before sunset (Bayoh *et al.*, 2010).

Socioeconomic status has often been linked with risk of malaria. Better schooling, improved housing and a higher income are commonly associated with reduced malaria risk (Tusting *et al.*, 2013). On Rusinga, areas with a higher risk as well as areas with a lower risk for malaria when residing in the highest SES category are identified. The local patterns of SES show that a positive association with malaria mostly affects the central western part of the island and the tip in the north-east (orange clusters), with an increased risk of malaria. The south-eastern part (green clusters) of the island, by contrast, yield clusters that show a reduced risk of malaria among those with the highest SES.

SES itself does not affect malaria directly; hence the components of SES were further explored. It was found that in most of the clusters where high SES is associated with increased malaria risk, most farmland and dwellings are owned by the occupants while house structure is predominantly poor. This could suggest that variables as owning land and a house, indicators for being in a high SES class, do not necessarily directly relate to reduced malaria risk. Thus even though people are in the highest SES class, the house structure could allow for considerable malaria risk because there is poor protection against mosquitoes entering the house. A higher education level of the head of household could indicate that there is more financial freedom within the family. This can possibly result in a higher expenditure on health care and malaria prevention, which would presumably lead to reduced malaria risk. The components of location of kitchen and wall structure in this SES PCA are proxies of exposure to mosquitoes. When people cook outside during sunset and at night-time they may be exposed to outdoor-biting mosquitoes. Finally and interestingly SES did not have a strong (Figure 6.5B) or significant relationship (Figure 6.6B) with malaria in the hot spots (Figure 6.2B). Thus, residing in a malaria hot spot was independent of house ownership, educational level or other SES factors.

A higher population density was associated with a slightly reduced risk of malaria in the GLR model, in keeping with previous findings from various studies in both urban and rural settings in Africa (Hay *et al.*, 2005). Higher population density has a large protective effect in some clusters farther from the lake and further from potential breeding sites, whereas the association between population density and malaria risk was positive in some clusters closer to the lake. It appears that the effect of a higher population density depended on proximity to possible breeding sites of malaria vectors near the lake shore. In a large simulation study (Smith *et al.*, 2004) the dynamics of a spatially heterogeneous human and mosquito population was modelled and it was suggested that where there are few mosquitoes or breeding sites, the chance of receiving an infective bite is reduced in densely populated areas whereas the chance or receiving an infective bite is not reduced in sparsely populated areas. On the other hand, if there are many breeding sites and many mosquitoes close to a densely populated area, the chance of malaria transmission increases considerably

compared to areas that are less densely populated where the chance or malaria transmission does not increase further with increasing mosquito numbers.
Other risk factors considered in the GLR model have all been suggested in previous literature as predictive for malaria risk. Remarkably, human age and mosquito counts as a proxy for exposure did not enter the final model. Young children (0-5 years) and adolescents typically have a higher risk of malaria because of different behaviour regarding malaria prevention and less well developed immune systems (Carneiro *et al.*, 2010). However, on Rusinga age was not significantly related to malaria, and there was no spatial heterogeneity in the effect of age on malaria. Furthermore, increased numbers of mosquitoes caught in some clusters were not accompanied by higher local prevalence. Screened eaves was not a significant predictor, but this can be explained by the fact that more than 90% of the households did not have screened eaves and therefore there was insufficient information relating to the impact of this variable. There was a fairly homogenous coverage of bed nets and IRS activities across the island in the year prior to the present study. Bed nets continued to be used, but no further IRS treatments took place. This lack of variability could explain why number of bed nets and IRS coverage were not significantly associated with malaria. NDVI and TWI were also rather homogeneous over the island and therefore not important predictors for malaria. Finally, the average distance to a clinic did not play a role in this model. On this relatively small island, there are five health clinics or dispensaries, and even the households furthest away from a health clinic are at a walking distance of only three km.
An advantage of this study is firstly the assumption that non-stationarity of underlying risk factors for malaria can improve model fit considerably and can subsequently be used to explore geographically varying factors responsible for spatial patterns of malaria. Local outcomes and relationships can shed light on why malaria persists in certain areas. Secondly, as the data collected for this analysis serves as the baseline survey for a large vector control study, this analysis can assist in exploring further research and explain why the interventions may ultimately perform better in some areas than in others. One could consider increasing the intensity of available malaria interventions near fishing beaches at night, account for poor housing structures and reduce the number of traps in a densely populated area where high population density is associated with lower risk of malaria.
It is essential to understand the degree by which the results could be influenced by the unit of analysis. The use of discrete zones to perform spatial analysis is very common (Fotheringham *et al*., 2001), but rather contradictory because geographical variation is a continuous process. Project clusters were defined and used to perform the intervention study, with the baseline malaria data described here. The number of clusters and population size per cluster were optimized and adopted for the rollout of the vector control intervention with optimal statistical power as well as community

acceptance (Oria *et al.*, 2014). Creation of 81 clusters with an even number of households per cluster was calculated to provide sufficient generalizability and randomness to detect a possible difference in malaria incidence (T. Smith, personal communication). As the intervention trial is analysed on basis of geographical divisions it was logical to use the same clusters for analysis of baseline data, which gave rise to this work. Spatial analyses are often performed on a similar scale at which this data was collected, for instance on village or county level (Wheeler, 2014). Published work stresses that a societal or biological rationale is important when constructing discrete geographical zones. The rationale behind using the project clusters in this study is because it will be valuable to know what factors will have influenced the outcome of the vector intervention study which was conducted on this cluster scale. However, using different discrete clusters or cluster sizes or individual level data may yield slightly different outcomes. More detailed variation in coefficients is yielded when using smaller units and vice versa (Fotheringham *et al.*, 1998). Additionally, when using an adaptive kernel function the radius of data included of local regression is variable. Also here it applies that smaller scale local regression usually leads to more variation in coefficients (Guo *et al.*, 2008), and this mostly leads to weaker or stronger local relationships rather than reversed relationships. Nonetheless, when first performing a global linear regression, one can be confident that the risk factors obtained are important predictors of malaria and that subsequently the local coefficients of GWR are justified, despite of varying strengths of the relationships being influenced by the scale chosen (Fotheringham *et al*., 2001).
Further limitations of this analysis are linked with the statistical methods used by GWR (Paez *et al.*, 2011). GWR has been criticized for lacking an integrated statistical framework because it represents a collective of local spatial regressions and a precise inference becomes imperfect. In understanding the varying coefficients one has to bear in mind that the coefficients that were estimated can be interpreted as an exploration and not as exact inference (Wheeler, 2014). Since this issue was raised, significance tests have been developed to reduce uncertainty about the relationships identified using this approach. These local tests were incorporated in our analysis, showing areas where relationships were more significant than in other areas. Another concern raised regarding GWR is that the technique yields local effects that can be inflated because of residual spatial autocorrelation and multicollinearity. Residual spatial autocorrelation occurs when regression residuals cluster spatially, violating the assumption of independence in a linear regression model. Even though GWR accounts for this by adding a random error term for observations, coefficients can become inflated due to clustering of residuals. In this analysis much care was invested in examining and testing for RSA, minimizing possible uncertainty in coefficients resulting from RSA. Finally, in recent years another limitation of GWR was put forward; inflation of local coefficients because of local multicollinearity

(Wheeler & Tiefelsdorf, 2005). If predictor variables locally indicate the same patterns, their effect on the outcome variable can be overestimated. Since this problem was raised several tools have been developed to assess the extent of local multicollinearity (Wheeler, 2007). In this analysis a measure of local multicollinearity by means of the condition number was incorporated, but it is concluded that this issue caused a negligible distorting effect on the local coefficients.

Conclusion

In this study, geographically-varying risk factors for malaria were modelled. The spatial heterogeneity of malaria risk factors is explored rather than concluding upon perfect inferences. The study reveals that predictor variables for malaria vary geographically even over small distances of several kilometres. The exploration demonstrates that assuming stationarity of risk factors by means of a global statistical model ignores spatial components that can yield useful information and improve model fit. Being part of the highest SES, working outdoors (during night time) and population density were most predictive for malaria patterns on Rusinga Island. When considering SES as a risk factor for malaria one has to bear in mind that this depends on the local setting and the components included, hence results need to be interpreted with caution. All relationships with risk factors were spatially heterogeneous and these varying effects can be used to explore for what reasons vector intervention at the island possibly may have dissimilar effects in different areas.

Authors' contributions

TS, NM, WT, AH, CM, WRM and TH designed the study, TH, NM, AdP, IK and KO designed and implemented the questionnaires and managed the database of the Health and Demographic Surveillance System, AH and WT designed the entomological monitoring study, TS and AR assisted with the spatial analysis and TH performed the statistical analyses. TH, AH and WT wrote the manuscript. All authors read and approved the final manuscript.

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Chapter 7

Stepped wedge cluster-randomised trial of the impact of mass mosquito trapping on malaria (SolarMal)

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Publication under review

Abstract

Background: Odour-baits can attract *Anopheles* mosquitoes indoors and outdoors. Here, we describe a large-scale trial of impacts of mass deployment of odour-baited traps [OBTs] on malaria transmission and disease burden. **Methods**: 4,358 households were provided with solar-powered mosquito trapping systems [SMoTS] on Rusinga Island, Lake Victoria, western Kenya (average population 24,879), using a stepped wedge cluster-randomised design. Fever and clinical malaria were monitored through repeated household visits six months prior to and throughout the two year roll-out period to the entire population. Random samples of households were monitored for *Plasmodium* parasite prevalence (three times per year) and mosquito densities (22 rounds). **Findings**: Clinical malaria incidence declined steeply during the first four months of intervention roll-out, leading to a reduction of 92.5% (95%CI: 89.6-94.5), compared to baseline. The unexpectedly low clinical incidence during roll-out precluded the pre-specified inference of effectiveness from clinical incidence data. Malaria prevalence measured by rapid diagnostic test [RDT] was 29.8% lower (95% CI: 20.9-38.0) in clusters with SMoTS compared to those without over the course of the roll-out. Densities of the major malaria vector, *Anopheles funestus*, declined precipitously, and were 69.2% (95% CI: 29.1-87.4) lower in clusters with SMoTS than in clusters without SMoTS. There was neglible effect on densities of *An. gambiae* s.l.. **Interpretation**: The substantial reduction in densities of *An. funestus* can account for the reduction in malaria prevalence in intervened areas compared with non-intervened areas. Odour-baited traps can be an effective malaria intervention comparable in potential impact to insecticide-treated nets.

Introduction

Long-lasting insecticidal nets [LLINs] and use of artemisinin combination therapies [ACTs] have substantially reduced malaria burden in the last decade (Bhatt *et al.*, 2015; Killeen, 2014). However additional vector-control interventions are needed because *Anopheles* mosquitoes biting at times and in places without LLINs, sustain residual transmission (Durnez & Coosemans, 2013). Existing tools are also threatened by insecticide and drug resistance (Das, 2015; Ranson *et al.*, 2011; WHO, 2015b)

Blends of synthetic chemical attractants can attract more vectors than a human (Mukabana *et al.*, 2012b; Okumu *et al.*, 2010b), motivating development of mass mosquito-trapping systems for malaria control (Hiscox *et al.*, 2012). This paper reports the first trial of odour-baited traps [OBTs] as a malaria control intervention. The study aimed to evaluate proof of principle for the elimination of malaria from Rusinga Island in Lake Victoria, western Kenya, by augmenting the existing strategies of the National Malaria Control Programme of the Government of Kenya (free LLINs and ACTs provided through public health centres) with mass trapping (Okumu *et al.*, 2010a). Rigorous testing of whether this can make elimination feasible required universal coverage with electrically-powered OBTs. Most households on Rusinga initially lacked electricity, so solar-powered mosquito trapping systems [SMoTS] were installed, providing lighting and mobile-phone charging alongside OBTs. A stepped wedge cluster-randomised design was used, in which the island population was assigned to 81 clusters of geographically contiguous households, and SMoTS were installed cluster-by-cluster. 4,358 households received SMoTS over a two year period.

The primary outcome of incidence of clinical malaria was assessed via active surveillance, with household visits to the entire population every four months. Effects on parasite prevalence and densities of host-seeking mosquitoes were also evaluated in sample surveys.

Methods

All residents of Rusinga Island (0°24′S 34°10′E), as enumerated in a Health and Demographic Surveillance System (HDSS) (Homan *et al.*, 2015) were eligible for participation. The standardised SMoTS included a solar panel mounted on the roof to power the OBT (Hiscox *et al*., 2016), two light bulbs, and a connection for charging mobile telephones (Figure 7.1). Traps ran automatically between dusk and dawn every night and were baited with a blend of synthetic organic attractants that mimic human odour along with the carbon-dioxide substitute 2-butanone (van Loon *et al.*, 2015). One SMoTS was installed for each household. Where there were two adjacent single-roomed households, one SMoTS was shared. Households were allocated to 81 clusters, each containing 50-51 households corresponding to the number of SMoTS that could be installed within one week. Groups of nine contiguous clusters formed a single metacluster, so that there were nine metaclusters covering the entire island (Figure 7.2). Metaclusters were large enough to limit dispersal of mosquitoes from neighbouring non-intervened areas into intervened areas (Guerra *et al*., 2014),

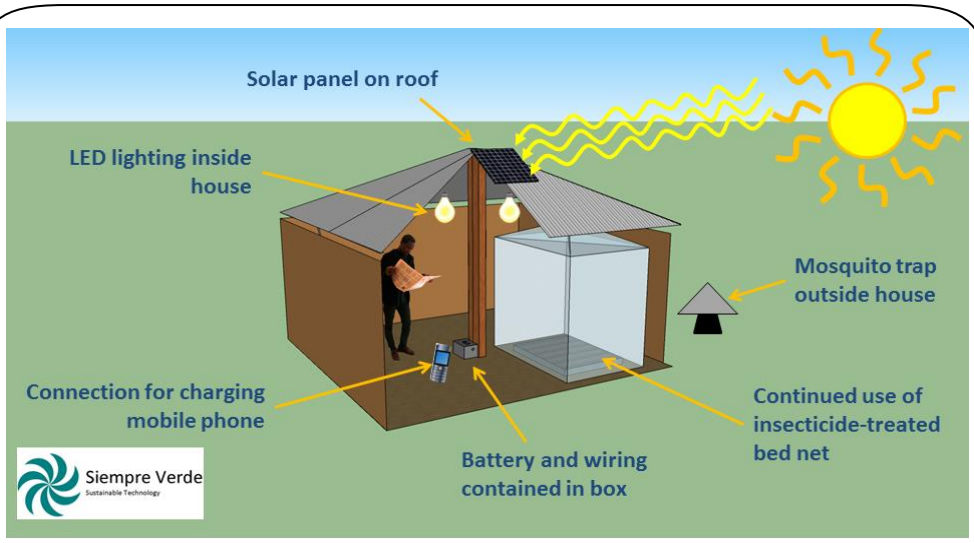

Figure 7.1: Solar-powered mosquito trapping system (SMoTS) in a house that is provided with a LLIN as well. (source: Oria, PA, Alaii J, Ayugi M, et al. *Trop Med Int Hlth* 2015; 20: 1048–1056)

whilst allowing measurements of possible spillover effects to neighbouring non-intervened areas. SMoTS installation lasted from June 2013 until June 2015, and was combined with and facilitated by a social science action research and communication strategy aimed at enhancing community support. This improved recipient understanding of the intervention and fostered programme learning during implementation (Oria *et al.*, 2015). Clinical data were collected during one complete

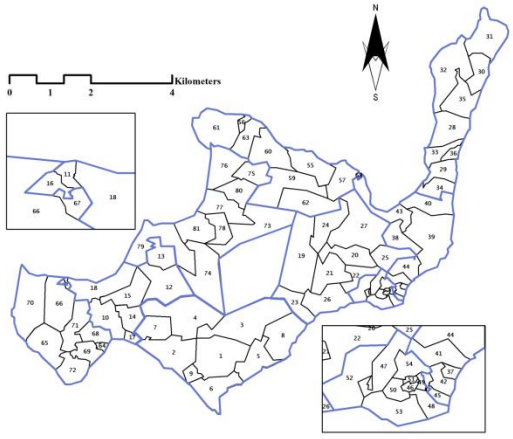

Figure 7.2: Map showing Rusinga Island with clusters (black boundaries, numbered 1-81 in the sequence of the roll-out) and metacluster boundaries (light blue).

round of HDSS prior to the commencement of the roll-out (January-June 2013). Parasitological and entomological surveys of randomly sampled households were conducted during a baseline period of 10 months (Sept 2012-June 2013) and over the roll-out period (Figure 7.3 and Supplementary Figures S7.1 and S7.2). Individual written consent for participation was requested from adults aged ≥18 years at the initial enumeration of the households and prior to collection of blood samples. For persons aged 13-17 years, individual assent alongside written consent of an adult was requested, and for those under 13 years of age written parental consent was solicited. The few people who declined to participate in this study were excluded from the enumeration and all analyses. Consent forms were signed by the recruiter and a witness. Informed verbal consent was provided by heads of household before participation in entomological studies. All participants were free to withdraw at any time without giving a reason. This study was approved by the Ethics Review Committee of the Kenya Medical Research Institute [KEMRI] as NON- SSC PROTOCOL NO. 350.

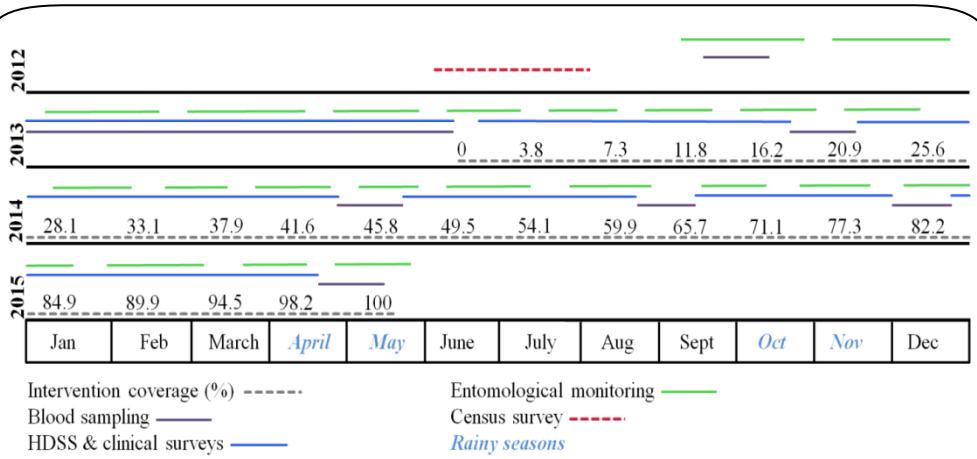

Figure 7.3: Project timeline showing the change in intervention coverage and key sampling activities taking place during each calendar month between 2012 and 2015.

Outcomes

Clinical malaria - The primary outcome was clinical malaria, diagnosed during continuous active HDSS surveillance of all individuals, with one round of household visits before the roll-out started and six further rounds during the two-year roll-out period. All individuals visited were asked about illness during the preceding two weeks. Temperatures were measured using an in-ear thermometer (Braun™ IRT 3020) in those reporting illness. Rapid Diagnostic Test [RDT] (*SD BIOLINE*™ Malaria Ag P.f/Pan *HRP-II*/pLDH) for *Plasmodium* were applied when temperatures ≥ 37.4°C. RDT positives were diagnosed with clinical malaria and provided with appropriate doses of Artemether–Lumefantrine (Coartem) or, in cases of pregnancy, age less than six months or severe symptoms, referred to a local health clinic (Shah *et al.*, 2015).

Malaria prevalence – The proportion of people harbouring *Plasmodium* parasites (prevalence) was recorded in surveys targeting 10% random samples of households (selected with replacement), with two surveys prior to the start of SMoTS roll-out and five more at approximately three-month intervals during roll-out. Each consenting individual in sampled households was tested by RDT and RDT-positives were treated with appropriate doses of Coartem or referred to a local health clinic. Mosquito densities – Entomological surveys were carried out at 6-8 week intervals from September 2012 until study end. 80 households were randomly sampled with replacement from the active HDSS database for each round. Each house was sampled for one night indoors and one night outdoors using a Mosquito Magnet-X® trap (American Biophysics corporation, North Kingstown, RI) baited with the MB5 blend and CO_2 produced by yeast and molasses fermentation (Mweresa *et al.*, 2014).Mosquitoes were sorted morphologically and members of the *Anopheles gambiae* sensu lato complex and *An. funestus* group were then identified to species level using PCR.

Sample size and randomisation

The stepped wedge randomised intervention schedule included the entire population of Rusinga in order to achieve mass coverage (Hiscox *et al*., 2016).

Intra-cluster correlation coefficients, estimated from 15,707 individuals visited during the baseline (pre-intervention) period, are given in Table S7.1. Based on these values, approximating the trial to a parallel Cluster Randomised Trial and assuming no change in the outcomes in the non-intervention arm (Hemming *et al.*, 2011), the trial had an 80% power to show a 23% reduction in clinical malaria over six surveys.

A large number of cluster randomisations was generated, each consisting of a distinct ordering of the 81 clusters. 27 of these randomisations complied with a series of

constraints relating both to statistical power and requirements of the community (which imposed some correlation structure on the orderings). One such randomisation (Hiscox *et al.*, 2012; Silkey *et al*., 2016) was selected in a public draw on the island (Oria *et al.*, 2014) (Figure 7.2). The nature of the intervention made masking of the allocation from participants or field workers impossible.

Statistical methods

The analytical plan finalised in September 2014 specified the inclusion of data of clinical and parasitological surveys and routine monitoring of mosquitoes up to the end of the next month after all SMoTS were installed (Silkey *et al*., 2016).

Intervention status (installation of traps) was classified week by week on an intention to treat basis (i.e., the whole cluster was classified as "intervened" or "not intervened" based on whether installation was completed in that cluster during that week). Clusters were excluded from analysis for weeks when SMoTS were being installed. There was no allowance for faulty solar panels or traps, or for delayed installation.

For the primary outcome of clinical malaria incidence and the secondary outcome of prevalence by RDT, several different effectiveness measures were calculated, in each case defined as:

$$\mathrm{e} = 1 - \frac{p_1}{p_0}$$

where p_1 is the proportion testing positive in the intervention group, and p_0 is the proportion in the comparator group. The primary analysis of protection is the contemporaneous comparison of intervention vs pre-intervention clusters, based on values of p_1 and p_0 computed from the entire roll-out period. Likelihood ratio tests were used for significance testing, using random effects logistic regression to allow for effects of intervention clustering and time period. Comparisons of clinical incidence (or prevalence) in the intervened population (June 2013–June 2014) with baseline (Oct 2012-June 2013) provided further evidence of overall programme impact. Random effects logistic models were again used to allow for intervention clustering. Further random effects models tested effects of individual level correlations in the outcomes, and modifying effects of sex, age LLIN use (Table S7.2), and any factors (among those listed in Table 7.1) that showed substantial imbalances. Akaike's Information Criterion [AIC] was used to compare model fit.

Logistic models were fitted using the R package *lme4*. The delta method (Oehlert, 1992) provided approximate model-based confidence intervals for the ratios p_1/p_0 and hence for each effectiveness measure.

Analogous analyses comparing mosquito densities used random-effects Poisson models, with effectiveness estimated as the ratio of numbers of mosquitoes caught in surveillance traps:

$$\mathrm{e} = 1 - \frac{d_1}{d_0}$$

where d_1 and d_0 are numbers of mosquitoes caught per surveillance trap.

Role of the funding source

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Findings

Data included

The analyses refer to 138 project weeks; the baseline comprised the first 38 project weeks, and the remainder spanned the period of SMoTS installation (June 2013-June 2015) (Figure 7.3). 34,041 distinct enrolled individuals, assigned to 4,847 households, consented to participate over this period (Figure S7.1).

Details of participation in each sample survey are in the Supplementary Appendix.

Comparability of groups

The roll-out resulted in very similar time-at-risk in intervention and pre-intervention arms (Table 7.2), and in similar intensities of entomological sampling in the two arms (Table 7.2). The trial was also well-balanced for most potential confounders. Further details of comparability are in the Supplementary Appendix.

Impact on clinical malaria

The overall incidence of clinical malaria decreased from an average of 0.17 clinical events per person-year of recall (103/15,707 interviews) during the 38-week baseline studies to 0.013 clinical events per person-year during the roll-out (56/113,186 interviews), corresponding to a 92.5% decline (95%CI: 89.6-94.5) (Table 7.2). Most of the decline occurred in the first few weeks of roll-out (Supplementary Appendix Table S7.4). A consequence of this decline in incidence during the baseline period was much lower power to detect a difference between intervened and non-intervened groups than anticipated. Although the contemporaneous comparison of incidence between the two arms indicated a substantial benefit of intervention, with only 23 episodes recorded in clusters with SMoTS and 33 episodes in non-intervened clusters, confidence intervals were broad and this difference was not statistically

Table 7.1: Comparison of potential continuous and discrete confounding factors between individuals at baseline, and individuals in intervened and non-intervened clusters. Data from individuals tested for malaria during prevalence surveys.

Variable	**Average baseline** (±SD) (N=3,164 people)	**Average intervened** (±SD) (N=6,550 people)	**Average not intervened** (±SD) (N=5,813 people)
Persons per sleeping room	2.2 (1.5)	2.2 (1.4)	1.9 (1.4)
LLINs per person (observed during HDSS)	0.6 (0.4)	0.5 (0.3)	0.5 (0.3)
Population density (people per 250 m^2)	12.9 (16)	14.1 (17.4)	14.6 (16.8)
TWI	7.4 (0.5)	7.4 (0.5)	7.3 (0.5)
NDVI	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)
Distance to lake (m)	540 (349.9)	516.9 (335.8)	531.8 (350.1)
	Proportion of population baseline	**Proportion of population intervened**	**Proportion of population not intervened**
Children < 5 years (%)	17.1	14.6	13.6
Children 5-15 years (%)	33.3	33.1	33.6
People > 15 years (%)	49.6	52.3	52.8
Reported ownership of nets (%) (during malaria testing)	72.6	79	61.2

TWI = topographic wetness index, NDVI = normalised difference vegetation index.

significant (adjusted effectiveness: 40.8%, 95% CI: -172.8-87.1, Likelihood Ratio χ^2=0.46, 1 degree of freedom (d.f.), P=0.5 Table 7.2). Correspondingly, the unadjusted comparison of the intervened clusters with baseline gave a highly statistically significant effectiveness of 93.8% (95% CI: 90.2-96.0, Pearson χ^2=306.7, 1 d.f., P<0.0001, Table 7.2) but sparsity of data prevented allowance for cluster and survey effects in this analysis.

Incidence of all reported illness also strongly decreased over time (adjusted effectiveness: 65.2%, 95%CI: 60.6-69.2, Likelihood Ratio χ^2=257.7, 1 degree of freedom, P<0.0001, Table 7.2), and incidence in reported illness in the control clusters compared with baseline also declined comparably (24.8% reduced to 9.1%, Table 7.2), indicating that the reductions in reported illness were not direct effects of the SMoTS intervention.

Impact on malaria prevalence

In contrast to clinical malaria, average prevalence in the intervention period was similar to baseline (Table S7.2). In the non-intervention arm prevalence was higher during much of the intervention period than at baseline, in particular at survey four (around week 48) which was associated with a temporary increase in average mosquito biting intensity (Figure 7.5A, 7.5B). There was no increase in prevalence in intervened areas (Figure 7.4).

Average prevalence in intervened clusters over the entire roll-out period was similar to the baseline prevalence of 23.9% (adjusted effectiveness: 3.7%, 95%CI: -9.5-15.5, Likelihood Ratio χ^2=1, 1 d.f., P=0.6, Table 7.2). There were consequently more data for malaria prevalence during the follow-up period than for clinical malaria.

The contemporaneous comparison of parasite positivity indicated a highly statistically significant effect of SMoTS (effectiveness estimate from random effects model: 29.8%, 95%CI: 20.9-38.0, Likelihood Ratio χ^2=30.6, 1 d.f., P<0.0001). Prevalence was lower in areas with SMoTS compared with non-intervention areas at each time point up to the final survey (by which time, coverage was almost complete). Low

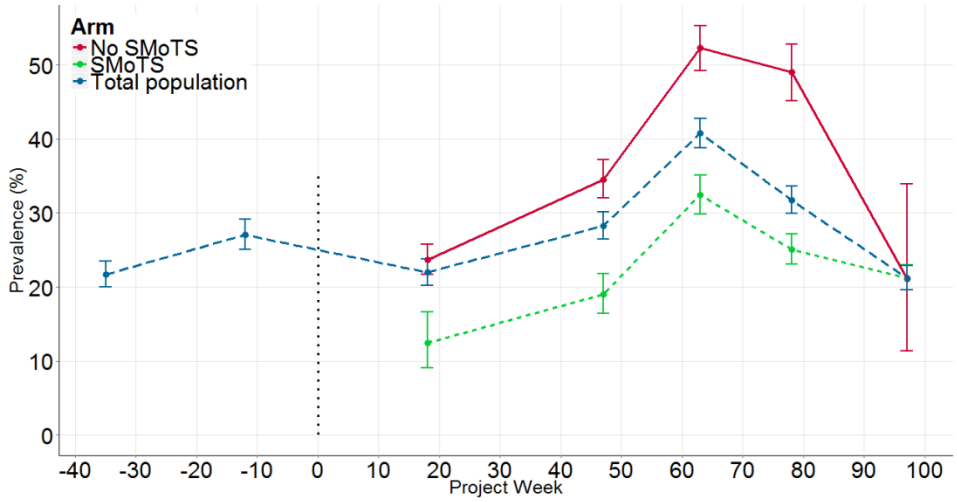

Figure 7.4: Graph showing malaria prevalence during each cross parasitology survey as an average of the whole study population (blue dashed line), of people with SMoTS (green dashed line) and of non-intervened people (solid red line). The dashed vertical line at week 0 indicates the commencement of the SMoTS roll-out. Error bars indicate 95% confidence intervals of the mean. Towards the end of the roll-out the confidence intervals of the non-intervened group become wide as mass coverage is reached and a small number of households are in the non-intervention arm.

prevalence values were measured in the first intervention clusters even when measured after just a few weeks of SMoTS usage (Figure 7.4; Table S7.5A).

Impact on mosquito densities

Overall, 3,528 trap-nights of mosquito monitoring recorded 1,073 female *Anopheles* mosquitoes. *Anopheles funestus* was the most abundant malaria vector during baseline (348/422=82%) with the remainder assigned morphologically to *An. gambiae* sensu lato.

Table 7.3: Intervention effectiveness measures on mosquito densities.

	All *Anopheles*	*An. funestus*	*An. gambiae* s.l .
Clusters with SMoTS			
Mosquitoes caught	212	52	160
Number of trapping nights	1290	1290	1290
Mean number of mosquitoes per trap	0.16	0.04	0.12
Control clusters			
Mosquitoes caught	439	258	181
Number of trapping nights	1370	1370	1370
Mean number of mosquitoes per trap	0.32	0.19	0.13
All clusters at baseline			
Mosquitoes caught	422	348	74
Number of trapping nights	868	868	868
Mean number of mosquitoes per trap	0.48	0.40	0.09
Contemporaneous comparison			
Unadjusted estimate of effectiveness (95% CI)	48.7% (39.7, 56.5)	78.6% (71.4, 84.3)	-6.1% (-16.1, 24.2)
Adjusted* estimate of effectiveness (95% CI)	42.2% (15, 61)	69.2% (29.1, 87.4)	10.8% (-43.5, 44.6)
Comparison of baseline with intervened clusters			
Unadjusted estimate of (95% CI)	66.2% (60.2, 71.2)	89.9% (86.6, 92.5)	-45.5% (-92.6,-10.9)
Adjusted* estimate of effectiveness (95% CI)	72% (59, 81.2)	92.1% (85.8, 95.8)	-18.8% (30, -102.9)

*Adjusted estimates are derived from Poisson models with random effects for the cluster and survey round

Far fewer *An. funestus* were caught in monitoring traps during roll-out than during baseline (Figure 7.5A, Table 7.3). The random-effects models indicated that *An. funestus* densities in the intervened clusters were reduced relative to those at baseline (point estimate 92.1%, 95%CI: 85.8-95.8, Likelihood Ratio χ^2=61.1, 1 d.f., P<0.0001 Table 7.3) with a smaller reduction in the non-intervened arm compared with baseline also observed (adjusted estimate 72.9%, see supplementary information Table S7.5B). The *An. funestus* density was significantly lower in the intervention arm compared with the non-intervention arm (adjusted effectiveness: 69.2%, 95%CI: 29.1-87.4, Likelihood Ratio χ^2=7.6, 1 d.f., P=0.005, Table 7.3). During the roll-out period only 47.6% of the anophelines (310/651) caught were *An. funestus*.

There was a negligible effect on *An. gambiae* s.l. densities in the comparison with baseline (adjusted effectiveness: -18.8%, 95%CI: -102.9-30.0, Likelihood Ratio χ^2=0.4, 1 d.f., P=0.5, Table 7.3) and by contemporaneous comparison (adjusted effectiveness: -6.1%, 95%CI: -16.1-24.2, Likelihood Ratio χ^2=0.2, 1 d.f., P=0.6, Table 7.3). The relative abundance of *An. gambiae* s.s. (15/70 *An. gambiae* s.l. at baseline (21.4%) and 63/311 (20.3%) subsequently) and *An. arabiensis* (78.6% at baseline and 79.7% subsequently) remained constant throughout the study.

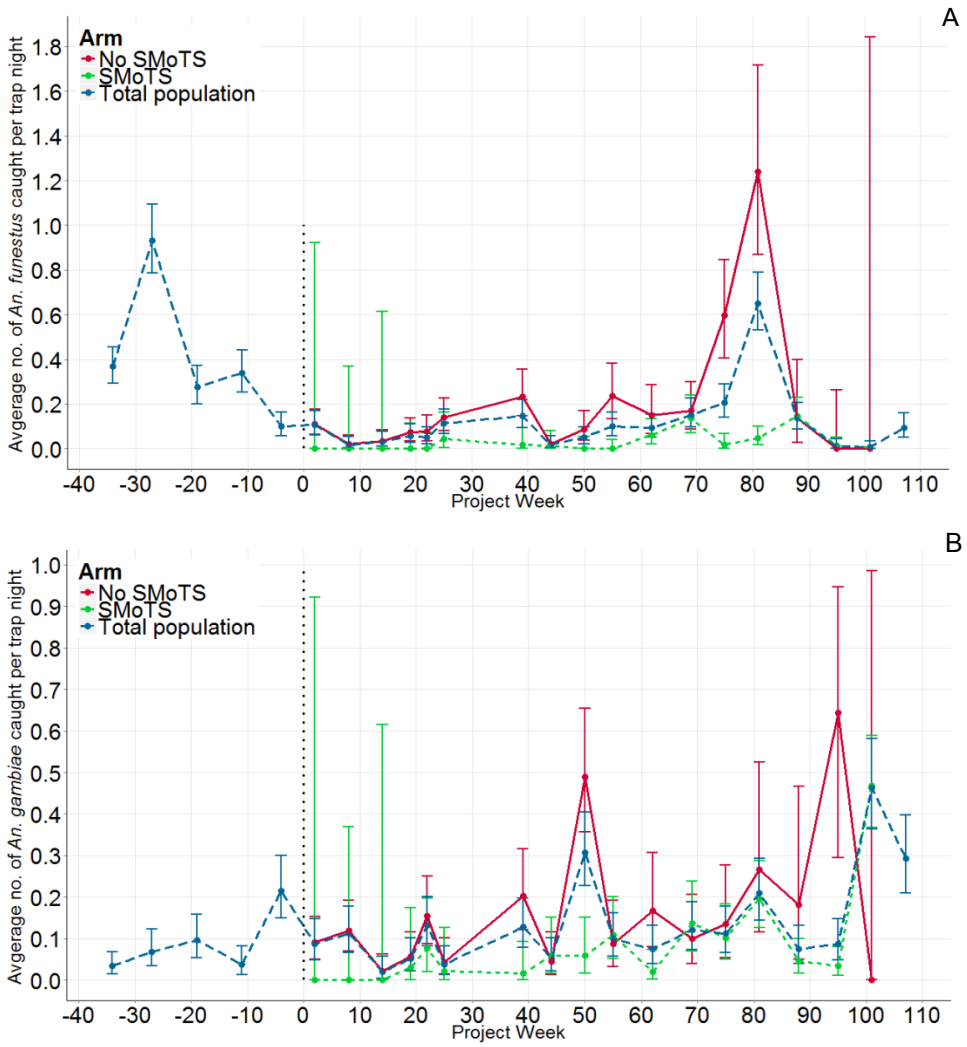

Figure 7.5: Mosquito populations over the course of the study A) Average number of *An. funestus* caught in sentinel traps during each round of entomological surveillance according to the intervention status of the household where sampling took place (blue dashed line indicates all households, green dashed line indicates households with SMoTS, solid red line indicates non-intervened households); B) Average number of *An. gambiae* s.l. represented in the same way as *An. funestus.* For both species mean values for each sampling round are plotted at the mid-way point of the round. Error bars indicate 95% confidence intervals of the mean.

Discussion

In this first trial of mass-mosquito trapping for malaria control the areas with SMoTS had significantly lower malaria prevalence than those without SMoTS. Malaria transmission, especially by *An. funestus*, declined more in intervened than in non-intervened areas. The stepped wedge roll-out design allowed for contemporaneous comparison between intervened and non-intervened clusters during the roll-out and showed sustained transmission reductions in intervened areas despite increased malaria prevalence in the control arm midway through roll-out.

The steep decline in clinical malaria incidence during the first few months is unlikely to be due to the intervention, as this reduction is already seen during the baseline period and even areas very remote from the SMoTS experienced a similar decrease. Moreover, the peak in prevalence in the non-intervened areas recorded during the middle of the intervention phase was not reflected in any resurgence in clinical incidence. Very possibly, there was a general increase in awareness of malaria on the island leading to improvement in treatment seeking and/or LLIN use, leading to the steep decline in clinical incidence. The parallel reduction in *An. funestus* populations observed in the non-intervened arm compared with baseline also corresponds with the reduction in clinical malaria, suggesting that seasonal effects on mosquito populations may also have contributed to the decline in clinical malaria during the first few months.

Attribution of the impact of the intervention on malaria to mass mosquito trapping thus hangs on the contemporaneous comparisons between trial arms. Although the power for the comparison of clinical incidence in intervened versus non-intervened clusters was lower than anticipated, and the efficacy estimate consequently not statistically significant, the point estimate of 41% was consistent with the measured effects on parasite prevalence and on mosquito densities. Together these data indicate that SMoTS introduction may have had a very rapid specific effect locally on malaria, which cumulated only gradually across the island during the roll-out.

The best estimate of effect on prevalence is of an overall reduction of 29.8% (95%CI: 20.9-38); similar in magnitude to the effects observed in insecticide-treated net trials (Hawley *et al.*, 2003; Lengeler, 2009). Untreated malaria infections last on average about eight months (Bretscher *et al.*, 2015) and many of the infections in the SMoTS arm must therefore have pre-existed the installation of the traps, and so could not be averted by the intervention. This implies a considerably larger effect of the SMoTS in averting new infections than in reducing prevalence, consistent with the point estimates of impact on clinical incidence or mosquito densities. The temporal trends in prevalence need interpretation in this context. Very low prevalences were observed

in the intervened clusters during the first survey after the start of roll-out, suggesting that the impact on new infections was rapid.

The reduction in densities of *An. funestus* (contemporaneous comparison of effectiveness 69.2%, 95%CI: 29.1-87.4) provides the strongest evidence that the SMoTS substantially reduced malaria transmission in a highly specific manner. While the *An. funestus* population crashed, *An. gambiae* s.l. (comprising both An*. arabiensis* and *An. gambiae s.s.*) continued to support some residual transmission; this may be ascribed to the more exophilic behaviour of *An. arabiensis*, which was dominant among the two *An. gambiae* s.l. species. This species may have been responsible for the continued transmission of malaria on the island. Continued entomological surveillance alongside maintenance of the traps and replacement of expired lures should indicate whether elimination can be achieved by sustaining the programme. The range of anophelines against which the baits are effective is not yet known, and there is an urgent need to evaluate potential impact in other settings.

In principle, effectiveness of SMoTS can also be incrementally improved, for instance by eave screening of houses to divert more mosquitoes into the traps (Kirby *et al.*, 2009), by improving the baits to capture more *An. arabiensis* and *An. gambiae s.s.* (Okumu *et al.*, 2010b), or through the combination of repellents and attractants in push-pull systems. Simulation modelling is being used to identify both the most promising avenues for continuing the Rusinga programme, and the characteristics of other settings and integrated programmes where OBTs will have most impact. OBTs are likely to be complementary to other novel intervention strategies such as intensified surveillance-response or mass vaccination.

Contributors

WT and WRM developed the study. WT, AH, TH, WRM, TAS, JA and CL designed the study, including analytical plan. AH, RWM, CKM, DM and WT led the study. TH, AH, CKM, PO, NM and AdiP collected data. TH, AH, NM, TAS analysed the data. TH made the figures. TH, AH, TAS and WT wrote the manuscript. All authors read and commented equally on the manuscript.

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The full trial protocol can be accessed in Hiscox et al. [submitted]. The SolarMal project was registered on the Dutch Trial Register (www.trialregister.nl) on 20 June 2012. Registration number NTR 3496.

Chapter 8

General discussion

With more than half of the world at risk of infection and more than 400,000 confirmed deaths each year, infection with the *Plasmodium* parasite transmitted by *Anopheles* mosquitoes is still a major health burden, predominantly in low and middle income countries (WHO, 2015b). By the middle of the 20th century malaria was eliminated or controlled in many parts of the world, but the control methods used were not able to permanently disrupt transmission and eradicate the disease (Snow, 2015). The control efforts were not sufficiently effective and were not applied effectively in many tropical countries, mostly for lack of funds. The health burden was acknowledged, and disruption of transmission by preventing malaria mosquitoes from biting humans using long lasting insecticidal nets [LLIN] and indoor residual spraying [IRS] with insecticides have been the foremost contributors to significant reductions in malaria burden since the year the turn of the millennium (Bhatt *et al.*, 2015; Murray *et al.*, 2012). Additionally, much progress has been made to control the disease through improved diagnosis and effective case management. Following these achievements malaria eradication is back on the table (Alonso *et al.*, 2011c).

However, the goal of malaria eradication and even maintaining the current level of control is under pressure as the current tools are severely threatened (Alonso *et al.*, 2013). Effective drugs to cure malaria are subject to increasing levels of parasite resistance (Ashley *et al.*, 2014). Furthermore, many malarious areas develop into low transmission settings whereby targeting the asymptomatic reservoir may become increasingly important in the attaining local elimination (Bousema *et al.*, 2014). Scientists are therefore urged to develop new effective and more sensitive diagnostic and monitoring tools for detection.

Moreover, vector control tools responsible for the prevention of infections are experiencing decreases in efficacy. Malaria mosquitoes are reported to become resistant to several insecticides used for IRS and on LLINs (Ranson *et al.*, 2011). Besides these physiological changes, in some regions mosquito feeding behaviour is changing due to selection pressure driven by vector control (Reddy *et al.*, 2011). This pressure fuels malaria transmission to occur earlier at the night and more often outdoors (Lwetoijera *et al.*, 2014; Russell *et al.*, 2013). Current malaria vector control in Sub Saharan Africa [SSA] is targeted at mosquitoes which express the typical nocturnal and endophilic feeding behaviour. In the face of malaria eradication, new effective vector control is urgently needed to further reduce malaria transmission (Alonso *et al.*, 2011b; Govella *et al.*, 2012).

This thesis describes the development and the outcomes of the first trial (SolarMal) of the impact on malaria by mass trapping of malaria vectors using an odour-baited mosquito trap [OBT] (Hiscox *et al.*, 2014). The proof of principle study aimed to trap host-seeking malaria mosquitoes to systematically shrink vector populations, disrupt

transmission and subsequently reduce malaria incidence and prevalence. To better understand the process of malaria reduction, the study was conducted on a naturally-isolated geographic area, Rusinga Island, Kenya. The mass trapping of vectors could be a sustainable way to augment present malaria control measures as it acts upon the host-seeking drive of the mosquito, the olfactory sense. The development of a detailed study protocol is described. An appropriate statistical design calibrated for the geography of the study area is presented and two new outcomes measures with respect for spatial contamination effects are proposed. A novel method of data collection and the implementation of a health and demographic surveillance are presented. The geographical heterogeneity of malaria prevalence and risk factors for malaria parasitaemia are studied. Finally the outcomes of mass trapping of vectors on vector populations and malaria prevalence and incidence are reported.

The key conclusion of this thesis is that OBTs are effective in trapping the dominant malaria transmitting vector on Rusinga Island. Transmission of malaria is anticipated to be disrupted as the effect prevalence of malaria in intervened areas was reduced by a magnitude similar to LLINs. It is concluded that the implementation of a stepped-wedge cluster randomized trial design, allowing for contemporaneous comparison between intervened and non-intervened areas, is an appropriate method to capture differences in disease outcomes when considering spill-over effects and universal coverage of the intervention. Furthermore, the adoption of computer tablets and OpenHDS, a digital data collection and management system, can be cost-effective, increase organisational efficiency and improve data quality when monitoring health and demography in low and middle income countries. Lastly, exploring varying risk factors for malaria can aid in strategically implementing malaria control measures.

As the first trial to report on the effect of mass trapping of mosquitoes on malaria, there are various aspects to be considered so that recommendations can be made to further explore the effects and mechanisms underlying such a malaria control intervention. Considering how OBTs can contribute to malaria control can best be illustrated using an epidemiological theoretical framework. The basic original reproductive number [R_0] and the entomologic inoculation rate [EIR] are quantities that can be used to explore whether an intervention may cause an effect on the transmission (Feachem *et al.*, 2009). Malaria mosquitoes are needed to transmit the parasite to another person and it is this transmission that determines whether the transmission level is decreasing or increasing (Kelly-Hope *et al.*, 2009). R_0 is the number of new infections arising from one particular infected individual in an entirely susceptible population and, for malaria, the value of R_0 depends on: a = human biting habit, m = mosquito density relative to humans, b = susceptibility of mosquito to parasite infection, p = daily mosquito survival, n = incubation period of parasite in

mosquito, r = human recovery rate from infection, s = sporozoite rate (proportion of mosquitoes infective) (Chitnis *et al.*, 2008; Dietz, 1993).

$$R_0 = \frac{ma^2bp^n}{-r(\ln p)}$$

The EIR is the number of bites per person per unit time and is obtained by multiplying the sporozoite rate (s) by the number of bites by malaria vectors, the human biting rate (MacDonald, 1957).

$$\mathrm{EIR} = mas$$

R_0 < 1 indicates a non-sustainable level of transmission ultimately resulting in the elimination of the pathogen. The relative number of mosquitoes is one of the most important predictors for whether malaria transmission can be sustained. OBTs can have a direct impact on R_0 by targeting several parts of the equation: the mosquito survival rate and subsequently the mosquito density relative to humans (Okumu *et al.*, 2010a). Also half of the parameters in the EIR equation are targeted when mass trapping mosquitoes effectively.

This thesis suggests that by complementing LLINs and case management, OBTs can have a significant effect on vectors and malaria as prevalence was lower in houses with the intervention compared to those without traps. However, it is not clear how exactly the addition of OBTs impacts mosquito populations and malaria epidemiology. Model-based estimates of R_0 and EIR are simplified theoretical equations that are practical for a broad understanding of malaria epidemiology, but we remain with various unanswered questions regarding the added value of mass trapping with OBTs to current malaria control.

An important hypothesis is that OBTs can aid in targeting the changing dynamics in vector behaviour by targeting outdoor biting and/or early evening biting mosquitoes because they can be positioned outside the house and could operate at whatever times of day are locally appropriate (Okumu *et al.*, 2010a). The selection pressure of current vector control methods on malaria mosquitoes increases the proportion transmission occurring outdoors, but until now no intervention tools are available to target these outdoor biting mosquitoes (Govella *et al.*, 2012).

During our baseline studies in the study area of Rusinga Island, most of the vector population was endophilic, endophagic and chiefly anthropophilic, *An. funestus* (Chapter 7). Surprisingly, few *An. gambiae s.s*. were collected, which species historically was more abundant than *An. funestus* (Bayoh *et al.*, 2010). A large effect

of the intervention was achieved on the population of this mosquito species, yet there is not enough evidence to assert that there was an effect on exophilic and exophagic mosquitoes (*An. arabiensis* (Mwangangi *et al.*, 2013)). Despite the lack of evidence of the impact on exophilic mosquitoes (i.e. *An. arabiensis*), a reduction of 60% in the major malaria vector (*An. funestus*) and 30% in malaria prevalence was achieved.

Prior to this study and after a decade of LLINs and IRS coverage in the study area, the prevalence of malaria halved to a prevalence between 30 and 40% (Olanga *et al.*, 2015). In areas where the effects of LLINs and IRS on malaria subsequently stabilised (WHO, 2015b), we conclude that the introduction of mass trapping using OBTs can further reduce transmission and prevalence. This may suggest that other parts of the mosquito life cycle and the model equations are targeted, reducing transmission where the current intervention tools have reached their maximal effect. Several studies emphasize that due to the development of insecticide resistance, *An. funestus* populations remerge, decreasing the efficacy of LLINs and IRS on indoor transmission (Lwetoijera *et al.*, 2014; McCann *et al.*, 2014). OBTs may assist in overcoming this concern, however, further research would be necessary to quantify how this intervention contributes to the reduction of transmission inside and outside of the residential extend.

In this thesis it is concluded that a large reduction in malaria vector densities must have led to the measured reduction in prevalence. Preliminary results indicate a dramatic decrease in the entomological inoculation rate (A. Hiscox, personal communication), confirming that the drop in malaria vector abundance and prevalence are most likely due to the intervention.

However, even though the SolarMal project monitored the parasitological and entomological outcomes very comprehensively and longitudinally, the results on the incidence of confirmed clinical malaria were ambiguous. Few clinical cases were detected in total, and during the baseline period the number of clinical cases already dropped toward near zero (Chapter 7). An explanation for this could lie in the fact that the epidemiology of malaria and vector composition in western Kenya has changed due to the effects of IRS and LLINs, leading to a strong decline in the *An. gambiae s.s*. population (Zhou *et al.*, 2011). A substantial prevalence may still be present, mostly as asymptomatic cases, but the number of individuals with clinical symptoms tends to drop as the transmission pressure decreases (Cotter *et al.*, 2013). Nevertheless, the asymptomatic carriers are often harbouring gametocytes and infectious (Bousema *et al.*, 2014), causing a low but continuous level of transmission. That is explained by the levels of malaria prevalence, as observed in this study. From the asymptomatic reservoir people will seek out treatment when they are sick, but will often be asymptomatic when visited at home (Sturrock *et al.*, 2013). The monitoring of

clinical malaria in our health and demographic surveillance system relied on these house visits, but did not consider the information collected by the local clinics. Making sure that sound data is obtained from these clinics requires an intense effort, but may have improved our estimates of clinical incidence (Zhou *et al.*, 2015). Another explanation for the low number of detected clinical events may lie in how strict the criteria were. This study required reported malaria symptoms accompanied by a body temperature of 37.4 or higher before testing for malaria with a RDT. Finally, the almost daily presence of project staff on the island, accompanied by regular malaria surveillance and house visits, may have induced a "Hawthorne effect", leading to unintended health seeking behaviour and LLIN use, resulting in non-specific but effective reductions in malaria incidence.

Notwithstanding the issue regarding the surveillance of the incidence of malaria, our HDSS has proven to be a strong instrument to monitor the outcomes of such a large field study. The quality and management of our data collection has been based on a completely digitized system (Chapter 3 and 5). Our HDSS is one of the first to operate using computer tablets to collect data and incorporates a near real time database with integrated quality checks. The data management platform used, OpenHDS, has been adopted to be the system of choice for all HDSSs by the overarching HDSS organization INDEPTH due to its cost effectiveness and organizational efficiency. Nevertheless, the piloting of OpenHDS yielded many questions and issues that should be addressed; mainly the empirical proof of its advantages over a paper-based method is still lacking. Some of the general key challenges of such HDSSs are the sharing of data (Sankoh *et al.*, 2011), the harmonization and generalizability of health data collection methods (Sankoh *et al.*, 2013) and the logistical management (Sankoh *et al.*, 2005). Ultimately, it is of great importance that HDSSs are further developed to accurately assess (malaria) health interventions, for their quality may be of comparable importance to the contribution of state of the art medicinal and analytical aspects.

These analytical aspects brought together into an experimental design, were most significant for SolarMal to successfully measure any possible difference. The use of a stepped wedge cluster-randomised trial [SWCRT] subtly incorporates the merits of a cluster randomised trial while allowing the complete study area to be covered by the intervention (Chapter 4). The design is appropriate to assess the achievability of local elimination of a vector borne disease. Estimates of the effects of incomplete coverage may be made by quantifying the degree of contamination of one trial arm to another. Simulations of possible experimental designs of this trial showed how generic transmission models can be used to for purposes of randomization strategies and optimization of cluster size. The use of a SWCRT as demonstrated here may be applied to a variety of infectious diseases transmitted via environmental reservoirs or

via arthropod vectors. After carrying out the most optimal experimental design, there were some issues important to mention for follow up trials. First of all, the SolarMal trial was designed to test the effect of OBTs on the incidence of malaria. To our surprise, this outcome returned fewer cases than expected and cases were too few to carry out a proper analysis. Preparing for an alternative outcome measure, should the primary parameter be unmeasurable, needs to be considered in a future study design. Additionally, when creating clusters for the experimental design, the arbitrary geographical borders do not account for social borders from for instance villages (Chapter 4). We found out that this can lead to some tension within the study population. Although we accounted for this in a later stage, it would be recommendable to consider this issue early on in the development of the SWCRT.

There are other challenges directly relating to the intervention tool used for this trial, the odour-baited trap. The number of mosquitoes relative to humans and the mosquito survival rate depend on several aspects; in the first case the relative attractiveness of the OBT compared to a human (Okumu *et al.*, 2010a; Okumu *et al.*, 2010c). The blend [MB5] of attractants used in this intervention (Mukabana *et al.*, 2012b; Verhulst *et al.*, 2009) was reported to be more attractive than a human odour (Okumu *et al.*, 2010b), however, the same level of efficacy is yet to be confirmed in field settings. Besides, there is some uncertainty about whether mosquitoes tend to directly prefer the trap over a human. Investigating to what degree mosquitoes are trapped by an OBT after being diverted from a human protected by a LLIN would reveal more about the efficacy of the OBT. Furthermore, research should be conducted into the relative attractiveness of the traps compared to a residence with several individuals. This natural source of human odour could possibly also assist in future developments of OBTs (Matowo *et al.*, 2013).

The attractiveness of an OBT does not depend on the blend alone as CO_2 has traditionally been considered essential in the host-seeking behaviour of malaria vectors (Takken *et al.*, 1999). Due to logistical constraints it would have been too labour intensive and costly to continuously provide all traps on the island with a natural CO_2 source like fermented yeast and molasses or gas cylinders with CO_2 .(Mweresa *et al.*, 2014) Therefore a pragmatic replacement was used, 2-butanone. Even though the efficacy of this CO_2 replacement is not as high as a natural CO_2 source, there is evidence that it its efficacy is substantial (Mburu, 2013; van Loon *et al.*, 2015). Improvement of such a CO_2 replacement should increase the relative attractiveness of the odour blend and with that the effectiveness of OBTs. Additionally, the OBT with the MB5 blend and 2-butanone were optimized and tested for only one species of malaria transmitting mosquitoes, *An. gambiae s.s.*. This thesis suggests that the effect of OBTs on *An. gambiae s.l.* on Rusinga, was insignificant (presumably because this comprised mainly *An. arabiensis*), whereas the most

prominent vector species on the Island, *An. funestus*, was critically affected by the intervention. The attractiveness of OBTs as intervention tool thus depends strongly on the vector species, and there is an urgent need to develop blends that are compatible with other major malaria transmitting mosquito species. Finally, there are indications that improvement of the physical design of the Suna trap can enhance trap catches by increasing its radius of effect and by improving its air flow mechanisms to prevent mosquitoes sensing the sucking power.

Putting this trial in a wider context evokes the question to what extent the addition of OBTs can contribute to the currently available tools for malaria control. Studies are being carried out to investigate the combined effect of IRS and LLINs (Okumu *et al.*, 2011). Although both LLINs and IRS target malaria mosquitoes within the home, they have shown significant effects when used as a stand-alone tool. However, it becomes clear that these two major interventions against malaria do not yield an extra protective effect when applied together (Pinder *et al.*, 2015). As OBTs have not been applied as a malaria control tool until the current trial, further investigation would be essential to elucidate what the relationships between OBTs and the existing malaria control interventions are. In the current trial on Rusinga LLINs were present in most households, and OBTs should be considered as an additional intervention tool. The study was, however, not designed to investigate the impact of OBTs in addition to that of LLINs.

Recently, the concept of a push-pull strategy has been studied in a field setting (Menger *et al.*, 2014b). This new research looks at the protective effect of “pushing” mosquitoes away from human occupied houses in combination with “pulling” or trapping them by means of OBTs (Menger *et al.*, 2015). The push is based on reducing mosquito house entry by screening the eaves between the walls and the roof with netting containing spatial repellents. In line with this concept, another study has revealed that screened eaves provided with air tubes covered in insecticides can act as an effective vector control method (Knols, 2015). The effectiveness of OBTs as control tool may complement and be even synergistic with these other existing or novel vector control measures.

Ultimately the question arises whether it would be possible to eliminate malaria by adding OBTs to the LLINs and case management. Elimination was the goal of SolarMal, and although the results point toward a partial disruption of transmission, substantial malaria prevalence is still present. Preliminary evidence of follow up surveys carries out after Island wide coverage indicate a rapidly decreasing malaria prevalence (W. Takken, personal communication). However, considering the persistent nature of the asymptomatic reservoir, it may not be feasible to attain elimination with only OBTs and the existing national control measures. A mass drug

administration may target most of the residual cases. Conversely, if due to the asymptomatic reservoir and or imported malaria cases elimination with OBTs in areas in SSA is not feasible, reduction to low transmission and hypo-endemicity may be possible. How subsequently the epidemiology of malaria would be affected by up-scaling of OBTs is an interesting topic of discussion. Selection pressure may even further change the mosquito populations to be essentially outdoor biting, further from the residential extend and during the day. It could also be plausible that transmission moves to hot spots of unprotected people. Mathematical models of malaria may further explore the effect of OBTs on transmission. Predictions of such models are of great importance; so that program managers can take into account what issues may arise after implementation.

More research must be conducted to ascertain the efficacy of OBTs alone as well as in combination with other malaria control tools. But not only should research be expanded to investigate variations within this spectrum, much value would lie in piloting similar field studies to evaluate the efficacy of OBTs in different settings. When transmission intensity is dropping continuously due to the interception of host-seeking mosquitoes by malaria control and potentially odour-baited traps, studying the heterogeneity of malaria epidemiology becomes more important (Snow, 2015). Malaria vectors, species of malaria, age categories at risk, climatological and environmental conditions are some of the important factors behind the complexity of local malaria epidemiology (Beck-Johnson *et al.*, 2013; Bousema *et al.*, 2012; Walker *et al.*, 2013). Over the last few years much emphasis has been put on the geographical distribution of malaria and its drivers. It becomes clearer that a one size fits all strategy is not enough to eliminate malaria from all these diverse epidemiological settings (Alonso *et al.*, 2011c). Carefully studying the local geographical distribution of the factors that play a role in malaria transmission may aid in deploying successful combinations of targeted interventions (Chapter 6). For instance, poor communities may be helped by different strategies than are being used in the somewhat richer communities; urban areas will need different approaches than rural regions; and high transmission settings may require another strategy than low transmission settings (Alonso *et al.*, 2013). In the SolarMal trial, all households received the intervention, but in future follow up studies a more cost-effective approach could lie in identifying areas where such vector control will have the largest impact (Woolhouse *et al.*, 1997).

These tailor made malaria control schemes involve detailed information about the area in question. Strategies to trial and implement novel malaria control methods require full understanding of and good communication with the population in such an area (Tindana *et al.*, 2007). The study described in this thesis is an example of a successful trial of a malaria control where community engagement was an essential

aspect (Oria *et al.*, 2014). Traps were provided to families in households who were then given responsibility and ownership over them. However, in contrast with LLINs, a complementary system to power the trap was needed. In each household a solar panel was installed linked to a battery which in turn provided electricity for the trap. The system was also equipped with two electric light bulbs and an outlet for charging mobile phones. Education and information about the project, the solar-powered mosquito trapping system [SMoTS], and the design of the experiment were important aspects for the community to cooperate with, understand and eventually to accept the trial (Oria *et al.*, 2015). In collaboration with representatives of the study site (key persons of stakeholder groups united into a community advisory board) the deployment of the trial was discussed and feedback gained from the community. In this way the community was comprehensively involved in the implementation of the project. Suggestions, ideas and interests of the population were communicated, and conversely, they were continuously informed about the ongoing work. Engagement of the community and a bottom-up approach in health promotion is generally understood to be an important aspect to create a platform to increase awareness about how the disease affects the community and how one can actively think of and create ideas about how to get rid of malaria (Tindana *et al.*, 2007; Whittaker *et al.*, 2015).

Finally, besides emphasizing the significance of community engagement for the successful implementation of malaria control, I want to further stress the importance of understanding the features and construction of such local environments. Primarily, preventable and curable diseases like malaria can only exist in low and middle income countries (Fosu *et al.*, 2007; Worrall *et al.*, 2005). The general socioeconomic state of such countries often prevents people from obtaining access to basic needs like health care, appropriate nutrition, education and good housing conditions (Owens, 2015; Teklehaimanot *et al.*, 2008). Endemic infectious diseases with a high morbidity are characteristics for an underprivileged situation (Deaton, 2014). Many billions of dollars are invested each year into the research and development of health systems and interventions, but despite acknowledging the situation, coordinated efforts to target the overlapping health goals are unexplored or unfruitful (Blas, 2013). Nevertheless, integrated vector management is a good example of an initiative that strives to involve common goals and resources to develop sustainable vector control (Beier *et al.*, 2008; WHO, 2011). I reason that this way of thinking could be expanded to not only bearing in mind developments in vector control, or even only considering the general discipline of health, but to ensure cooperation of all parts of society that are in need of development. A more holistic framework led by progressive policy makers may take to heart the socioeconomic developments in society (Utzinger *et al.*, 2013). At a small scale the SolarMal trial managed to achieve such an approach. Over 25,000 individuals were provided with a novel malaria control tool, but simultaneously, they were provided with sustainable energy from solar panels that

also enabled them to use electricity for other purposes (i.e. electric LED lights and phone charging). Most importantly, the provision of LED lights allows people to read and see at night without using polluting kerosene lamps. The introduction of mobile phone chargers may have empowered people to have better communication and access to information. In conclusion, multisectoral approaches, community involvement and transdisciplinary research are key notions for a more equal, sustainable, healthy and effective development of low and middle income countries. To beat the challenges in malaria control of this time, the combining of knowledge regarding the mosquito life cycle, the epidemiology of malaria and societal areas, are key in developing robust and environmentally sustainable interventions that are embraced and sustained by the people affected.

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Summary

The parasites belonging to the genus P*lasmodium* are the cause of the second deadliest infectious disease in the world, malaria. Sub Saharan Africa harbours more than 90% of malaria attributable mortality and morbidity, and most deaths occur in children under 18 years old. Malaria is transmitted to humans by a bite of a P*lasmodium* infected arthropod vector from the genus *Anopheles*. Halfway the 20th century malaria was successfully eliminated from most developed countries, nonetheless in the third world effective control remains a laborious challenge. Intensive efforts undertaken to control and eventually eradicate malaria during the past decade have led to substantial reductions in morbidity and mortality. Conversely, scientists became increasingly aware that with the current preventative and curative tools against malaria successful eradication seems unlikely. Not only do current tools not suffice to attain that goal, their efficacy to control malaria as it is, maybe severely threatened. Proper treatment and diagnosis are becoming increasingly less effective because of the adaptive nature of the parasite. Parasites get resistance against drugs and carriers are more often found to have subclinical infections. Likewise prevention of malaria, by vector control, becomes less effective. Malaria vectors become resistant to insecticides and transmission patterns are shifting away from where preventive measures are functional: outside and during the day. It this gap where the SolarMal project experimented with a novel malaria vector control tool, complimentary to existing malaria control methods: odour-baited mosquito traps that mimic human beings to lure and kill mosquitoes to eventually reduce malaria. The ultimate aim of this thesis was to seek proof of principle of the effect of mass trapping of malaria vectors on malaria and mosquito densities by rolling out over 4000 odour-baited mosquito traps at household level on Rusinga Island, Kenya.

Chapter 2 is a study protocol of the SolarMal project and provides a general understanding of how the objectives of the project are translated into a research design. The study comprises of a medical, an entomological and a sociological discipline. A multidisciplinary strategy is presented in which the intervention is explained. Experimental designs of all disciplines are introduced including time frames, participant eligibility, and randomisation. Furthermore, a general overview of the data collected and how it is evaluated and analysed using health and demographic surveillance and monitoring is provided.

In chapter 3 a novel data collection and management platform is presented. The health and demographic surveillance as well as other disciplines in the project are an example of one of the first fully digital data collection systems in a low and middle income country. The development of digital questionnaires and the conducting of these by means of Open Data Kit software enabled the project to efficiently collect data. All residential structures were documented by GPS, and data of individuals attached. Converting the geo-located data to a geodatabase and displayed with

Google Earth mobile made navigating from house to house an easy task. By daily uploading of data to the server at the project campus, scientists have access to a near real time database. Once uploaded to the server, data is transferred to the OpenHDS database in which the demography of the study population is updated accordingly. Data quality was further increased by a tool that looked for inconsistencies.

In chapter 4 we explore what experimental design would fit the SolarMal project best. A stepped wedge cluster-randomized trial [SWCRT] design was chosen to make sure that the whole area would cross over from the control to the intervention arm over a period of two years. As elimination was the goal, universal coverage was required. Subsequently, strategies for randomization and crossover of clusters that could measure a possible intervention effect best were simulated with a generic model of disease transmission. Considering sufficient numbers and sizes of clusters a hierarchical SWCRT would best measure a possible effect of OBTs on Rusinga Island. Special care was given to quantifying spill over effects into the control arm. Finally, two new measures of intervention effectiveness are proposed.

Chapter 5 reports on the outcomes of the health and demographic surveillance system on Rusinga Island. Running an HDSS is a thorough but complex method to monitor intervention effects in an area where health surveillance is minimal. As part of the overarching HDSS institution, INDEPTH, data collection methods and reporting are harmonious with many other HDSSs around the world. Demographic parameters are calculated and the HDSS practices are described.

Chapter 6 uses the baseline cross sectional prevalence surveys to elucidate how the epidemiology of malaria on Rusinga Island. Firstly, the malaria distribution and hot spots are identified. Consequently, a standard epidemiological model and a geographically weighted regression are compared, and used to identify risk factors for malaria. The latter model, taking into account non-stationarity, performs better and is able to produce geographically varying risk factors. The strength of the relationship of risk factors for malaria are heterogeneous over the whole island, and for instance social economic status and occupation are strong predictors of malaria in some areas but less in other areas. Considering these risk factor distributions can aid in guiding the implementation of malaria intervention methods.

Chapter 7 presents the main outcomes of the SolarMal project. The impact of OBTs on the prevalence of malaria is pronounced in the contemporaneous comparison between the intervened and the intervened arm. Comparison of baseline data with the intervened clusters does not yield significant effects. A strong decline in cases of clinical malaria was observed starting already in the baseline period, and therefore we

cannot attribute this decline to the intervention. Effects on the most prominent malaria vector were large, whereas other vectors did not suffer under the intervention.

Chapter 8 is a general discussion of the work provided. The most important implications of the thesis are discussed underscoring the societal and scientific relevance, and putting the research in a wider perspective. Unaddressed issues are raised and recommendations for further research are provided.

Appendices

Supplementary material chapter 4

Table S4.1: Power at rollout week 60 (simulation week 100) for the hierarchical design

Simulated effectiveness: $\hat{e}_i = 30\%$, significance level $a = 0.1\%$							
r	$\overline{y_r}(0)$	$\hat{e}_1(t)$	$\hat{e}_2(t)$	$\hat{e}_3(t)$	$\hat{e}_4(t)$	$\hat{e}_5(t)$	$\hat{e}_6(t)$
0.5	0.1	1	0.94	1	0.98	0.89	0.52
0.5	0.2	1	0.93	1	0.99	0.9	0.52
0.5	0.5	0.99	0.8	1	0.97	0.83	0.4
0.5	0.8	0.95	0.41	0.99	0.84	0.58	0.18
1	0.1	1	0.99	1	0.8	0.8	0.66
1	0.2	1	0.98	1	0.84	0.73	0.58
1	0.5	0.99	0.95	1	0.79	0.63	0.45
1	0.8	0.91	0.66	0.99	0.5	0.44	0.29
1.5	0.1	1	0.99	1	0.54	0.94	0.88
1.5	0.2	0.99	0.99	1	0.54	0.79	0.74
1.5	0.5	0.98	0.97	1	0.45	0.56	0.48
1.5	0.8	0.88	0.78	0.99	0.25	0.41	0.36
Simulated effectiveness: $\hat{e}_i = 80\%$, $a = 0.1\%$							
r	$\overline{y_r}(0)$	$\hat{e}_1(t)$	$\hat{e}_2(t)$	$\hat{e}_3(t)$	$\hat{e}_4(t)$	$\hat{e}_5(t)$	$\hat{e}_6(t)$
0.5	0.1	1	0.99	1	1	1	0.82
0.5	0.2	1	0.99	1	1	1	0.84
0.5	0.5	1	0.98	1	1	1	0.81
0.5	0.8	1	0.91	1	1	1	0.67
1	0.1	1	1	1	0.99	1	0.92
1	0.2	1	1	1	1	1	0.87
1	0.5	1	1	1	1	0.99	0.8
1	0.8	1	0.99	1	1	0.97	0.72
1.5	0.1	1	1	1	0.86	1	1
1.5	0.2	1	1	1	0.93	1	0.99
1.5	0.5	1	1	1	0.97	0.99	0.87
1.5	0.8	1	0.99	1	0.97	0.94	0.77

Table S4.2: Power at rollout week 60 (simulation week 100) for the oil drop design.

Simulated effectiveness: $\hat{e}_i = 30\%$, significance level $a = 0.1\%$							
r	$\overline{y_r}(0)$	$\hat{e}_1(t)$	$\hat{e}_2(t)$	$\hat{e}_3(t)$	$\hat{e}_4(t)$	$\hat{e}_5(t)$	$\hat{e}_6(t)$
0.5	0.1	1	0.90	1	0.99	0.93	0.53
0.5	0.2	1	0.89	1	0.99	0.94	0.54
0.5	0.5	0.99	0.72	1	0.98	0.88	0.41
0.5	0.8	0.95	0.37	1	0.86	0.64	0.18
1	0.1	1	0.97	1	0.91	0.84	0.64
1	0.2	1	0.97	1	0.93	0.82	0.59
1	0.5	0.99	0.92	1	0.88	0.74	0.48
1	0.8	0.93	0.6	0.99	0.6	0.52	0.28
1.5	0.1	1	0.98	1	0.75	0.84	0.63
1.5	0.2	1	0.98	1	0.77	0.82	0.61
1.5	0.5	0.99	0.95	1	0.69	0.76	0.51
1.5	0.8	0.91	0.71	0.99	0.41	0.52	0.31
Simulated effectiveness: $\hat{e}_i = 80\%$, $a = 0.1\%$							
r	$\overline{y_r}(0)$	$\hat{e}_1(t)$	$\hat{e}_2(t)$	$\hat{e}_3(t)$	$\hat{e}_4(t)$	$\hat{e}_5(t)$	$\hat{e}_6(t)$
0.5	0.1	1	0.98	1	1	1	0.84
0.5	0.2	1	0.98	1	1	1	0.87
0.5	0.5	1	0.97	1	1	1	0.84
0.5	0.8	1	0.86	1	1	1	0.68
1	0.1	1	1	1	0.99	1	0.88
1	0.2	1	1	1	1	1	0.87
1	0.5	1	0.99	1	1	0.99	0.84
1	0.8	1	0.97	1	1	0.99	0.75
1.5	0.1	1	1	1	0.94	1	0.88
1.5	0.2	1	1	1	0.97	1	0.88
1.5	0.5	1	1	1	0.99	1	0.9
1.5	0.8	1	0.99	1	0.98	0.99	0.82

Table S4.3: Power at rollout week 60 (simulation week 100) for the random design

Simulated effectiveness: $\hat{e}_i = 30\%$, significance level $a = 0.1\%$							
r	$\overline{y_r}(0)$	$\hat{e}_1(t)$	$\hat{e}_2(t)$	$\hat{e}_3(t)$	$\hat{e}_4(t)$	$\hat{e}_5(t)$	$\hat{e}_6(t)$
0.5	0.1	1	0.93	1	0.99	0.90	0.51
0.5	0.2	1	0.93	1	0.99	0.9	0.52
0.5	0.5	0.99	0.79	1	0.98	0.83	0.41
0.5	0.8	0.95	0.41	1	0.85	0.59	0.18
0	0.1	1	0.99	1	0.83	0.82	0.67
0	0.2	1	0.98	1	0.87	0.74	0.56
0	0.5	0.99	0.95	1	0.81	0.64	0.45
0	0.8	0.92	0.66	0.99	0.53	0.45	0.29
0.5	0.1	1	0.99	1	0.58	0.95	0.91
0.5	0.2	1	0.99	1	0.59	0.86	0.78
0.5	0.5	0.99	0.97	1	0.5	0.62	0.51
0.5	0.8	0.9	0.78	0.99	0.28	0.45	0.37
Simulated effectiveness: $\hat{e}_i = 80\%$, $a = 0.1\%$							
r	$\overline{y_r}(0)$	$\hat{e}_1(t)$	$\hat{e}_2(t)$	$\hat{e}_3(t)$	$\hat{e}_4(t)$	$\hat{e}_5(t)$	$\hat{e}_6(t)$
0.5	0.1	1	0.99	1	1	1	0.82
0.5	0.2	1	0.99	1	1	1	0.84
0.5	0.5	1	0.98	1	1	1	0.81
0.5	0.8	1	0.91	1	1	1	0.67
0	0.1	1	1	1	0.99	1	0.92
0	0.2	1	1	1	1	1	0.87
0	0.5	1	1	1	1	0.99	0.8
0	0.8	1	0.99	1	1	0.97	0.72
0.5	0.1	1	1	1	0.86	1	1
0.5	0.2	1	1	1	0.93	1	0.99
0.5	0.5	1	1	1	0.97	0.99	0.87
0.5	0.8	1	0.99	1	0.97	0.94	0.77

Table S4.4: Median effectiveness measures and 95% confidence interval widths for the hierarchical design, summarized over 80 replicates and 10 geographies

						95% CI width						95% CI width		
r	E_s	$\overline{y_r}(0)$	$\hat{e}_1(t)$	$\hat{e}_2(t)$	$\hat{e}_3(t)$	$\hat{e}_1(t)$	$\hat{e}_2(t)$	$\hat{e}_3(t)$	$\hat{e}_4(t)$	$\hat{e}_5(t)$	$\hat{e}_6(t)$	$\hat{e}_4(t)$	$\hat{e}_5(t)$	$\hat{e}_6(t)$
0.5	0.3	0.1	0.35	0.08	0.14	0.31	0.23	0.2	0.3	0.32	0.12	0.36	0.38	0.43
0.5	0.3	0.2	0.33	0.06	0.13	0.21	0.15	0.13	0.28	0.31	0.11	0.24	0.25	0.28
0.5	0.3	0.5	0.25	0.03	0.09	0.12	0.07	0.07	0.22	0.24	0.08	0.13	0.13	0.14
0.5	0.3	0.8	0.15	0.02	0.05	0.07	0.03	0.04	0.13	0.15	0.04	0.07	0.07	0.07
0.5	0.8	0.1	0.74	0.14	0.28	0.2	0.23	0.21	0.7	0.72	0.29	0.23	0.22	0.37
0.5	0.8	0.2	0.72	0.12	0.27	0.15	0.15	0.15	0.68	0.71	0.28	0.17	0.16	0.26
0.5	0.8	0.5	0.66	0.08	0.23	0.12	0.08	0.11	0.63	0.66	0.22	0.13	0.12	0.14
0.5	0.8	0.8	0.55	0.05	0.17	0.11	0.04	0.09	0.53	0.55	0.14	0.11	0.11	0.08
0	0.3	0.1	0.23	0.09	0.12	0.32	0.23	0.21	0.16	0.21	0.1	0.37	0.46	0.44
0	0.3	0.2	0.21	0.08	0.11	0.22	0.15	0.13	0.14	0.2	0.09	0.25	0.31	0.29
0	0.3	0.5	0.16	0.05	0.08	0.12	0.07	0.07	0.11	0.16	0.07	0.14	0.16	0.14
0	0.3	0.8	0.09	0.03	0.04	0.07	0.03	0.03	0.06	0.09	0.04	0.07	0.09	0.07
0	0.8	0.1	0.54	0.21	0.29	0.26	0.23	0.21	0.42	0.52	0.25	0.35	0.34	0.39
0	0.8	0.2	0.52	0.19	0.27	0.2	0.16	0.16	0.4	0.5	0.23	0.26	0.25	0.26
0	0.8	0.5	0.44	0.15	0.22	0.15	0.1	0.12	0.34	0.43	0.19	0.18	0.17	0.14
0	0.8	0.8	0.31	0.09	0.14	0.12	0.06	0.08	0.24	0.31	0.11	0.13	0.13	0.08
0.5	0.3	0.1	0.17	0.1	0.12	0.33	0.23	0.21	0.07	0.15	0.09	0.39	0.78	0.77
0.5	0.3	0.2	0.16	0.09	0.11	0.22	0.15	0.14	0.07	0.14	0.09	0.26	0.51	0.5
0.5	0.3	0.5	0.12	0.07	0.08	0.12	0.07	0.07	0.05	0.11	0.07	0.14	0.25	0.24
0.5	0.3	0.8	0.06	0.03	0.04	0.06	0.04	0.03	0.03	0.06	0.04	0.07	0.13	0.12
0.5	0.8	0.1	0.41	0.25	0.29	0.3	0.23	0.22	0.22	0.39	0.24	0.42	0.61	0.66
0.5	0.8	0.2	0.4	0.24	0.28	0.23	0.17	0.17	0.2	0.37	0.23	0.3	0.42	0.44
0.5	0.8	0.5	0.32	0.18	0.22	0.16	0.11	0.12	0.17	0.31	0.18	0.19	0.25	0.23
0.5	0.8	0.8	0.2	0.11	0.13	0.12	0.07	0.08	0.11	0.2	0.11	0.12	0.16	0.13

Table S4.5: Bias defined as the difference between median estimates and median $\hat{e}_i$, hierarchical design, summarized over 80 replicates and 10 geographies

r	E_s	$\overline{y_r}(0)$	Bias $\hat{e}_2(t)$	Bias $\hat{e}_3(t)$	Bias $\hat{e}_4(t)$	Bias $\hat{e}_5(t)$	Bias $\hat{e}_6(t)$
0.5	0.3	0.1	0.28	0.21	0.05	0.03	0.24
0.5	0.3	0.2	0.26	0.2	0.05	0.02	0.22
0.5	0.3	0.5	0.22	0.16	0.03	0.01	0.17
0.5	0.3	0.8	0.13	0.1	0.01	0	0.1
0.5	0.8	0.1	0.6	0.45	0.04	0.01	0.45
0.5	0.8	0.2	0.6	0.45	0.04	0.01	0.45
0.5	0.8	0.5	0.58	0.44	0.03	0.01	0.44
0.5	0.8	0.8	0.5	0.38	0.02	0	0.41
1	0.3	0.1	0.14	0.11	0.08	0.02	0.14
1	0.3	0.2	0.13	0.1	0.07	0.01	0.12
1	0.3	0.5	0.11	0.08	0.05	0.01	0.09
1	0.3	0.8	0.06	0.05	0.03	0	0.05
1	0.8	0.1	0.33	0.25	0.12	0.02	0.29
1	0.8	0.2	0.32	0.24	0.12	0.02	0.28
1	0.8	0.5	0.29	0.22	0.1	0.01	0.26
1	0.8	0.8	0.22	0.17	0.07	0	0.2
1.5	0.3	0.1	0.07	0.05	0.1	0.02	0.08
1.5	0.3	0.2	0.06	0.05	0.09	0.02	0.07
1.5	0.3	0.5	0.05	0.04	0.06	0.01	0.05
1.5	0.3	0.8	0.03	0.02	0.03	0	0.03
1.5	0.8	0.1	0.16	0.12	0.2	0.03	0.17
1.5	0.8	0.2	0.16	0.12	0.19	0.03	0.17
1.5	0.8	0.5	0.14	0.1	0.15	0.01	0.13
1.5	0.8	0.8	0.09	0.07	0.1	0	0.09

Table S4.6: Median effectiveness measures and 95% confidence interval widths for the oil drop design, summarized over 80 replicates and 10 geographies

						95% CI width						95% CI width		
r	E_s	$\overline{y_r}(0)$	$\hat{e}_1(t)$	$\hat{e}_2(t)$	$\hat{e}_3(t)$	$\hat{e}_1(t)$	$\hat{e}_2(t)$	$\hat{e}_3(t)$	$\hat{e}_4(t)$	$\hat{e}_5(t)$	$\hat{e}_6(t)$	$\hat{e}_4(t)$	$\hat{e}_5(t)$	$\hat{e}_6(t)$
0.5	0.3	0.1	0.36	0.07	0.14	0.31	0.23	0.2	0.31	0.34	0.12	0.36	0.37	0.44
0.5	0.3	0.2	0.34	0.06	0.13	0.21	0.15	0.13	0.3	0.32	0.11	0.25	0.25	0.29
0.5	0.3	0.5	0.26	0.03	0.09	0.12	0.07	0.06	0.24	0.25	0.08	0.14	0.13	0.14
0.5	0.3	0.8	0.15	0.01	0.05	0.07	0.03	0.03	0.14	0.15	0.04	0.08	0.08	0.07
0.5	0.8	0.1	0.76	0.12	0.28	0.19	0.23	0.19	0.72	0.74	0.29	0.23	0.21	0.39
0.5	0.8	0.2	0.74	0.11	0.27	0.15	0.15	0.13	0.71	0.73	0.28	0.18	0.17	0.27
0.5	0.8	0.5	0.68	0.08	0.23	0.12	0.08	0.08	0.66	0.68	0.23	0.14	0.13	0.15
0.5	0.8	0.8	0.57	0.04	0.17	0.13	0.04	0.05	0.55	0.57	0.14	0.14	0.13	0.09
0	0.3	0.1	0.25	0.08	0.12	0.32	0.24	0.2	0.19	0.24	0.1	0.39	0.45	0.41
0	0.3	0.2	0.24	0.07	0.11	0.23	0.15	0.13	0.18	0.23	0.09	0.27	0.29	0.27
0	0.3	0.5	0.18	0.05	0.08	0.13	0.07	0.06	0.14	0.18	0.07	0.15	0.16	0.13
0	0.3	0.8	0.1	0.03	0.04	0.07	0.03	0.03	0.08	0.1	0.04	0.09	0.09	0.07
0	0.8	0.1	0.58	0.19	0.28	0.27	0.23	0.19	0.49	0.57	0.26	0.38	0.33	0.37
0	0.8	0.2	0.56	0.17	0.27	0.23	0.16	0.13	0.47	0.55	0.25	0.31	0.26	0.26
0	0.8	0.5	0.49	0.13	0.22	0.2	0.09	0.08	0.4	0.48	0.2	0.26	0.22	0.14
0	0.8	0.8	0.35	0.08	0.15	0.19	0.05	0.05	0.29	0.35	0.12	0.23	0.2	0.08
0.5	0.3	0.1	0.2	0.09	0.12	0.33	0.22	0.2	0.12	0.19	0.09	0.4	0.58	0.54
0.5	0.3	0.2	0.18	0.09	0.11	0.23	0.14	0.13	0.11	0.18	0.09	0.28	0.39	0.36
0.5	0.3	0.5	0.14	0.06	0.08	0.13	0.07	0.06	0.08	0.14	0.07	0.16	0.2	0.17
0.5	0.3	0.8	0.08	0.03	0.04	0.08	0.03	0.03	0.04	0.08	0.04	0.09	0.11	0.09
0.5	0.8	0.1	0.47	0.23	0.29	0.32	0.23	0.19	0.32	0.47	0.26	0.47	0.48	0.47
0.5	0.8	0.2	0.45	0.22	0.27	0.26	0.17	0.13	0.3	0.44	0.25	0.39	0.36	0.33
0.5	0.8	0.5	0.37	0.17	0.22	0.22	0.1	0.08	0.24	0.37	0.2	0.32	0.26	0.18
0.5	0.8	0.8	0.25	0.1	0.14	0.2	0.06	0.05	0.16	0.24	0.12	0.25	0.22	0.1

Table S4.7: Bias defined as the difference between median effectiveness estimates and median $\hat{e}_i$, oil drop design, summarized over 80 replicates and 10 geographies

r	E_s	$\overline{y_r}(0)$	Bias $\hat{e}_2(t)$	Bias $\hat{e}_3(t)$	Bias $\hat{e}_4(t)$	Bias $\hat{e}_5(t)$	Bias $\hat{e}_6(t)$
0.5	0.3	0.1	0.29	0.22	0.05	0.03	0.25
0.5	0.3	0.2	0.28	0.21	0.04	0.02	0.23
0.5	0.3	0.5	0.23	0.17	0.02	0.01	0.18
0.5	0.3	0.8	0.14	0.1	0.01	0	0.11
0.5	0.8	0.1	0.63	0.47	0.04	0.01	0.46
0.5	0.8	0.2	0.63	0.48	0.03	0.01	0.46
0.5	0.8	0.5	0.61	0.46	0.03	0	0.46
0.5	0.8	0.8	0.53	0.4	0.02	0	0.43
1	0.3	0.1	0.17	0.13	0.07	0.01	0.15
1	0.3	0.2	0.16	0.12	0.06	0.01	0.14
1	0.3	0.5	0.13	0.1	0.04	0	0.11
1	0.3	0.8	0.08	0.06	0.02	0	0.06
1	0.8	0.1	0.4	0.3	0.1	0.01	0.32
1	0.8	0.2	0.39	0.29	0.09	0.01	0.31
1	0.8	0.5	0.35	0.26	0.08	0.01	0.29
1	0.8	0.8	0.27	0.2	0.06	0	0.23
1.5	0.3	0.1	0.11	0.08	0.08	0.01	0.11
1.5	0.3	0.2	0.1	0.07	0.08	0.01	0.09
1.5	0.3	0.5	0.08	0.06	0.06	0	0.07
1.5	0.3	0.8	0.04	0.03	0.03	0	0.04
1.5	0.8	0.1	0.24	0.18	0.16	0.01	0.21
1.5	0.8	0.2	0.24	0.18	0.15	0.01	0.21
1.5	0.8	0.5	0.21	0.15	0.13	0	0.18
1.5	0.8	0.8	0.15	0.11	0.09	0	0.13

Table S4.8: Median effectiveness measures and 95% confidence interval widths for the random design, summarized over 80 replicates and 10 geographies

						95% CI width						95% CI width		
r	E_s	$\overline{y_r}(0)$	$\hat{e}_1(t)$	$\hat{e}_2(t)$	$\hat{e}_3(t)$	$\hat{e}_1(t)$	$\hat{e}_2(t)$	$\hat{e}_3(t)$	$\hat{e}_4(t)$	$\hat{e}_5(t)$	$\hat{e}_6(t)$	$\hat{e}_4(t)$	$\hat{e}_5(t)$	$\hat{e}_6(t)$
0.5	0.3	0.1	0.35	0.08	0.14	0.30	0.23	0.20	0.30	0.32	0.12	0.36	0.37	0.43
0.5	0.3	0.2	0.33	0.06	0.13	0.21	0.15	0.13	0.28	0.31	0.11	0.25	0.25	0.27
0.5	0.3	0.5	0.25	0.04	0.09	0.11	0.07	0.06	0.22	0.24	0.08	0.13	0.13	0.14
0.5	0.3	0.8	0.15	0.02	0.05	0.07	0.03	0.03	0.13	0.15	0.04	0.07	0.07	0.07
0.5	0.8	0.1	0.74	0.14	0.28	0.19	0.23	0.19	0.7	0.73	0.29	0.23	0.21	0.37
0.5	0.8	0.2	0.72	0.12	0.27	0.15	0.15	0.13	0.69	0.71	0.27	0.17	0.16	0.25
0.5	0.8	0.5	0.66	0.08	0.23	0.11	0.07	0.07	0.63	0.66	0.22	0.13	0.12	0.14
0.5	0.8	0.8	0.55	0.05	0.17	0.11	0.04	0.05	0.53	0.55	0.14	0.12	0.11	0.08
0	0.3	0.1	0.24	0.09	0.12	0.32	0.23	0.2	0.16	0.22	0.1	0.37	0.46	0.44
0	0.3	0.2	0.22	0.08	0.11	0.22	0.14	0.13	0.15	0.2	0.09	0.26	0.31	0.28
0	0.3	0.5	0.16	0.06	0.08	0.12	0.07	0.06	0.11	0.16	0.07	0.14	0.16	0.14
0	0.3	0.8	0.09	0.03	0.04	0.07	0.03	0.03	0.07	0.09	0.04	0.08	0.09	0.07
0	0.8	0.1	0.54	0.21	0.29	0.26	0.22	0.18	0.42	0.53	0.25	0.36	0.34	0.38
0	0.8	0.2	0.52	0.19	0.28	0.2	0.15	0.13	0.41	0.51	0.23	0.28	0.25	0.26
0	0.8	0.5	0.45	0.15	0.22	0.16	0.08	0.08	0.35	0.44	0.19	0.2	0.18	0.14
0	0.8	0.8	0.31	0.09	0.14	0.14	0.04	0.05	0.25	0.31	0.11	0.16	0.15	0.08
0.5	0.3	0.1	0.18	0.1	0.12	0.32	0.22	0.2	0.08	0.15	0.09	0.38	0.76	0.76
0.5	0.3	0.2	0.16	0.1	0.11	0.22	0.14	0.13	0.07	0.15	0.09	0.26	0.5	0.49
0.5	0.3	0.5	0.12	0.07	0.08	0.12	0.07	0.06	0.05	0.11	0.07	0.14	0.24	0.22
0.5	0.3	0.8	0.06	0.03	0.04	0.06	0.03	0.03	0.03	0.06	0.04	0.08	0.12	0.11
0.5	0.8	0.1	0.42	0.26	0.3	0.29	0.21	0.19	0.22	0.4	0.24	0.44	0.6	0.64
0.5	0.8	0.2	0.4	0.24	0.28	0.23	0.15	0.13	0.21	0.38	0.23	0.32	0.42	0.42
0.5	0.8	0.5	0.32	0.18	0.22	0.17	0.08	0.08	0.17	0.31	0.18	0.22	0.24	0.21
0.5	0.8	0.8	0.21	0.11	0.13	0.13	0.05	0.05	0.11	0.2	0.11	0.16	0.17	0.12

Table S4.9: Bias defined as the difference between median $\hat{e}_i$ and median effectiveness, random design, summarized over 80 replicates and 10 geographies

r	E_s	$\overline{y_r}(0)$	Bias $\hat{e}_2(t)$	Bias $\hat{e}_3(t)$	Bias $\hat{e}_4(t)$	Bias $\hat{e}_5(t)$	Bias $\hat{e}_6(t)$
0.5	0.3	0.1	0.27	0.21	0.05	0.03	0.23
0.5	0.3	0.2	0.26	0.2	0.05	0.02	0.22
0.5	0.3	0.5	0.22	0.16	0.03	0.01	0.17
0.5	0.3	0.8	0.13	0.1	0.01	0	0.11
0.5	0.8	0.1	0.6	0.45	0.04	0.01	0.45
0.5	0.8	0.2	0.6	0.45	0.04	0.01	0.45
0.5	0.8	0.5	0.58	0.44	0.03	0.01	0.44
0.5	0.8	0.8	0.5	0.38	0.02	0	0.41
1	0.3	0.1	0.15	0.11	0.08	0.02	0.14
1	0.3	0.2	0.14	0.1	0.07	0.01	0.13
1	0.3	0.5	0.11	0.08	0.05	0.01	0.1
1	0.3	0.8	0.06	0.05	0.03	0	0.06
1	0.8	0.1	0.34	0.25	0.12	0.02	0.3
1	0.8	0.2	0.33	0.25	0.12	0.02	0.29
1	0.8	0.5	0.3	0.22	0.1	0.01	0.26
1	0.8	0.8	0.23	0.17	0.07	0	0.2
1.5	0.3	0.1	0.07	0.05	0.1	0.02	0.08
1.5	0.3	0.2	0.07	0.05	0.09	0.01	0.07
1.5	0.3	0.5	0.05	0.04	0.06	0.01	0.05
1.5	0.3	0.8	0.03	0.02	0.03	0	0.03
1.5	0.8	0.1	0.17	0.13	0.2	0.03	0.18
1.5	0.8	0.2	0.16	0.12	0.19	0.02	0.17
1.5	0.8	0.5	0.14	0.11	0.15	0.01	0.14
1.5	0.8	0.8	0.1	0.07	0.1	0	0.09

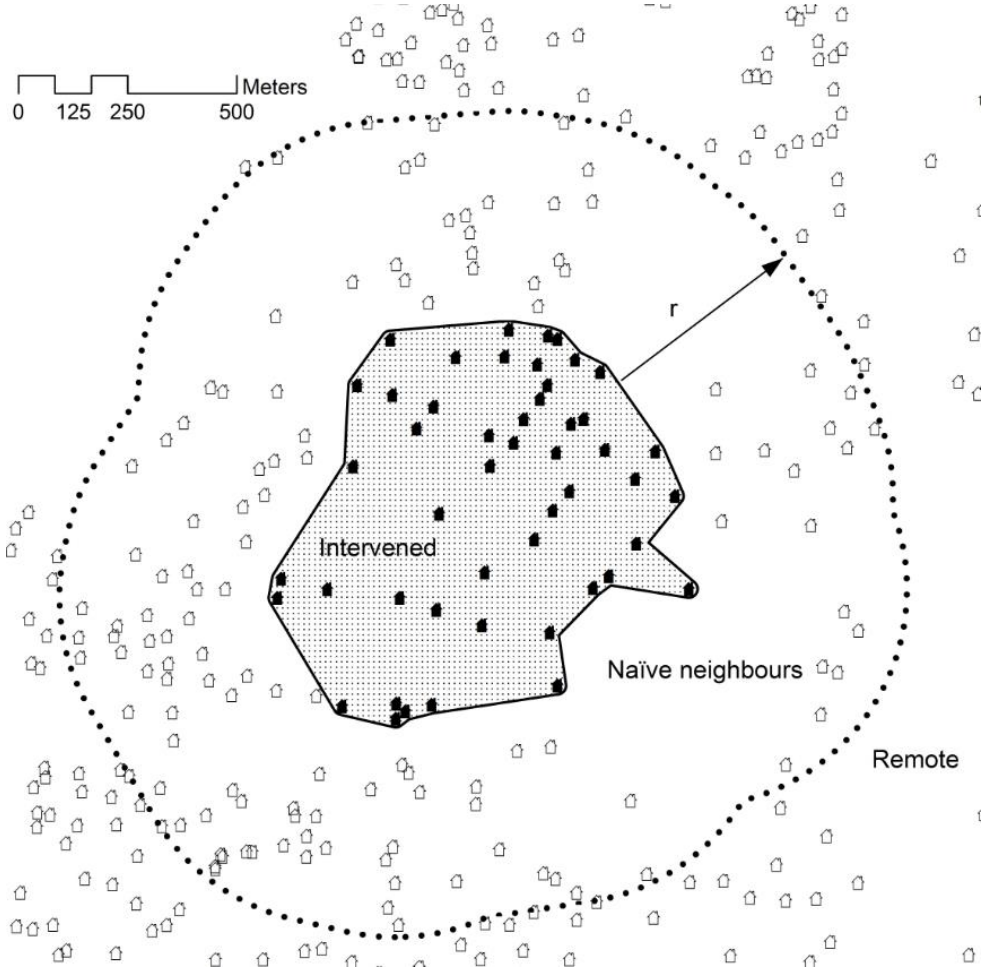

Figure S2.1: Household assignments during an intermediate time-step of the simulation for a small proportion of the surface illustrating how the intervened, neighbour and remote zones are assigned

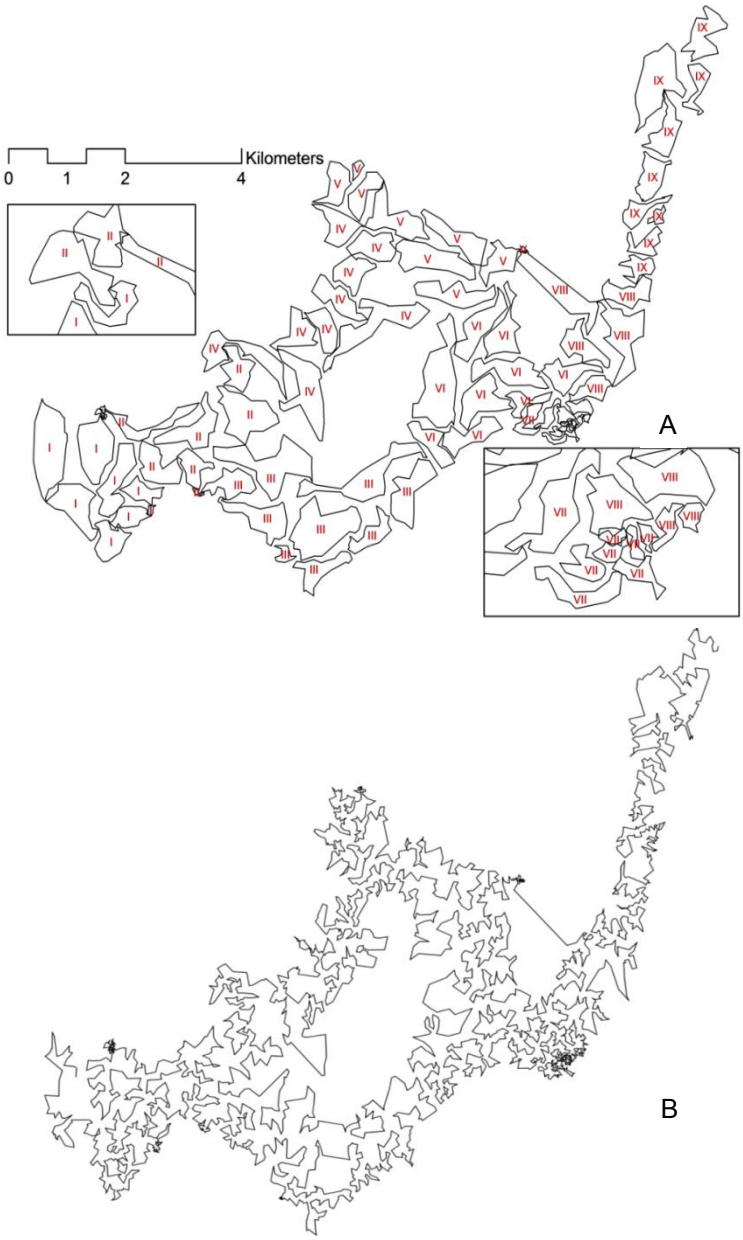

Figure S2.2: A: minimal spanning tree algorithm applied across the geographic locations of households of Rusinga Island to find an efficient (minimum distance) one-way path connecting all households. B: households were counted off in groups of 50 from a starting point on the south-west corner of the island along the one-way path to construct a total of 81 clusters. Each group of nine clusters is further combined into a metacluster, here denoted from I-IX.

Supplementary material chapter 7

Introduction

This document reports analyses carried out in order to estimate the effect of the introduction of odour-baited traps [OBTs] for trapping malaria mosquitoes on Rusinga Island, western Kenya. Outcomes analysed are parasite positivity in humans (measured using RDTs), clinical malaria, and mosquito densities. These analyses are complementary to those reported in the main paper entitled "Stepped wedge cluster-randomised trial of the impact of mass mosquito trapping on malaria (SolarMal)" (Homan *et al*., 2016). Together these two documents correspond to the analyses prescribed in the analytical plan of the Solarmal trial (Hiscox *et al*., 2016) , with the exception of certain planned analyses that are excluded for the reasons given below.

Numbers of participants in the trial

The numbers of participants in the trial at each survey round are given in Figures S7.1 and S7.2.

Characteristics of trial participants at baseline and during roll-out

The parasite positivity in humans (measured using RDTs), and clinical malaria for the baseline period are summarised in Table 7.1 and baseline mosquito densities in Table 7.2 of the main paper (Homan *et al*., 2016). The averages of other potential modifying factors at baseline are tabulated in Table 7.3.

A more complete set of potentially modifying factors is listed in Table S7.3, along with the proportions of responses in each category, both at baseline, and at the five subsequent parasitological surveys, at each of which a 10% random sample of households were included. The values tabulated are counts of responses in the categories indicated and percentages of the total number of responses aggregated over all surveys included.

Power and sample size rationale

Table S7.1 gives the intra-cluster correlation coefficients for both malaria prevalence and clinical malaria based on the data of the baseline studies. The power depended on the correlation between observations on the same individuals at sequential HDSS visits. We could not determine this level of correlation from the single baseline enumeration visit. A lower bound for the minimum detectable effect size is given by the value that would be achieved by a single visit per person, occurring halfway through the rollout. Using previously published formulae, this implied that the design had at least 80% power to detect approximately 52% reduction in clinical incidence (Hemming *et al.*, 2013). Conversely, a parallel CRT with six repeated visits and independent outcomes for each visit should have had power to detect (in the worst case of complete correlation between successive visits) an approximately 23% reduction in clinical incidence. Analogous calculations for prevalence, using a baseline malaria prevalence of 23.9% (RDT prevalence rate during the baseline survey for this project) and sample size of around 1,860 persons (10% of the population that was initially enumerated for this project) suggest that a single prevalence survey should have had 80% power to detect a 27% reduction in prevalence. Six repeated surveys carried out, might have power to detect effects as small as an 11% reduction in prevalence, assuming that correlations between repeated observations were small.

Analyses of effectiveness

Analyses of effectiveness of the SMoTS against parasite positivity in humans (measured using RDTs), clinical malaria, and mosquito densities are also reported in Tables 7.1 and 7.2 of the paper. These tables consider comparisons between the intervened clusters and (i) the status of the population prior to the intervention (baseline): this is a before-and-after comparison of the direct effect of the intervention; (ii) the non-intervened clusters during the roll-out of the intervention: this is a contemporaneous comparison of the direct effect of the intervention.

This document contains analyses that are complementary to those presented in the main paper as follows:

(a) Analysis of modifying effects of potential confounders

The analyses presenting in Tables 7.1 and 7.2 do not include any adjustment for potential confounders. For the outcome of clinical malaria incidence, for which the data are extremely sparse, no additional adjusted analyses were carried out. Adjusted analysis of parasite prevalence by RDT are presented below in Table S7.2; the adjusted estimates of effectiveness are similar to the unadjusted estimates.

(b) Temporal pattern of clinical malaria incidence

Because clinical malaria was infrequent during the follow-up period and hence the data are sparse the temporal pattern of clinical malaria is not given in the paper. Table S7.4 provides additional information on the temporal pattern of clinical malaria in both trial arms.

Planned analyses not included in these reports.

In addition to analyses of the outcomes reported in the main paper and in this document, the analytical plan envisaged:

- *Corresponding analyses of all-cause human mortality*: analyses of all-cause mortality are not included here because the relatively high levels of migration (>10% annually) would lead to underestimates or overestimates of cases of death, given that the older people are likely to return to their "ancestral home" at the time of death.
- *Analysis of sporozoite positivity in mosquitoes and of mosquito survival*. These analyses will be reported elsewhere.

(c) Analysis of effects on additional outcome measures

Additional outcomes were analysed for the outcomes of parasite positivity by RDT, and mosquito densities. These comprise comparisons between: (i) the non-intervened clusters during the intervention and the baseline: (a before-and-after comparison of

the indirect effect of the intervention); (ii) the overall population during the intervention and the baseline: this is a before-and-after comparison of the overall effect of the intervention (Halloran *et al.*, 1997); (iii) the non-intervened households close to SMoTS with non-intervened households further away, using several different distance cutpoints (Table S7.5A, S7.5B): this provides an estimate of the spill-over effect of the intervention; (iv) the intervened clusters, with non-intervened clusters remote from the nearest SMoT: this provides an estimate of the direct effect of the intervention, with adjustment for the diluting effect of spill-over from the intervention into neighbouring areas.

Table S7.5A reports these complementary analyses for the outcome of parasite positivity by RDT. Table S7.5B reports these analyses for mosquito densities (disaggregated by mosquito species complex) (Halloran *et al.*, 1997).

Participation: Demographic surveillance and clinical incidence surveillance

A total of 34,538 individuals were enrolled at some point during the trial. Figure S7.1 gives the active number of enrolled individuals in the HDSS at the beginning of each round, the numbers of immigrants/emigrants or enumerated (later), they were also subject to the active case detection. 15-20 % of the enrolled individuals were not sampled because they migrated out, passed away or were not available at the time of survey. The analyses refer to 138 project weeks; the baseline comprised the first 38 project weeks, and the remainder spanned the period of SMoTS installation (June 2013 until June 2015) (Figure 7.2). 34,041 distinct enrolled individuals, assigned to 4,847 households, consented to participate over this period (Figure S7.1).

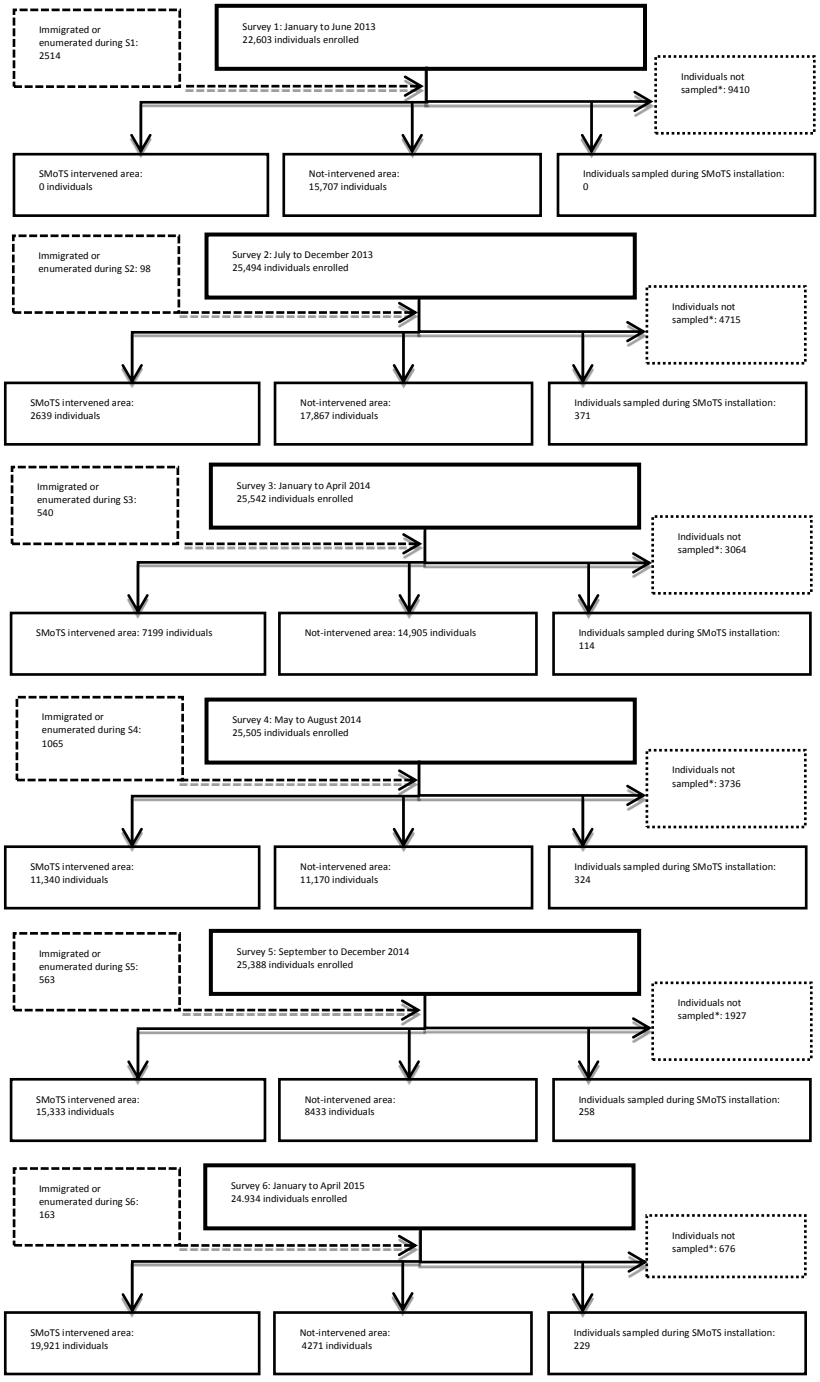

Figure S7.1: Participation diagram; demographic and clinical malaria surveillance

Participation: Demographic surveillance and clinical incidence surveillance

A total of 12,187 individuals were randomly selected to participate in one or more of the seven cross-sectional surveys (16,029 RDTs). 11,970 individuals were tested by RDT resulting in 15,627 RDT test results available for analysis. On 1402 occasions an individual that was randomised to be sampled* could not be found, had migrated out or had passed away. 2516 individuals were sampled twice, 442 individuals three times, and 84 individuals more than three times. The first two surveys served as baseline.

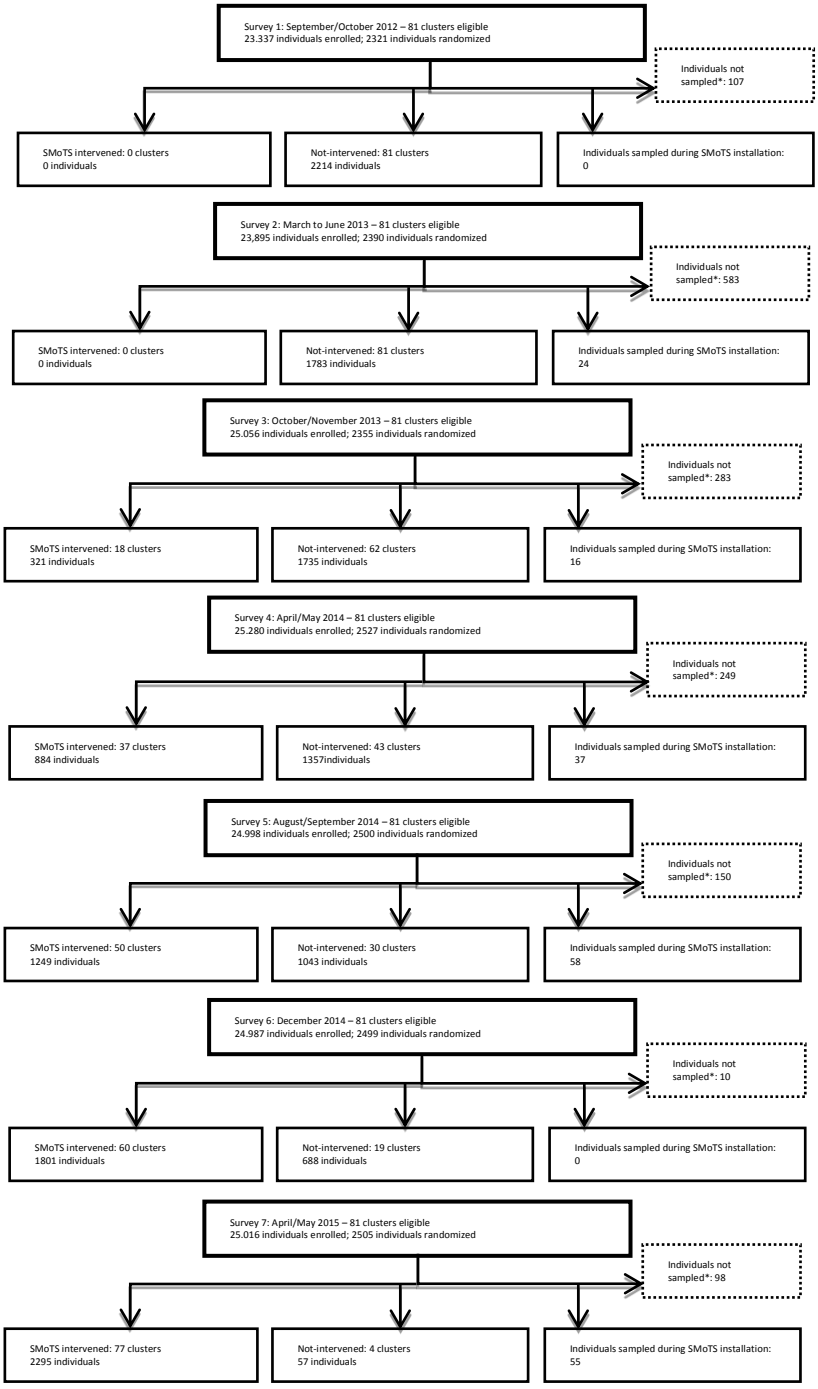

Figure S7.2: Participation diagram; prevalence surveys

A mean of 24,879 individuals were enumerated at each of the seven survey rounds, with the difference between the total enrolled population and mean population reflecting high rates of local movement of fishermen. SMoTS were allocated to 4,358 households. The difference in total number of households enrolled compared to number of households receiving SMoTS was due to an increasing number of households on the island during the course of the study. A total of 12,187 individuals were randomised in at least one of the seven cross sectional parasitological surveys during this whole period, resulting in 15,627 RDT test results prior to the exclusion of RDT results from those whose household was undergoing SMoTS installation during the week when the RDT was taken (Figure S7.2). Of this total 2,516 individuals were sampled twice (20.6%), 442 individuals three times (3.6%), and 84 individuals more than three times (0.7%).

Comparability of groups

The roll-out resulted in approximately the same time-at-risk in both the intervention and pre-intervention arms of the trial (Table 7.1), and in similar intensities of entomological sampling in the two arms (Table 7.2). The trial was also reasonably balanced for most potential confounders, including age (Table 7.3), occupancy, Topographic wetness index (TWI, a measure of potential water accumulation), Normalised Difference Vegetation Index (NDVI), and distance to the lake (a proxy for distance to mosquito breeding sites). Population density was slightly higher in the intervened and non-intervened arms after baseline. Comparisons for other potentially relevant factors are presented as supplementary information (Table S7.3).

Reported LLIN ownership among people tested for malaria in 10% cross-sectional surveys changed from 73% during baseline, to 79% in the intervened arm and 61% in the not-intervened arm during the rollout. These differences may reflect reporting bias, since observations by the field team of LLIN use (Table 7.3) found no difference between arms. Controlling for reported LLIN use also made little difference to estimated effects of SMoTS on RDT positivity (Table S7.2).

Table S7.1: Intra-cluster correlation and power calculations

	Clinical malaria	Parasitaemia
Sampled during baseline	15,707	3093
RDT+ during baseline	103 (0.01%)	733 (23.69%)
Intra-cluster correlation	0.006	0.0655
Effective sample size	7914	907
Power	80%	80%
Minimal detectable effect size, 1 survey	52%	27%
Minimal detectable effect size, 6 surveys	23%	11%

Table S7.2: Estimates of effect of the intervention on parasitaemia, adjusted for potential confounding factors

	Effectiveness
Contemporaneous comparison	
Estimate* of effectiveness (95% CI)	29.3% (25.4, 33.1)
Estimate** of effectiveness (95% CI)	28.1% (19.6, 35.8)
Comparison of baseline with intervened clusters	
Estimate* of effectiveness (95% CI)	1% (-6.3, 7.4)
Estimate**of effectiveness (95% CI)	4.6% (-8.7, 16.3)

*Adjusted estimates derived from binomial models controlling for age, gender, occupation and bed nets reported.

**Adjusted estimates derived from binomial models with random effects for the cluster and survey round; controlling for age, gender, occupation and bed nets reported

Table S7.3: Potential risk factors by trial arm

	Baseline (%)	Number positive: Baseline	Intervened (%)	Number positive: (Inter-vened)	Non-intervened (%)	Number positive: non-intervened
Sex distribution						
Males	46.6	1441	46.8	3068	47.5	2751
Location of kitchen						
Kitchen outside, in the open	35.5	1098	37.2	2439	41.5	2402
Kitchen in main living area	15.9	491	16.8	1099	20.4	1184
Separate kitchen building	23.9	740	20.6	1352	20	1157
Separate kitchen room in house	3.3	101	3.1	205	2.6	152
In another house	11.3	348	11.3	738	9.6	556
Outside at day, inside at night	5.7	175	9.8	642	4.7	273
Unknown	4.5	140	1.1	75	1.2	70
Dwelling						
Own dwelling	76	2351	76.6	5018	76.7	4446
Rent dwelling	15.8	488	17.6	1151	19	1099
Other	3.7	114	4.7	306	3.1	179
Unknown	4.5	140	1.1	75	1.2	70
Source of electricity						
No electricity	85.2	2635	55.5	3638	88.8	5147
Connected to main power supply	2.5	76	2.3	152	2.8	163
Generator	0.6	20	0.4	24	0.6	35
Battery	0.9	28	1	66	1	59
Solar power	6.3	194	39.6	2595	5.5	320
Unknown	4.5	140	1.1	75	1.2	70
Source of light						
1. Kerosene powered light	86.8	2686	56.3	3688	89.3	5172
2. Candle light	0.1	2	0	3	0.2	10
3. Electric light	5.7	177	38.5	2524	4.8	281

4. Other	0.9	27	0.6	39	0.5	29
1 and 2	0	1	0.1	9	0.6	35
1 and 3	1.9	60	3.2	211	3.3	192
2 and 3	0	0	0	1	0.1	5
Unknown	4.5	140	1.1	75	1.2	70
Level of education head of household						
Pre-school education	1	30	0.8	55	1.6	92
Primary school	59.7	1846	62.9	4120	61.9	3588
Secondary school	26	804	24.5	1602	27.6	1597
Higher education	4.6	143	6.7	440	6.2	360
Non-standard	3.6	111	3.5	228	1.1	63
Other	0.6	19	0.5	30	0.4	24
Unknown	4.5	140	1.1	75	1.2	70
Wall structure of house						
Stone	0.7	21	1.4	90	0.3	20
Wood and mud	62.7	1940	62.8	4114	65	3765
Brick and block	17	526	17.4	1141	18.8	1088
Mud and cement	8.8	271	9.3	607	6.5	377
Iron and sheet	6.3	195	7.8	511	8.1	467
Wood	0	0	0.1	6	0	0
Other	0	0	0.1	6	0.1	7
Unknown	4.5	140	1.1	75	1.2	70
Floor structure of house						
Earth, dung or sand	10.7	332	49.4	3233	30.5	1768
Carpet	47.9	1481	11	718	30.7	1781
Cement	36.5	1130	38.1	2496	37.2	2158
Tiles or linoleum	0.3	10	0.3	17	0.2	14
Other	0	0	0.2	11	0.1	3
Unknown	4.5	140	1.1	75	1.2	70
Mosquito house entry						
Open Eaves	85	2629	86.7	5677	88.5	5129

Openings in the house	3.3	103	4.3	284	4.7	271
Open eaves and openings in house	0.7	21	0.7	47	0.5	28
Screened eaves	5.8	179	6.5	426	4.4	254
Screened eaves, openings in house	0.7	21	0.6	41	0.7	42
Unknown	4.5	140	1.1	75	1.2	70
When were bed nets acquired						
1-3 months ago	2.1	66	5.2	342	4.7	275
3-6 months ago	8.7	269	8.7	573	10.1	587
>6 months ago	68.7	2126	60.9	3991	69	3997
Bed nets of mixed Age	11	340	17.6	1150	9	522
No bed nets	0.3	10	0.3	20	0.7	40
Unknown	9.1	282	7.2	474	6.4	373
Bed nets reported						
Bed net(s) in House	72.6	2247	79	5174	61.2	3545
No Bed net(s) in House	22.8	706	19.9	1301	37.6	2179
Unknown	4.5	140	1.1	75	1.2	70
Occupation						
Fishing	8.5	263	8.4	551	10.2	592
Farming	3.2	99	2.1	139	2.5	146
Construction	0.7	23	0.7	45	0.7	43
Other outdoor	15.6	483	19.2	1258	17.0	984
Clerical, other Indoor	2.5	77	2.5	167	2.7	157
Housewife	5.4	168	3.7	242	5.0	287
Students and school children	44.4	1372	45.6	2987	42.4	2457
Children under 5	15.2	469	13.5	885	15.3	889
Jobless	3.7	113	2.9	189	3.2	184
Retired	0.8	26	0.9	60	0.5	30
Unknown	0.0	0	0.4	27	0.4	25

Table S7.4: Clinical events by round

	SMoTS			No SMoTS			Total population		
Round	Person /years	Clinical events per p/y	RDT+	Person /years	Clinical events per p/y	RDT+	Person /years	Clinical events per p/y	RDT +
1	0.0	-		597.2	0.173	103	597.2	0.173	103
2	101.0	0.049	5	685.0	0.045	26	807.2	0.038	31
3	275.7	0.040	11	571.4	0.014	6	861.8	0.020	17
4	434.7	0.002	1	428.3	0.000	0	877.5	0.001	1
5	587.7	0.007	4	323.5	0.006	1	923.7	0.005	5
6	763.9	0.003	2	163.8	0.000	0	938.0	0.002	2

Table S7.5A: Complementary analyses of effectiveness in reducing parasite prevalence by RDT.

	Clinical malaria	RDT+/N (%)	Parasitaemia	RDT+/N (%)	Reported illness previous two weeks	RDT +/N (%)
Comparison of baseline with non-intervened clusters						
Unadjusted estimate of effectiveness (95% CI)	91.1% (86.9, 94)	103/1570 7 (0.66), 33/56,793 (0.06)	-45.8% (36.2, 56.1)	733/309 3 (23.7), 2002/57 95 (34.6)	62.4% (60.9, 63.8)	3914 /15,7 07 (24.9), 5326 /56,7 93 (9.4)
Adjusted estimate of effectiveness (95% CI)	93% (87.3, 96.2)		-38.3% (-20.3, -59)		66.4% (62.9, 69.6)	
Comparison of baseline with all clusters during roll-out						
Unadjusted estimate of effectiveness (95% CI)	93.4% (90.7, 95.2)	103/1570 7 (0.66), 56/11318 (0.05)	-21.5% (-13.7, -29.8)	733/309 3 (23.7), 3556/12, 345 (28.8)	73.6% (72.7, 74.5)	3914 /15,7 07 (24.9), 11,3 38/1 13,1 86 (10)
Adjusted estimate of effectiveness (95% CI)	95.2% (90.1, 97.7)		-15.2% (-18.1, -30.3)		81.3% (79.3, 83)	
Comparison of intervened clusters, with non-intervened clusters >100m from nearest SMoT						
Unadjusted estimate of effectiveness (95% CI)			33.9% (29.9,	3556/12, 345		

	37.7)	(28.8), 1673/4667 (35.8)
Adjusted estimate of effectiveness (95% CI)	32.4% (22.9, 40.7)	
Comparison of intervened clusters, with non-intervened clusters >300m from nearest SMoT		
Unadjusted estimate of effectiveness (95% CI)	34.4% (30.3, 38.3)	3556/12,345 (28.8), 1478/4092 (36.1)
Adjusted estimate of effectiveness (95% CI)	33.1% (23.4, 41.5)	
Comparison of intervened clusters, with non-intervened clusters >500m from nearest SMoT		
Unadjusted estimate of effectiveness (95% CI)	35.1% (30.9, 39.1)	3556/12,345 (28.8), 1330/3643 (36.5)
Adjusted estimate of effectiveness (95% CI)	33.6% (23.5, 42.3)	
Comparison of intervened clusters, with non-intervened clusters >700m from nearest SMoT		
Unadjusted estimate of effectiveness (95% CI)	32.7% (30, 37.1)	3556/12,345 (28.8), 1084/3084 (35.1)

Adjusted estimate of effectiveness (95% CI)	31.5% (20.8, 40.7)	
Comparison of intervened clusters, with non-intervened clusters >900m from nearest SMoT		
Unadjusted estimate of effectiveness (95% CI)	29.5% (24.2, 34.3)	3556/12,345 (28.8), 917/2730 (33.6)
Adjusted estimate of effectiveness (95% CI)	27.9% (16.3, 37.9)	
Comparison of non-intervened clusters ≤100m from nearest SMoT, with non-intervened clusters >100m from nearest SMoT		
Unadjusted estimate of effectiveness (95% CI)	-8.3% (-25.6, 6.7)	125/322 (38.8), 1673/4666 (35.9)
Adjusted estimate of effectiveness (95% CI)	-5.7% (-37.2, 18.5)	
Comparison of non-intervened clusters ≤300m from nearest SMoT, with non-intervened clusters >300m from nearest SMoT		
Unadjusted estimate of effectiveness (95% CI)	1.1% (-8.9, 10.2)	320/896 (35.7), 1478/4092 (36.2)
Adjusted estimate of effectiveness (95% CI)	2.8% (-18.5, 20.2)	

Comparison of non-intervened clusters ≤500m from nearest SMoT, with non-intervened clusters >500m from nearest SMoT		
Unadjusted estimate of effectiveness (95% CI)	5.7% (-3.6, 12.3)	468/1345 (34.8), 1330/3643 (36.5)
Adjusted estimate of effectiveness (95% CI)	7.7% (-10.8, 23)	
Comparison of non-intervened clusters ≤700m from nearest SMoT, with non-intervened clusters >700m from nearest SMoT		
Unadjusted estimate of effectiveness (95% CI)	-6.3% (-14.7, 1.4)	714/1908 (37.4), 1084/3080 (35.2)
Adjusted estimate of effectiveness (95% CI)	-6.1% (-24.8, 9.8)	
Comparison of non-intervened clusters ≤900m from nearest SMoT, with non-intervened clusters >900m from nearest SMoT		
Unadjusted estimate of effectiveness (95% CI)	-16.1% (-25.1, -7.9)	881/2258 (39), 917/2730 (33.6)
Adjusted estimate of effectiveness (95% CI)	-19.5% (-40.9, -1.3)	

n.a. this random effects model could not be fitted owing to sparse data. Adjusted estimates are derived from binomial models with random effects for the cluster and survey round.

Table S7.5B: Effects on entomological outcomes, comparison of baseline with non-intervened clusters and the total population during intervention. And spatial effects for different radii.

	All *Anopheles*	Mosquitoes/ trapping nights	*An. funestus*	Mosquitoes/ trapping nights	*An. gambiae s.l.*	Mosquitoes/ trapping nights
Comparison of baseline with non-intervened clusters						
Unadjusted estimate of effectiveness (95% CI)	34.1% (24.7, 42.3)	422/868, 439/1370	53% (44.9, 60.0)	348/868, 258/1370	-55% (-18.8, -104.2)	74/868, 181/1370
Adjusted estimate of effectiveness (95% CI)	52.3% (31.9, 66.9)		72.9% (56.3, 83.4)		-33.2% (22.5, -130.5)	
Comparison of baseline with all clusters during roll-out						
Unadjusted estimate of effectiveness (95% CI)	49.7% (43.1, 55.4)	422/868, 651/2660	70.9% (66.1, 75.1)	348/868, 310/2660	-50.4% (-17.7, -94.7)	74/868, 341/2660
Adjusted estimate of effectiveness (95% CI)	63.2% (48.3, 63.2)		84.2% (73.5, 90.6)		-26.2% (-107.4, 22.3)	
Comparison of intervened clusters, with non-intervened clusters >100m from nearest SMoT						
Unadjusted estimate of effectiveness (95% CI)	51.5% (42.8, 58.9)	212/1290, 413/1220	79.9% (73.2, 85.3)	52/1290, 245/1220	9.9% (-11.8, 27.5)	160/1290, 168/1220
Adjusted estimate of effectiveness (95% CI)	43.4% (15.2, 62.3)		69.6% (27.7, 87.9)		12.2 (-44, 46.4)	
Comparison of intervened clusters, with non-intervened clusters >300m from nearest SMoT						
Unadjusted estimate of effectiveness (95% CI)	51.9% (43.2, 59.5)	212/1290 ,372/1088	80.5% (73.9, 85.7)	52/1290, 225/1088	8.2% (-14.9, 26.6)	160/1290, 147/1088
Adjusted estimate of effectiveness (95% CI)	43.4% (14.9,		71.% (31.2,		10.7% (-48.8, 46.2)	

	62.5)		88.3)			
Comparison of intervened clusters, with non-intervened clusters >500m from nearest SMoT						
Unadjusted estimate of effectiveness (95% CI)	51.5% (42.4, 59.3)	212/1290, 314/926	80.8% (74.1, 86)	52/1290, 194/926	4.3% (-21.5, 24.4)	160/1290, 120/926
Adjusted estimate of effectiveness (95% CI)	39.6% (6, 61.3)		67.6% (16.1, 88)		7.4% (60.7, 46.3)	
Comparison of intervened clusters, with non-intervened clusters >700m from nearest SMoT						
Unadjusted estimate of effectiveness (95% CI)	36.8% (23.4, 47.8)	212/1290, 206/792	69.9% (58.3, 78.5)	52/1290, 106/792	1.8% (-26.5, 23.3)	160/1290, 100/792
Adjusted estimate of effectiveness (95% CI)	35.3% (-1.3, 58.9)		65.1% (6.1, 87.4)		3.9% (-72.3, 45.8)	
Comparison of intervened clusters, with non-intervened clusters >900m from nearest SMoT						
Unadjusted estimate of effectiveness (95% CI)	32.8% (17.8, 44.9)	212/1290, 174/712	69.8% (57.8, 78.6)	52/1290, 95/712	11.8% (47, 14.3)	160/1290, 79/712
Adjusted estimate of effectiveness (95% CI)	31% (-9.6, 56.8)		62.6% (-8.3, 87.3)		-1.6% (81.6, 42.6)	
Comparison of non-intervened clusters ≤100m from nearest SMoT, with non-intervened clusters >100m from nearest SMoT						
Unadjusted estimate of effectiveness (95% CI)	70.5% (42.4, 87.4)	70/7, 413/1220	57.3% (12.4, 83.2)	6/71, 245/1220	89.6% (53.9, 99.4)	70/1, 168/1220
Adjusted estimate of effectiveness (95% CI)	64.4% (22.6, 91.7)		35.5% (-310.3, 95)		86.5% (-17.5, 99.7)	
Comparison of non-intervened clusters ≤300m from nearest SMoT, with						

non-intervened clusters >300m from nearest SMoT						
Unadjusted estimate of effectiveness (95% CI)	30.5% (7.2, 49.2)	48/202, 372/1088	37.8% (8.5, 59.5)	26/202, 225/1088	19.4% (-23.3, 49.9)	22/202, 147/1088
Adjusted estimate of effectiveness (95% CI)	1% (-72.8, 44)		-162.6% (-549, -10)		54.7% (-0.8, 81.7)	
Comparison of non-intervened clusters ≤500m from nearest SMoT, with non-intervened clusters >500m from nearest SMoT						
Unadjusted estimate of effectiveness (95% CI)	14.1% (-6.6, 31.4)	106/364, 314/926	25.3% (0.3, 44.8)	57/364, 194/926	3.9% (-43.8, 26.1)	49/364, 120/926
Adjusted estimate of effectiveness (95% CI)	75% (61.8, 84.3)		83.5% (71.1, 91.4)		53.5% (3.7, 80.6)	
Comparison of non-intervened clusters ≤700m from nearest SMoT, with non-intervened clusters >700m from nearest SMoT						
Unadjusted estimate of effectiveness (95% CI)	-65.2% (-100, -36.4)	214/498, 206/792	-117.6% (-180, -69.6)	145/498, 106/792	-9.7% (-48.8, 19.5)	69/498,100/792
Adjusted estimate of effectiveness (95% CI)	28.9% (-11.1, 55.7)		4.1% (71.1, 91.4)		49% (6.3, 74.5)	
Comparison of non-intervened clusters ≤900m from nearest SMoT, with non-intervened clusters >900m from nearest SMoT						
Unadjusted estimate of effectiveness (95% CI)	-74.2% (-111.7, 43.6)	246/578, 174/712	-102.3% (-161.2, -57.1)	156/578, 95/712	-40.3% (-90.1, -3.8)	90/578, 79/712
Adjusted estimate of effectiveness (95% CI)	-24.6% (-106.3, 25.3)		-22.7% (-164.4, 0.44.6)		-11% (-129.6, 47.6)	

Adjusted estimates are derived from Poisson models with random effects for the cluster and survey round.

Acknowledgement

Before applying for this PhD position, I knew I was drawn to work that involved working with people, in an environment where I would be able to contribute to the general life quality with those people. And in tropical disease research one could have such an impact by strengthen public health. However, at first I thought that a PhD wouldn't involve much applied work on human life conditions and health. Nevertheless, when the opportunity arose to work on a pragmatic project that focusses on developing a new vector intervention against malaria and at the same time improving life conditions by providing solar panels and lights, I knew I would enjoy it.

Therefore, I firstly want to express gratitude to my promoters Willem Takken and Tom Smith for offering this opportunity to me. Besides, I have to thank them for guiding me through this mind boggling expedition of wisdom, education, adventure and data. Although I had the luxury to have worked with so many likeminded and interesting people, Willem and Tom always stood in the vanguard of the project aiding me in the numerous challenges that I encountered. After a sneak preview in the kitchen of malaria science I know I should cherish them for their get-at-able character and knowledgeability.

Ja Luo Rusinga, ero kamano ahinya, wabironenore. I want to thank everybody on the Island of Rusinga for being part of the study, for being such a cheerful crowd and being part of my experience. Although I never learned the language, the culture and way of living have deepened my views on and definitions of humans.

The ento family at Wageningen University is a very extraordinary family. There seems to be a harmonious mindedness that connects people. Not only because of the 40-50 people counting open work space. Also the joint coffee breaks and the social agenda made it a pleasure to work there, and a good environment to get to know people and different parts of work within the science of entomology.

Then the vector group, inevitably when one is affiliated to this group you are drawn to all the amazing work that is created and done there. There were always new ideas and developments, new student projects and new results. And despite being an epidemiologist in an entomologist world, I really think that the research done and work ethos have broaden my horizon, and provided me with a special way of looking at malaria science. Thanks Sander, Niels, Jeroen, Leon, David, Jetske, Gillian and Leon.
And then Alex Hiscox, of whom I have learned many things. Much of my work I discussed with her and her input as a colleague, and as a friend was valuable.

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The real hard day-to-day data collection and logistical work was extensive in the SolarMal project, and for this I want to thank the whole team based at *icipe* Mbita. The crew comprised of a health and demographic surveillance team, entomologist, parasitologists, sociologists and technicians. It was impressive how efficient this machine worked, and through good communication, discussion and hard work I am proud of what was accomplished. The numerous times I was with the team, I felt a harmonious vibe where it was comfortable to work and learn from each other. Besides work, I really enjoyed sharing moments of ugali, sukuma, kuku choma and ohangla dance and music and all the other countless experiences that took place in and around Mbita Point. A big thank you to: Prisca Oria, Dan Masiga, Richard Mukabana, Collins Mweresa, Kennedy Okoth, Elizabeth Okello, Winnie Ogonda, Violet Bolo, Pauline Okode, David Odhiambo, Kennedy Ojijo, Hilary Kennedy, Thomas Odhiambo, Lillian Awuor, Charles Otieno, Molly Ariko, Faith Kyengo, Ibrahim Kiche, Kelvin Onoka, Patrick Sawa, Bruno Otieno, Philemon Omusula, Andrew Abuya, Anthony Muthai Kibet, Margaret Ayugi, Francis Okomo, Maurine Santino , Jared Odhiambo, Tom Gumba, Jackton Arija and Charles Wambua.

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Thanks to my friends for being a friend: in Utrecht, Wageningen other parts of the Netherlands, Basel, Mbita and elsewhere were a solid basis to share life with. I certainly consider myself lucky to have such a diversity of good friends.

And finally I want to express my endless respect and gratitude for being always there for me: my girlfriend, Esther Bogte, and family, Floor Oliveiro, Wieger Homan, Silver Oosterbaan, Floris de Waal, Louky Wark, John Nagelmaeker and Storm de Waal.

Tobias

Curriculum Vitae Tobias Homan

Tobias Homan was born 22nd of January 1985 in Krommenie, The Netherlands. During his 14 years of attending primary and secondary schooling at the Kees Boeke Werkplaats Kindergemeenschap special attention was given to subjects like nature, equality and arts. With a creative mother and a father in science he got the chance to explore the world at an early age. It became clear to him that wealth and health are not equally distributed, and he pursued to choose a study that could contribute to the general health of people in developing countries. He started a BSc Health Sciences at the Vrije Universiteit Amsterdam, a study looking at health in a broad sense; from sociology to medicine and from psychology to epidemiology. Subsequently, he got enrolled to the MSc Health Sciences and graduated for two specialising differentiations: International Public Health and Policy Organization in Health Care. For the first specialisation he constructed an epidemiological risk factors study for *Ascaris lumbricoides* in a village in central Venezuela. At the Universidad de Carabobo almost half a year was spend on developing the study and conducting fieldwork, lab work and analysis. For the second specialisation he worked with the Ghana Health Service to investigate the mechanism and process of overtreatment of malaria in the Greater Accra region. During the beginning of his study period he worked as a bike messenger, not the worst job as tour cycling is one of his big passions. In the last years of his studies he worked as a research assistant for the Amsterdam University College and the Universiteit van Amsterdam. When the vacancy for the SolarMal project came to his attention, he immediately knew this project would suit him well. Applied science, working with a challenging tropical disease in a transdisciplinary context combined with aspects of general development. After the PhD track he pursues a position in science or at a nongovernmental organisation within the area of the epidemiology of disease in low and middle income countries. Ultimately to be involved in the vanguard of the crossroad between developmental studies and health sciences.

List of publications

Scientific articles

Homan T, Hiscox A, Mweresa C, Masiga D, Mukabana WR, Oria PA, Maire N, Di Pasquale A, Alaii J, Leeuwis C, Smith TA, Takken W. Stepped wedge cluster-randomised trial of the impact of mass mosquito trapping on malaria (SolarMal).
Publication under review

Homan T, Di Pasquale A, Kiche I, Onoka K, Hiscox A, Mweresa C, Mukabana WR, Takken W, Maire N. Innovative tools and OpenHDS for health and demographic surveillance on Rusinga Island, Kenya.
Published in *BMC Research Notes* 8:397 (2015)

Homan T, Di Pasquale A, Onoka K, Kiche I, Hiscox A, Mweresa C, Mukabana WR, Masiga D, Takken W, Maire N. Profile: The Rusinga Health and Demographic Surveillance System, Western Kenya (2016).
Publication in press, *International Journal of Epidemiology*

Homan T, Maire N, Hiscox A, Di Pasquale A, Kiche I, Onoka K, Mweresa C, Mukabana WR, Ross A, Smith TA, Takken W. Spatially variable risk factors for malaria in a geographically heterogeneous landscape, western Kenya: an explorative study.
Published in *Malaria Journal* 15:1 (2016)

Menger DJ, Omusula P, Holdinga M, **Homan T**, Carreira AS, Vandendaele P, Derycke J, Mweresa C, Mukabana RW, van Loon JJA, Takken W. Field Evaluation of a Push-Pull System to Reduce Malaria Transmission.
Published in *PLoS ONE* 10(4) (2015)

Hiscox A*, **Homan T***, Mweresa C, Maire N, Di Pasquale A, Masiga D, Oria PA, Alaii J, Leeuwis C, Mukabana WR, Takken W, Smith TA. Mass mosquito trapping for malaria control in Western Kenya: study protocol for a stepped-wedge cluster-randomised trial (2016).
Publication under review

Silkey M, **Homan T**, Maire N, Hiscox A, Mukabana WR, Takken W, Smith TA. Design of trials for interrupting the transmission of endemic pathogens (2015).
Publication under review

Homan T, Hiscox A, Mukabana WR, Masiga D, Smith TA, Takken W, Maire N. Spatial patterns of the effect of odour-baited mosquito traps on malaria vectors, prevalence and transmission.
Manuscript in preparation.

Hiscox A, Otieno B, **Homan T**, Mukabana WR, Masiga D, Smith TA, Takken W. Impact of odour baited traps on entomological measures of malaria transmission on

Rusinga Island.
Manuscript in preparation.

Masiga D, Kibet A, **Homan T**, Hiscox A, Smith TA, Takken W. Diagnostic performance of RDTs, microscopy and HRM PCR over the course of malaria vector control by odour baited traps.
Manuscript in preparation

Oral and poster presentations
Homan T, Hiscox A, Smith TA, Mukabana WR, Takken W. A geographically heterogeneous context and spatially varying risk factors for malaria at Lake Victoria.
Published in *Tropical Medicine & International Health* PS1.358.LB (2015)

Hiscox A, Maire N, Kiche I, Silkey M, **Homan T**, Oria PA, Mweresa C, Otieno B, Ayugi M, Bousema T, Sawa P, Alaii J, Smith TA, Leeuwis C, Mukabana WR, Takken W. The SolarMal Project: innovative mosquito trapping technology for malaria control.
Published in *Malaria Journal* 11-S1-O45 (2012)

Hiscox A, **Homan T**, Vreugdenhil C, Otieno B, Kibet A, Mweresa C, van Lammeren R, Mukabana WR, Takken W. Spatial heterogeneity of malaria vectors and malaria transmission risk estimated using odour-baited mosquito traps.
Published in *Malaria Journal* 13-S1-P41 (2014).

Homan T, Hiscox A, Di Pasquale A, Kiche I, Mweresa C, Mukabana W, Smith TA, Takken W, Maire N. Measuring outcomes of the first trial of odour-baited mosquito traps for malaria control using a state of the art health and demographic surveillance system.
Published in Malaria Journal 13-S1-P97 (2014)

Homan T, Hiscox A, Smith TA, Maire N, Mukabana WR, Mweresa C, Oria PA, Ayugi M, Kiche I, Otieno B, Kibet A, Onoka K, Di Pasquale A, Alaii J, Leeuwis C, Masiga D, Takken W. Reduction of malaria by mass trapping of mosquitoes – a new tool for disease control.
ASTMH conference, Philadelphia, USA (2015).

Homan T, Hiscox A, van Lammeren R, Smith TA, Mukabana WR, Takken W. The SolarMal project: risk factors for malaria before commencing a vector based control intervention, Rusinga Island, Kenya. *Multilateral Initiative on Malaria (MIM)* conference, Durban, SA (2013).

Homan T, Di Pasquale A, Kilimba T, Maire N. OpenHDS for mobile data capture in INDEPTH HDSS Sites. Advanced Progress and Immediate Opportunities: Experience with implementing openHDS in the operation of a new site: SolarMal and the Rusinga Island HDSS, Mbita, Kenya.
INDEPTH Network Workshop, Johannesburg, SA (2013).

PE&RC Training and Education Statement

With the training and education activities listed below the PhD candidate has complied with the requirements set by the C.T. de Wit Graduate School for Production Ecology and Resource Conservation (PE&RC) which comprises of a minimum total of 32 ECTS (= 22 weeks of activities)

Review of literature (4.5 ECTS)

- Impact of odour-baited traps on the incidence and prevalence of malaria on Rusinga Island, Kenya

Writing of project proposal

- Impact of odour-baited traps on the incidence and prevalence of malaria on Rusinga Island, Kenya

Post-graduate courses (2.5 ECTS)

- Geostatistics; SENSE (2013)
- Introduction to R; SENSE (2014)

Laboratory training and working visits (2 ECTS)

PCR and ELISA; Icipe, Kenya (2013)

Deficiency, refresh, brush-up courses (4 ECTS)

- Introduction to ARC GIS; WUR (2013)
- ARC GIS tools; WUR (2013)

Competence strengthening / skills courses (2 ECTS)

- Academic English, scientific writing; Wageningen in'to Languages (2012)

PE&RC Annual meetings, seminars and the PE&RC weekend (1.5 ECTS)

- PE&RC Weekend (2012)

- PE&RC Annual PhD day (2012- 2013)

Discussion groups / local seminars / other scientific meetings (7.5 ECTS)

- AIGHD and AMC Amsterdam – Malaria maternal and infant health (2012)
- Yelrem symposium (2012-2015)
- Entomology day – NEV (2012-2015)
- Vector group meetings (2012-2016)
- PhD Student meetings Entomology (2012-2016)
- De anatomische les (2013-2014)
- College Tour – Bill Gates on funding research for tropical disease (2014)

International symposia, workshops and conferences (8.9 ECTS)

- 6th Multilateral initiative on malaria meeting; Durban, South Africa (2013)
- 12th INDEPTH Meeting; Johannesburg, South Africa (2013)
- 3th Challenges in malaria research; Oxford, UK (2014)
- 9th ECTMIH Meeting; Basel Switzerland (2014)
- 64th ASTMH Meeting; Philadelphia, USA (2015)

Lecturing / supervision of practical's / tutorials (3 ECTS)

- Biology of infectious disease (2014-2015)

Supervision of MSc students (9 ECTS)

- Epidemiology and risk factors of malaria
- Geographic risk factors for malaria
- Land use as predictor for malaria

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rond hete kolen

Wat als malariamuggen
niet konden vliegen,
wat als ze niet konden bijten,
fluisterend zoemen, fier
mooi prooi wezen –

was de wereld dan rond?

Ik wil niet op haar stampen,
wil om haar kunnen dansen