THE EVALUATION OF EASY ACCESS GROUPS AS A TOOL FOR MALARIA SURVEILLANCE IN CHIKHWAWA, MALAWI.

Thesis submitted in accordance with the joint requirements of

The University of Liverpool and the University of Malawi for the degree of

Doctor of Philosophy

by

Sanie Samuel Sogoyan Sesay

July 2014

Liverpool School of Tropical Medicine

Dedication

To my wife and lifelong partner, Regina whose unflinching love and support gave me the courage and determination to accomplish this feat.

To my children, Samuel, Joshua, Ruth and Ethan, who had to accommodate my intermittent absence while I chased my dream.

The evaluation of Easy Access Groups as a Tool for Malaria Surveillance in Chikhwawa, Malawi

Sanie Samuel Sogoyan Sesay

Introduction: Malaria is a major public health problem in Malawi and a lack of decline has been observed in the past decade despite the scaling up of control interventions. Continued surveillance for malaria is needed to evaluate the effects of the increased malaria control efforts, but obtaining estimates of malaria control indicators through population-based surveys is logistically and financially challenging. Surveillance in easy access groups (EAGs) provides a complimentary approach to measure malaria control indicators in different risk strata, but there is limited evidence on the comparability of measurements from such surveys and household surveys in the same population. We report the evaluation of several EAGs in the background of a concurrent continuous population-based household survey in the same catchment population.

Methodology: Between May 2011 and April 2013, within a 707km^2 high transmission rural area of Chikhwawa district in Southern Malawi, we conducted two continuous EAG surveys, one in children attending EPI clinics for "well child" visits and any accompanying sibling below 5 years, and one in all pregnant women attending ANC, to determine population estimates and geospatial heterogeneity of malaria burden and uptake of control interventions. We evaluated the accuracy of the EPI clinic survey by comparing to a random probability sample of the same age strata in the population, and used a combined geostatistical model to estimate and adjust for any residual bias. In the ANC survey we used a similar combined geostatistical model including a probability sample of women of childbearing age (15 to 49 years) from the population to validate our estimates. We also compared the performance of continuous surveillance in children attending EPI clinics with that of household surveys in determining short- to medium-term temporal trends in malaria control indicators.

Results: When we compared average estimates from the EPI clinic survey and a contemporaneous probability sample of the same population age strata, our results indicated that controlling for geospatial bias improved the accuracy and geospatial representativeness of estimates from this EAG. Our results also suggest that spatio-temporal models may be more appropriate to present short- to medium-term trends in malaria control indicators. When we used a combined geostatistical model including women attending ANC and a contemporaneous random sample of women of childbearing age in the population, our results indicated that primigravidae less than 20 years were the most likely risk strata in pregnancy to detect geographic variation in *Pf*PR. This risk strata however seemed less sensitive to small scale variations in transmission compared to children attending EPI clinics. We believed this to be due to a combination of higher age specific immunity in pregnant women attending ANC and decreased level of spatial accuracy due to the use of village-level coordinates in the ANC survey compared to household-level coordinates for children in the eMIS.

Conclusions: Surveillance in EAGs is promising complementary low-cost approach to monitor and/or target malaria control interventions. The use of a hybrid sampling methodology combining the EAG sample with a small probability sample of the population could resolve bias in the geospatial representativeness of the data. This method of surveillance urgently needs to be evaluated in other transmission settings.

Table of contents

List of tables

List of figures

Acknowledgements

I would like to thank the children and guardians of the Lower Shire River valley for their patience and willingness to participate in such a novel survey, the village leaders and community advisor group members for consenting to have these studies to be carried out in their communities, and helping us to inform the villagers about the studies and facilitating participation. I am indebted to the health facility staff in Chikhwawa District Hospital for assisting us in conducting the surveys. I send special thanks to the staff of the EPI clinic, ANC clinic, General OPD and Paediatric Surgical Ward in helping me implement the facility based surveillance. Dr. Elizabeth Nkosi the District Medical Officer for assisting in the administrative procedures required in setting up the study in the hospital and facilitating health facility staff cooperation; and Mr. Harvey Mkandawire the District HMIS coordinator for making hospital morbidity and mortality data available to guide the implementation of the study. I am also grateful to Mr. Adams Chavula of the Southern Regional Office of the Department of Climate Change and Meteorological Services in Malawi, for making climatic data in the study area available for use in our analyses.

This work would not have been possible without the endless efforts of staff at the Malawi-Liverpool Wellcome Trust (MLW). I am especially grateful to my outstanding project staff, Mrs. Evelyn Udedi, Mr. Chipiliro Moffat and Mr. Wilson Mataka, whose hard work and dedication made this work a success. I am grateful to staff of the ACTia study, especially Mr. Paul Chipeta and Miss Patience Korea for helping with the administration of the study; and Mr. Malango Msukwa and the staff of the Data Department for guidance in setting up the study electronic databases and data management issues. Thanks to the laboratory staff of the MLW for tolerating my continuous demands and producing high quality data, especially those in the ACTia who graciously accommodated my demands despite the high case load of the clinical trial. This work would have not been possible without the

assistance of the support staff of the MLW who arranged for equipment, supplies and logistics. I gratefully acknowledge the contribution of many scientists at the MLW, whom during the past four years help shape this research venture. I am very grateful for the friendship, support and advice I received from Prof. Robert Heyderman, the Director of the MLW, whose office was always open to PhD students.

This PhD was a joint effort at the College of Medicine (Malawi) and the Liverpool School of Tropical Medicine. I am grateful to Miss Helen Wong of the Liverpool School of Tropical Medicine (LSTM) for all her kind assistance in arranging all the logistics from the LSTM end. Thanks to you, I did not feel far from home when working in Liverpool. My thanks also to Dr. Brian Faragher for help with statistical issues, Prof. Paul Garner for his help on the review of previous evidence of evaluation of EAGs, and Dr. Anna Maria van Ejik for her critique of the ANC EAG. I am grateful to Dr. Wilson Mandala of the College of Medicine (CoM) who had to deal with incessant requests from MCDC students, yet was always please to see us at any time, whatever the problem. You taught us that there was no crisis that could not be solved by dialogue over a cup of tea and some lemon creams.

My sincere thanks go to my primary supervisor Dr. Anja Terlouw, who gave me the privilege of being one of her students and whose guidance, support and confidence enabled me to complete this work. Prof. David Lalloo, my secondary supervisor for always being there when I lost my way, struggled for inspiration, or lost all will to continue. The completion of this thesis is as much a testament to the support of my supervisors as it is to my will to get the job done. I am extremely grateful to my expert advisory panel, Prof. Feiko ter Kuile and Dr. Caroline Jeffery, for their encouragement and continued interest in my work. I am very grateful to Mr. Emanuele Giorgi of Lancaster University for gracefully

accommodating my frequent requests and helping me out with the geospatial analysis of the data.

Lastly, I sincerely thank my wife and kids for enduring my long absence from home and for their continuing support and encouragement.

This work would not have been possible without funding from the Malaria Capacity Development Consortium (MCDC) which is funded by Wellcome Trust (Grant number WT084289MA).

Declaration

The work in this thesis is the result of a collaborative research project between the EvalMal study and the ACTia study in Chikhwawa, Malawi. My involvement was mainly in the conduct of the EvalMal study and the details of my (SSSS) contribution to the work in this thesis is presented below. The geospatial analysis in this thesis was done with the help of Emanuele Giorgi (EG) of Lancaster University.

Study activity	**Responsible parties**
Project management:	
Project supervision	SSSS
Training of study staff	SSSS
Development of SOPs	SSSS
QC of study procedures	SSSS & Senior research nurse
Physical assessment of study participants	Research nurses
Informed consenting process	Research nurses & field worker
Determination of eligibility	Research nurses
Questionnaire administration	Research nurses
Specimen collection and processing	Research nurses
Laboratory tests:	
Rapid diagnostic tests	Research Nurses
Haemoglobin assessment	Research Nurses
Malaria microscopy	Laboratory technicians
QC of laboratory tests	Senior laboratory technician and MLW laboratory manager.
Data entry:	
EPI Clinic survey	Research nurses
ANC survey	MLW data entry clerks
Trauma survey	Research nurses
Market survey	MLW data entry clerks
Data cleaning	SSSS & MLW Data Manager
Data analysis	
General data analysis	SSSS
Geospatial data analysis	SSSS & EG

Abbreviations & Acronyms

ABER	Annual blood examination rate
ACT	Artemisinin combination therapy
ACTia	ACTs in action study
ADB	African Development Bank
ANC	Antenatal Clinic
API	Annual parasite incidence
APR	Anaemia (Hb < 8.0g/dl) prevalence rate
C	Vectorial capacity
CCTA	Commission for Technical Co-operation in Africa South of the Sahara
CDH	Chikhwawa District Hospital
CI	Confidence interval
COMREC	College of Medicine Research and Ethics Committee
CSA	Chondroitin sulfate-A
DDT	Dichloro-diphenyl-trichloroethane
DHS	Demographic and Health Surveillance System
DPT	Diphtheria Pertussis Tetanus
EA	Enumeration area
EAG	Easy Access Group
EIR	Entomological inoculation rate
ELISA	Enzyme-linked immunosorbent assay
eMIS	expanded Malaria Indicator Survey
EPI	Expanded Programme on Immunization

EvalMal	The evaluation of EAGs as a tool for malaria surveillance in Chikhwawa Malawi Study
GLM	Generalized linear model
GMAP	Global Malaria Action Plan
GPS	Global positioning systems
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information System
HRP2	Histidine rich protein 2
IFA	Indirect fluorescent antibody
IPTi	Intermittent preventive treatment in infants
IPTp	Intermittent presumptive treatment in pregnancy
IPTp-SP	IPT with SP
IRS	Indoor Residual Spraying
ITN	Insecticide Treated Net
LA	Artemether-Lumefantrine
LBW	Low birth weight
LLIN	Long-lasting insecticide treated net
LOWESS	Locally Weighted Scatterplot Smoothing
LQAS	Lot quality assurance sampling
LSM	Larval source management
LSTMREC	Liverpool School of Tropical Medicine Research Ethics Committee
M&E	Monitoring and evaluation
malERA	Malaria Research Eradication Agenda
MCH	Maternal and Child Health
MCML	Monte Carlo maximum likelihood estimation

MDA	Mass drug administration
MDG	Millennium Development Goals
MDHS	Malawi Demographic and Health Survey
MERG	Monitoring and Evaluation Reference Group
MICS	Multiple Cluster Indicator Surveys
MIP	Malaria in Pregnancy
MIS	Malaria Indicator Survey
MLW	Malawi-Liverpool-Wellcome Trust
MoH	Ministry of Health
MSP	Merozoite surface protein
NID	National immunization day
NIHR	National Institute for Health Research
NMCP	National Malaria Control Programme
NMSP	National Malaria Strategic Plan
OD	Optical density
OPD	Out-patient Department
PCR	Polymerase chain reaction
PDA	Personal digital assistant
PfAPI	*Plasmodium falciparum* annual parasite incidence
***Pf*EIR**	*P. falciparum* entomological inoculation rate
***Pf*PR**	*Plasmodium falciparum* prevalence rate
***p*LDH**	*plasmodium* Lactate Dehydrogenase
PMI	President's Malaria Initiative
PPR	Parasite prevalence rate
PR	Parasite Rate

PREGACT	Safe and efficacious artemisinin-based combination treatments for African pregnant women with malaria
***Pv*API**	*Plasmodium vivax* annual parasite incidence
***Pv*PR**	*Plasmodium vivax* prevalence rate
R_0	Basic reproductive rate
RBM	Roll Back Malaria Programme
RD	Risk difference
RDT	Rapid diagnostic test
REDCap	Research Electronic Data Capture
rMIS	rolling Malaria Indicator Survey
RR	Risk ratio
SD	Standard deviation
SES	Socioeconomic status
SMC	Seasonal Malaria Chemoprevention
SOP	Standard operating procedure
SP	Sulfadoxine–pyrimethamine
SPR	Slide positivity rate
T3	Test, Treat, Track Initiative
TA	Traditional authorities
U5MR	Under-fives mortality rate
UNICEF	United Nations Children Fund
WHO	World Health Organisation
WHOPES	WHO Pesticide Evaluation Scheme
WINPEPI	Windows Program for epidemiologists

Chapter 1: Introduction and objectives

1.1 Topic overview

1.1.1 Introduction

Malaria is the most important human parasitic infection with an estimated 3.3 billion, or 40 percent of the world's population, at risk for malaria. Malaria is a protozoan disease caused by over 100 parasite species and infection has been found in a wide range of vertebrates including reptiles and birds. Malaria is transmitted by *Anopheles* mosquitoes and five species of the genus *Plasmodium* are responsible for all human infections: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*(Snow and Gilles, 2002). The greatest global clinical burden is due to *P. falciparum* and *P. vivax*. *P. falciparum* predominates in sub-Saharan Africa and parts of Oceania (Gething et al., 2011; Gething et al., 2012), whilst *P. falciparum* and *P. vivax* are roughly equally prevalent in most of Asia and South and Central America (Gething et al., 2011; Gething et al., 2012). Ongoing malaria transmission is present in 97 countries, and, in 2012, it caused an estimated 207 million cases and 627 000 malaria deaths (WHO, 2013a). Young children and pregnant women are at greatest risk of malaria-related morbidity and mortality, especially in areas of stable transmission. Sub-Saharan Africa bears the brunt of the burden of malaria with more than 80% of all malaria cases and 90% of all malaria deaths(WHO, 2013a). Most cases of morbidity and mortality are caused by *P. falciparum* though recently *P. vivax* is proving to be an important cause of morbidity and mortality (Tjitra et al., 2008; Kochar et al., 2009; Price et al., 2009). *Plasmodium knowlesi*, a zoonotic infection originally found in *Macaca fascicularis* monkeys is further emerging as a cause of severe and fatal human disease (Cox-Singh et al., 2008; Kantele and Jokiranta, 2011; William et al., 2011; Antinori et al., 2013).

Over the past decade, an increase in funding to support malaria control has allowed the widespread deployment of proven interventions in many endemic countries, contributing to substantial reductions in malaria morbidity and mortality in some countries (Nyarango et al., 2006; Bhattarai et al., 2007; Erhart et al., 2007; Sharp et al., 2007; Ceesay et al., 2008; O'Meara et al., 2008a; Rodrigues et al., 2008;

Ceesay et al., 2010). A major turning point for malaria control was the call for renewed effort at achieving malaria eradication by Bill and Melinda Gates in October 2007 (Roberts and Enserink, 2007). These led to renewed motivation for malaria control and the re-establishment of the global agenda of malaria elimination with possible eradication(Tanner and de Savigny, 2008). A rigorous scientific consultative process involving more than 250 scientists, the Malaria Eradication Research Agenda (malERA) initiative(WHO, 2008), was set up to ascertain knowledge gaps and new tools that will be needed to eradicate malaria globally and to complement the Global Malaria Action Plan (GMAP)(RBM, 2008a). A research agenda for malaria eradication was published in a Public Library of Science (PLoS) Medicine monographic volume(malERA, 2011a) to guide the research and development priorities for malaria eradication. Around the same time, a paradigm shift occurred from improving malaria control and reducing morbidity and mortality, to the development of tools interventions and strategies to interrupt transmission and lead to the ultimate eradication of parasitic infection from the human population. National Malaria Control Programs (NMCPs) are now tasked with obtaining accurate timely estimates of malaria transmission to determine the health impact of deployed control interventions through nationally representative population surveys; a process that will become increasingly intensive as transmission intensity falls(Hay et al., 2008). As the current indication is that malaria transmission intensity will continue to fall in endemic areas (Snow et al., 2012), there is an urgent need to develop complementary, robust and cost-effective methods to provide timely estimates of malaria transmission intensity to track control progress.

To appreciate the need for the development of novel tools for malaria surveillance, an understanding of the current tools to monitor control progress and the effect of the changing global malaria epidemiology on current tools is required, and this is described briefly in the two next sections.

1.1.2 Current tools to evaluate control progress

Currently, the most endorsed tools to evaluate control progress are nationally representative household surveys like Malaria Indicator Surveys (MISs)(RBM MERG, 2005; MEASURE Evaluation et al., 2013b), Demographic and Health Surveys (DHSs)(ICF International, 2012a) and UNICEF Multiple Indicator Cluster Surveys (MICSs) (UNICEF, 2012d) that are designed to provide summary estimates of progress of different public health interventions at the national level.

Demographic and health surveys are standardized, household surveys that collect a wide range of data on population, health and nutrition(ICF International, 2012a). They are intended to provide decision-makers in participating countries with reliable information and analyses useful for informed policy choices. Since the inception of DHS in 1985, more than 275 DHSs have been conducted in more than 90 countries. Multiple indicator cluster surveys are designed to provide up-to-date, high quality data to monitor the health situation of children and women around the world, in order to monitor progress toward national goals and global commitments, including the Millennium Development Goals (MDGs)(Child Info, 2012). Since its inception in 1995, 240 MICSs have been conducted in approximately 100 countries worldwide. Both DHSs and MICSs provide accurate estimates of all-cause mortality rates in children < 5 years old, useful in countries with high malaria burden. They also provide estimates for the prevalence of febrile illness in children in a two-week period. This is difficult to interpret as an indicator of malaria morbidity and has now been dropped as a MIS indicator(MEASURE Evaluation et al., 2013b).

To complement the ongoing efforts of DHSs and MICs, the World Health Organisation's (WHO's) Roll Back Malaria Partnership (RBM) developed MISs as a standalone tool designed to collect nationally representative population estimates of key malaria-specific household coverage indicators (e.g. coverage with indoor residual spraying or IRS) and morbidity indicators from the population at risk for

malaria (e.g. parasite prevalence in children less than five years old)(RBM MERG, 2005; MEASURE Evaluation et al., 2013b). Since its inception in 2005, more than 25 MISs have been completed.

1.1.3 The changing global malaria epidemiology and its impact on malaria surveillance

The changing global malaria epidemiology has presented NMCPs with several new challenges in deriving accurate estimates of control progress. Firstly, there are different priorities for surveillance at different levels of transmission intensity and phases of control(WHO, 2012a; WHO, 2012b). This requires re-orientation of the program focus as transmission intensity falls. Timely estimates of control progress allow NMCPs to make an informed choice on when to restructure their control strategy to minimize wastage of resources. The long interval between currently recommended surveys (usually 3-5 years) limits the monitoring of short- to medium-term changes in control progress, which would give NMCPs forewarning on when to adapt their control strategy. Secondly, as transmission drops, NMCPs will be faced with the logistically and financially demanding task of carrying out ever larger population surveys, to reach the elimination threshold. Once elimination is achieved a complete program reorientation is required to focus on measuring malaria incidence by malaria case detection through a comprehensive system of passive and active surveillance (Hay, Smith & Snow 2008). Thirdly, as malaria transmission intensity continues to fall, the distribution of transmission will become localized and a more targeted approach involving detecting and eradicating hotspots will become increasingly important (Bousema et al., 2012).

The Wold Health Organization defines a focus of malaria transmission as a geographic area with current or previous transmission containing the continuous or intermittent epidemiological factors necessary for malaria transmission (WHO, 2007b). A hotspot is consequently defined a usually smaller region of a focus of

malaria transmission where transmission intensity exceeds the average level (Bousema et al., 2012). In order to be able to measure heterogeneity in transmission and potentially capture hotspots, the collection of spatially representative data will be required (Clements et al., 2013). Because the two-stage cluster sampling technique of the nationally representative household surveys does not always include all districts and the number of clusters within a district is small(MEASURE DHS, 2013a), data from these surveys is not representative at the district level unless a specific attempt is made to collect an appropriate sample from every district which would drastically increase the total sample size. Though hotspots vary in size, they are usually $1km^2$ (Bousema et al., 2012) and the collection of geographic information as recommended during MISs (MEASURE DHS, 2012) is inadequate to detect hotspots due to the small number of enumeration areas sampled, and the small number of households assessed per enumeration area (MEASURE DHS, 2013a). The total sample size required using the MIS technique in order to adequately measure heterogeneity and target 'hotspots' would be logistically and technically challenging for NMCPs.

Finally, the recent levelling off of malaria funding at US$ 2.5 billion in 2012 (short of the US$ 5.1 billion required to achieve universal coverage of malaria interventions) resulting in a consequent levelling off of control progress(WHO, 2013a) means that NMCPs will face above challenges with little or no increase in funding. Developing novel tools to provide timely estimates of malaria control progress at the district and sub-district level, complementary to currently recommended tools, is of critical importance as malaria transmission intensity falls and its distribution becomes more localized. This thesis examines whether surveillance in easily accessible sub-groups of the population is one such potential tool.

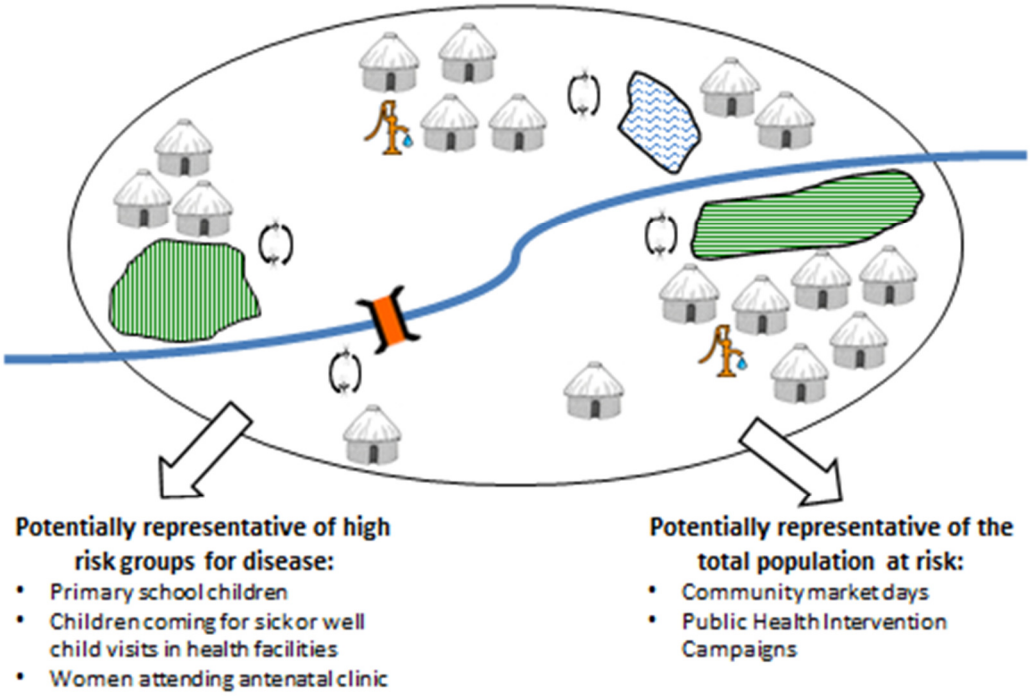
1.1.4 The easy access group concept

Individuals from several human settlements with different ecological characteristics may routinely assemble in one geographic location (e.g. a school or a clinic) for a variety of reasons in a way that makes them easy to access and logistically attractive to sample; or may be accessible as part of an activity that either makes the whole population or sub-set of the population available to surveillance (e.g. mass drug administration and catch-up vaccination campaigns respectively). These so called easy access groups (EAGs) (Figure 1) might be opportunistically surveyed to derive estimates of disease burden and uptake of public health interventions. The identification and selection of individuals to be surveyed becomes simplified resulting in cost saving due a reduction in the personnel and logistics required when compared to household surveys (Brooker et al., 2009). EAGs potentially representative of high risk groups for malaria morbidity and mortality include school children, children coming to health facilities for sick or well visits and women attending antenatal clinics (ANC) (Figure 1). EAGs potentially representative of the population at risk of malaria infection include all patients reporting to health facilities, people exposed to a public health intervention survey and people attending community market days (Figure 1). This thesis attempts to evaluate the evidence available on these potential EAGs and assesses the most promising for district or sub-district level surveillance.

In order to evaluate EAGs as a potential tool for malaria surveillance, the validity of estimates of control progress derived from EAGs needs to be assessed and in case any inherent bias is observed, whether this can be resolved by appropriate statistical techniques. Though several studies have explored EAGs as a surveillance tool, only a few have compared their obtained estimates to population surveys (Ndyomugyenyi and Kroeger, 2007; Skarbinski et al., 2008; Mathanga et al., 2010; Gahutu et al., 2011; Oduro et al., 2011b; Stevenson et al., 2013), only one study has attempted to improve the accuracy of estimates by statistical techniques

(Mathanga et al., 2010). None have used geospatial statistical methods to resolve bias in estimates.

Figure 1: The Easy Access Group concept



1.2 Rationale for the study

Determining whether EAGs can be used to reliably monitor the burden of transmission and uptake of control interventions could have important public health implications as this offers a potentially cost effective surveillance tool at district level that may be complementary to nationally representative surveys especially in the interval between surveys. This is particularly important as malaria endemic countries scale-up existing evidence-based malaria prevention and control strategies including the use of insecticide treated bed nets (ITNs), IRS, chemoprevention (intermittent presumptive treatment in pregnancy (IPTp) and

Seasonal Malaria Chemoprevention (SMC) and prompt effective diagnostic testing and treatment, to achieve universal coverage targets.

In the past decade, malaria transmission in Malawi has remained relatively stable in the context of increasing coverage with control interventions (Roca-Feltrer et al., 2012a; Okiro et al., 2013). Progress in control interventions has been substantial in recent years with an increase in the proportion of children under the age of five years who slept under an ITN at night from 25.0% in 2006 (National Statistical Office, 2007) to 55.4% in 2010 (Ministry of Health (MoH) Malawi, 2010). This increasing coverage of control interventions is expected to have a measurable impact on malaria transmission which makes it an opportune time to validate such a tool by comparing estimates from EAGs to a 'gold' standard MIS in the same geographic area.

1.3 Study aims and objectives

Aim: To determine if measurement of malaria control indicators from children coming for well child visits at the EPI Clinic and women attending ANC could be a comparable alternative to that from a standard population-level household survey in the same catchment population.

Primary objective: To determine if average estimates of control intervention coverage and malaria transmission derived by surveys in children coming for well child visits at the EPI Clinic aged 6 to 59 months are significantly different from a 'gold' standard household survey of a probability sample of a similar age strata in the population (i.e. the rMIS/eMIS).

Plasmodium falciparum prevalence (*Pf*PR) was selected as the primary indicator of malaria transmission as it forms a reliable indicator of endemicity (Hay et al., 2008; Gething et al., 2011). Moderate to severe anaemia (Hb<8.0g/dl) was chosen as the secondary indicator to assess the transmission as it has been shown to be a reliable indicator that reflects the impact of malaria interventions (Korenromp et al., 2004; RBM et al., 2009). Intervention trials have shown that malaria control reduces the prevalence of moderate-to-severe anaemia (i.e. Hb<8g/dL) more so than it reduces the prevalence of milder anaemia (i.e. Hb<11g/dL) (Korenromp et al., 2004).

Secondary objectives:

1. To compare the performance of surveillance in children aged 6 to 59 months coming for well child visits at the EPI Clinic versus a population-based household survey in the same age strata in determine geospatial patterns in the distribution of key malaria control indicators.
2. To determine whether any significant bias (i.e. differences in average and spatial estimates of burden and intervention coverage from children coming for well child visits compared to gold standard MIS estimates) can be adjusted for by classical and geospatial statistical techniques.
3. To determine the potential of surveillance in children coming for well child visits in providing estimates of temporal trends in control intervention coverage and malaria transmission.
4. To assess the feasibility of surveillance in women attending ANC as a tool for providing accurate estimates of spatial heterogeneity in *Pf*PR by comparing to a contemporaneous probability sample of children aged 6 to 59 months from the same catchment population.

1.4 Thesis Outline and Chapters

1.4.1 Overview of Thesis Outline

The thesis consists of four sections. The first section consists of introductory chapters providing an overview of the topic, the study rationale, review of literature and a systematic review of studies comparing EAGs to population estimates of control progress. The second section covers a description of the study design and methods of the overall study. The third section is the results section including four results chapters corresponding to the study specific objectives. The fourth and final section includes a chapter that consolidates the main findings in the form of a general discussion with recommendations on surveillance in EAGs and areas for future research.

1.4.2 Thesis Sections and Chapters

Section I: Introduction and Literature Review

- Chapter 1: An introductory chapter including the rationale and objectives.
- Chapter 2: A review of the literature describing the current understanding of the epidemiology of malaria, development of malariometry and sampling methods for malaria surveillance.
- Chapter 3: Provides the theoretical basis for surveillance in EAGs, a summary of current evidence on potentially suitable EAGs, and a qualitative and quantitative summary of the evidence on surveillance in these EAGs in the form of a systematic review.

Section II: Design and Methods

- Chapter 4: An overview of the study design and methodology, study outcomes, study area, survey procedures and statistical analysis.

Section III: Easy Access Groups

- Chapter 5: Evaluates surveillance of children coming for well visits as a tool for measuring malaria control progress, including resolving any bias in estimates by classical and geospatial statistical techniques.

- Chapter 6: Evaluates surveillance of children coming for well visits as a tool for measuring temporal trends in malaria control progress.
- Chapter 7: Evaluates the surveillance of women attending antenatal clinics as a tool for measuring population *P. falciparum* prevalence.

Section IV: Discussion and recommendations

- Chapter 8: Discusses the main findings of chapters 4 to 6 and provides recommendations for surveillance in EAGs and future research.

Chapter 2: Literature review

2.1 Introduction

Malaria transmission intensity affects most aspects of its epidemiology including the disease at-risk groups, the development of acquired immunity and the pattern of morbidity and mortality (Snow et al., 1997; Snow and Marsh, 2002; Struik and Riley, 2004; Reyburn et al., 2005; Desai et al., 2007). Accurate and timely estimates of malaria transmission intensity are therefore necessary to evaluate options for malaria control in different regions, plan an appropriate intervention strategy and to evaluate control progress. We are at an exciting time for malaria control because we have the roadmap for elimination (Feachem and The Malaria Elimination Group, 2009; PLoS Medicine, 2011). The recent worrisome trend of levelling off of malaria funding to an average of 4% per year between 2009 and 2013, compared to an average of 43% per year between 2005 and 2009 (WHO, 2013a) could however jeopardize progress with malaria control and eventual elimination. In order not to lose the gains in control already made, we need to develop robust cost-effective approaches to monitor control progress that are complementary to currently validated tools. EAGs could provide a low cost approach to malaria surveillance complementary nationally representative household surveys, as has been suggested for school surveys (Gitonga et al., 2010).

The term malariometry is applied to the epidemiological measure of capability of a geographic area to support active malaria transmission (i.e. its endemicity) (Bruce-Chwatt et al., 1973), and may broadly be classified as direct and indirect epidemiological measures of risk of malaria transmission. Indirect measures gauge malaria endemicity through surrogate indicators such as rainfall, humidity, temperature, altitude, spleen rates, antibody titres, anaemia and patterns of antimalarial drug use. The inclusion of the measurement of environmental variables (e.g. rainfall, temperature, altitude) as indirect measures is based on the fact that these key variables govern the activity and abundance of *Anopheline* mosquitoes and thus their ability to transmit malaria, if there is an available pool of infectious humans. Direct measures involve the assessment of the risk of malaria

infection which normally involves confirmation of malaria infection (by microscopy, rapid diagnostic test (RDT) or polymerase chain reaction (PCR)), and is usually presented in the form of epidemiological indices with a variety of denominators representing the population at risk over a specified time period.

This chapter describes the current understanding of the epidemiology of malaria, development of malariometry, sampling methods for malaria surveillance, theoretical basis for surveillance in EAGs, and provides a summary of the current evidence on EAGs that offer the opportunity for the surveillance of malaria at a district level. The EAGs mentioned in this chapter were selected either because there was historical evidence that they had been used for malaria surveillance or they satisfied the criteria for surveillance including cost, usefulness and quality e.g. representativeness, simplicity and acceptability (Thacker et al., 1988).

2.2 The evolution of malariometry

This section strives to describe the evolution of malariometry from the lessons learned from earlier efforts, to the advent of mathematical modelling and development of new technology to assist measuring indices (e.g. PCR) and finally consensus on the current measures of endemicity. Most efforts to classify malaria endemicity focused on *P. falciparum* malaria as it was considered the main threat at that time, but recent attempts have been made to classify the endemicity of P. vivax malaria (Gething et al., 2012). Historical landmarks in malaria control and eradication efforts are mentioned where they impacted on the development of malariometry as we know it today.

2.2.1 Earlier efforts at malariometry

The first documented method of malariometry was the introduction of the spleen rate (the proportion of the population with palpable splenomegaly) by Dempsey in India in 1847. From then on, as more information about malaria

became apparent, there was active and prolonged debate as how to classify the information from malariometric surveys into endemicity, and consensus was only achieved relatively recently (Hay et al., 2008; Gething et al., 2011). The first practical attempt to use malariometry to aid control efforts was the US Army's campaign using environmental management control malaria in Havana and in the Panama Canal, as part of public health control measures during the US' occupation (Le Prince and Orenstein, 1916a; Le Prince and Orenstein, 1916b). The impact of these control measures on the population was assessed using records of the number of deaths due to malaria per 10,000 population in Havana (Le Prince and Orenstein, 1916a) or the monthly percentage of malaria cases amongst employees of the Isthmian Canal Commission admitted to hospital in the Panama Canal (Le Prince and Orenstein, 1916c). These indicators were successfully able to illustrate the effect of the control programme with malaria being declared effectively eradicated from both areas in 1914.

Despite the success of the metrics deployed in the US Army's malaria eradication campaign, the first attempt at consensus to classify the endemicity of malaria was during the Malaria conference in Equatorial Africa held under the joint auspices of the Commission for Technical Co-operation in Africa South of the Sahara (CCTA) and WHO in 1950 in Kampala, Uganda (WHO, 1951) (Table 1), more than a hundred years after the initial classification of endemicity suggested by Dempsey. This system of classification categorized endemic areas into hypo-, meso-, hyper- and holoendemic on the rates of splenomegaly in children aged 2-9 years (Table 1). This classification was short-lived and the consequent discovery that adults in holoendemic regions had a high frequency of palpable splenomegaly despite a considerable degree of immunity (Metselaar, 1956) questioned the reliability of such a classification. A revised classification was proposed by Mestelaar & Van Thiel in 1959 based on asexual parasite rate (PR) by microscopy during malariometric surveys and this was later adopted (WHO, 1963) (Table 1). This classification was also not without controversy at the time as it was more invasive because of the requirement for blood sampling, was logistically more

complex, and the epidemiological index suggested it was affected by seasonality (WHO, 1963).

Table 1: Classification of malaria endemicity based on splenomegaly and parasitaemia

Endemicity	**Spleen rates** (WHO, 1951)	**Parasite rate** (WHO, 1963)
Hypoendemic	0 – 10% in children aged 2 – 9 years	< 10% in children aged 2 – 9 years as a rule; may be higher for parts of the year
Mesoendemic	11 – 50% in children aged 2 – 9 years	11 – 50% in children aged 2 – 9 years
Hyperendemic	Constantly > 50% in children aged 2 – 9 years; also high in adults (over 25%)	Constantly > 50% in children aged 2 – 9 years
Holoendemic	Constantly over 75% in children aged 2 – 9 years; low in adults, adult tolerance of malaria infection high	Constantly > 75% among infants aged 0 – 11 months

2.2.2 The Ross-Macdonald model

At the time of the Malaria Conference in Equatorial Africa, George Macdonald was an important voice of opposition to this system of classification preferring the stable-unstable classification of endemicity (Macdonald, 1952) developed from the dynamic model of transmission used by Sir Ronald Ross (1857 – 1932) to describe the lifecycle of malaria in anopheline mosquitoes and humans (Ross, 1916; Ross and Hudson, 1917b; Ross and Hudson, 1917a). Macdonald developed this model due to improved information about the population dynamics of anopheline mosquitoes at the time and summarized the model in what has become known as the Ross-Macdonald model below(MacDonald, 1957a):

$$R_0 = \frac{ma^2bcp^n}{r(-lnp)} \qquad (1)$$

where

'R_0' is the expected number of hosts who would be infected by a single infectious person, introduced into an otherwise naive population, after one generation of the parasite i.e. the basic reproduction rate

'm' the ratio of anopheline mosquitoes to human beings,

'a' the human biting rate (number of bites on a human being per anopheline mosquito per day),

'b' the transmission efficiency of infected anopheline mosquito to a human being,

'c' the transmission efficiency of an infected human being to an anopheline mosquito,

'p' the proportion of anopheline mosquitoes surviving daily,

'n' the duration of sporogony (days)—the process of parasite development occurring in the anopheles mosquito that follows sexual union of gametes and ends with the formation of infective sporozoites, and

'r' the rate of recovery of the human being from infection (days), so that 1/r is the human infectious period.

Using this model, Macdonald successfully showed that the stability of malaria transmission was determined by a stability index defined as the average number of blood feeds a female anopheline mosquito takes in humans throughout its adult lifespan (Macdonald, 1952):

$$Stability\ index = \frac{a}{-lnp} \quad (2)$$

Stable transmission that was not sensitive to climatic variation and resistant to control efforts was achieved with stability indexes higher than 2.5. Unstable malaria transmission that was extremely sensitive to climatic variations and control efforts was achieved with stability index values less than 0.5 and in between stability was variable (Macdonald, 1952).

Macdonald introduced the concept of the use of the basic reproduction rate (R_0) as an indicator of endemicity and that the objective of control was to reduce to R_0 less than 1.0 and maintain it at that level until the number of cases eventually diminished to zero. The mathematical modelling done by Macdonald indicated the strong impact of adult mosquito mortality on interrupting transmission (Macdonald, 1956b; MacDonald, 1957a) and that together with the efficacy of dichloro-diphenyl-trichloroethane (DDT) used as IRS at the time (WHO, 1951) were the key motivating factors resulting in adoption of the Global Malaria Eradication Plan (GMEP) at the 8th World Health Assembly in Mexico in 1955 (WHO, 1973).

2.2.3 Metrics derived directly from the Ross-Macdonald model

Other malariometric indicators were derived from the Ross-Macdonald model focusing on the activity of the anopheline mosquito: the vectorial capacity (C) and the entomological inoculation rate or EIR (h'). Of these, the later was to become more widely used as a method of assessing endemicity.

The vectorial capacity, which is a quantitative index of a mosquito population's capacity to transmit malaria, was later suggested as another vector-based malariometric (Garrett-Jones, 1964). Vectorial capacity (C) defined as the average number of inoculations with a specified parasite resulting from one case of malaria in unit time that the population will distribute to man if all female mosquitoes biting the case became infected and summarized as the equation below:

$$C = \frac{ma^2p^n}{-lnp} \qquad (3)$$

The vectorial capacity is a direct derivation from the Ross-Macdonald equation (Macdonald, 1957b) and all variables on the right side of the equation are the same as in equation (1). Vectorial capacity's principal function was to assess the impact of control interventions, where for example a consistent downward trend would indicate effectiveness of control interventions (Garrett-Jones, 1964).

The EIR was another suggested vector-based malariometric derived from the Macdonald-Ross equation (Macdonald, 1957b). The equation for the EIR (h) is as follows:

$$h' = mas \tag{4}$$

The variables 'm' and 'a' are the same as in equation (1), and 's' is the proportion of mosquitoes with sporozoites in their salivary glands. The EIR was considered a more reliable vector-based malariometric than vectorial capacity as it provided both a measure of exposure to infective bites and transmission intensity (Burkot and Graves, 1995) and could be used to evaluate the suitability of vector control methods (Coosemans et al., 1992).

2.2.4 Improvements on the Ross-Macdonald model through mathematic modelling

Since first proposed by Ross and Macdonald, mathematical models have provided greater insights into malaria controls and have aided the measurement of change in malaria endemicity and hence their impact (Najera, 2000; McKenzie and Samba, 2004). The use of such models in the Global Malaria Eradication Program (Macdonald, 1956a) and the information from important studies like the Garki Project (a large population-based longitudinal study of human malaria in the absence of control interventions in Garki District, Kano State, Nigeria) (Molineaux et al., 1980), led to their improvement including the consideration of the effect of other key variables like human immunity and seasonality (Aron, 1988; Smith and McKenzie, 2004; Smith et al., 2005; Smith et al., 2007b). Smith et al then proposed a model (Smith et al., 2007b) using the estimates of annual EIR and PR from studies of 121 African populations (Hay et al., 2005) to validate their assumptions. According to Smith et al 2007:

$$R_0 = E\frac{c_0 b_0}{r}\frac{(1 + S\sigma\bar{X})}{\sigma\bar{X}}B_E(1 + \alpha) \tag{5}$$

where

'R_0' is the expected number of hosts who would be infected by a single infectious person, introduced into an otherwise naive population, after one generation of the parasite

'c' the infectivity of humans to mosquitoes: the probability that a mosquito becomes infected from a bite on an infected human

'b' the infectivity of mosquitoes to humans: the probability that a human becomes infected from a bite by an infectious mosquito

'1/r' the expected time to naturally clear a simple infection

'E' the EIR

'S' the stability index: the expected number of bites taken by a vector over its lifetime.

'σ' the sampling bias index: the proportion of mosquitoes that become infected after biting a human divided by the proportion of people with detected parasites

'α' the biting disparity index: the squared coefficient of variation of the human biting rate

'B_E' the susceptibility bias index: the infectivity of mosquitoes in a naïve population divided by the infectivity of mosquitoes in an endemic population

The model proposed by Smith et al further corroborated the significance of R_0 as an indicator to measure malaria endemicity and thus control progress(Smith et al., 2007b).

At this stage in the evolution of malariometry, there was consensus that basic reproductive number (R_0) was the most appropriate way to measure endemicity. However, due to difficulties in its direct measurement (Dietz, 1993; Smith et al., 2007b), Hay et al 2008 suggested the measurement of the *P. falciparum* parasite rate (*Pf*PR) and the *P. falciparum* EIR (*Pf*EIR) as suitable proxies throughout the range of endemicity (Hay et al., 2008). Using public domain data on the annual

parasite incidence of *P. falciparum* from 85 countries, combined with other medical intelligence data, remote sensing surfaces and biological models, Gething et al 2011 further suggested the measurement of the *P. falciparum* parasite rate in 2 to 10 year olds (*Pf*$PR_{2\text{-}10}$) (Gething et al., 2011). In the same paper Gething et al 2011 noted that levels of malaria endemicity were spatially heterogeneous and that this state was temporally dynamic necessitating the generation of accurate maps that need to be regularly updated.

2.3 Current malariometric indicators

The evolution of malariometry with time resulted in the development and application of many approaches to measure malaria risk and not all of the current indicators are intended to measure endemicity. Some indicators are intended to measure impact of control (e.g. anaemia), and others to improve the interpretation of other measures (e.g. serology) or to detect when a change is required in the control strategy (e.g. infant parasite prevalence as a percentage of the total population prevalence).

2.3.1 Measures of prevalence of infection in the population

Parasite prevalence rate

The parasite prevalence rate (PPR) is a measure of the prevalence of asexual peripheral blood-stage infection in a population (equation (6)) and has been the most evaluated metric of malaria endemicity (Guerra et al., 2007). It is actually a proportion as measurement is usually at one time point in the year (i.e. point prevalence), and so its value can be affected by within- and between year variations (like seasonality and sudden changes weather pattern respectively). Despite this PPR is a good metric to assess short- to medium term impact of scaling up of malaria control efforts, as it sensitive to changes in transmission intensity.

$$PPR = \frac{No.\,people\ with\ parasitaemia}{Total\ number\ of\ people\ examined} \times 100 \qquad (6)$$

Table 2: The pros and cons of using RDTs and microscopy to determine PPR during population-based surveys (Adapted from: Household Survey Indicators for Malaria Control (MEASURE Evaluation et al., 2013a))

	Rapid Diagnostic Test	**Microscopy**
Pros	• Use requires less training than microscopy • Results are rapid (within 15 minutes), thus facilitating timely treatment. • In survey settings, costs are lower than microscopy • Currently available RDTs have sensitivity and specificity comparable to routine microscopy	• Historically, considered the gold standard for malaria diagnosis • Permits speciation and quantification of parasites. • Can detect low infection (<200 parasites/µl), assuming skilled microscopist • Historical comparisons possible assuming comparable skill of microscopists and consistency of methods of quantification over time. • Slides can be stored and re-examined, enabling retrospective quality control
Cons	• Individuals may test positive by Histidine Rich Protein 2 (HRP2)-based RDTs within 14 days after effective treatment for malaria, as antigens often persist after treatment • Variation may exist between brands and types of RDTs (including the antigens are detected) and this could affect the comparability of survey results. • Tests that detect other species do not identify which is present • Quantification of parasites is not possible • Sensitivity is low for low parasite densities	• Practical difficulties preparing blood films in the field. • Slides must be transported and stored. • Results take longer (more than 15 minutes) • In survey settings, costs are higher than RDTs • Skilled microscopists are not always available and this might affect the quality of speciation and quantification • Intra-observer variation is likely to occur between microscopists.

Since the majority of malaria infections and gametocyte carriage are asymptomatic regardless of transmission (Park et al., 2000; Pinto et al., 2000; Alves et al., 2002; Bousema et al., 2004; Macauley, 2005; Laishram et al., 2012), the parasite prevalence rate assessed through population-based cross-sectional surveys is a better measure of endemicity than the prevalence in clinical cases. Diagnostic confirmation of the presence of infection during this surveys is normally through microscopy or RDT (MEASURE Evaluation et al., 2013a). Though microscopy is

historically considered as the "gold" standard for the diagnostic confirmation, RDTs are increasingly being view as a suitable objective particularly where P. falciparum accounts for more than 90% of all malaria infection and low level infections (<200 parasites/μl) are uncommon (MEASURE Evaluation et al., 2013a). The use of RDTs has some advantages over microscopy in survey settings as they provide timely results and have comparable sensitivity and specificity (Table 2). There is also a mechanism in place for the regular evaluation of the performance of RDTs through the WHO Product Testing Programme and this information is updated regularly with the most recent report being Round 3 (WHO, 2011a).

Polymerase chain reaction (PCR) has been reliably used as a complementary tool in malariometric surveys (Satoguina et al., 2009; Takem et al., 2013), but because of cost and the requirement of advanced laboratory facilities, PCR has been more of a research tool for the quality control of speciation and quantification (Stich et al., 2006; Ebrahimzadeh et al., 2007; Schachterle et al., 2011; Asih et al., 2012; Fancony et al., 2013). Recent developments with molecular-based isothermal tests means that field deployment of PCR is now possible (Oriero et al., 2014), and this has promising prospects for malaria surveillance given the fact that plasmodium DNA can be recovered from alternative specimens like saliva (Nwakanma et al., 2009; Estevez et al., 2011). Polymerase chain reaction has great potential in the detection of sub-microscopic infection (Golassa et al., 2013; Mosha et al., 2013) which will be of increasing importance as transmission falls (Harris et al., 2010; Golassa et al., 2013).

The classification of malaria of endemicity based on PPR was a subject of much debate and consensus was only achieved recently as part of the development of the Malaria Atlas Project (Guerra et al., 2007; Hay et al., 2008; Gething et al., 2011; Gething et al., 2012) and efforts to guide malaria control and eradication strategy based on classification of malaria risk (Hay et al., 2008) (Table 3and Table 4). This represented a revision of the classification proposed earlier by Metselaar & Van

Thiel (WHO, 1963) and an expansion to include classification of the endemicity of *P. vivax* (Gething et al., 2012). The recommendation of both systems of classification is that the endemicity be classified by the species specific PPR in population at risk. Gething et al 2011 went further to specify that the population at risk as children aged 2 to 10 years influenced by the earlier work of Smith et al, who tested algorithms for the age-standardization of *Pf*PR and concluded that that age group was the most appropriate the purposes of comparing studies and mapping malaria endemicity (Smith et al., 2007a). The age at risk for *P. vivax* infection was considered to be all individuals aged 1 to 99 years, and the all-age infection prevalence the appropriate measure to classify endemicity (Table 4) (Gething et al., 2012).

Table 3: Current classification of *P. falciparum* malaria endemicity by *P. falciparum* Prevalence Rate (*Pf*PR)

Endemicity	***Pf*PR** (Hay et al., 2008)	***Pf*PR$_{2-10}$** (Gething et al., 2011)
Intense stable (hyper-holoendemic)	≥40%	≥40%
Moderate stable (hypo-mesoendemic)	5.1 – 39.99%	5.1 – 39.99%
Unstable endemic	≤5.0%	≤5.0%
Non-endemic	*	*
Malaria free	*	*

*At this point *Pf*PR is not a reliable estimate of endemicity and *P. falciparum* annual parasite incidence (*Pf*API) is preferred.

Despite the recent evidence, it is still the policy-recommended approach to assess national-level PPRs for *P. falciparum* in children aged 6-59 months during population-based surveys; and that the PPR in older age groups should only be measured when there is no clear age pattern in infection, prevalence is low, malaria transmission is unstable or information is required for the modelling of malaria incidence (MEASURE Evaluation et al., 2013a). However, the assessment of parasite prevalence in children aged 2 to 9 years old is recommended for the continuous

facility-based surveillance of malaria cases at all stages of control (WHO, 2012a; WHO, 2012b).

Table 4: Current classification of *P. vivax* malaria endemicity by *P. vivax* Prevalence Rate (*Pv*PR)

Endemicity	***Pv*PR$_{1\text{-}99}$** (Gething et al., 2012)
Stable	≥1.0%
Unstable	<1.0%
Unstable and high Duffy antigen negativity (>90%)	<1.0%
Risk free	*

*At this point P*vf*PR is not a reliable estimate of endemicity and Plasmodium vivax annual parasite incidence (*Pv*API) is preferred.

Anaemia prevalence rate (APR)

Although anaemia (Hb<8.0g/dl is not specific to malaria, the APR (equation (7)) has remained a policy-recommended measurement to assess the impact of malaria control efforts (RBM, 2003; Korenromp et al., 2004), due the 60% reduction in the risk of moderate-to-severe anaemia (Hb<8.0 g/dL) observed in a quantitative review of the impact of malaria control on haemoglobin distributions and anaemia prevalences in children under 5 in malaria-endemic Africa (Korenromp et al., 2004). This cut-off point appeared to be more specific for assessing the impact of malaria control measures than the lower cut-off point of Hb<7.0g/dl recommended for the classification of nutritional anaemia (WHO, 1968; DeMaeyer and Joint WHO/UNICEF Nutrition Support Programme, 1989), and the higher cut-off point for any anaemia (Hb<11.0g/dl) (Korenromp et al., 2004). The development of the HemoCue® Hb Point-of-care test (HemoCue AB, Ängelholm, Sweden) greatly simplified the measurement of the haemoglobin distribution during large-scale household surveys by providing an accurate, portable, and relatively low cost solution to the assessment of haemoglobin in the field than previous methods like the direct and indirect measurement of cyanmethaemoglobin (Sari et al., 2001).

$$APR = \frac{No.of\ children\ aged\ 6-59\ months\ with\ Hb < 8\ g/dL}{Total\ no.of\ children\ aged\ 6-59\ months\ examined} \times 100 \qquad (7)$$

APR unlike PPR is not designed to measure or classify endemicity but to measure impact of malaria control interventions, which is no surprise based on the evidence for its validity as an indicator (Korenromp et al., 2004). This means that unlike PPR, APR cannot be used to guide strategy during the phases of control or elimination. Another potential shortcoming to the use of APR is the fact that normal haemoglobin distributions vary with altitude and adjustment factors are required when at high altitude (CDC, 1998). APR is also affected by seasonal variation where transmission is seasonal and this makes the values sensitive to the timing of surveys in these regions. Caution is advised in the interpretation of APR given the problems with its specificity particularly in areas with low malaria transmission, given other anaemia determinants such as paediatric HIV/AIDS, malnutrition and helminth infections (MEASURE Evaluation et al., 2013a).

2.3.2 Measures of incidence of infection in the population

The accurate measurement of malaria incidence required the diagnostic confirmation of every case of malaria in the population of interest. This necessitates a comprehensive surveillance system comprising passive case detection (through the detection of malaria cases as they present at any point in the healthcare system). This can be supplemented by active case detection (by household surveys at regular intervals) to minimize missing cases that occur in the population that do not report to health facilities. The indices were defined during the Global Malaria Eradication Programme and continue to be used to date: annual parasite index, annual blood examination rate and slide positivity rate.

Annual parasite index

The metric used to illustrate malaria incidence is the annual parasite incidence or API (equation (8)).

$$API = \frac{Annual\ parasite\ incidence\ rate}{Total\ population\ at\ risk} \times 1000 \quad (8)$$

Estimates of API are only deemed valid if the ABER exceeds 10% (Black, 1968; Pampana, 1969). The API is usually expressed per 1000 of the population of the administrative area it represents. Annual parasite incidence is often presented together with ABER and SPR as they are interrelated (equation (9)) (Ray and Beljaev, 1984):

$$API = \frac{(ABER \times SPR)}{10} \quad (9)$$

The division by 10 is required as API is presented per 1000 of the population whilst ABER and SPR are presented as percentages.

Annual blood examination rate

The annual blood examination rate (ABER) is a representation of the degree of diagnostic effort made to identify cases of malaria by active and passive case detection (equation (10)). Blood slides from sources other than the actual detection of cases (e.g. population surveys and follow-up of cases) are excluded from the calculation.

$$ABER = \frac{No.of\ blood\ smears\ examined\ during\ the\ year}{Population\ under\ surveillance} \times 100 \quad (10)$$

Slide positivity rate

The Slide Positivity Rate (SPR) among the blood smears collected through both active and passive surveillance can yield accurate information on distribution of malaria infection in the community over a period of time (equation (11)). The SPR is a measure of prevalence among suspected cases of malaria, but is sometimes considered a proxy measure of malaria incidence (Subbarao et al., 1988; Jensen et al., 2009; Lee et al., 2010). The experience with SPR as an indicator of impact is mixed, with some studies showing a concurrent reduction as malaria incidence

drops (Metzger et al., 2009; Lee et al., 2010) whilst others show little change as incidence falls (Metzger et al., 2009).

$$SPR = \frac{No.of\ blood\ smears\ positive\ for\ malaria}{Total\ no.of\ blood\ smears\ examined} \times 100 \quad (11)$$

2.3.3 Entomological inoculation rate

The EIR is the an estimation of the daily number of infective mosquito bites received per person (equation (4)) (MacDonald, 1957a), and the values are usually expressed per year. For the EIR value to be representative of yearly vector activity, frequent assessments must be done at least monthly (or more frequently) for one year or at least one transmission season; in order to capture the effect of changing environmental conditions on vector activity. The annual EIR was considered the most accurate malariometric for assessing endemicity (Burkot and Graves, 1995) and may be necessary for measuring changes in transmission in highly endemic areas. However its limited precision and accuracy and the lack of standardised methods for collection, means that alternate indicators like PPR should be considered especially in low transmission settings (Tusting et al., 2014).

The EIR is usually estimated by deriving the human biting rate (the product of *ma*) and the sporozoite index(*s*) (equation (4)). The most direct way to measure the human biting rate is by the human bait catch (WHO, 1975), which entails collecting all the mosquitoes that attempt to feed on exposed individuals. Because it involves a team waiting at a suitable location, usually all night, capturing all the mosquitoes that attempt to feed on exposed humans, it is expensive and technically difficult to replicate. It is also unethical in areas of drug-resistant malaria. It is unique in the fact that it directly samples human-biting mosquitoes and is thus the most direct method to assess human biting rate (Goff et al., 1997). Other sampling methods, like pyrethrum spray collections and light and exit traps, depend on mosquito behaviours that are less directly associated with feeding attempts (Garret-Jones, 1970; Service, 1993). Methods of assessing human biting rate depend on

accurate sampling of all mosquitoes that have actually attempted feed on exposed individuals, and since this is technically challenging, there is the risk of sampling bias which fortunately has been explored in detail (Lines et al., 1991; Faye et al., 1992; Mbogo et al., 1993; Davis et al., 1995; Smith, 1995) allowing correction factors to be used where sampling is obviously biased (Port et al., 1980).

Measurements of the sporozoite index (s) require the number of infective mosquitoes (those with sporozoites in their salivary glands) in the local population to be determined (WHO, 1975). Ideally, but not always, the sporozoite index is derived from the human biting rate sample. The traditional method was to dissect all sampled mosquitoes for their salivary glands and to identify malaria sporozoites by microscopy (Shute et al., 1965; Pringle, 1966), but recently enzyme-linked immunosorbent assay (ELISA) techniques to detect *Plasmodium* circumsporozoite antigens from mosquito head and/or thorax samples are increasingly being favoured to the traditional method, due to their higher sensitivity and capability for speciation (Burkot et al., 1984) .

Based on the EIR, malaria endemic regions can be classified into high transmission when the EIR is greater than 10 infective bites per person per year, and low transmission when the EIR is less than 1 infective bite per person per year (Hay et al., 2000). The main disadvantage is EIR is the lack of standardization in the entomological methods used in its estimation (Githeko et al., 1996).

2.3.4 Basic reproduction rate

The basic reproduction rate is the average number of secondary infections produced from one infected individual introduced into a non-immune host population (equation (1)). The concept of R_0 originated from demography in the late 1800s where it is usually called the 'net reproduction rate' (Dietz, 1993). The term 'basic reproduction rate' was introduced to epidemiology in 1952 by Macdonald

(Macdonald, 1952) in the context of malaria: 'The number of infections distributed in a community as the direct result of the presence in it of a single primary non-immune case.' The average R_0 determines the endemicity, and essentially for malaria to be endemic in an area, R_0 must be greater than 1.0. Macdonald further suggested a classification of malaria endemicity by the level of R_0 (Macdonald, 1952) that was recently improved upon by Hay et al (Hay et al., 2008) using data from the Malaria Atlas Project (Table 5) (Hay and Snow, 2006).

Table 5: Classification of *P. falciparum* malaria endemicity by $Pf R_0$

Endemicity	***Pf*R$_0$** (Macdonald, 1952)	***Pf*R$_0$** (Hay et al., 2008)
Intense stable (hyper-holoendemic)	$\geq$2.5	$\geq$10
Moderate stable (hypo-mesoendemic)	1.2 – 2.49	1.4 – 9.99
Unstable endemic	1 – 1.19	1 – 1.39
Non-endemic	0 – 1	0 - 1
Malaria free	0	0

2.3.5 Serology

Earlier attempts to measure malaria antibody prevalence in an attempt to estimate endemicity relied on the indirect fluorescent antibody technique (IFA) (Voller and O'Neill, 1971; Druilhe et al., 1986). The widespread use of IFA was however limited by the requirement for cultured parasites, expensive fluorescence microscopes and the subjective time-consuming process of slide manipulation. This was superseded by the much more efficient method of measurement of antimalarial antibodies by Enzyme Linked Immunosorbent Assay (ELISA) (Esposito et al., 1988; Ramasamy et al., 1994). The results of these assays are presented as seroprevalence (equation (12)) (i.e. presence or absence of antibody) and the magnitude of antibody response in seropositives. Of these seroprevalence has been shown to be a reliable indicator of endemicity when interpreted with other indicators (Druilhe et al., 1986), and the impact of control interventions can be inferred from a change in the age-specific seroprevalence (Bruce-Chwatt et al., 1973; Drakeley et al., 2005). The

cut-off for seropositivity has been historically defined as the mean optical density (OD) plus 3 standard deviations derived from a sample of individuals not exposed to malaria (Lobel et al., 1973; van der Kaay, 1976). More recently statistical modelling has been suggested to resolve the potential bias of the immunological background of the naïve sample, and the use of mixture models widely used to establish a diagnostic cut-off point from sample of the population of interest for serological assays of other diseases (Baughman et al., 2006; Hardelid et al., 2008; Rota et al., 2008).

$$Seroprevalence = \frac{No.of\ specimens\ positive\ for\ an\ antigen}{Total\ no.of\ specimens\ examined} \times 100 \quad (12)$$

The main advantage of measurement of seroprevalence compared to other malariometrics is the fact since it reflects cumulative exposure to infection (Corran et al., 2007), it is relatively resistant to short-term changes in transmission like seasonality. The level of parasitaemia in human blood is influenced by acquired immunity (Struik and Riley, 2004) and in some regions seasonality (Bouvier et al., 1997), and this means that measures based on the detection of parasitaemia may underestimate endemicity in regions with high endemicity (due to high levels of acquired immunity leading to rapid clearance of parasites from the circulation) and during the dry season (due to reduced transmission). Seroprevalence is thus useful as a supplementary measure of transmission intensity and in areas with low transmission (Shekalaghe et al., 2009), where PPR and EIR can be insensitive, it offers an accurate way of assessing endemicity and detection focal areas of infection (Wanjala et al., 2011; Olotu et al., 2012). Another advantage is that the possibility of the collection and storage of serological samples on filter papers, and that fact that current ELISA-based antibody assays are robust, relatively low tech, and inexpensive (Biswas, 2004; Corran et al., 2008) has greatly simplified the use of serology during population surveys. However the fact that exposed individuals remain seropositive for many months and even years (Luby et al., 1967; Collins et al., 1968; Struik and Riley, 2004) make serology inappropriate to measure individual level risk. Though this persistence of seroprevalence is potentially useful in the retrospective detection of cases during epidemics or sources of transmission during

eradication efforts (Luby et al., 1967; Bruce-Chwatt et al., 1973; Lobel et al., 1976; Tikasingh et al., 1980), there are no currently available serological assay system that can reliably serve as a quantitative measure of malaria infection.

2.3.6 Measures of infectivity

The infectivity of the population is usually estimated through the prevalence and density of gametocytes. This measure is most frequently used for *P. falciparum* due to the fact that there is a distinct distribution of asexual parasites and gametocytes in time in the human population, and the fact that *P. falciparum* gametocytes are the easiest to recognise in a blood smear because of their conspicuous size and shape. It is only a proxy measurement of infectivity as the volume of blood usually examined in a blood smear (100 fields of thick film correspond to about 0.25μl of blood) is far less than what the vector ingests during a blood meal (about 2 μl). Direct measurement of infectivity involves feeding vectors on the general population (Muirhead-Thomson, 1951; Muirhead-Thomson, 1954) to determine those carrying infectious gametocytes which is usually difficult to justify ethically but is still applied under specific experimental conditions (Tchuinkam et al., 1993; Toure et al., 1998; Robert et al., 2000). Since the prevalence of gametocytes declines with increasing age in malaria endemic regions (Genton et al., 1995; Snow and Gilles, 2002), this measure should be age-specific. Gametocyte prevalence in young children (i.e. children less than 5 years old) may serve as an indicator of risk and can allow the comparison between different location and time points.

2.3.7 All-Cause Under-Five Mortality Rate

The all-cause under-five mortality rate (U5MR) is a measure of the probability of dying between birth and exactly five years of age expressed per 1,000 live births (equation (13)). The reasoning behind the use of U5MR as a metric of control progress stems from the fact that malaria accounts for a significant

proportion of the deaths in children less than 5 years globally (7.4% or 0·564 million, 95% CI 0·432, 0·709 million) (Liu et al., 2012). In areas of stable endemicity, the proportion of deaths in children less than 5 years due to malaria is likely to be higher and scaling up of control interventions should have an impact on all-cause under five mortality trends.

$$U5MR = \frac{No.\,of\ deaths\ in\ children < 5\ years}{Total\ no.\,of\ live\ births} \times 1000 \qquad (13)$$

At the national level, under-five mortality can be measured using a number of different methods, including registration of births and deaths via vital registration systems, national population censuses and/or data collected via household surveys. Where a well-functioning vital registration system does not exist or a national population census is prohibitive, it is preferred that U5MR be derived from household surveys (e.g. DHSs and MICSs) using direct or indirect methods. To ensure reliable results when using household surveys, U5MR is calculated for a five-year period to make sure there are enough cases. The indirect method also referred to as the Brass method (Brass and Coale, 1968), is the method preferred in most MICSs and involves converting the proportion of children who have died among women in a certain age group into the probability of dying by an exact childhood age, and then indirectly derive the U5MR using model life tables and strong assumptions as to age patterns and time trends. The direct method in used in DHSs and uses a birth history including information on all children born their survival status and (for non-surviving children) their age at death, in order to calculate the probability of dying before age five from children exposed to mortality during the five-year period before the survey. The life history synthesized from age-specific mortality rate represents synthetic cohort, and using the synthetic cohort life table approach (Ryder, 1965), the measures derived from this cohort mortality probabilities for small age segments based on real cohort mortality experience are combined into larger age segments that correspond to the age group of interest (in this case children aged less than five years). The main advantage of this metric is the fact that it can be measured reliably and does not suffer from limitations of methods to identify malaria-specific deaths. The main disadvantage

of this metric is the fact that changes in U5MR may, however, be influenced by a variety of factors other than malaria control (for an example an increase in overall standard of living may decrease U5MR).

2.3.8 Malariometric indicators for Malaria in Pregnancy

Pregnant women are a unique sub-group of the population when it comes to *P. falciparum* transmission because there is an interaction between a transmission specific effect (Gilles et al., 1969; Brabin, 1983; McGregor et al., 1983; Desai et al., 2007) and a parity-specific effect with infections being more common in primigravidae (Fried and Duffy, 1996). When transmission is high and stable, most infections being asymptomatic, severe malaria syndromes are relatively uncommon, and the main clinical effect is anaemia (Gilles et al., 1969; Fleming, 1989; Shulman and Dorman, 2003) and low-birth weight babies (Brabin, 1991; Shulman and Dorman, 2003; Duffy and Fried, 2005). Severe syndromes like cerebral malaria are more common in low transmission settings and maternal and foetal mortality is high (Duffy and Fried, 2005). In low transmission settings, there is reduced development of parity-specific immunity and a parity-specific effect is not clearly demonstrated (Desai et al., 2007). A further complexity is due to the fact that HIV infection modifies this parity-specific risk leading to increased frequency and density of malaria infections (Steketee et al., 1996; van Eijk et al., 2003; ter Kuile et al., 2004). To date, there is limited data on the epidemiological pattern of *P. vivax* malaria in pregnancy but there is some evidence from low transmission settings that infection is similarly more common in primigravidae, and that it can result in stillbirths and low birth weight (LBW) (Nosten et al., 1999; Singh et al., 1999; Machado Filho et al., 2014).

A number of core malariometric indicators for malaria in pregnancy formulated in relation to these epidemiological patterns of infection have been designed by WHO to assess progress in the delivery of interventions for the control of malaria in pregnancy (WHO, 2007a) and these are what are being used to date,

though there has been call that these be updated (Brabin et al., 2008). The two key malariometric indices for assessing endemicity are the percentage of low birth-weight singleton live births by parity (birth weight less than 2500 g obtained within 24 h of birth, regardless of gestational age) and the percentage of screened pregnant women with severe anaemia (Hb < 7 g/dl) in third trimester by gravidity (WHO, 2007a). These indicators are meant to be measured through nationally representative household surveys.

Percentage of low birth-weight singleton live births by parity

This science behind the use of this malariometric is based on the fact that the consequences of malaria in pregnancy including malaria-associated anaemia and their effects on the foetus are known to result in LBW (Brabin, 1991; Shulman and Dorman, 2003; Duffy and Fried, 2005). Since the risk for LBW has been shown to be higher in primiparous compared to multiparous women (Brabin, 1991; Shulman and Dorman, 2003; Duffy and Fried, 2005) , this indicator is derived for both (Equation (14)). Since LBW can be due to both small-for-gestational age and prematurity, and since the former is difficult to determine in most resource poor settings, the two are often not differentiated when deriving estimates of this malariometric.

$$Percentage\ LBW = \frac{No.of\ LBW\ singleton\ live\ births}{Total\ no.of\ singleton\ live\ births} \qquad (14)$$

This indicator is best measured through nationally representative surveys due to the fact that facility-based estimates are dependent on the number of women who deliver in health facilities who are not usually representative of the number of women delivering in the community (Singh et al., 2013). The main shortcoming of this approach is the fact that this usually requires a large sample size from the population to ensure precise estimates as pregnant women are not present in every household. The women surveyed may also not be able to exactly remember all the birth weights of their children or may report them incorrectly. Promoting childbirth in health facilities where infants are weighed at birth is likely to improve the quality

of data on birth weight as data will be recorded in the mother's ANC card. Low birth weight in developing countries has long since been known to be due to variety of factors other than malaria, like poor gestational nutrition, low pre-pregnancy weight, short maternal stature and general morbidity and episodic illness (Kramer, 1987). Where there is a significantly high prevalence of these other causative factors, this indicator is likely to over-estimate the endemicity of malaria. It can also be affected by the uptake and coverage of MIP control interventions like IPTp (Kayentao et al., 2013)and ITNs (Eisele et al., 2012). Where uptake and coverage is high, this will reduce the prevalence of anaemia and this indicator is likely to under-estimate endemicity. These are the main reason why WHO recommends caution in the interpretation of this indicator(WHO, 2007a).

Percentage of screened pregnant women with severe anaemia in third trimester by gravidity

The reasoning behind the use of this malariometric is based on the fact that anaemia is a recognised outcome of malaria in pregnancy (Gilles et al., 1969; Fleming, 1989; Shulman and Dorman, 2003) especially among primigravidae living under holoendemic or perennial malaria exposure. As the risk for anaemia has been shown to be higher among primigravidae than multigravidae, measurement of anaemia must be differentiated by gravidity. Severe anaemia is defined as a haemoglobin concentration less than 7.0g/dl (Stoltzfus, 1997), but recently there has been discussion on whether this cut-off should be revised to 8.0g/dl (Savage et al., 2007; Brabin et al., 2008) or a normogram should be used to determine a cut-off based on the distribution of haemoglobin values in a sample of pregnant women (Savage et al., 2007).

$$Percentage\ of\ pregnant\ women\ with\ severe\ anaemia = \frac{No.of\ women\ with\ Hb < 7.0g/dl\ in\ the\ 3rd\ trimster}{No.of\ women\ screened\ for\ anaemia\ in\ the\ 3rd\ trimester} \quad (15)$$

This indicator is best measured through nationally representative surveys despite the higher level of ANC attendance when compared to deliveries (UNICEF,

2013) for a variety of reasons. Firstly, haemoglobin screening may not be available in all health facilities, particularly in resource-poor settings. Secondly, screening, if done, is usually clinical and performed during the first ANC clinic visit. Finally, the methods of assessment may not be standardised and the cadre of health staff available may differ between the health centres leading to variations in accuracy. This indicator for MIP is prey to similar shortcomings as the previous indicator. A large sample size is required from the population to ensure precision in estimates, and since anaemia in pregnancy is multifactorial in origin (Savage et al., 2007; Brooker et al., 2008b; Lee and Okam, 2011; Ayoya et al., 2012), values must be interpreted with caution. One major fact that must be considered when interpreting this indicator is the fact that it is recommended that this indicator be measured in the third trimester. This means that it can be affected by iron supplementation (Haider et al., 2013) and maternal deworming (Brooker et al., 2008b), and where there is good uptake and coverage of these interventions, this indicator is likely to under-estimate anaemia prevalence.

2.4 Current malaria control and elimination strategy

2.4.1 Vector Control Interventions

The intensity and pattern of malaria transmission in an area is largely due to the abundance and feeding habits of vectors. As a result, vector control interventions are targeted to reduce human-vector contact and/or reduce vector abundance at the population level (WHO, 2013a). Insecticide treated mosquito nets (including LLINs and conventional nets treated with an insecticide), IRS and larval source management are the current vector control interventions endorsed by WHO. The WHO currents recommends universal coverage with ITNs (defined as one ITN for every two people at risk of malaria) (WHO, 2006), and urges a switch-over to WHO Pesticide Evaluation Scheme (WHOPES) certified LLINs (WHO, 2013b) in which the net's fibre is coated or incorporated with pyrethroids insecticide (e.g. permethrin) for all endemic countries. Free mass distribution campaigns every

three years or less, complemented with continuous distribution programmes (e.g. through antenatal and routine immunization services) are advised as the approach to achieve universal coverage (WHO, 2013c). Coverage with ITNs in sub-Saharan Africa has increased steadily from 2000 to 2012 with 3% of household owning at least one ITN in the former compared to 56% in the latter, with a slight decline to 54% in 2013 (WHO, 2013a).

IRS involves the application of residual insecticides to the inner surfaces of dwellings to target Anopheles mosquitoes that rest on walls after having taken a blood meal. Spraying of at least 80% (and ideally 100%) of houses, structures and units (including domestic animal dwellings) in the targeted area in any round of spraying is recommended by the WHO (WHO, 2013d). Again, WHOPES endorses twelve insecticides belonging to four main categories for IRS: organochlorines (e.g. DDT), organophosphates (e.g. Malathion), carbamates (e.g. Bendiocarb) and pyrethroids (e.g. deltamethrin) (WHO, 2009). In the African region, the proportion of the population protected by IRS in countries with ongoing transmission rose from less than 5% in 2005 to 11% in 2010, but fell slightly to 8% in 2012 (WHO, 2013a). Insecticide resistance is one of the main challenges to the success of vector control strategies requiring its use, driven by the previous heavy reliance in pyrethroids. To date, resistance in the vector has been identified in at least 64 malaria-endemic countries worldwide (WHO, 2013a). This led to WHO issuing the Global plan for insecticide resistance management in malaria vectors, urging the development and implementation of comprehensive insecticide resistance management to reduce the chance of significant resistance (WHO, 2012d).

Larval source management (LSM) is the management of aquatic habitats that are potential larval habitats for mosquitoes in order to prevent the completion of immature stages of mosquito development (WHO, 2013e). There are four categories of LSM: habitat modification or permanent alteration of the environment (e.g. surface water drainage), habitat manipulation or temporary environmental

changes (e.g. drainage clearance), biological control by introduction of natural enemies into larval habitats (e.g. predatory fish) and the regular application of biological or chemical insecticides to water bodies or larviciding (e.g. *Bacillus thuringiensis* subsp. *israelensis* (*Bti*)). Larviciding is the most widely used LSM and in 2012 the WHO Interim Position Statement on the role of larviciding in sub-Saharan Africa (WHO, 2012c), recommend larviciding in urban areas where breeding sites are relatively few, fixed and easily accessible, arid regions were habitats are few and fixed for most of the year, and in the East African highlands where a field trial in 2009 (Fillinger et al., 2009) demonstrated the effectiveness of larviciding in conjunction with LLINs.

Another promising vector control strategy that is currently been studied is house improvement as means of reducing house entry of malaria vector entry as a means of reducing transmission (Atieli et al., 2009; Kirby et al., 2009). House modifications reduced the vector density in intervention household (Atieli et al., 2009; Kirby et al., 2009) and anaemia in children (Kirby et al., 2009) compared to controls, but did not seem to result in significant decreases in parasitaemia in children (Kirby et al., 2009). This method is promising with good social acceptability (Kirby et al., 2010) but more research needs to be done before it can be adopted as a viable control strategy.

2.4.2 Preventive chemotherapy

Preventive chemotherapy is the use of complete treatment courses of antimalarial in at-risk groups to reduce malaria-related morbidity and mortality by preventing the consequences of infection. Currently WHO endorses intermittent preventive treatment in pregnancy (IPTp), intermittent preventive treatment in infants (IPTi), and seasonal malaria chemoprevention (SMC) as preventive chemotherapy. Sulfadoxine–pyrimethamine (SP) is the drug currently recommended for intermittent preventive treatment in pregnancy (IPTp), because of its safety profile and the fact that it can be delivered as a single dose under

observation by a health worker. Recent scientific evidence from a review of 7 clinical trials conducted in Africa in areas of stable transmission and different levels of SP resistance revealed that 3 or more doses of IPTp-SP yielded better clinical outcomes for the mother and the newborn than the standard two doses of IPTp-SP in all gravidae and HIV groups (Kayentao et al., 2013). Intermittent preventive treatment in pregnant women has been adopted into policy by 36 sub-Saharan African countries with moderate to high malaria transmission in 2012. From household survey data from 2010 to 2012 in 13 of those countries, a median of 64% of pregnant women attending ANC received at least one dose of IPTp in 2012, 38% received at least two doses and 23% received at least three doses (WHO, 2013a).

Intermittent preventive treatment for infants with SP with the DPT2, DPT3 and measles vaccines (a total of three doses) during routine immunization is the currently recommended for sub-Saharan Africa countries with moderate to high malaria transmission. Initial evidence for the partial protection in the first year of life against clinical malaria and anaemia, and reduction in hospital admissions was first demonstrated in a pivotal trial in Tanzania (Schellenberg et al., 2001), and this has been substantiated by several consequent trials (Aponte et al., 2009; Gosling et al., 2009; Odhiambo et al., 2010; Schellenberg et al., 2011; Willey et al., 2011). Doubts on the effectiveness of this strategy given the widespread resistance to SP (Naidoo and Roper, 2011) has limited the implementation of this strategy in many malaria-endemic countries and to date only Burkina Faso has instituted a national policy for IPTi.

The third preventive chemotherapy strategy is seasonal malaria chemoprevention, the intermittent administration of full treatment courses of an effective antimalarial during the malaria season to prevent malarial illness in children aged 3 and 59 months (WHO, 2011b). The use of SMC is only recommended in areas of highly seasonal malaria transmission in the Sahel sub-region region where the combination amodiaquine plus SP is still effective (Cairns

et al., 2012). Since WHO released its recommendation on SMC in August 2013 (WHO Global Malaria Programme, 2012), two countries have adopted the approach and several countries have expressed the desire to adopt the policy.

2.4.3 Diagnosis and treatment of malaria

The WHO urges that in every country with ongoing malaria transmission, the diagnosis in every suspected malaria case should be confirmed (by microscopy or RDT), every confirmed case treated with a quality assured artemisinin combination therapy (ACT), and every malaria case tracked in a surveillance system. This forms the basis of WHO's T3: Test, Treat and Track Initiative (WHO, 2012e). The objectives of diagnosis and treatment are to reduce patient morbidity and mortality by rapid cure, reduce the population parasite pool by completely clearing a patient of malaria infection, and to prevent the emergence and spread of resistance by using effective combination therapy (i.e. ACTs) but it is accepted that there are a few challenges to this strategy (Bastiaens et al., 2014). Firstly, sustaining the supply of RDTs to rural areas has been difficult and drug stock outs are common (Shillcutt et al., 2008; Proietti et al., 2011). Secondly, even where tests are available, adherence to the results amongst healthcare workers is poor (Hamer et al., 2007; Reyburn et al., 2007; Bisoffi et al., 2009; Ansah et al., 2010), and over-use of antimalarials is likely particularly in low transmission settings (Mwanziva et al., 2008; Bastiaens et al., 2011). Thirdly, the cost-effectiveness of this strategy depends on the transmission settings, this strategy is cost-effective even if there is poor adherence to results (Lubell et al., 2008). However in high transmission settings given the imperfect sensitivity of tests under field conditions, poor adherence to results and supply maintenance issues, presumptive treatment is more cost-effective than diagnosis-based treatment (Lubell et al., 2008).

Current recommendations are that uncomplicated *P. falciparum* malaria should be treated by one of five ACTs based on the therapeutic efficacy in the area of planned use: artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus

mefloquine, artesunate plus SP, and dihydroartemisinin plus piperaquine (WHO, 2010). *Plasmodium vivax* malaria should be treated with chloroquine monotherapy only in areas where this drug is effective, and in areas with chloroquine resistance *P. vivax* malaria should be treated with an ACT other the artesunate plus SP. Severe malaria should be treated with injectable artesunate, followed by a complete course of an effective ACT as soon as the patient can take oral medications, based on the evidence from two large multicentre trials in South East Asia and sub-Saharan Africa (Dondorp et al., 2005; Dondorp et al., 2010). This control strategy should be supported by therapeutic drug efficacy studies to allow for measurement of the clinical and parasitological efficacy, and the emergence of drug resistance.

2.4.4 Monitoring, Evaluation and Surveillance of Malaria

Monitoring, evaluation and surveillance of malaria is fundamental to malaria programme design and implementation. Monitoring is a continuous process of collecting and utilizing data on programme implementation with the aim of verify whether the project activities are happening according to planning and whether adjustments are required to ensure satisfactory progress (WHO et al., 2011). Monitoring must provide the project management with timely information (in the form of administrative data, inputs, processes, outputs and sometimes outcomes and impacts) during the course of the programme to make it possible to take efficient and appropriate decisions. The information is acquired through routinely collected data or specific surveillance systems, field observation reports, progress reports, rapid assessment, program review meetings.

Evaluation involves a much more comprehensive programme assessment, usually done at discrete time points (often the midpoint and end of implementation period), that focuses on the expected long term outcomes and impacts of the programme in order to assess the programmes' effectiveness, relevance, impact and cost-effectiveness (i.e. its population effects) (WHO et al., 2011). The information required is acquired through data for monitoring as well as population-based

surveys, vital registration and specific studies (e.g. treatment efficacy). Evaluation may assess whether activities have been undertaken as planned (normative evaluation) or whether changes in malaria transmission are attributable to programme efforts (impact evaluation).

The Monitoring and Evaluation (M&E) Framework for malaria control programmes consists of a series of activities, namely, Assessments and Planning, Inputs, Processes, Outputs, Outcomes (intermediate effects), and Impact (long-term effects) (Figure 2). In the context of malaria program scale-up, M&E has historically focused on measuring disease burden to detect impact, specifically measuring morbidity and mortality through routine sources of data (e.g. health facility reports), Demographic and Health Surveillance systems (DHS), and health facility surveys (Figure2A) (RBM, 2010). However, as malaria transmission drops due to improved control and we approach the elimination threshold, measurement of malaria-specific morbidity and mortality by these methods will not produce accurate estimates of ongoing malaria transmission. As a result, there was a paradigm shift in thinking resulting in a change in priority from the burden reduction to the interruption of transmission (Figure 2B) (malERA, 2011b).

Current malaria M&E focuses on detecting infections (with or without symptoms) and measuring transmission dynamics as the primary indicators of interest. Impact is usually assumed when there is detectible burden reduction (measured through impact indicators) with concurrent coverage scale-up (measured through outcome indicators) in the absence of any other explanatory factor (RBM, 2008b). In reality, this type of evaluation requires rigorous experimental design, including the measurement of all other possible explanatory factors (e.g. rainfall) to make a causal association between program inputs and resulting impacts, a mandate seldom achievable by most NMCPs. For this reason, current policy emphasis is on the measurement of outcome indicators rather than impact indicators (MEASURE Evaluation et al., 2013a).

Figure 2: (**A**) Previous Malaria M&E framework (**B**) Current Malaria M&E framework (Source: PLoS Collections, (malERA, 2011b), open source)

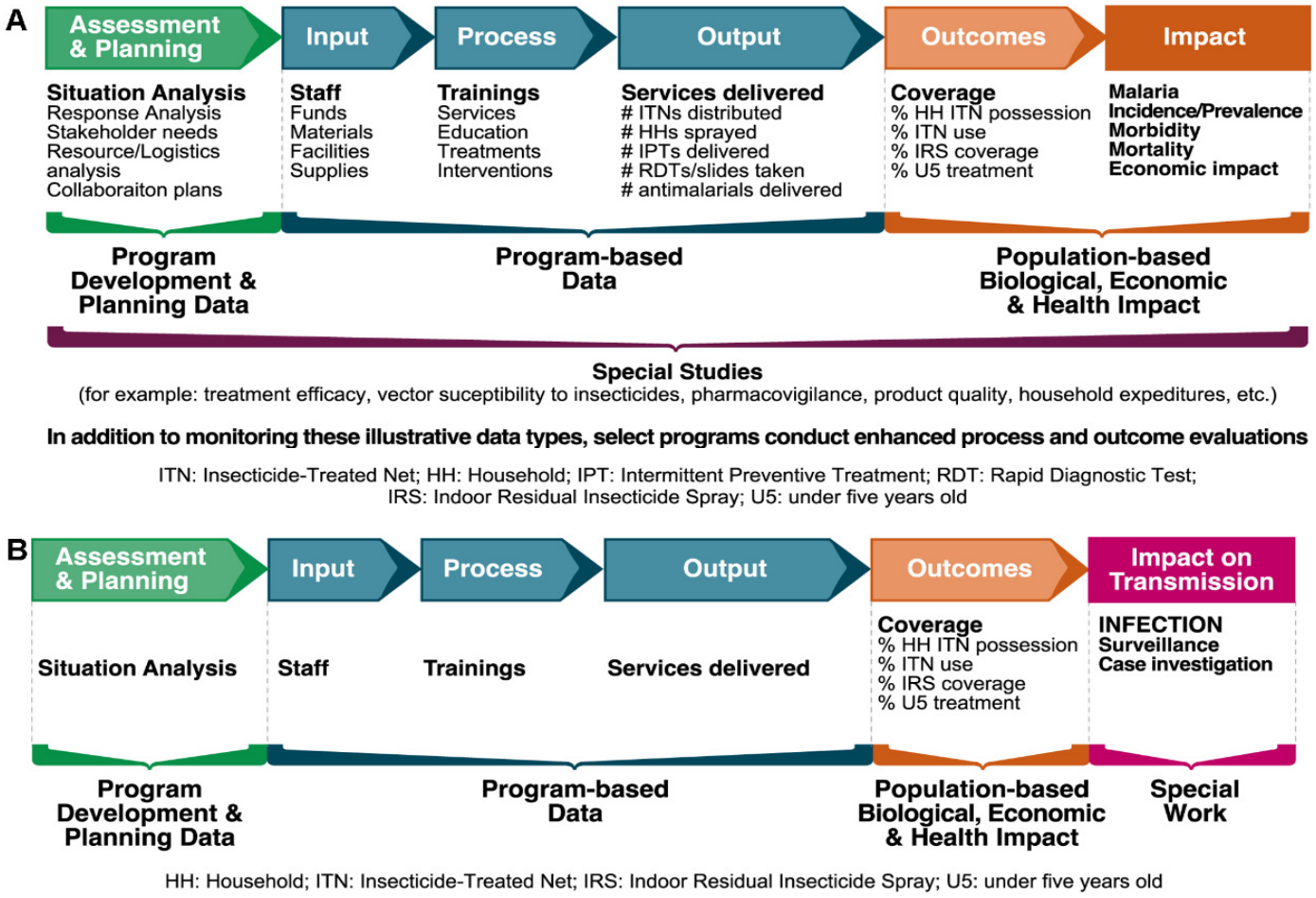
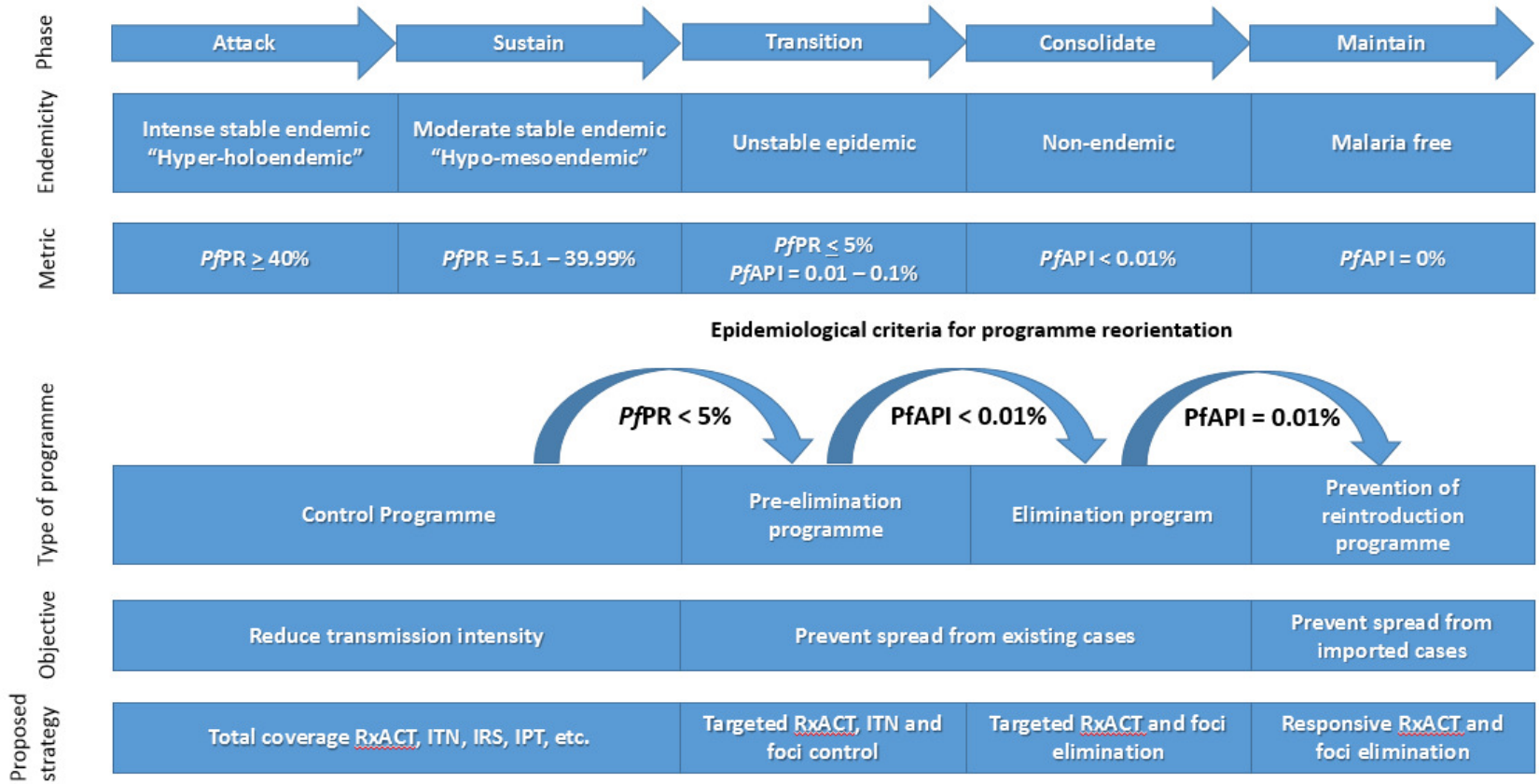


Figure 3: Endemicity classification, appropriate metric and programme strategy at different stages of control and elimination
(Adapted from Lancet Infectious Diseases (Hay et al., 2008) & Malaria elimination: A field manual for low an moderately endemic countries (WHO, 2007c))



Measurement of impact indicators is still necessary however as part of normative evaluation in other to guide programme efforts through phases of control. Previously, the phases of controls were divided into preparatory, attack, consolidation and maintenance according to the WHO Global Malaria Eradication Programme (Black, 1968; Pampana, 1969; Najera and Global Partnership to Roll Back Malaria, 1999), and measurement of the *Pf*PR and API were meant to guide programmes as to which phase in control continuum they currently were in and so which control strategy to employ. These phases have since been adapted to attack, sustain, transition, consolidate and maintain (Hay et al., 2008) with key epidemiological criteria indicating when a reorientation in programme strategy is required (Figure 3).

Where transmission is stable (hyper- to mesoendemic), appropriate metric is *Pf*PR (usually estimated from data from population-based surveys) and the strategy adopted by NMCPs should be that of a control programme focusing on the reduction of transmission intensity through scale-up of proven interventions, for example accurate diagnosis and treatment with artemisinin combination therapy or ACT (RxACT). When transmission becomes unstable both *Pf*PR (usually estimated from data from population-based surveys) and API (from a combination of active and passive surveillance) should be measured and the strategy should be that of a pre-elimination programme focusing on the prevention of spread from existing cases through targeted RxACT and ITN distribution campaigns, and detection and control of foci of infection (i.e. hotspots). As transmission continues to fall, the strategy becomes that of a control programme with continued focus on prevention of spread from existing cases but with a strategy of targeted treatment and foci elimination. When elimination is achieved, the strategy becomes that of a prevention of reinfection programme and the main objective is the prevention of spread from imported cases. When a country has zero locally acquired malaria cases for at least three consecutive years, as proven by reliable data it can request WHO to certify its malaria-free status.

Despite the availability of WHO guidelines (WHO, 2007a), monitoring and evaluation programmes for malaria control in pregnancy still remain poorly developed. The current control strategies for MIP are constructed with in relation to the epidemiological patterns of infection, with focus on IPTp, ITNs and prompt effective case management of malaria and anaemia in stable transmission (high to medium) settings, and ITNs and prompt and effective case management in unstable transmission settings (WHO/AFRO, 2004). Recommended indicators for monitoring and evaluation of MIP control programmes are consequently structured based on this control strategy with LBW by parity and percentage with severe anaemia (Hb<7.0g/dl) in the third trimester by gravidity as the main impact indicators (WHO, 2007a). The appropriateness for the cut-off for severe anaemia most likely to be due to malaria infection is still being debated (Savage et al., 2007; Brabin et al., 2008). There are also are no indicators to monitor the number of clinical cases, efficacy of IPTp or the burden of malaria infection. Impact indicators are recommended to be measured during nationally representative household surveys, whilst other indicators are to be measured by facility-based surveys (WHO, 2007a). It has been suggested therefore that these indicators be updated (Brabin et al., 2008), and given the high rates of ANC attendance (UNICEF, 2013), data to guide decision-making in the control of MIP could also be derived from facility based surveys (Parise et al., 2003), an approach that is appealing based on the prohibitive sample size required to get precise estimates of burden from current impact indicators.

2.5 Sampling strategies for malaria surveillance, monitoring and evaluation

Surveys of human population measure and count the occurrence of a particular attribute in the human population at a particular time within a locality (Law and Pascoe, 2013). Sometimes it is possible to survey all the individuals making up the population of interest, such as demographic and health surveillance

systems (DHS), but usually the population of interest is too large to survey everyone and we usually study a subset: the sample. The sample is made of sub-divisions that maybe natural (such as households) or artificial (such as a rectangular area on a map bearing no relation to natural subdivisions) termed sampling units (Yates, 1981). The structure of all sampling units available for survey is referred to as the sampling frame, for example in sampling in a human population, the sampling frame will be the list of all households in the study area (Yates, 1981). The whole aggregate of sampling units is referred to as the population of sampling units (Yates, 1981). In most cases, the sampling frame and the population of sampling units are congruent, but sometimes it may not be feasible to include the whole population in the sampling frame for logistic reasons.

When the sample is collected using a sampling strategy that results in a representative subset of the population, it is possible to infer the properties of the population from the properties of the sample. As long as a representative subset of the population of interest is the end result, sampling is advantageous when compared to census in that data is cheaper to collect as a smaller number of sampling units are required and fewer people are needed to collect and analyse the data. Sample surveys are frequently quicker to administer, analyse and process, and because there are fewer cases make it possible to collect more data about each than would have been possible in a census. The method of selecting a sample to survey is classically divided into two broad categories: probability and non-probability sampling (Law and Pascoe, 2013). Choosing between these approaches is a matter of evaluating the issues of validity and credibility, against a realistic assessment of alternative both in time and effort. This section intends to give an overview on the sampling strategies currently used for malaria surveillance, monitoring and evaluation.

2.5.1 Censuses

The most common example of a situation where it is possible to sample the whole population (i.e. a census) in order to derive measures of transmission intensity is that of a Demographic and Health Surveillance System (DHS). A DHS consists of monitoring demographic and health characteristics of a population living in a well-defined geographic area through the collection of data prospectively and longitudinally (INDEPTH Network, 2002; Sankoh and Binka, 2005). Where these DHSs are in malaria-endemic countries, they can be used to measure trends in malaria morbidity and mortality at the population level and even potentially measure the impact of control interventions (Monasch et al., 2004; Kaatano et al., 2009; Alba et al., 2011; Kouanda et al., 2013). Cause-specific mortality (including that due to malaria) in DHSs are assessed by verbal autopsy and some sites have followed trends for over 10 years (Hammer et al., 2006; Deressa et al., 2007; Kamugisha et al., 2007; Becher et al., 2008; Kaatano et al., 2009; Sacarlal et al., 2009), despite doubts about the sensitivity and specificity (INDEPTH, 2002; Rowe, 2005; Setel et al., 2006).

Data from a DHS can allow us to study geographical heterogeneity in transmission if all the possible data points are linked to GPS coordinates. The main disadvantage of a DHS is the fact that due to the intensive nature of data collection activities, it generally cannot be applied over wide geographic areas or large population. The data from a DHS may not be representative of the whole country as the selected site may not be typical of the whole country especially given the variability in transmission intensity. Where it exists within a district, the data from a DHS can be useful for district programme management.

2.5.2 Probability sampling

A probability sample is one in which each person in the population has an equal, or at least a known, chance (probability) of being selected (International

Epidemiological Association, 2008). There are different types of probability samples (Table 6) but they are all structured to give an average estimates of the property of interest in population with its precision. They are often regarded more favourably by survey researchers as they are more likely to produce representative samples and facilitate estimates of sample accuracy which allow inferences to be made to a wider population.

Table 6: Probability sample designs

Type of sampling	**Strategy to select sampling units**
Simple random	After sub-division into sampling units, the requisite number of sampling units to satisfy the sample size are selected at random from the sampling frame.
Stratified	After sub-division into groups called 'strata' containing the same of differing number of sampling units (uniform sampling fraction and non-uniform sampling fraction respectively), sampling units are selected at random from each strata.
Systematic	After the sample frame is assembled and listed, a random start point is designated from which sampling units are selected at equal intervals until the desired sample size is achieved.
Cluster	After each sampling unit of the population of sampling units is assigned to a naturally occurring group of 'cluster' and a random selection of clusters is made until the desired sample size (in terms of sampling units) is achieved.

A random sample is the simplest type of a rigorously selected sample and is sometimes the basis of much more complex sampling methods (Table 6). The aim of random sampling is to ensure that every sampling unit (whether that be an individual, household, or geographic area) in the sampling frame has an equal chance of being selected, so that the measurement of a particular variable can be generalized to the population with a calculable degree of confidence. Classical random sampling usually means sampling without replacement, in which once the sampling unit has been selected, it is no longer a part of the sampling frame and is thus not eligible for re-selection, as it is more efficient than sampling with replacement in producing representative samples. A disadvantage is that this

approach focuses on a random sample of the whole population whilst in some cases estimates from a sub-group of the population (e.g. a key disease at-risk group like pregnant women) may be more desirable. Finally, respondents may be widely dispersed; hence, data collection costs might be higher than those for other probability sample designs such as cluster sampling. In practice many large-scale malaria surveys do not use random sampling because of the excessive costs associated with sample selection and instead opt for a compromise which often utilizes stratified, multistage, or random sampling (MEASURE DHS, 2013b).

In stratified sampling, the main purpose is to improve the precision of the overall population estimates by improving the precision of the corresponding estimates of sub-divisions of interest termed domains of study (e.g. high and low transmission intensity) (Table 6) (Yates, 1981). This strategy is useful if the aim is to compare groups and is most effective when sampling units are reflected in the same proportions as those in the strata in the population. The accuracy of the overall estimates will increase if there are large differences in estimates of the attribute of interest between strata, as the strata will be represented in their correct proportions, whereas in a random sample these may be subject to sampling errors if too little of one strata is sampled. Systematic sampling is only possible when a list of sampling units of the sampling frame is available (Table 6). The main disadvantage is that stratified sampling requires more effort in terms of preparation for sampling, executing the sample design, and analysing the data collected. Information on stratification variables is required for each element in the population, and selection of stratification variables may be difficult if a study involves a large number of variables.

Systematic sampling (or interval random sampling) does not strictly result in a fully random sample (Table 6). Systematic sampling may be classified into three major types: linear systematic sampling, circular systematic sampling, and repeated (or replicated) systematic sampling. In linear sample, we move down the

list until completion and then stop whilst in cyclic sampling, we return to the start of the list and continue selecting sampling units. Whilst both linear and circular systematic sampling aim to produce a single sample, repeated systematic sampling involves the selection of multiple samples from the target population by using multiple random start locations to select smaller systematic samples which are then combined into a single sample. The main advantage is that systematic sampling is easier, simpler, less time-consuming, and more economical than simple random sampling. However, if the sampling interval is related to periodic ordering of the elements in the sampling frame there may be increased variability in in the result.

In most cases, it is impossible or impractical to create a sampling frame of the whole target population, and/or the target population is widely dispersed geographically, making data collection costs by the aforementioned method of random sampling relatively high. In such situations, a cluster sample is more realistic. Cluster sampling involves selection of natural aggregates of population elements (e.g. villages) (Table 6) and is usually classified according to the number of stages in the sampling process: single-stage sampling, two-stage sampling, and multistage sampling. Each stage involve repetition of listing the sampling frame and randomly selecting sampling units until the last stage element sampling is achieved. Sampling with probability proportional to size is another variant of cluster sampling that aims to ensure every element in the population having an equal chance of inclusion in the sample. The probability of selecting a cluster is dependent on the proportional distribution of its elements in the target population thus obtaining a self-weighting sample e.g. the number of households to be randomly selected in a village depending on the proportion of households in the village compared to the total population.

In summary, probability sampling is structured to give an average estimate and its precision for a geographic area and is currently the policy-recommended approach for population-based surveys intended to produce average estimates of

control progress to guide decision making at the national level (Hancioglu and Arnold, 2013; MEASURE DHS, 2013b). At the district or sub-district level, in order to make timely decisions and to target interventions to achieve maximum efficiency, we need timely data that takes account of the heterogeneity in distribution of transmission intensity, and thus we need to balance the statistical validity versus the likelihood that the data results in the correct decision in terms of the next control step. The sample size required to achieve this by probability sampling is logistically challenging and financially prohibitive and we need to explore alternate sampling strategies that could be more efficient.

2.5.3 Non-probability sampling

In non-probability sampling, the chance of each sampling unit being selected from the population of sampling units is unknown (Law and Pascoe, 2013). Non-probability samples may not provide a sample that is representative of the population, but never the less is a rich source of data. Using a non-probability sample to infer properties of the population should be approached with caution because we don't know the probability of how well we have represented the population of interest and neither can we directly determine the precision of estimates from such a sample. However, some non-probability samples are routinely used in malaria surveillance, for example health facility-based surveys and school surveys. Health facility-based surveys are currently a policy recommended complementary surveillance tool at different phases of control and elimination (WHO, 2012a; WHO, 2012b). The common misconception when using such samples is that by using probability sampling techniques to select sampling units from such a sampling frame (i.e. the sampling units available to be sampled in the health facility or school) results in a non-probability sample that can now been reliably generalized either to the whole population (for non-age restricted facility surveys) or a particular risk strata of the population (for age-restricted restricted health facility surveys, ANC surveys and school surveys). This is not the case, selecting a smaller probability sample from a larger non-probability sample only

ensures the selection of a representative sample of the larger non-probability sample which has already been selected by natural systems (e.g. health seeking behaviour, socioeconomic status, proximity, etc.), and the selected sample is still thus subject to all the shortcomings of a non-probability sample.

The main advantage of non-probability sampling is that the natural systems in place allow us to easily select and recruit the sample, making non-probability sampling cheaper and more straightforward to administer than probability sampling as it doesn't require a sampling frame. Non-probability sampling include convenience sampling (also called accidental or haphazard sampling), purposeful sampling (also called purposive or judgemental sampling) and snowball sampling. In convenience sampling, sampling units are selected based on availability and accessibility which gives an element of randomness and therefore reduces the opportunity for bias (Law and Pascoe, 2013). EAGs are convenience samples that are either potentially representative of a disease at risk group (e.g. school children) or the population (e.g. opportunistic surveys during public health intervention campaigns). The potential disadvantage of this approach is that people who are accessible and willing to participate may be significantly different from those that are not accessible and/or not willing to participate.

Purposeful sampling involves selection sampling with the objective of obtaining detailed information on one or more specific pre-defined groups of the population for in-depth study (Law and Pascoe, 2013), for example, sampling only households who have recently received and ITN for an in-depth investigation of the source and direct or indirect costs (if any). Purposive sampling can be very useful when you need to reach a targeted sample quickly and where sampling for proportionality is not the primary concern. This type of sampling can only be representative of the targeted population. In snowball sampling, the researcher identifies a sampling unit of interest, ask them to recommend another person (such

as a friend) who is also sampled and so on (Law and Pascoe, 2013). This method is used extensively in market research for commercial networks, but the results are likely to be highly correlated due to the relationship between individuals in the sample.

2.5.4 Novel sampling approaches

The advent of improvement in our knowledge of statistics and improvement in computer technology and statistical programmes have enabled us to develop and test novel sampling approaches including the use of mathematical modelling (Sarndal et al., 2003). Of these, the most promising for malaria M&E and surveillance are hybrid sampling (Hedt and Pagano, 2011), lot quality assurance sampling (LQAS) (Dodge and Romig, 1929; Shewhart, 1931) and geo-spatial sampling.

Hybrid sampling

Using hybrid prevalence estimators to collect information from convenience samples is a novel concept that has been explored mathematically (Hedt and Pagano, 2011) but is yet to be implemented in practice. Hybrid prevalence estimators are derived by combining data from a convenience sample with that of a simple random sample of the population. According to mathematical modelling done by Hedt and Pagano, hybrid sampling provides gains in efficiency resulting in decreased sample size requirement by combining a relatively small, and presumably far less expensive, random sample to convenience sample (Hedt and Pagano, 2011). Combining both samples eliminates the bias from the convenience sample and legitimises the use of powerful inferential tools that are usually associated with a random sample. The decreased sample size of a hybrid sampling approach is likely to reduce the complexity and cost of surveillance at the district level compared to the cluster randomised sampling approach of a household survey, thus favouring more frequent surveys and data-driven programme management. Despite the sound mathematical reasoning behind this concept,

hybrid sampling is yet to receive global acceptance as a surveillance strategy for malaria as there are hardly any examples described in the literature. Whilst hybrid sampling may be an answer to the need for timely estimates for control progress, it still results in an average estimate with no cognisance of the geospatial distribution of transmission.

Lot Quality Assurance Sampling

Lot quality assurance sampling (LQAS) was developed in the late 1920s to control the quality of output in industrial production processes (Dodge and Romig, 1929; Shewhart, 1931). It involves the assessment of a small batch of a manufactured sample of products for quality, and if the defective items in the sample exceeds a predetermined number (decision rule), then the lot is rejected. The sample size is statistically determined, based on the desired production standards and the corresponding decision rule (Dodge and Romig, 1929). Since the 1980s, LQAS has been increasingly used in the health sciences and has gained considerable appeal in a wide range of applications (Lanata and Black, 1991; Valadez, 1991; Valadez and Devkota, 2002; Robertson and Valadez, 2006). In this case, the definition of the lot should be defined, based on geographical or administrative boundaries, usually at district or sub-district level, where there is a responsible officer present and accountable for corrective actions. The main advantage of LQAS is that a smaller sample size is required to classify areas according to performance than would be required by a probability sampling approach in household surveys (Robertson et al., 1997). Lot quality assurance sampling as a means of assessing control progress is a relatively new strategy that has been assessed at the local level (Dias et al.; Okoh et al., 2006; Ministry of Health of Eritrea, 2008; Laly et al., 2009) and at the national level (Biedron et al., 2010).

In order to make data driven decisions at the district level using LQAS, the exact value of the indicator is not required like in household surveys, rather its position above or below a set threshold defined according to the requirement for

control interventions. This will identify communities with inadequate control progress for targeted control providing all possible geographic locations are sampled. The main shortcoming of this approach is that it deals with a threshold and exact estimates of the degree of coverage or endemicity will be unavailable making it impossible to determine sub-threshold changes. Lot quality assurance sampling is receiving more and more acceptance but needs to be tested across the endemicity spectrum before it can be confirmed as a legitimate surveillance strategy.

Geospatial sampling

Spatial representation of epidemiological data in the form of a map facilitates interpretation, synthesis and recognition of any changing frequency and pattern of infected cases and the appearance of clusters of infection. This is key as control strategies are usually applied at different spatial levels – from administrative regions like district to the unit of coverage assessment, the household (MEASURE Evaluation et al., 2013a). The availability of geospatial data on malaria transmission and improved availability software capable of carrying out spatial analytic methods have enabled the development of detailed risk maps of malaria transmission at both the global level (Guerra et al., 2007; Hay et al., 2008; Gething et al., 2011; Gething et al., 2012) and national level (Alegana et al., 2013). Geo-spatial representation of disease risk is a powerful approach in that it communicates to key decision makers the spatial differences in control progress in a region of interest and facilitates spatial targeting of control interventions. Environmental data (e.g. rainfall, temperature and humidity) need to be collected as well as this may help in determining the epidemiological significance of the spatial distribution in a particular geographic region (Hay et al., 1998; Hay et al., 2006).

To provide accurate geospatial estimates of infectious disease with spatial variation like malaria, it is necessary to find optimal sampling locations in the area of interest in order to get representative data. Sampling from this type of

distribution is analogous to previously discussed major sampling strategies, and are categorised into simple random, systematic, stratified and cluster sampling. A simple random spatial sampling scheme consists of choosing a set of random sampling points in in an area of interest in such a manner that each location has an equal probability of being selected (Ripley, 2004). This process is repeated until the desired sample size is achieved. This method is simple to carry out but there is the risk of over- or under-sampling in some areas leading to a sample that is not spatially representative (Griffith and Amrhein, 1997).

In systematic geospatial sampling, after determining the sample size, we construct a sampling frame consisting of a row of sampling units (usually using a natural linear organisation of the population like points along a main access road), then randomly select a starting point from one end of the sequence and sample at equal intervals from that point (Ripley, 2004). The main benefit of this approach compared to simple random geospatial sampling is the fact that it results in a good spread of sampling points in the area of interest. This method however relies on the preposition that the points selected are not significantly different from those in between the sampling points which may not always be the case. There is also a danger of resulting with data that is not spatially representative if coincides in frequency with a regular pattern in the landscape (e.g. irrigation schemes) (Griffith and Amrhein, 1997).

In stratified geospatial sampling, the survey area is divided into non-overlapping strata either as a set of regular blocks or into natural areas based on factors such as vegetation pattern (Ripley, 2004). Sampling points are then randomly selected until the desired sample size for the whole area of interest is achieved. Because some sub-regions of the study area may exhibit more marker spatial variation than others (Cressie, 1993), smaller strata are preferred in areas where we expect a wide spectrum of spatial variation.

Cluster geospatial sampling may be practical when there is a natural spatial proximity of desired sampling units e.g. households in a village. In this method of sampling, clusters are randomly selected from our area of interest, then either the whole cluster or a random sample of the cluster is selected depending on the resources or sample size (Ripley, 2004). If the probability of selecting a cluster is dependent on the proportional distribution of its elements in the target population we will obtain a self-weighting sample. This method of geospatial sampling is advantageous to the other methods as it requires only the list of available clusters unlike the others which require the details of the whole sampling frame.

Combining data from EAGs and probability samples using generalised linear geostatistical models is a promising new geospatial sampling approach(Giorgi et al., In press). With the assumption that the data from the probability sample is an accurate geospatial representation of the prevalence of a particular attribute of interest (e.g. *P. falciparum* parasitaemia), the joint model allows for biased sampling and temporal variation, and leads to gains in efficiency of estimation and spatial prediction. The paper used the data from samples from two serial standard MISs combined with that of an EAG sample from the same study area to construct accurate malaria prevalence maps. This model indicates that a using hybrid sampling approach combining data from EAG and random sampling to derive spatial maps and guide in the targeting of malaria control interventions urgently needs to be evaluated(Giorgi et al., In press).

2.6 Survey designs for malaria surveillance, monitoring and evaluation

2.6.1 Nationally representative household surveys

Malaria Indicator Surveys

The Roll Back Malaria (RBM) Partnership was launched in 1998 by numerous global partners, in order to provide a coordinated global approach to fighting malaria. In 2002, the RBM Monitoring and Evaluation Reference Group (MERG) was established to act as an advisory body for the RBM Partnership Board on all matters pertaining to monitoring and evaluation of RBM initiatives at the international, regional, and national levels. The mandate of MERG was to provide technical advice on state-of-the-art approaches for the monitoring and evaluation of malaria programs. In 2005, the RBM Survey and Indicator Guidance task produced a comprehensive package of tools to guide NMCPs in carrying out household-level surveys relevant for assessing core malaria indicators (i.e. MISs) (RBM MERG, 2005). These guidelines and indicators are regularly updated with the most recent version containing 13 outcome indicators and three impact indicators (Table 7) (MEASURE Evaluation et al., 2013a). MISs are expected to be applicable to different endemic settings as a tool for measuring coverage of control interventions that target the household (e.g. IRS).

In the light of the global progress in malaria control by 2010, RBM updated the GMAP goals, objectives and targets in June 2011 (WHO and RBM, 2011). The updated objectives are as follows:

1. Reduce global malaria deaths to near zero by end 2015
2. Reduce global malaria cases by 75% by end 2015 (from 2000 levels)
3. Eliminate malaria by end 2015 in 10 new countries (since 2008) and in the WHO Europe Region

The targets necessary to achieve these objectives include achieving and sustaining universal access to prompt and effective diagnostic testing and treatment at all

sectors of health care, universal access to and utilization of prevention measures (including ITNs) and accelerate development of surveillance systems (WHO and RBM, 2011). The updated targets necessitated a revision of indicators resulting in 5 new and two updated outcome indicators (Table 7) (MEASURE Evaluation et al., 2013a) . Both outcome and impact indicators are included in the Household and Women's Questionnaires.

The population of interest for MISs are those at most risk for malaria infection, women of reproductive age (15-49 years old) and children less than 5 years of age, living within malaria endemic or epidemic-prone areas (MEASURE DHS, 2013b). MISs use probability sampling so their feasibility depends on the availability of a suitable sampling frame that entirely covers the target population. The preferred sampling frame is a list of geographic areas consisting of a convenient number of dwelling units (clusters) which serve as a counting units from a recently completed population census (i.e. enumeration areas (EAs)) (MEASURE DHS, 2013b). The geographic extent of the sampling frame is determined by the perceived distribution of endemic and/or epidemic-prone malaria based on climatic and entomological factors (Snow et al., 2003; Bryce et al., 2005). In countries with endemic and/or epidemic-prone malaria throughout, the sampling frame should cover the entire country (stratified by urban and rural residence). In countries with endemic and/or epidemic-prone malaria throughout (excluding readily identifiable regions within the Sahel or Sahara deserts), the sampling frame should include the whole country. In countries that contain malaria-endemic regions intermittently, regions without endemic and/or epidemic-prone malaria should be excluded from the sampling frame if conditions are not favourable for transmission (e.g. mean ambient monthly temperatures below 18° C) or treated as a separate survey domain if there is still a risk of transmission.

Table 7: Household Survey Indicators for Assessing Progress towards GMAP Targets (Source: Household Survey Indicators for Malaria Control, *(MEASURE Evaluation et al., 2013a)* with kind permission)

Intervention	Outcome indicator description
Prevention	
Vector Control via ITNs and IRS	1. Proportion of households with at least one ITN 2. Proportion of households with at least one ITN for every two people **(NEW)** 3. Proportion of population with access to an ITN within their household **(NEW)** 4. Proportion of population that slept under an ITN the previous night 5. Proportion of children under five years old who slept under an ITN the previous night 6. Proportion of pregnant women who slept under an ITN the previous night 7. Proportion of existing ITNs used the previous night **(NEW)** 8. Households covered by vector control: Proportion of households with at least one
IPTp	9. Proportion of women who received three or more doses of IPTp for malaria during ANC visits during their last pregnancy **(UPDATED)**
Case Management	
Diagnosis	10. Proportion of children under five years old with fever in the last two weeks who had a finger or heel stick
Treatment	11. Proportion of children under five years old with fever in the last two weeks for whom advice or treatment was sought **(NEW)** 12. Proportion receiving an Artemisinin-based Combination Therapy (ACT) (or other appropriate treatment), among children under five years old with fever in the last two weeks who received any antimalarial drugs **(NEW)**
Impact measure	**Impact Indicator description**
Morbidity indicators	13. Parasite prevalence: proportion of children aged 6-59 months with malaria infection 14. Anaemia prevalence: proportion of children aged 6-59 months with a haemoglobin
Mortality indicator	15. All-cause under five mortality rate (U5MR)

Determination of sample size for a MIS is a balance between the level of precision at the national level and at the domain level (if there are domains) and how detailed an analysis is required with capability of the implementing organization and the funding available. The minimum required sample size is the sum of the sample sizes required for all RBM indicators over all domains (if any) for

which desired precisions are guaranteed, providing this can be covered by the funding available. Sample selection for a MIS is a two-stage stratified cluster sampling procedure developed by ICF International's DHS program (ICF International, 2012b). In the first stage, every EA in the country is assigned a measure of size equal to the number of households or its population. Since countries are usually divided into geographic regions or administrative units (which are further sub-divided into districts), the main sampling frame is thus distributed over these administrative units and usually stratified by type of residence (urban vs. rural). A sample of EAs with a predetermined sample size is then independently selected in each stratum with probability proportional to its size. In the selected EAs, all dwellings and households are listed to provide a sampling frame for household selection to correct for possible errors in the existing main sampling frame. A fixed number of households are then selected from each EAs by systematic sampling from a randomly determined point. Systematic sampling is preferred to simple random sampling because it provides a stratification effect with respect to the variables on which the frame is sorted (implicit stratification) thus preventing the unexpected concentration of sample points in certain areas that can occur with simple random sampling (ICF International, 2012b).

Data collection on RBM indicators is via a combination of household interviews and blood sample collection for assessment of haemoglobin and malaria parasite infection, usually conducted during or right after the rainy season. Before each household interview, the household members are listed and eligible respondents are selected for interview and/or assessment.

Demographic and Health Surveys

Demographic and Health Surveys were designed to collect data on several population, health and nutrition indicators (including Millennium Development Goal indicators (MDGs)) in order to guide the policy choices of decision-makers

(ICF International, 2012a). The DHS program is implemented by ICF International, a private consulting firm in Calverton, Maryland, USA (formerly called Macro International Inc.), typically carried out by government organizations. The target population for the DHS survey is all women age 15-49 and children under five years of age living in residential households, but most surveys now include all men age 15-59 (Aliaga and Ren, 2006). The selection of the sampling frame, determination of sample size and sample selection are the same as above, but data is collected on a much wider spectrum of indicators than in a MIS surveys. Demographic and Health Surveys are not specifically tailored for malaria surveillance but produce reliable estimates of current RBM indicators including ITN use in children less than five year old, ITN use in pregnant women, the proportion of women who received intermittent presumptive treatment (IPTp) for malaria during a recent pregnancy and the U5MR (ICF International, 2012a).

Multiple Indicator Cluster Surveys

Multiple Indicator Cluster Surveys were first developed by UNICEF, to support countries measure progress towards an internationally agreed set of goals that emerged from the 1990 World Summit for Children (UNICEF, 2012d). Over the following years the indicators evolved to accommodate other major international commitments including MDGs, United Nations General Assembly Special Session on HIV/AIDS and the Abuja targets for malaria; whilst still maintaining its focus as key data source to measure progress in meeting commitments made to children. MICS are typically carried out by government organizations, with the technical support and financial assistance of UNICEF and its partners. The target population for a MICS are women aged 15 to 49 years, and children under five and in other age groups. The current round of MICS (MICS5) is scheduled from 2012 – 2014 (UNICEF, 2012b). The MICS questionnaires collects several malariometric indicators of which the key indicators to assess endemicity are the under-five mortality rate and the 2-week period-prevalence of fever in children < 5 years old. The interpretation of the latter indicator as a measure of malaria endemicity has

been much debated and its reliability is doubtful (Einterz and Bates, 1997; Lubanga et al., 1997; Dunyo et al., 2000).

Vital Registration Systems

A vital statistics system is defined as the total process of collecting information on vital events (e.g. births and deaths) in the population by civil registration or enumeration on the frequency of occurrence of specified and defined vital events through regular censuses or population registers, and compiling, processing, analysing, evaluating, presenting and disseminating these data in statistical form (United Nations, 2001). Systems of vital registration can sometimes provide relevant information for malaria surveillance especially for the determination of U5MR at the national level (MEASURE Evaluation et al., 2013a). The problem with this form of surveillance is due to completeness as recent estimates indicate that almost one-third of 135 million births and over two-thirds of approximately 57 million deaths worldwide were unregistered or unrecorded (Oomman et al., 2013).

2.6.2 District and sub-district level surveys

The distribution of malaria infection depends on environmental, climatic, and ecological suitability for vectors and transmission. As a result, the distribution of malaria endemicity globally is spatially heterogeneous (Gething et al., 2011; Gething et al., 2012). This is one of the reasons for the adoption of a spatial progressive approach to malaria control and elimination referred to as shrinking the malaria map (Feachem and The Malaria Elimination Group, 2009). At the sub-national level, infections tend to cluster in geographic foci of varying size or hotspots that maintain a higher level of transmission than the immediately surrounding areas, and act as a reservoir of parasites throughout the year thus contributing significantly to the population parasite pool (Bejon et al., 2010; Bousema et al., 2012). The current MIS sampling guidelines try to address this by suggesting explicit stratification into specific domains for high- and low-intensity

malaria transmission (MEASURE DHS, 2013b). This approach requires recent accurate knowledge of heterogeneity in transmission which is not available, will increase the sample size and complexity of the survey, and being part of a national MIS may not be able to offer timely estimates to monitor control progress.

Continuous facility-based surveillance of clinical cases

An alternative approach will be to carry out continuous sub-district surveillance to supplement national efforts particularly in the interval between national household surveys. Continuous facility based surveillance of clinical cases have also been suggested by the WHO, taking into consideration the fact that estimates from this EAG are affected by health facility attendance, diagnostic testing and reporting rates (WHO, 2012a; WHO, 2012b). If the facility use rates and reporting rates are known, then estimates can potentially be adjusted for these factors. This approach like that of nationally representative household surveys is targeted at providing average estimates (in this case of incidence of confirmed cases) and not the geographic heterogeneity distribution in the facility's catchment area. The spatial distribution of malaria must be taken into consideration by NMCPs because targeting hotspots with control measures will have a greater effect than uniform resource allocation (Carter et al., 2000; Bousema et al., 2012). This strategy will become crucial as transmission intensity drops and transmission becomes increasingly focal.

Rolling malaria indicator surveys

The novel "rolling" methodology of surveys proposed by Roca-Feltrer et al 2012 which consists of monthly cross-sectional surveys is a promising approach that could provide timely estimates of parasite and anaemia prevalence to detect short- to medium term control progress (Roca-Feltrer et al., 2012). In this approach, the total sample size is calculated to provide accurate estimates of the geographic area of interest (e.g. a district) with proportionality to village size. Then using small

mobile survey teams, the surveys are 'rolled' using the same questionnaire tool and indicators as a standard MIS so that data is collected continuously (e.g. monthly), depending on the availability of resources, timing of control interventions and seasonality (Roca-Feltrer et al., 2012). This methodology can generate geographically relevant data on control progress and could support district-level malaria control strategies (Rowe, 2009a). For now, this promising approach has only being carried out under experimental settings and should urgently be evaluated in real life settings to fully assess the full economic and financial cost of this potential complementary M&E tool.

2.7 Conclusion

As malaria transmission declines in sub-Saharan Africa and other regions of the world, it is necessary to robustly evaluate the impact of control programmes. The current funding climate implies that developing cost and time effective approaches to measure transmission reduction using precise and accurate indicators in a time and cost effective approach is an urgent requirement. This is of particular importance to NMCPs for two reasons. Firstly, NMCPs need timely data to be able plan their overall strategy and change focus accordingly at the different phases of malaria control. Secondly, in order to be able to effectively target interventions, NMCPs need geospatial data on the uptake of malaria control interventions and transmission intensity, preferably at the district/sub-district level. This is not currently provided by current tools, and there is a definite need for the development of less logistically and financially demanding novel supplementary tools that can provide this data. The next chapter provides a review of potential sub-groups of the population that are easily accessible, the so-called EAGs, which could potentially be suitable for surveillance at the district/sub-district level.

Chapter 3: Systematic Review of Potential Easy Access Groups

3.1 Introduction

Theoretically any spontaneous or premeditated aggregations of sufficient members of the general population or key disease at-risk groups that allows the possibility of surveillance for a certain disease or health state is a potential EAG. However a proposed EAG has to satisfy certain basic characteristics before being suitable for disease surveillance. Thacker et al devised a method of evaluating the quality of surveillance systems based on seven criteria: sensitivity, specificity, representativeness, timeliness, simplicity, flexibility and acceptability all of which should be directly linked to usefulness and cost (Thacker et al., 1988). The main criteria for the selection for appropriate EAGs is whether or not the information provided is cost-effective and useful in contributing to the understanding of the local epidemiology of malaria and/or results in a prompt control response leading to reduction of transmission (Table 8). A trade-off has to be made between the suitability of the surveillance and some aspects its quality. For using RDTs to detect clinical infection might reduce costs of maintaining a microscopy lab but might result in a loss of specificity and inability to quantify parasitaemia (Abba et al., 2011).

Continuous monitoring of data from EAGs will allow estimation of temporal trends and georeferencing the data by determining the origin participants by direct questioning would allow estimation of the geographic distribution of health events of interest, and the latter has been by data from facility-surveys (Schellenberg et al., 1998; Kazembe et al., 2006). Bias in average estimates from EAGs could be corrected by appropriate statistical techniques if the degree and direction of the bias is known, by applying the appropriate corrective factor (Kilian et al., 2013). Even with some imprecision in geospatial representativeness, the data from EAGs can be used to as a guide for resource allocation using alternate sampling approaches like LQAS (Dias et al.; Okoh et al., 2006; Ministry of Health of Eritrea, 2008; Laly et al., 2009). If more average estimates or geospatial representativeness is required this can be achieved by hybrid sampling combining

with a random sample (Hedt and Pagano, 2011) or a spatially representative sample (Giorgi et al., In press) of the population respectively. Based on these criteria and historical evidence, suitable EAGs for district level surveillance include primary school children, the population attending health facilities, pregnant women attending ANC or coming for deliveries, the population exposed to public health intervention surveys and community market days.

Table 8: Definition of criteria evaluating the suitability of EAGs for malaria surveillance (adapted from (Thacker et al., 1988))

Attribute	**Definition**
Suitability	
Usefulness	Contributes to understanding the epidemiology of malaria in the study area. Generates a suitable prompt public health response by impacting policies and/or control response.
Cost-effective	The direct and indirect costs should be justifiable in relation to the benefits attained.
Quality	
Sensitivity	The ability of the surveillance system to measure presence of relevant impact indicators.
Specificity	The ability of the surveillance system to identify the absence of relevant impact indicators.
Representativeness	Accurately reflects the spatio-temporal distribution of key health events and uptake of public health control measures in the population or key at-risk groups.
Timeliness	Ability to provide timely estimates of key health events in order to guide control efforts.
Simplicity	Easy to understand and implement.
Flexibility	Ability to be easily adapted to include new or emerging problems, other health events, population sub-groups or key disease at-risk groups.
Acceptability	Willingness of persons conducting surveillance and those providing data to generate accurate, consistent and timely data. Acceptability to other key stakeholders, the community, health planners, donors, etc.

3.2 Overview of potential EAGs

3.2.1 Primary school children

Primary school surveys were commonly used in the early approaches to malaria surveillance and control (Boyd MF, 1949), but were abandoned in part due to financing constraints and a shift in the goals of control programmes from malaria elimination to morbidity control (Brooker et al., 2009). School parasite surveys were re-introduced as part of rapid assessments of malaria in urban sub-Saharan Africa in 2005 (Wang et al., 2005), since then school surveys have been assessed as a potential surveillance tool at national and subnational level (Gitonga et al., 2010; Ashton et al., 2011). Age-stratified studies in different transmission settings illustrate a similar pattern of a rapid rise in *P. falciparum* prevalence rate (*Pf*PR) from birth attaining maximum in the 5 to 10 year age group (Gupta et al., 1999a; Gupta et al., 1999b), then a decline to a relatively stable level throughout adolescence and adulthood (Baird et al., 1993; Baird, 1995). This means that the typical age range of primary school children in Africa of 5 to 14 years will capture the *Pf*PR peak. Surveillance in school children is attractive as they are increasingly becoming a target of malaria control interventions (Brooker et al., 2008a) and studies in Uganda showed that children reliably reported on household bed net and use (Ndyomugyenyi and Kroeger, 2007), and more importantly were able to differentiate treated from un-treated bed nets (Ndyomugyenyi and Kroeger, 2007). School surveys are a therefore a very attractive potential EAG, but the representativeness of the surveyed population needs to be assessed given the substantial variations in primary school enrolment rates between different regions in sub-Saharan Africa (Table 9) (Filmer and Pritchett, 1999). School surveys may under-represent malaria transmission intensity in countries with high to moderate transmission and thus higher burden in younger children (Table 9).

3.2.2 Population attending health facilities

Specific surveillance in the population attending formal health facilities (Table 9) offers an improved method of collecting information on community

malaria burden than an HMIS (Owusu-Agyei et al., 2007; Chanda et al., 2009; Asante et al., 2011), because it is less susceptible to problems of the latter such as incomplete reporting and lack of confirmation of diagnosis (Cibulskis et al., 2011; Afrane et al., 2013). However, the representativeness of burden estimates from sick individuals still depends largely on the availability of alternative non-formal sector facilities and health seeking behavior; the latter being a key factor that determines health facility utilization rates in times of illness (Table 9) (Agyepong and Kangeya-Kayonda, 2004; Erhart et al., 2007; Rowe et al., 2009). Malaria cases during such surveillance are usually defined as all fever cases associated with a threshold level of *P. falciparum* parasitaemia and this can drastically overestimate the population burden at all levels of endemicity (Roucher et al., 2012). This is however changing with the introduction of RDTs as part of WHO's T3 Initiative (WHO, 2012e). Burden estimates from the population attending health facilities regardless of their illness status is a potential method of deriving estimates of transmission intensity from the population at the lower end of the endemicity spectrum (Oduro et al., 2011b), as it would capture the *Pf*PR peak age shift due to the inclusion of older children (Carneiro et al., 2010).

Alternatively we can consider sub-groups of the population attending health facilities for non-morbidity episodes like children coming for "well child" visits. Well child visits include those coming for scheduled immunization visits and growth monitoring. These children are not sick and thus are probably less susceptible to bias due to health facility utilization as there are limited options to receive public health interventions like lifesaving vaccines from non-formal health facilities. Children coming for immunization visits are the most promising as global immunization coverage is nearly 79% (UNICEF, 2012a). They are usually accompanied by their mothers (women of child-bearing age) and sometimes by an older sibling who is also a source of data on parasite prevalence. Immunization clinics are usually distributed country-wide and it is relatively easy to derive estimates of district-level immunization coverage. The EPI platform has also successfully been used to deliver malaria control measures (Mathanga et al., 2009),

and surveillance in this EAG will allow direct measurement of the impact of the intervention in that age strata. Though there were earlier attempts to evaluate the feasibility of this EAG (Delacollette C, 1990; Some et al., 1997), there have only been two attempts to validate the estimates in direct comparison with a population survey (Skarbinski et al., 2008; Mathanga et al., 2010). Coverage rates of public health interventions have proven to be similar between vaccinated and unvaccinated children if population vaccine coverage is over 60% (Cibulskis et al., 2012).

3.2.3 Pregnant women attending ANC and coming for delivery

Pregnant women merit special consideration as a unique EAG separate from non-pregnant people attending health facilities, because pregnancy makes a woman more susceptible to malaria regardless of endemicity (McGregor, 1984; Desai et al., 2007). There is parity specific susceptibility to the consequences for both mother and child (Brabin, 1983) now known to be due to a phenotypically distinct sub-population of *P. falciparum* that produces *Pf*EMP1 adherent mainly to placental chondroitin sulfate-A (CSA) (Duffy and Fried, 2003; Fried et al., 2006). Despite the increased risk of malaria in pregnancy, to date there is no integrated strategic approach to surveillance of malaria control in pregnancy (Brabin et al., 2008). In areas with high to moderate transmission intensity, there is increased *P. falciparum* prevalence in the placental and peripheral blood which decreases with gestation (Gilles et al., 1969; Brabin, 1983; McGregor et al., 1983) due to parity-specific immunity (Fried and Duffy, 1996), and if not treated during pregnancy would remain until delivery. Surveillance in pregnant women attending ANC or coming for delivery would not only offer an opportunity to assess the impact of interventions in a specific risk category but will also allow us to extrapolate information about transmission intensity to the population (Table 9). Currently only the prevalence of low birth weight (<2500g) by parity and the prevalence of third trimester anaemia (Hb<8.0g/dl) are the recommended impact indicators (WHO, 2007a) but peripheral and/or placental parasitaemia at delivery has also been

suggested (Parise et al., 2003). Since ANC attendance is high and most women attend ANC at least once during their pregnancy (73%), even in least developed countries (UNICEF, 2012c), this makes them an attractive EAG for malaria surveillance (Table 9). Pregnant women are scheduled to attend ANC at regular intervals until delivery and they build up pregnancy-specific malaria immunity over the course of infections. The prevalence of parasitaemia at the first antenatal booking is likely to reflect transmission pressure in women who have not yet received any control intervention for malaria in pregnancy. The prevalence in primigravidae at delivery may be taken as a reflection of the effects of interventions against malaria in pregnancy in high to moderate transmission settings. The wide geographic distribution of antenatal clinics (like vaccination clinics) and the ability to detect different levels of transmission through surveillance in ANCs (Newman et al., 2003) would make the data from this EAG representative at the district level. It is also relatively easy to derive district level information on ANC attendance and the proportion of deliveries that take place in formal health facilities. One significant advantage that ANC surveillance has over surveillance in non-pregnant health facility attendants is that pregnant women are routinely screened at antenatal booking for anaemia, syphilis and HIV. Thus adding screening for malaria may not require an additional fingerpick.

3.2.4 Public Health Intervention campaigns

Large population-based public health intervention control campaigns like mass ITN distribution campaigns, national immunization days (NIDs) and mass drug administration (MDA) offer an excellent opportunity to integrate malaria surveillance (Table 9). These campaigns cover a large cross-section of the population in a relative short period of time. There are no examples for malaria but the NID platform was successfully utilized to implement a concurrent nutritional survey and estimate coverage of health and social welfare services in almost 3 million children in Brazil (Santos et al., 2008b). The size of the NIDs platform allowed inferences about different subgroups of underprivileged children that had never before been studied in such detail, including state-level data from the semi-

arid region and information on specific vulnerable populations. NIDs are currently used for global poliomyelitis eradication (Birmingham et al., 1997) but it is highly likely that as other vaccine preventable diseases near the eradication threshold, there will be other such NIDs. Malariometric surveys could be integrated into other public health campaigns. Mass drug administration (MDA) campaigns are a particularly attractive option are they are currently used for the control of several tropical diseases such as vitamin A deficiency and trachoma, and onchocerciasis (Smits, 2009). Mass drug administration campaigns for filariasis has been successfully explored as a potential platform for malaria surveillance (Mitja et al., 2013).

3.2.5 Community market days

Regular market days are common in most developing countries and are another potential EAG. This may be particularly attractive in areas where villages are far apart and communities are nomadic as the logistic requirement to do a household survey in such circumstances may be prohibitively expensive. Cross-sectional surveys during market days have been explored as a tool to estimate vaccination coverage in children (Oladokun et al., 2009), the community burden of diarrhoeal disease in under-fives and use of oral rehydration solutions (Omokhodion et al., 1998) and loiasis (Ibidapo et al., 2008). Collection of samples for screening/diagnosis purposes has been shown to be possible in a survey of undiagnosed hypertension and proteinuria in a market population (Fatiu et al., 2011). The most conclusive evidence for the potential of market surveys as an EAG for disease surveillance comes from the use of market surveys to determine the population prevalence of filarial and non-filarial elephantiasis in Ethiopia, Rwanda and Burundi (Oomen, 1969; Price, 1976). The data from these market surveys not only accurately represented population prevalence (Oomen, 1969), but were able to demonstrate heterogeneity in prevalence due to differing exposure to soil containing volcanic lava (Price, 1976). Though there are no published examples for malaria, markets are conveniently centrally located and in some cases situated in

border towns which makes them important for monitoring cross-border transmission as transmission falls (Kitvatanachai et al., 2003; Wesolowski et al., 2012).

3.3 Systematic review

3.3.1 Methods

Search strategy

Medline, PubMed®, ScienceDirect®, Web of Knowledge® and CINAHL® bibliographic databases without language restrictions from inception to 31st October 2013 for articles with the following search terms in the keywords, title or abstract: "malaria" AND "survey"; or "malaria" AND "monitoring" AND "evaluation"; or "malaria" AND "transmission" AND "measurement. We also searched the online WHO Document centre (WHO, 2013f) for any up to date relevant policy documents; and grey literature from WHO historical documents on malaria (1947-2000) database (WHO/MAL, 2012).

To determine which abstracts on these EAGs were eligible for further review we searched the resulting pooled database for the mention of the following keywords in the abstract:

(1) "school AND survey" and "school AND monitoring AND evaluation"

(2) "health AND facility OR centre AND survey" and "health AND facility OR centre AND monitoring AND evaluation"

Table 9: Characteristics of EAG surveys

Easy Access Group	Pros	Cons
Primary school children	• Identification and selection of individuals for survey simplified. • Compliance likely to be high. • Schools are widely distributed allowing the potential of detecting hotspots. • Surveys can be further simplified using LQAS. • Has been successfully implemented at programmatic level and is already a validated form of surveillance. • Suitable for continuous surveillance. • Could easily be integrated with school public health programmes like deworming campaigns.	• Sampling bias: Socio-Economic Status. May represents more affluent section of the community from families who can send their children to school. May underestimate malaria, as children who are sick will likely stay at home. • May under-represent malaria transmission intensity in countries with high to moderate transmission and thus higher burden in younger children (under-fives).
Population attending health facilities	• Includes at-risk groups for malaria so less individuals need to be surveyed compared to a population-based survey. • Potentially representative where there is good health facility utilization and wide geographic distribution of health facilities. • Population vaccine coverage for well child visits can be estimated from district health figures. • Identification and selection of individuals for survey simplified. • Surveys can be further simplified using LQAS. • Has been evaluated as a surveillance tool. • Suitable for continuous surveillance. • Could easily be integrated with the HMIS	• Sampling bias: Affected by health facility utilization rates so may only represent those with good health seeking behaviour. • Since invasive sampling is not routinely done in all people attending health facilities, implementation may require evaluation. • Needs to be validated as a form of surveillance.
Pregnant women attending health facilities	• At-risk group for malaria so less individuals need to be surveyed compared to a population-based survey	• Sampling bias: Affected by ANC attendance and proportion of women who opt to deliver in hospital

Easy Access Group	Pros	Cons
	• Suitable for continuous surveillance. • Potentially representative where there is good ANC attendance and geographic distribution of ANCs. • Population ANC attendance can be estimated from district health figures. • Identification and selection of individuals for survey simplified. • Surveys can be further simplified using LQAS. • Invasive sampling part of routine ANC care to assess HIV, STIs and anaemia in pregnancy so addition of assessment of parasitaemia may not require an additional sample. • Can be easily integrated into current ANC strategy.	so may only represent those with good health seeking behaviour or higher socio-economic status. • Needs to be validated as a form of surveillance.
Public health campaigns	• Represents a large cross-section of the population of interest. • Has been successfully evaluated before with surveillance of other diseases.	• Not suitable for continuous surveillance. • Needs to be validated as a form of surveillance.
Community market days	• Represents a large cross-section of the population of interest. • Has been successfully evaluated before with surveillance of other diseases. • Suitable for continuous surveillance.	• Sampling bias: May only represent the more affluent section of the community that can afford to attend market days. • Needs to be validated as a form of surveillance.

(3) "antenatal clinic AND survey", "antenatal clinic AND monitoring AND evaluation", "delivery AND survey", "delivery AND monitoring AND evaluation"

(4) "market AND survey" and "market AND monitoring AND evaluation"

(5) "public health intervention AND survey" and "public health intervention AND monitoring AND evaluation"

Inclusion criteria

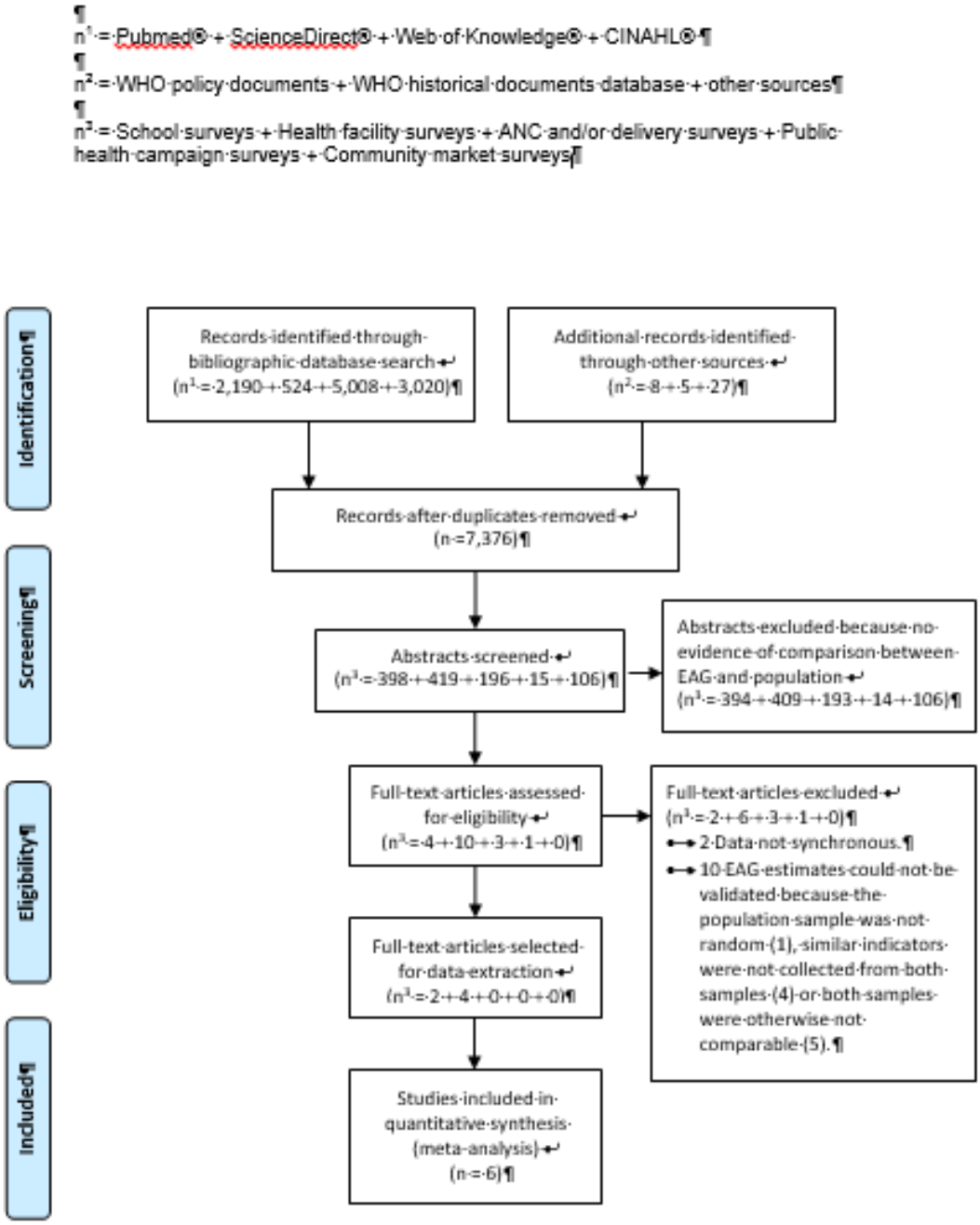
The abstracts of all EAG studies were examined and the articles of abstracts where there was specific mention of comparison between an EAG and population sample were selected for a full text review (Figure 4). Only studies where estimates of malaria control indicators from cross-sectional surveys in EAGs were compared to a synchronous random population sample, in the same age group, district or catchment area were included in the systematic review.

Selection of studies

Twelve of the eighteen studies selected for full review did not meet the inclusion criteria (Figure 4). Two studies were excluded because the data collected was not synchronous between the EAG and population sample (Stewart et al., 2009; Mitja et al., 2013). In eleven studies the validity of EAG estimates could not be determined either because the population sample was not random (Rulisa et al., 2013), similar indicators were not collected from both samples (Parise et al., 2003; Nyarango et al., 2006; Hanson et al., 2009; Marchant et al., 2011), or both samples were otherwise not comparable (Onori, 1967; Bouma et al., 1996; Rodrigues et al., 2008; Pacific Malaria Initiative Survey Group, 2010; Sahu et al., 2013).Of the included studies, one author extracted data on the EAGs and comparator population in relation to characteristics of the sampling process (units, method frame) and the results. Data extraction from the selected publications was done by two independent un-blinded authors. In the designated studies data was extracted on the first author, year of publication, study duration, malaria transmission

intensity, selection criteria, sampling methodology, sample size, sampling unit(s) and estimates of control progress (e.g. *Pf*PR).

Figure 4: PRISMA Flow Diagram for studies comparing estimates between EAG and population surveys



* PRISMA stands for Preferred Reporting Items for Systematic Reviews and Meta-Analyses and is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses (http://www.prisma-statement.org/).

We contacted the primary authors where there was insufficient data in the publication for analysis or missing information. The comparability of key estimates of control progress was determined by calculating the absolute difference in the prevalence with their respective 95%Cis and p-values.

3.3.2 Results

Description of studies

Six studies all from sub-Saharan Africa, satisfied the inclusion criteria and were included in the systematic review (Figure 4). EAG populations were from primary schools, EPI clinics, dispensaries, and the outpatient department (OPD) of hospitals and health centres (Table 10). Two surveys compared estimates from school surveys to population estimates (Ndyomugyenyi and Kroeger, 2007; Stevenson et al., 2013), four studies compared estimates from health facilities (including sick and/or well child visits) with population estimates (Skarbinski et al., 2008; Mathanga et al., 2010; Gahutu et al., 2011; Oduro et al., 2011b).

Comparison of estimates

Table 11 illustrates a comparison of the crude estimates of *P. falciparum* parasitaemia from EAGs with a probability sample from the population. In the study in a mesoendemic region in Rwanda, where *Pf*PR was determined by PCR, the estimates derived from sick children attending OPD of a hospital and health centre where not significantly different from that from the population. In a study involving serial surveys in six districts with different endemicity in Malawi where *Pf*PR was determined by microscopy, estimates from children attending EPI clinics were significantly higher than that of the population in 2005 (absolute percentage risk difference or RD = 6.2%, 95% CI 2.4%, 10.0%, p = 0.0017) but was not significantly different in the follow-up survey in 2008 (RD = -0.7%, 95% CI -2.5%, 1.2%, p = 0.4044). In the Gambia where transmission was mesoendemic, a study comparing estimates *Pf*PR determined by microscopy, determined that estimates

derived from all patients presenting at health centres (regardless of diagnosis) were significantly higher than that of the catchment population rainy season (RD = 11.6%, 95% CI 10.0%, 13.2%, $p < 0.001$) and slightly lower in the dry season (RD = -1.0%, 95% CI -1.6%, -0.5%, $p < 0.001$). In a study in Kenya comparing estimates of *Pf*PR determine by RDT from primary school children and that of the catchment population within 600m of selected schools, estimates from the EAG sample significantly overestimated that of the population.

Table 12 is a comparison of estimates of APR between EAGs and a population sample. In the Gambia, EAG estimates of APR were significantly higher than that in the population in both the dry and the rainy season. In Malawi, in both surveys in 2005 and 2008, APR estimated from children aged 6 to 30 months attending EPI clinic for well child visits was not significantly different from that in the population.

Table 13 is a comparison of estimates of seroprevalence between EAGs and a probability sample of the population. In the Gambia, there was little change in seroprevalence to MSP119 between seasons but in the rainy season estimates from a sample of all patients reporting to health centres regardless of diagnosis were significantly higher than that of the population in the rainy season and significantly lower than population values in the dry season. Stevenson et al. 2013 compared estimates for seropositivity for MSP1 and/or AMA1 in primary school children in classes 2 – 6 with all children aged more than 6 months in households within 600m of each selected school, and estimates from the EAG were not significantly different from that of the population sample (RD = 0.4%, 95% CI -1.7%, 2.5%, $p = 0.7224$).

Ndyomugyenyi et al. 2007 compared estimates of household ITN possession obtained by direct questioning of primary school children aged ten years or more with that of from household heads and spouses of a randomly selected school

catchment village (Table 14). Estimates of ITN possession from this EAG were not significantly different from the population. Table 15 is a comparison of crude percentage estimates of household ITN use (i.e. the number of under-fives who slept under an ITN the previous night) between different EAGs and a probability sample of the population. In the serial surveys conducted in Malawi by Mathanga et al 2010, the estimates from the mothers of children attending EPI Clinics overestimated population household ITN use in 2005 (RD = 12.1%, 95% CI 9.5%, 14.7%, $p < 0.001$) and underestimated population household ITN use in the follow-up survey in 2008 (RD = -4.3%, 95% CI -8.3%, -0.4%, $p = 0.0305$). In Tanzania, the study by Skarbinski et al 2008 compared estimates of household ITN use from mothers of children coming for sick and well child visits and in two different health facility catchment populations and estimates derived from both groups significantly over-estimated population coverage (Table 15).Only one study compared the estimates of IRS coverage between an EAG and the population (Table 16). A study done in Kenya, illustrated that estimates of household IRS coverage derived from primary school children in classes 2 – 6 underestimated population values from the community adjacent to the schools (RD = -3.4%, 95% CI -5.3%, -1.5%, $p < 0.001$).

Potential limitations

First, the search strategy may not have identified all the relevant papers a there may be other sources of grey literature that may have been missed. Secondly, we phrased our search terms as basic as possible to allow a wider inclusion of possible papers and in this regard we may have missed some very specifically title papers that the search terms may not have been able to detect. Thirdly, all the articles included in the systematic review were from sub-Saharan Africa and our results may not be generalizable elsewhere. Finally, our literature search was guided by categories of EAG which we theorized would be suitable for malaria surveillance and we may have missed publications on other possible EAGs.

Table 10: Description of studies comparing estimates between EAG and population surveys

Study	Study year(s)	Country	Geographic unit of comparison	Site(s)	Malaria endemicity	EAG			Population		
						Participants	Sampling methods	Sampling Units	Participants	Sampling methods	Sampling Units
Gahutu et al. 2011	2012	Rwanda	District	Huye	Meso-	Sick children < 5 years attending health facilities	Successive	Hospital (1) Health centre (1)	Children < 5 years living in households	Stratified random	Villages (24), then households (600)
Mathanga et al. 2010	2005 & 2008	Malawi	District	Phalombe Blantyre Chiradzulu Mwanza Lilongwe Rumphi	Multiple	Well children 6-30 months attending EPI clinics	Systematic	2005: EPI clinics (12)	Children aged 6-30 months living in households	Stratified random, probability proportional to enumeration area	Enumeration areas (30), then households (1739)
							Systematic	2008: EPI clinics (12)		Modified EPI cluster survey	Enumeration areas (30), then households (10034)
Ndyomugyenyi et al. 2007	2005	Uganda	District	Hoima	Hyper-	Primary school children ≥ 10 years	Purposeful[a]	All primary schools (39)	Household heads or spouses	Stratified random	Villages (39), then households (2798)
Oduro et al. 2011	2008	Gambia	Country	Albreda Kaur Yorobawol Gambisara Bureng Gunjur	Meso-	All patients attending health facilities	All on day of survey	Health centre (6)	All villagers	Age-stratified random	Villages (18), then compounds (2160)

Study	Study year(s)	Country	Geographic unit of comparison	Site(s)	Malaria endemicity	EAG			Population		
						Participants	Sampling methods	Sampling Units	Participants	Sampling methods	Sampling Units
Skarbinski et al. 2008 (Skarbinski et al., 2008)	2005	Tanzania	District	Lindi	Holo-	Children < 5 years coming for sick and well child visits	Stratified cluster sampling (Lindi)	Lindi: Hospital (5) Health centre (5) Dispensary (5)	Household members	Stratified random, probability proportional to enumeration area (Lindi)	Enumeration areas (22), then households (574) (Lindi)
				Rufiji			All (Rufiji) on day of survey	Rufiji: Health centre (4)		Simple random (Rufiji)	Households (1727) (Rufiji)
Stevenson et al. 2013 (Stevenson et al., 2013)	2010	Kenya	District	Rachuonyo Kisii	Meso-	Primary school children in classes 2-6	Government primary schools (46)	Gender-stratified random sampling	All children > 6 months living in compounds	Simple random sampling, within 600m of each school	Compounds (unknown)

Table 11: Comparison of crude percentage estimates of *P. falciparum* parasitaemia between EAG and population survey

***P. falciparum* prevalence**	**EAG sampling unit**	**EAG survey**		**Population survey**		**Absolute percentage risk difference (95% CI)**	**p-value**
		Events (n/N)	**Percentage prevalence (95% CI)**	**Events (n/N)**	**Percentage prevalence (95% CI)**		
Rwanda (Gahutu et al., 2011)[a,d]							
Huye 2010	Hospital	15/101	14.9 (7.9, 21.8)	88/545	16.2 (13.1, 19.2)	-1.3 (-8.9, 6.3)	0.7440
Huye 2010	Health centre	22/103	21.4 (13.4, 29.3)	88/545	16.2 (13.1, 19.2)	5.2 (-3.3, 13.7)	0.1963
Malawi (Mathanga et al., 2010)[b,e]							
Multiple 2005	EPI clinic	464/1516	30.6 (28.3, 32.9)	195/799	24.4 (21.4, 27.4)	6.2 (2.4, 10.0)	0.0017
Multiple 2008	EPI clinic	247/1871	13.2 (11.7, 14.7)	607/4337	13.9 (12.8, 14.9)	-0.7 (-2.5, 1.2)	0.4044
Gambia (Oduro et al., 2011b)[b,f]							
Multiple 2011	Health centre	1088/4543	24.0 (22.7, 25.2)	478/3870	12.4 (11.3, 13.4)	11.6 (10.0, 13.2)	<0.001
Multiple 2011[g]	Health centre	46/4101	1.1 (0.8, 1.4)	80/3716	2.2 (1.7, 2.6)	-1.0 (-1.6, -0.5)	<0.001
Kenya (Stevenson et al., 2013)[c]							
Multiple 2010	Primary school	1256/4888	25.7 (24.5, 26.9)	580/3742	15.5 (14.3, 16.7)	10.2 (8.5, 11.9)	<0.001

[a]*Pf*PR assessed by PCR

[b]*Pf*PR assessed by microscopy

[c]*Pf*PR assessed by RDT

[d]Sick child visits

[e]Well child visits

[f]All patients regardless of diagnosis

[g]Dry season survey, all other surveys done in the rainy or immediate post-rainy season

Table 12: Comparison of crude percentage estimates of anaemia (Hb < 8.0g/dl) prevalence between EAG and population survey

Anaemia prevalence	EAG sampling unit	EAG survey		Population survey		Absolute percentage risk difference (95% CI)	p-value
		Events (n/N)	Percentage prevalence (95% CI)	Events (n/N)	Percentage prevalence (95% CI)		
Gambia (Oduro et al., 2011b)[a]							
Multiple 2011	Health centre	440/4543	9.6 (8.8, 10.6)	283/3870	7.3 (6.5, 8.1)	2.4 (1.2, 3.6)	<0.001
Multiple 2011[a]	Health centre	317/4101	7.7 (6.9, 8.6)	127/3716	3.4 (2.8, 4.0)	4.3 (3.3, 5.3)	<0.001
Malawi (Mathanga et al., 2010)[c]							
Multiple 2005	EPI clinic	299/1636	18.3 (16.4, 20.2)	184/926	19.9 (17.3, 22.4)	-1.6 (-4.8, 1.6)	0.3216
Multiple 2008	EPI clinic	295/1909	15.5(13.8, 17.1)	649/4461	14.6 (13.5, 15.6)	0.9 (-1.0, 2.8)	0.3518

[a] All patients regardless of diagnosis.

[b]Dry season survey, all other surveys done in the rainy or immediate post-rainy season.

[e]Well child visits

Table 13: Comparison of crude percentage estimates of seroprevalence between EAG and population survey

Seroprevalence	EAG sampling unit	EAG survey		Population survey		Absolute percentage risk difference (95% CI)	p-value
		Events (n/N)	Percentage prevalence (95% CI)	Events (n/N)	Percentage prevalence (95% CI)		
Gambia(Oduro et al., 2011b)[a,d]							
Multiple 2011	Health centre	1122/4543	24.7 (23.4, 26.0)	736/3870	19.0 (17.8, 20.3)	5.7 (3.9, 7.4)	<0.001
Multiple 2011[c]	Health centre	696/4101	17.0 (15.8, 18.1)	712/3716	19.2 (17.9, 20.4)	-2.2 (-3.9, -0.5)	0.0119
Kenya (Stevenson et al., 2013)[b]							
Multiple 2010	Primary school	2536/4888	51.9 (50.5, 53.3)	1927/3742	51.5 (49.9, 53.1)	0.4 (-1.7, 2.5)	0.7224

[a]$MSP1_{19}$ positivity derived using a cut-off optical density (OD) three standard deviations from the mean OD of naïve Europeans.

[b]MSP1 and AMA1 positivity derived by defining a cut-off OD using the mixture model.

[c]Dry season survey, all other surveys done in the rainy or immediate post-rainy season.

[d]All patients regardless of diagnosis.

Table 14: Comparison of crude percentage estimates of household ITN possession between EAG and population survey

Proportion of households with at least one ITN	**EAG sampling unit**	**EAG survey**		**Population survey**		**Absolute percentage risk difference (95% CI)**	**p-value**
		Events (n/N)	**Percentage prevalence (95% CI)**	**Events (n/N)**	**Percentage prevalence (95% CI)**		
Uganda (Ndyomugyenyi and Kroeger, 2007)							
• Hoima 2005	Primary school	814/3602	22.6 (21.2, 24.0)	629/2798	22.5 (20.9, 24.0)	0.1 (-2.0, 2.2)	0.9106

Table 15: Comparison of crude percentage estimates of household ITN use between EAG and population survey

Proportion who slept under an ITN the previous night	EAG sampling unit	EAG survey		Population survey		Absolute percentage risk difference (95% CI)	p-value
		Events (n/N)	Percentage prevalence (95% CI)	Events (n/N)	Percentage prevalence (95% CI)		
Malawi (Mathanga et al., 2010)							
• Multiple 2005[a]	EPI clinic	943/1909	49.4 (47.2, 51.6)	1703/4565	37.3 (35.9, 38.7)	12.1 (9.5, 14.7)	<0.001
• Multiple 2008[a]	EPI clinic	601/1637	36.7 (34.4, 39.1)	380/926	41.0 (37.9, 44.2)	-4.3 (-8.3, -0.4)	0.0305
Tanzania (Skarbinski et al., 2008)							
• Lindi 2005[a]	Hospital, health centre, dispensary	164/444	36.9 (32.5, 41.4)	78/354	22.0 (17.7, 26.4)	14.9 (8.7, 21.1)	<0.001
• Lindi 2005[b]	Hospital, health centre, dispensary	81/193	42.0 (35.0, 48.9)	78/354	22.0 (17.7, 26.4)	19.9 (11.7, 28.1)	<0.001
• Rufiji 2005[a]	Health centre	656/911	72.0 (69.1, 74.9)	241/455	53.0 (48.4, 57.6)	19.0 (13.6, 24.5)	<0.001
• Rufiji 2005[b]	Health centre	386/522	74.0 (70.2, 77.7)	241/455	53.0 (48.4, 57.6)	21.0 (15.1, 26.9)	<0.001

[a]Well child visit.

[b]Sick child visit.

Table 16: Comparison of crude percentage estimates of IRS coverage between EAG and population survey

IRS coverage	EAG sampling unit	EAG survey		Population survey		Absolute percentage risk difference (95% CI)	p-value
		Events (n/N)	Percentage prevalence (95% CI)	Events (n/N)	Percentage prevalence (95% CI)		
Kenya (Stevenson et al., 2013)							
• Multiple 2010	Primary school	3441/4888	70.4 (69.1, 71.7)	2762/3742	73.81 (72.4, 75.2)	-3.4 (-5.3, -1.5)	<0.001

3.4 Conclusion and application to this thesis

A comprehensive review of the validation of estimates of control progress from multiple EAGs has been carried out in the previous section to allow robust comparison of the validity of the estimates against contemporaneous data from a probability sample from the population. Previous work has focused on validating average estimates which do not give an idea of the heterogeneity in control progress and this is a clear limitation. Not surprisingly, there was a great deal of variability in the accuracy of estimates from different EAG samples. In different transmission settings and except in few situations, average estimates from EAGs were biased. The main potential of surveillance in EAGs as a sub-national M&E tool will be to provide evidence of heterogeneity in control progress thus facilitating a targeted response, complementary to the information from nationally representative household surveys. Research is required to assess the best sampling approaches to maximise the potential of EAGs to either be geospatially representative or at least identify communities with poor control progress for catch-up campaigns. Research is also required in statistical techniques to control for any geospatial bias in order to improve the spatial representativeness of EAGs. The studies included in the review only included primary school surveys and facility-based surveys in children and adults. This is not surprising as historically, these are the EAGs have been used to derived proxy population estimates. Other EAGs should be explored providing there is a reasonable basis to suggest its suitability for malaria surveillance.

In this thesis, the potential for EAGs to offer estimates of the heterogeneity in control progress including methods of dealing with geospatial bias is explored with the help of a spatial statistician. Surveillance in children attending EPI clinics for well child visits and women attending ANC is explored in the same catchment area as a gold standard MIS, to enable comparison with an accurate probability sample and determination of any spatial bias.

Chapter 4: Design and methods

4.1 Introduction

This study aimed to evaluate surveillance in various EAGs as a tool to measure malaria control progress in the catchment area of CDH in Chikhwawa District, Malawi. Limitations in funding, led to only the most promising EAGs being evaluated in detail (i.e. children attending EPI clinics for well child visits and women attending ANC), whilst others were explored as potential tools for further research. The assessed indicators and related study procedures were harmonised between all EAGs included in the study and an ongoing standard MIS in the same geographical area was considered the gold standard approach.

4.2 Study area and population

4.2.1 Geography of the study region

Malawi is a land-locked country located in south-east Africa lying along the East African Rift Valley between latitudes 9° and 18° South, and longitudes 33° and 36° East. It is bordered by Mozambique to the east and south east, Zambia to the west and Tanzania to the north (Figure 5). Malawi has a total surface area of 118,500 km^2 with highly variable terrain made up of plateau, highlands and valleys (FAO, 2007). The geography is dominated by Lake Malawi (formerly referred to as Lake Nyasa) comprising about 20% of the total land area. Malawi has a population of 13 million people (National Statistical Office, 2013). The country is divided into three regions (Northern, Central and Southern Regions) which are divided into 29 administrative areas, and further sub-divided into traditional authorities (TAs) Malawi is divided into three topographical zones: (1) the lakeshore zone including Karonga, Nkhata Bay, Nkhotakota, Salima, Dedza and Mangochi districts; (2) the highland zone covering Chitipa, Rumphi, Mzimba, Kasungu, Mchinji, Lilongwe, parts of Dedza, parts of Ntcheu, Blantyre, parts of Mulanje, central parts of Zomba, central parts of Thyolo, and northwest parts of Mwanza; and (3) the lowland zone covering Balaka, eastern parts of Ntcheu, southern parts of Mwanza, Chikwawa, Nsanje, parts of Thyolo, parts of Mulanje, part of Blantyre and parts of Zomba.

Malawi also has diverse altitude ranging from 50m above sea level in the Lower Shire River valley to about 3000m at the highest point of the Mulanje Massif in Southern Malawi. This diverse topographical landscape influences climatic conditions with the highlands being cooler and less humid and the lowlands being hotter and more humid.

This study was conducted in the catchment area of Chikhwawa District Hospital (CDH), defined by a 15km radius of CDH in Chikhwawa District located in the lower Shire River valley in Southern Malawi. Figure 6 is a map of all the villages in the study catchment area including Chikhwawa district hospital. Chikhwawa District, highlighted in blue on the map.

Chikhwawa is in the Southern Region and has a total population of 434,648 (National Statistical Office, 2013). Chikhwawa District Hospital is a government owned health facility with no user fees and is the main referral hospital for the district. The catchment area of CDH is approximately 707 km^2, estimated to contain a population of around 120,000 individuals, and is demarcated by the following natural borders: to the north east by the Rift Valley escarpment, to the west by the lower Shire River, and to the south by Nchalo sugar plantation and Lengwe National Park. Chikhwawa District's main topographic features are the Shire river valley (which is along the Great African Rift Valley) and the Thyolo-Chikhwawa Escarpment. The Shire River, which is the only outlet from Lake Malawi, meanders southwards for distance of approximately 700 km, passing through Chikhwawa District to its confluence with the Zambezi River (Chimatiro, 2004). The Shire River is usually divided into the upper, middle and lower sections and generates most of Malawi's electricity through hydroelectric plants at Kapichila and Tedzani falls. It supports abundant fisheries, and provides freshwater for irrigation in Malawi's plantations. The lower Shire River extends from the Kapichila Falls to the end of Ndindi marshes at the border with Mozambique (Chimatiro, 2004). The Shire River frequently changing course as it passes through the Lower Shire valley, leading to

the formation of oxbow lakes, lagoons and islands. The altitude of the Shire River valley falls gradually from 107m at Chikhwawa town to 61m at the inland port of Nsanje (Chimatiro, 2004).

The floodplains of the lower Shire River are one of the seventeen major floodplains in Africa and of direct benefit to the local population due to fishing (Bulirani et al., 1999), irrigation for agriculture and grazing for livestock (Kalowekamo, 2000). Seasonal changes to water flow and sediment deposition make this area prone to flooding during the months of highest rainfall, January and February. The flood plains retain water from the peak of the rainy season till the end of April, when the water levels start to recede till July and September when the water levels in the flood plain are at their lowest, and start to rise again in October (Chimatiro, 2004).

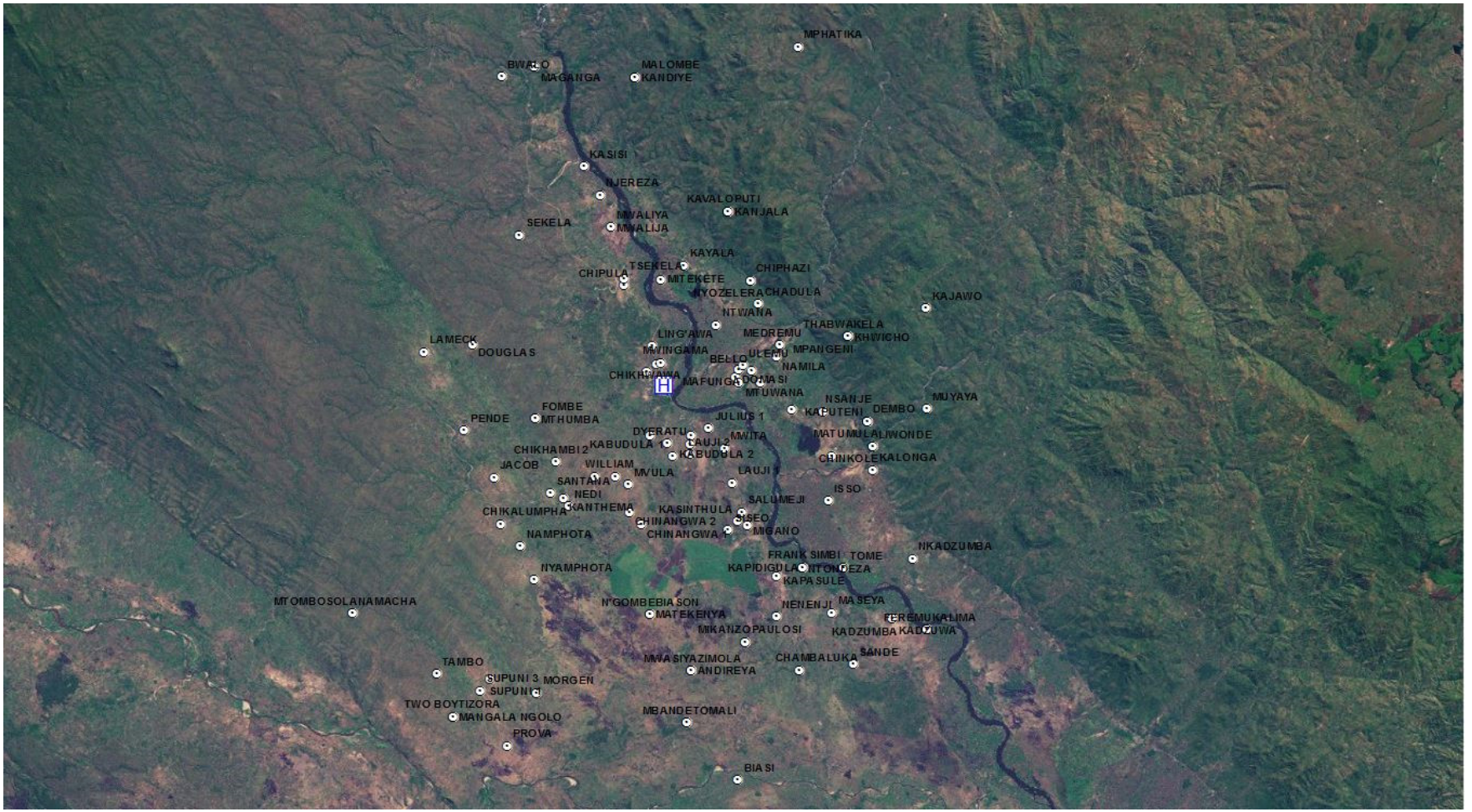
4.2.2 Climate

The climate of Malawi is subtropical, relatively dry and strongly seasonal with a warm and wet season from November to April (during which 95% of annual rainfall occurs), a cool dry winter season from May to August (mean temperature range 17° to 27° C), and a hot dry season from September to October (mean temperature range 25° to 37° C) immediately preceding the rainy season (Malawi Metereological Services, 2006). Humidity ranges from 50% in the hot dry season to 87% in January to February, the wettest months of the rainy season. The climate of different regions is heavily influenced by the topography. Meteorological data from the study area shows clear related seasonal peaks in total monthly rainfall and mean monthly temperature. The total annual rainfall during the 2011-2 and 2012-13 rainy season was higher than the two preceding years, as clearly illustrated by the tri-monthly moving average trend line) (Figure 7). The rainfall peak appears to lag behind the temperature peak.

Figure 5: Map of Southern Africa

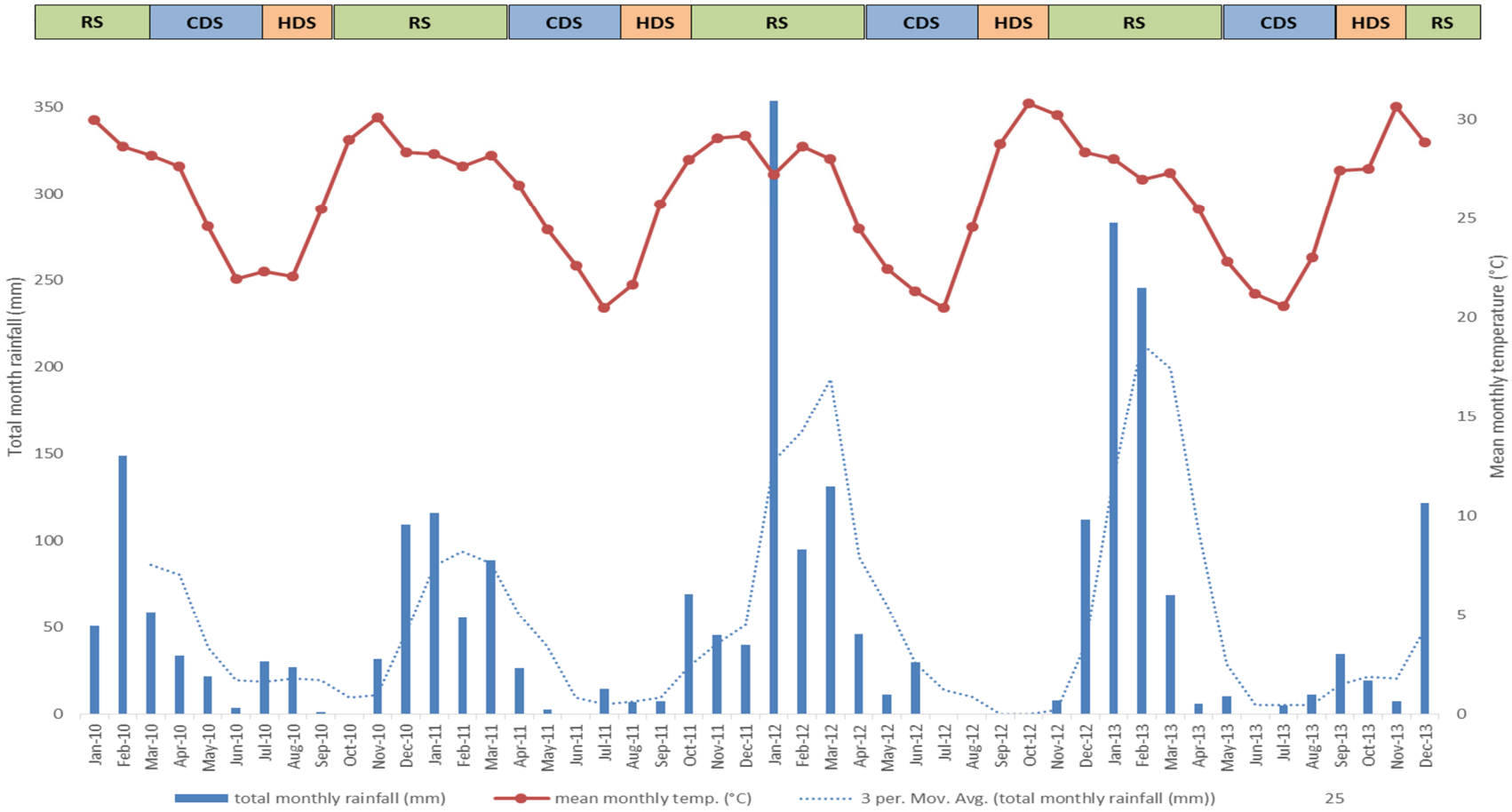
Created using ArcGIS® software by ESRI.

Figure 6: Map of Lower Shire River valley showing study villages



Created using ArcGIS® software by ESRI.

Figure 7: Monthly climatic conditions in the study area from 2010 to 2013 (copyright Malawi Meteorological Services, with permission)



Key: CDS = Cold dry season, HDS = Hot dry season, RS = Rainy season.

From the mean monthly temperature, optimal conditions for sporogony (i.e. 25 to 30 °C) (Gilles, 2002) is maintained yearly from September to April. Throughout the year the mean monthly temperatures are still high enough for some transmission to occur, with the temperature in the coldest months of the year (June and July) being well above the temperature below which sporogony ceases (i.e. 16°C) (Gilles, 2002).

4.2.3 Malaria epidemiology

The entire population of Malawi is at least under moderate transmission with overall transmission in the country classified as mesoendemic with variations in transmission intensity due to season and topography (Bennett et al., 2013). By 2010, 71% of the population lived in areas of mesoendemic transmission, 27% lived in areas with hyperendemic transmission, 1% were at risk of holoendemic transmission and only 0.2% were at risk of hypoendemic transmission (Okiro et al., 2014). Transmission is highest in areas with high temperatures during the peak rainy season (December to April), particularly along the lakeshore(Slutsker et al., 1996) and lowland areas of the lower Shire Valley(Mzilahowa et al., 2012).

Malaria transmission in the study area occurs throughout the year with some intensification during the rainy season (Mzilahowa et al., 2012). The low altitude in most of the Lower Shire River valley and the rising of the water table during the rainy season results in the formation a floodplain of ponds and marshes that are excellent breeding sites for the mosquitoes. The main vectors determined by PCR in a recent study were *Anopheles gambiae sensu lato* and *Anopheles funestus*, which are present year round with *An. gambiae s.l.* being most common in the region's single annual wet season when most of the malaria transmission occurs (Mzilahowa et al., 2012). The same study determined the EIR from two villages within Chikhwawa district but just outside the study area to be 183 infective bites per person per year. The nationwide MIS, preceding the work in this thesis, reported that in the Southern Region of Malawi (containing Chikhwawa District),

*Pf*PR (by microscopy) and APR (Hb < 8.0g/dl) in children aged 6 to 59 months were 42.3% and 13.6% respectively (Ministry of Health (MoH) Malawi, 2010). By 2012, the *Pf*PR (by microscopy) and APR in the Southern Region in children aged 6 to 59 months had changed to 8.5% and 23.9% respectively (NMCP (Malawi) and ICF International, 2012). The *Pf*PR determined by RDT was also determined in this survey and was 39.1% in the Southern Region of Malawi.

4.2.4 Malaria control

In 2005, there were substantial increases in both PMI and Global Fund support for Malawi to increase the coverage of control measures (Mtonya and Chizimbi, 2006). After a successful pilot study of the integration of free long lasting insecticide treated net (LLIN) distribution into the routine Expanded Programme of Immunization (EPI) clinic attendance in two districts in 2007, Malawi's ITN policy was changed focusing more on LLINs and the use of multiple approaches to scale up coverage. This included routine distribution through ANC clinics and EPI clinics and periodic catch-up campaigns targeting rural areas every two to three years (Ministry of Health (MoH) Malawi, 2011; Skarbinski et al., 2011).

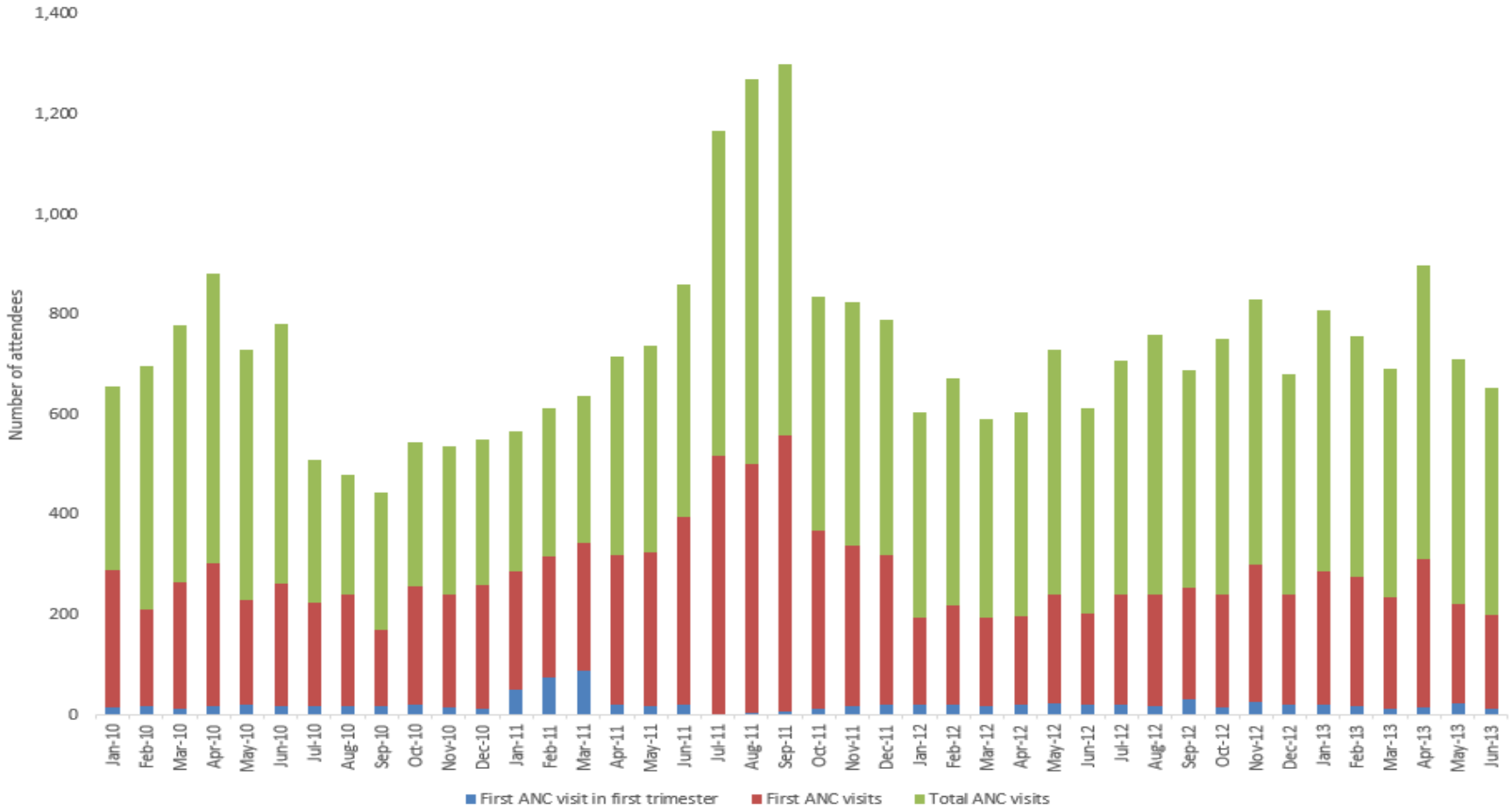
Before the Ministry of Health launched its IRS in Nkhotakota district in 2007, there were African Development Bank (ADB) supported small-scale IRS projects using pyrethroid insecticides in two rural areas of Ntchisi district in 2006. Two private sector initiatives had further been in place since the late 1990s involving Paladin Africa (an Australia-based global uranium mining company and Illovo Malawi (a subsidiary of Illovo Sugar Limited, South Africa). These employed several malaria control strategies including IRS with pyrethroids in the case of Paladin and a combination of pyrethroids and organophosphates in the case of Illovo. Due to the encouraging results of the pilot study, the NMCP supported by developmental partners like PMI, carried out two IRS rounds in seven target districts (including Chikhwawa) from 2010 to 2011 (NMCP (Malawi), 2012). During

the first IRS round in Chikhwawa District (January to February 2011), 86,661 out of 99,955 targeted structures (87%) were successfully sprayed. During the second round in November to December 2011, 101,785 out of 120,709 targeted structures (84%) were successfully sprayed. In both cases, there were reports of residents refusing to be included in IRS activities (NMCP (Malawi), 2012).

Based on the recommendations of the National Malaria Advisory Committee to develop an evidence based treatment strategy, drug efficacy studies were carried out in three sites in Malawi ((Rumphi, Nkhotakota and Machinga). Based on this evidence and its efficacy in neighbouring countries, Artemether-Lumefantrine (AL) was recommended to replace Sulphadoxine-Pyrimethamine (SP) as first line treatment for malaria in May 2006 (Malenga et al., 2009). From 2005 to 2010, the national policy was the presumptive treatment of children aged less than five years and diagnostic testing for all persons older than five years before the administration of appropriate treatment. During that time, the main malaria diagnostic was microscopy.

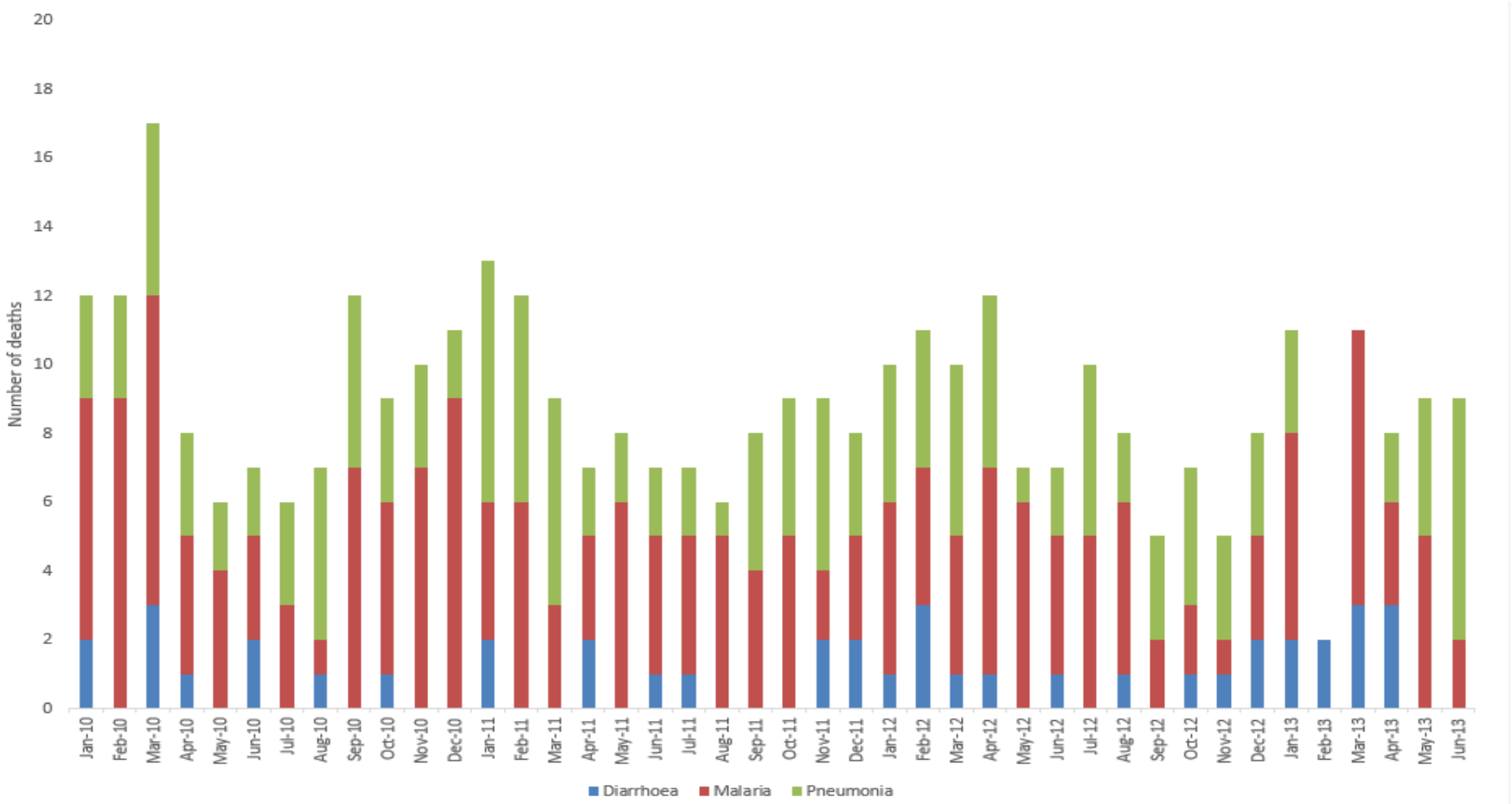
A Malaria Program Review was undertaken in 2010 to assess the performance and to help in the development of a new strategic focus (NMCP (Malawi), 2010), leading to the development of the third National Malaria Strategic Plan or NMSP III (2011 to 2015). The key objectives of this strategic plan included achieving universal coverage of all interventions to attain 80% utilization rate of the interventions. This resulted in the mass distribution of LLINs nationwide in 2012, change from pyrethroid to an organophosphate for IRS and scaling up diagnostic testing using RDTs (Ministry of Health (MoH) Malawi, 2011). Results from two studies in Chikhwawa District further highlighted that access to prompt diagnosis and treatment was affected by distance and costs with poorer households and those living in hard-to-reach areas being less likely to access malaria treatment (Masangwi et al., 2010; Ewing et al., 2011).

Figure 8: Monthly ANC attendance at CDH during the period of the study (copyright CDH HMIS, with permission)



Categories not mutually exclusive.

Figure 9: Monthly mortality in under-fives admitted at CDH during the study period by the three most common primary diagnoses (copyright CDH HMIS, with permission)



Categories are mutually exclusive.

The 2010 MIS showed that coverage with control interventions in the Southern Region (which contains Chikhwawa District) was low; the proportion of households with at least one ITN was 59% and the percentage of children who slept under an ITN the previous night was 56% (Ministry of Health (MoH) Malawi, 2010). There were no estimates for IRS coverage as this was before the first spray round. The 2012 MIS, did not show much improvement in coverage of control interventions; the proportion of households with at least one ITN was 51% and the percentage of children who slept under an ITN the previous night was 60% and the percentage with IRS in the past 12 months was 12% (NMCP (Malawi) and ICF International, 2012).

4.2.5 Population of the lower Shire River valley

The main occupation of the population of the lower Shire River valley is subsistence farming of maize, rice, and seasonal vegetables, and animal husbandry (mainly poultry). There is some small-scale cash crop cultivation (e.g. rice, cotton and sweet potatoes), which together with fishing and trading provide the needed cash. Chikhwawa town is the main trading hub of the district. Mang'anja and Sena are the dominant tribes in the district; while Chichewa, Chinyanja and Chisena are the dominant languages. According to the Malawi Demographic and Health Survey (MDHS) in 2010, in the Southern Region, the majority of males and females (aged six years and over) have some primary school education (61.7% and 63.3% respectively) (Malawi National Statistical Office and ICF Macro, 2011).

4.2.6 Maternal health

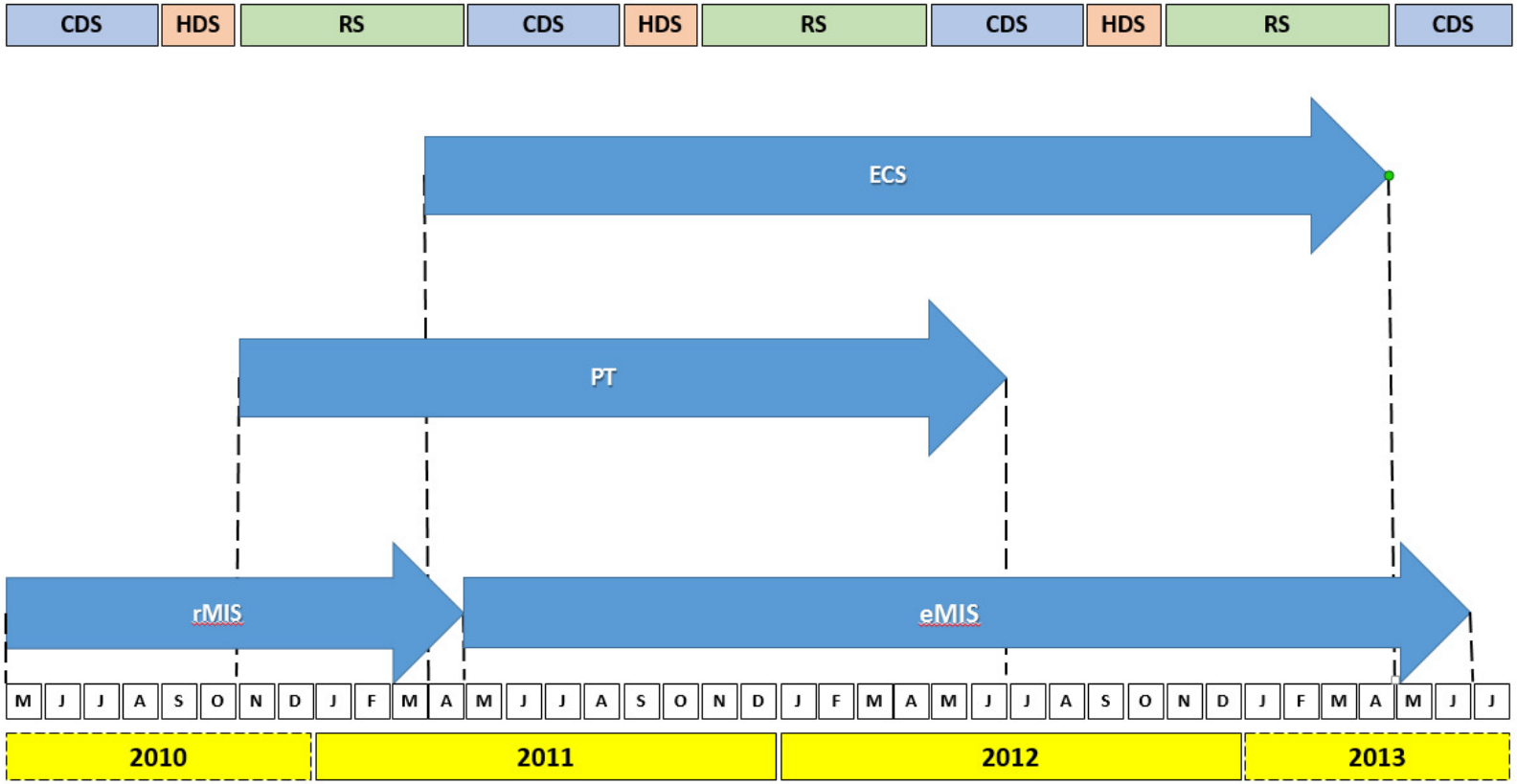
According to data from the MDHS in 2010, 95.4% of women received antenatal care from a skilled attendant (doctor, clinical officer, nurse, or midwife) during their most recent pregnancy (Malawi National Statistical Office and ICF Macro, 2011). The first ANC visit in rural areas like Chikhwawa District was at a

median 5.6 months in 2010, and 94.7 % of women aged 15-49 years who had a live birth in the five years preceding the survey had received antenatal care at least twice (Malawi National Statistical Office and ICF Macro, 2011). Data from the district health management and information system (HMIS) corroborated the evidence that most first time ANC attendees from the hospital's catchment area came after the first trimester and this trend was preserved throughout the period of the study (Figure 8). Less than 50% of all ANC visits were due to first time attendees, and there was an increase in the total ANC attendance during the period of recruitment of the PREGACT trial (November 2010 to June 2012) (Figure 8).

4.2.7 Child health

Data from the 2010 MHDS indicated that nationally, 71.8% of all infants and 80.9% of all children aged 12 – 23 months were likely to have received all basic vaccinations (BCG, measles, and three doses each of DPT or pentavalent (DPT-HepB-Hib) and polio vaccine (excluding polio vaccine given at birth)) (Malawi National Statistical Office and ICF Macro, 2011). Higher educational and socioeconomic status were associated with higher vaccination rates. In the Southern Region, 83.1% of all children aged 12 – 23 months were likely to have received all basic vaccinations (Malawi National Statistical Office and ICF Macro, 2011). The prevalence of severe (-3SD below weight-for-height or length) and moderate (less than -2SD but greater than -3SD weight-for-height or length) malnutrition in under-fives was low in the Southern Region, 1.4% and 4.0% respectively). Data from the district HMIS indicated that in the total catchment area, most of the deaths in under-fives were due to malaria and pneumonia and this trend was maintained throughout the study period (Figure 9). There did not appear to be a clear seasonal trend in malaria deaths which could either be to incomplete reporting or missed deaths in the community that were not recorded in the HMIS. The absence of cases of pneumonia in February and March 2013 probably represented incomplete reporting rather than a complete absence of deaths due to pneumonia.

Figure 10: Study timelines



Key:
CDS = Cool dry season, HDS = Hot dry season, RS = Rainy season.
rMIS = rolling MIS, eMIS = expanded MIS, ECS = EPI Clinic survey, PT = PREGACT trial,

4.3 Sample size determination

This section presents an overview of the sample size determination for the studies discussed in the result chapters. The sample size determination for the rMIS/eMIS has been presented elsewhere (Roca-Feltrer et al., 2012b). Sample sizes for EAGs was calculated using WinPepi® version 2.21 (Abramson, 2011). Win Pepi® is a freeware computer program, and is the Windows version of the DOS-based PEPI (an acronym for Windows Program for epidemiologists) package.

4.4 Study procedures

4.4.1 Overall study management

In the EAG surveys, the study staff consisted of two study research nurses and a field worker. In the household survey the study staff consisted of two mobile teams of a research nurse and a field worker each and both supervised by a senior field worker. Prior to all surveys study staff were trained in obtaining informed consent, administering the questionnaire, carrying out the physical assessment of participants, collecting finger prick blood specimens, performing haemoglobin assessments, carrying out and interpreting RDTs, and collecting filter paper specimens. Only the research nurses were allowed to administer treatment. The training was guided by procedure specific SOPs which were harmonised across all studies except the ANC survey. Slide microscopy was done by microscopists employed by the ACTia trial. A quality control system was put in place to ensure that all study staff involved in lab procedures received regular standardized training (every 3 to 4 months) throughout the study period. Management of all surveys was centralized and the project manager of the ACTia study was responsible for the overall management of research related activity in Chikhwawa. Additional assistance for data management, laboratory supervision and research governance was provided by the Data Management, Laboratory and Research Governance Departments of the Malawi-Liverpool-Wellcome Trust (MLW) respectively.

Health and safety of study staff was centrally managed by the MLW. The MLW has a Health and Safety Manual which all new staff are introduced to and are urged to follow. Post-exposure prophylaxis treatment is provided to all staff free of charge and Hepatitis B vaccinations are provided free of charge to all staff that will be exposed to human body fluids as part of their work.

4.4.2 Study population and timelines

This study involved three cross sectional surveys as follows (Figure 10):

1. The first survey and the main comparator was the monthly rolling MIS (rMIS) which started in May 2010 and lasted until June 2013. The rMIS was a continuous prospective monthly household survey in 50 villages within the catchment area of CDH that was part of an ongoing trial on the safety and effectiveness of combination therapies with repeated treatments for uncomplicated *P. falciparum* malaria over a three-year period supported by the ACT consortium (ACT Consortium, 2014). Data collection on malaria control indicators was done through an adapted version of the standard National MIS (MEASURE Evaluation et al., 2013a). The main difference between the rMIS methodology and that of a standard MIS was that the total sample size was 'rolled' over 12 months (Roca-Feltrer et al., 2012b). The 50 villages were randomised into two groups to be surveyed every six (to adjust for seasonal variation) and within each village a random sample of households were selected by proportionality to size (Roca-Feltrer et al., 2012b). In May 2011, the rMIS was expanded to include women aged 15 to 49 years and children aged 5 to 15 years (i.e. the eMIS).
2. The second survey involved data from the screening and enrolment logs of the PREGACT trial. This trial studying "Safe and Efficacious Artemisinin-based Combination Treatments for African Pregnant Women with Malaria ((ClinicalTrials.gov, 2014) started enrolling participants in November 2010. Data was collected retrospectively starting in November 2012, after the end of active recruitment in June 2012.

3. The third survey involved children attending EPI clinics for "well" child visits from late April 2011 to April 2013. This consisted of a continuous prospective MIS in children reporting to the EPI Clinic of CDH, their parents or guardians and any accompanying sibling. The EPI Clinic sample used for the comparison with the population sample was restricted to participants from any village within a 15 km radius of CDH (i.e. the same geographic catchment area as the rMIS/eMIS), but all surveyed children reporting to the EPI clinic were recruited to get an unbiased sample from the total hospital catchment area. Children were selected on alternate days and no particular attempt was made to select or avoid a particular day because of high case loads. To adjust for month-to-month variations in health facility attendance, the total sample size 'rolled' over 12 months similarly to the population survey.

4.4.3 Enrolment

Household survey

The mobile study team, usually comprised of a study nurse and field worker, introduced themselves to the household. The person responsible for healthcare decision-making was consented and then interviewed using the adapted MIS questionnaire. If that individual was not available on the first visit, up to two revisits were made to collect information from that individual. In the rMIS/eMIS, households to be surveyed were randomly selected from a list of all enumerated households whilst in the eMIS households were selected randomly from the centre of the village using the spin the bottle approach. After administration of the MIS questionnaire, a blood sample was collected from children under five years of age (in the rMIS/eMIS) who slept in the household the previous night for the assessment of haemoglobin level and the presence of malaria parasites by RDT and microscopy. In the rMIS/eMIS, children under five years of age, a blood sample was further collected from older children and women of childbearing age who slept in the household the previous night for the same laboratory tests.

EPI Clinic survey

Information about the study was delivered by the study nurse as part of the routine public health information delivered by government health staff at the Maternal and Child Health Unit of CDH. Then, the parents or guardians of all children with an age greater than 4 months but less than 15 years, resident in Chikhwawa District (for more than 6 months), who came to the EPI Clinic for "well child" visits (i.e. immunization and routine nutritional assessment), were approached for participation in the study. Accompanying siblings aged less than 15 years were also offered participation in the study. Participants were surveyed as they from the start of well child clinic at 9:00am until the EPI Clinic closed usually around midday. Due to the administration of the MIS MERG questionnaire, physical and laboratory assessments which usually took about 45 minutes in total, only an average recruitment of 3 to 4 children per day was possible by a single research nurse.

All participants surveyed were first screened for study eligibility, and if they satisfied all of the inclusion criteria and none of the exclusion criteria, they were approached for consent before being enrolled in the study. Children who had the following conditions were excluded from participation: participation in another study that was either an intervention study or might have interfered with the EvalMal study, severe malnutrition (less than -3SD weight-for-height), known HIV infection, previous enrolment in the EvalMal study and lack of consent from the parent or guardian. The screening details of all participants, whether enrolled or not, were recorded in a screening and enrolment log.

ANC survey

All women aged 15 years and above attending the ANC between the 20th of November 2012 and the 19th of June 2012 were considered to be eligible for screening to be enrolled in the PREGACT trial (ClinicalTrials.gov, 2014). The results from this eligibility screening were recorded in the trial screening and enrolment

log and all women screened in the PREGACT trial were included in the retrospective review.

4.4.4 Overview of the WHO/MERG National MIS package

The MIS package is sub-divided into core components, biologic components and complementary documents.

Core Components

The core components are as follows:

1. The Household Questionnaire
2. The Women's Questionnaire
3. The Interviewer's Manual
4. The Supervisor's Manual
5. Guidelines for the MIS Interviewer Training
6. Household Listing Manual
7. Guidelines for Sampling for the MIS
8. Tabulations for Key Malaria Indicators

The core components are structured to provide essential guidance for the conduct of MISs. The Household Questionnaire contains questions on basic demographic information, listing of household members, selected household assets (used to calculate an asset-based wealth index), IRS coverage, ITN possession and use. It also includes a section for recording anaemia and parasitaemia status of key groups at risk of disease(RBM, 2013). The Women's Questionnaire contains questions on recent birth history, pregnancy status, and use of intermittent preventive treatment with sulfadoxine-pyrimethamine during pregnancy. It also

includes a section to collect information on care seeking and access to prompt treatment with antimalarials for children with reported fever (RBM, 2013). The Interviewer's and Supervisor's Manuals serve to facilitate the jobs of interviewers and field supervisors respectively. The Guidelines for MIS Interviewer Training are general guidelines for organizing and conducting the training of the field staff, to ensure a standard approach to data collection using the Household and Women's Questionnaires. The Guidelines for Sampling for the MIS recommend probability sampling using a pre-existing sampling frame, with a two-stage cluster sample selection. It also provides details on the selection of an appropriate sampling frame, sample design and sample size determinations. The final sampling frame is usually all the households in a cluster, which need to be enumerated prior to selection of a sample of households from interviews. The Household Listing Manual offers guidance on the organisation of logistics required to locate clusters and define the sampling frame by listing all households including quality control issues of listing procedures. It is thus complementary to the Guidelines for Sampling for the MIS. Finally, there is the "Tabulations for Key Malaria Indicators" document which provides recommended tables for presenting results obtained from the Household and Woman's Questionnaires for the key RBM coverage indicators in standardized format allowing comparison with other such surveys.

Biologic Components

These consist of the Anaemia and Malaria Field Testing Manual which provide an overview of procedures for conducting anaemia and malaria parasitaemia testing (using the HemoCue® system and using rapid diagnostic tests or microscopy respectively) in the field during household surveys. This is to ensure a standard approach to these surveys to allow the results to be compared with other such surveys.

Complementary documents

The complementary documents in the MIS package were the following:

1. Calculating the Cost of the MIS
2. Incorporating Geographic Information into MEASURE Surveys: A Field Guide to GPS Data Collection

Table 17: Key information on study participants obtained for each of the surveys

	EAG surveys		**Population surveys**	
Information collected	**EPI Clinic survey**	**ANC survey**	**rMIS**	**eMIS**
Household questionnaire				
Demographic characteristics	√	√*	√	√
Household assets	√		√	√
General malaria knowledge	√		√	√
ITN possession and use	√		√	√
IRS	√		√	√
History of fever in children	√		√	√
Use of antimalarial drugs	√		√	√
Axillary temperature	√		√	√
Haemoglobin measurement	√	√*	√	√
Malaria testing (RDT and microscopy)	√	√*	√	√
Women's questionnaire				
Information on current pregnancy		√*		√
Information on previous pregnancies		√*		√
Site of last delivery				√
Previous ANC attendance				√
IPTp use				√

*In the ANC survey, the only demographic information available was the age, village and TA of origin. Haemoglobin assessment and malaria microscopy was done in women who had a positive RDT. The household or women's questionnaire was not specifically used in the ANC survey but some pertinent information on these variables could be extracted from the trial screening and enrolment log.

Calculating the Cost of the MIS was adapted from Chapter 2 of the United Nations Children's Fund (UNICEF) Multiple Indicator Cluster Survey (MICS) Manual (UNICEF, 2012d) and guides how to develop an appropriate budget for a MIS survey. The guide consists of a costing framework to help standardize the process of figuring survey costs by providing a breakdown of expenditures within each type of activity. This guide is to ensure a standard approach to the costing of MISs and to help NMCPs to determine which activities need donor funding. The Field Guide to GPS Data Collection is a relatively new addition to the MIS package and addresses the geocoding of household- or cluster-level survey measurements. It guides the measuring of spatial patterns of disease or coverage of interventions in order to facilitate a targeted approach to control.

The main study tool was a locally adopted form of the MIS household questionnaire and part of the women's questionnaire (Table 17). The other aspects of the MIS package were used for guidance on certain aspects of the study for example in training of study staff of development of standard operating procedures (SOPs) for key study steps. All study SOPs and procedures were standardized in all surveys except the ANC survey.

4.4.5 Study flow

Other than the ANC survey which involved the retrospective collection of data from the screening and enrolment log of the PREGACT trial, the study flow in the other surveys was as illustrated in Figure 11.

Recruitment

After informed consent was acquired in the EPI Clinic Survey and the eMIS, the participant was assessed for inclusion in the study. This involved confirmation of Malawian citizenship through the participant's health passport, confirmation of residence in the Chikhwawa District from the health passport and/or direct

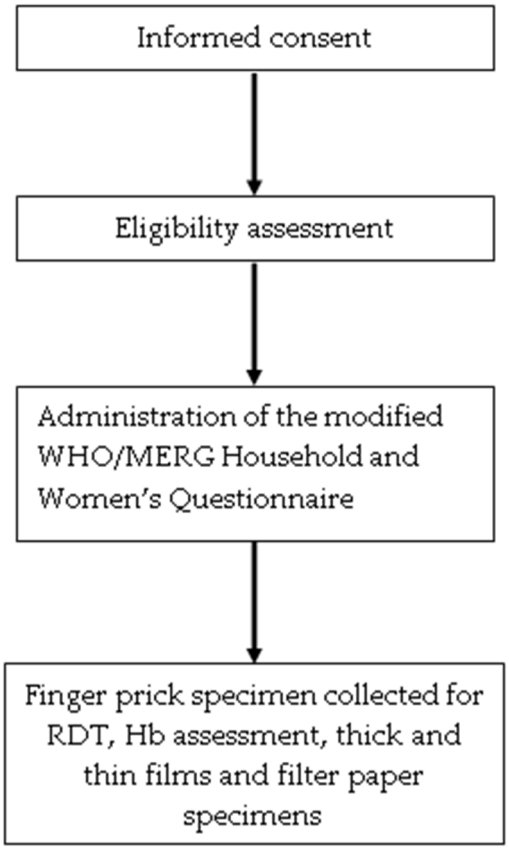
questioning, and determination of age from the health passport and/or direct questioning. In the case of children, whether or not the child was enrolled in an intervention study was determined by examining the child's health passport for the sticker containing the identification bar code of children enrolled in the ACTia trial, and when this was not available, by direct questioning of the parent or guardian. The HIV status of the participant was also determined from the health passport and if not available by direct questioning. In the EAGs, previous participation in the study was determined by a mixture of direct questioning and review of the screening and enrolment log.

In the ANC survey since data was collected retrospectively, pages of the screening and enrolment log with the column containing the name of the participant occluded where photocopied by the PREGACT study team, and this was the main source of information used for data entry. Where script was illegible or missing, this was sent back to the PREGACT team in the form of a data query.

Physical assessment

After administration of the modified WHO/MERG MIS questionnaire, enrolled children underwent physical assessment which included determination of nutritional status (by mid-upper arm circumference (MUAC) in the eMIS and rMIS, and by weight-for-height in EAG surveys) and axillary temperature measurement using an electronic thermometer (OMRON® Ecotemp Basic Electronic Thermometer, OMRON Healthcare Europe B.V.). In the EAG surveys, height of children was measured using a height measure (Seca® 213 Height Measure / Stadiometer, Seca, UK), length of children who couldn't stand was done using measuring boards (S0114530 Baby/infant length-height measuring system/SET-2, UNICEF). Weight was assessed using electronic scales (Seca 803 Clara Digital Personal Scale, Seca, UK).

Figure 11: Study flow



Investigations

After physical assessment, the participant's eligibility for enrolment was determined and individuals suitable for survey were asked to give a finger prick blood specimen for assessment of haemoglobin level (HemoCue® 301, HemoCue AB, Ängelhom, Sweden), malaria infection by RDT (First Response® Malaria Ag. pLDH/HRP2 Combo Card Test, Premier Medical Corporation Ltd., India) and a blood smear. A filter paper specimen was also collected for serology. Unless there was a clinical indication, for example fever or a history of fever, the microscopy slides were stained and read later.

Concurrent blood specimens were also collected from all consenting parents/guardians of children attending EPI clinic and assessed for haemoglobin

level, malaria infection by RDT and a thick and thin film. A filter paper blood spot specimen was also collected for serology.

Management

All children attending the EPI Clinic who were found to have malaria (fever and/or history of fever in the past 48 hours and a positive RDT) were referred for treatment to, if less than five years old, the Maternal and Child Health(MCH) Clinic and else the Outpatient Department (OPD). Children in the EPI Clinic Survey with significant anaemia (Hb < 8.0g/dl) were treated with generic Ferrous Fumerate suspension if less than five years old and generic Fefol tablets if aged five years or older. Children with severe anaemia (Hb < 5.0g/dl) in the EPI clinic survey were referred for transfusion.

All children in the household survey (i.e. rMIS/eMIS) found to have malaria and/or anaemia were referred to the nearest health facility for treatment. All children who had asymptomatic parasitaemia were treated with dispersible artemether-lumefantrine (Coartem® Dispersible, Novartis Pharma Nederland, The Netherlands) provided by the study team. Pregnant women screened in the PREGACT trial that had malaria and/or anaemia but were not suitable for enrolment were referred back to the ANC for treatment. Those who were suitable for recruitment were enrolled and randomized to receive one of the artemisinin combination therapies (ACTs) in the trial.

4.4.6 Laboratory procedures

Haemoglobin assessment

Haemoglobin was assessed using the HemoCue® 301 system (HemoCue® 301, HemoCue AB, Ängelhom, Sweden). The selected finger was cleaned with an alcohol swab, and pricked at the pulp slightly to the side. The first drop of blood was wiped with a dry swab and then the collecting end of the HemoCue cuvette

was placed next to the finger prick specimen until filled with capillary blood. The sides of the cuvette were then cleaned with a dry swab and the cuvette place in the HemoCue device for assessment. The HemoCue® machines were validated every two months using low, normal and high controls for the HemoCue Hb 301 system (Eurotrol Hb 301 Control, HemoCue AB, Ängelhom, Sweden).

Rapid Diagnostic Test

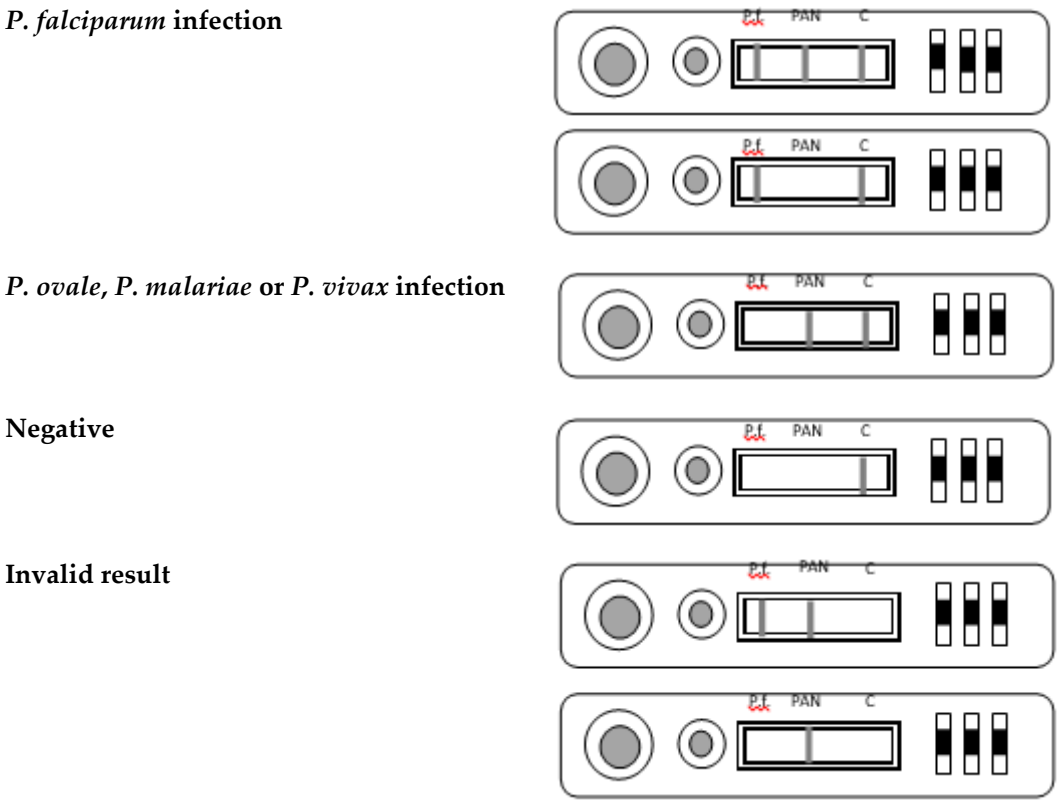
The RDT used in all surveys was the First Response® Malaria Antigen pLDH/HRP2 Combo Test (First Response® Malaria Ag. pLDH/HRP2 Combo Card Test, Premier Medical Corporation Ltd., India). This test was selected because of its performance in round three of WHO's product testing for RDTs (WHO, 2011a). It is a rapid test for the detection of *Plasmodium falciparum* malaria Histidine-rich Protein 2 (HRP) and plasmodium Lactate Dehydrogenase (pLDH) in human blood(Premier Medical Corperation Limited, 2012). *Plasmodium falciparum* HRP-2 is a protein molecule present in the parasite throughout the erythrocytic cycle. Plasmodium Lactate Dehydrogenase is a metabolic enzyme that is actively produced by all human malaria parasite species during their growths in red blood cells. This test contains a membrane strip that is coated with monoclonal antibodies in the form of two separate lines. Test line 1 consists of monoclonal antibody specific to HRP2 of P. falciparum and test line 2 consists of monoclonal antibody to all four of the plasmodium species that cause malaria (i.e. falciparum, vivax, malariae, and ovale). Test line 3 is the control line should appear irrespective of reactive or non-reactive sample. The test was interpreted according to the manufacturer's instruction summarized in Figure 12.

Malaria microscopy

A thick and thin film specimen was collected from each surveyed participant, however the method of quantification of parasitaemia detailed below was only done in the EPI Clinic Survey and eMIS. Both thick and thin films were

stained with Field's stain which is a water-based "Romanovsky" stain that consisting of two solutions (solution A and solution B).

Figure 12: Interpretation of First Response® Malaria Antigen pLDH/HRP2 Combo Test (Adapted from (Premier Medical Corperation Limited, 2012))



Since all malaria microscopy was done centrally as part of the ACTia trial, the results of the quantification of parasitaemia where not ready by the time the thesis was submitted. It is intended that these results together with those from the parents/guardians will be used to validate the accuracy of *Pf*PR determined by RDT in the study.

Serology

A filter paper blood spot specimen was collected from each trial participant in the study. Serological analysis for AMA1 and $MSP1_{19}$ is planned after the submission of the thesis as a future direction of research as to whether geospatial heterogeneity in seroprevalence could be accurately measured by the assessed

EAGs. The results from the parents/guardians will be used in addition to that of enrolled children in the EPI clinic survey to model the age-specific seroprevalence.

4.5 Ethical considerations

4.5.1 Ethical approval

The population survey which was considered the gold standard approach was a sub-study of the ACTia trial (ACT Consortium, 2014), and both the initial survey (i.e. the rMIS) and the expanded survey (i.e. the eMIS) were approved by the College of Medicine Research and Ethics Committee (COMREC) and the Liverpool School of Tropical Medicine Research Ethics Committee (LSTMREC). The main EAG study involving children attending EPI Clinics was approved by both COMREC and LSTMREC. It was possible to explore women attending ANC due to the availability of further funding from the Malaria Capacity Development Consortium and the ACT Consortium, and these were added as amendments which were also approved by both COMREC and LSTMREC. Annual reports were submitted to both bodies under the appropriate study IDs (COMREC P08/10/971 and LSTMREC 10.79) and approval was renewed annually.

4.5.2 Study ethical considerations

The main ethical issue is the fact that unless the surveyed individual is parasitaemic or anaemic and consequently receives treatment, there is usually no direct individual benefit in taking part in the survey (RBM, 2007). The pain and inconvenience was however justified given the fact that information from the survey can improve the malaria control program, clinical services and health knowledge. Other ethical issues include confidentiality of the data collected and the protection of human subjects needed to be fully considered when geocoding MIS clusters and making the data available with longitude and latitude coordinates (RBM, 2013). The confidentiality of enrolled participants in the rMIS/eMIS was

ensured by restricting access to the full database to authorized individuals in the study only.

Collection of blood specimens is classified as low risk in children (McIntosh et al., 2000) and finger prick specimens have less risk than venous specimens, so only finger prick specimens were collected. According to the current National Institute for Health Research (NIHR) in the UK, study related blood losses should not exceed 3% of total blood volume during a period of four weeks and should not exceed 1% at any single time (McIntosh et al., 2000). The total volume of blood is estimated at 80 – 90ml/kg body weight and 1% is 0.8ml. A drop of blood is estimated at 0.05ml so total blood collection for the purposes of the study is estimated to be 0.4ml (8 drops of blood).

4.5.3 Informed consent

Written informed consent was obtained for each surveyed participant before administration of the study questionnaire and blood sampling in the EPI Clinic Survey and the eMIS. The information sheets and consent forms were translated into the most common local dialect (i.e. Chichewa) and were printed in both English and Chichewa (Annex 1). The information sheet included information about the research question, the eligibility for participation, details on study procedure, risks and benefits, confidentiality, voluntary participation and who to contact if more information was required. The exploratory nature of the research was explained and parents or guardians were informed that they could refuse to take part without any repercussions and that they could also withdraw consent at any time during the survey process. If the parent or guardian could read, s/he was allowed to read the English version of the consent form and make a decision. If the parent or guardian could not read, the consent form was read out in the parent or guardian's local language by study staff in the presence of an impartial witness (i.e. not associated with the study) who could understand both English and the local language used for the consenting process. The parent or guardian was required to

document consent (if given) by signing the consent form if they could write or a thumb print if they couldn't. If an impartial witness was needed, s/he was also required to sign the consent form to document that they witnessed the consent process and the parent or guardian was given an accurate representation of what was written on the English and Chichewa versions of the consent forms. If consent was acquired, a copy of the consent form in Chichewa was retained by the parent or guardian. Emancipated minors below the age of 18 years who were married were allowed to sign their own consent forms.

4.5.4 Confidentiality

The names of participants and identification information were only recorded on the consent forms and screening and enrolment log; which were both kept in a secure cabinet accessible only to the head research nurse and principal investigator. From then on, the participant would only be identified in the database and laboratory specimens by an assigned study number. Data collection in EPI Clinic Survey was via an electronic database on Netbooks both of which were password locked and access restricted to authorized members of the study team. Data collection in the rMIS and eMIS was in electronic databases on PDAs both of which were password locked and access restricted to authorized members of the study team. The participants will not be identified in any resulting publications or reports.

4.6 Data Management

4.6.1 Household survey

In the household survey, data was collected electronically in PDAs (Somo 650®, Socket Mobile, Newark, California) programmed in Visual CE® 11.1 language (Syware Incorporation, Cambridge, Massachusetts). During the survey, data was backed up onto a secure digital card and PDAs were returned to the

Chikhwawa field site daily where they were aggregated into a Microsoft Access database.

4.6.2 EAG surveys

Except for the ANC Survey, where data was collected respectively from a paper-based screening and enrolment log, study data was collected and managed using REDCap electronic data capture tools hosted at the Data Management Department of the MLW. REDCap® (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies (Harris et al., 2009; Vanderbilt University, 2014). REDCap® provides a web-based interface for validated data entry with audit trails to track data manipulation and export. It also includes automated procedures for seamless data export to common statistical packages and import from external sources. Data was directly entered in the database with a validation component to check data, and decision rules and skip patterns analogous to that in a standard MIS questionnaire. Data was single entered in Netbooks (Toshiba NB500 12Z, Toshiba UK) on-site in the EPI Clinic surveys. Both the netbooks and REDCap® databases were set-up to allow only password access. Data collected on site was stored in a back-end MySQL databases (Oracle Corporation, 2014) in the netbooks. Data was backed-up weekly both locally in a pen-drive with encryption software bought for this specific purpose and on the ACTia trial server. Remote data back-up on the MLW server was also done weekly by sending both files through e-mail to the MLW data supervisor copying in the principal investigator. If there was lack of an internet connection the netbook and/or the USB pen drive containing the data were transported to Data Management Department at the MLW for back-up. Data cleaning, verification, and merging of the final datasets for analysis was conducted in Stata version 13.1® (StataCorp, Texas, USA).

4.7 Data analysis and statistical methods (overview)

All data analysis except the geospatial analysis was done in Stata version 13.1® (StataCorp, Texas, USA). Geospatial analysis was done in R version 3.0 (The R Project for Statistical Computing). The data from the first overlapping year of the EPI Clinic Survey and eMIS were used for the comparison of estimates of control progress between that EAG and the geographic catchment population of CDH. The data from the first overlapping year of the PREGACT trial and the eMIS were used for comparison of estimates of *Pf*PR between that EAG and women of childbearing age in the geographic population of CDH. The data from the rMIS, PREGACT trial, EPI Clinic Survey and eMIS were used for the temporal analysis. Though microscopy was done in all surveyed participants except for those in the PREGACT trial, *Pf*PR in this thesis refers *P. falciparum* prevalence rate determined by RDT unless stated otherwise.

Different statistical methods were used in the different surveys to address the uniqueness of each data set and the objectives of the study. In-depth details of the statistical techniques used to present data will be described in each results chapter. Only a summary of the core statistical methods in this thesis is presented in this chapter.

To assess the performance of the surveillance in children attending the EPI clinic in providing accurate annual population estimates of malaria control indicators, average estimates of malaria control indicators in this EAG were compared those from a probability sample of the population in the same area. Univariate analysis was done to detect associations between the key outcome variables and possible predictors. Multivariate log binomial regression models were used to calculate the risk ratios and risk differences of the estimates of indicators and their respective 95% confidence intervals in both surveys. The likelihood ratio test was used to determine potential predictors in the multivariate regression model. To model spatial variation in the distribution of control indicators, we used

geostatistical binomial models extending the geostatistical framework to allow for potential biased sampling in the EPI survey, with the assumption that the household survey provides accurate population estimates. We used Monte Carlo maximum likelihood methods to fit both models to the data, a technique that had previously been explored with the same data set and was detailed in a separate publication(Giorgi E, 2015).

To compare the performance of surveillance in children attending EPI clinics in determining temporal trends in malaria control indicators, we compared the monthly trends in this EAG with trends from the population survey. Autocorrelation and partial autocorrelation coefficients were calculated using the monthly data on *Pf*PR and APR to assess for seasonality and the significance of any lag was determined using the Portmanteau (Q) test for white noise. Smoothed trends derived by locally weighted scatterplot smoothing, to adjust for random month to month variation, were compared between the EPI clinic survey and the population survey.

To assess the feasibility of surveillance in women attending ANC in providing accurate population estimates of *Pf*PR these rates were compared to a population survey of all women of childbearing age (i.e. 15 to 49 years). Predictors exhibiting a significant relationship with PfPR in a univariate linear regression model were further explored using a multivariate linear regression on combined data from both surveys. To model spatial variation in *Pf*PR in pregnant women in the population, we used geostatistical binomial models correcting for the effect of pregnancy by assuming that the data on pregnancy in women of childbearing age from the population survey accurately represents the situation in the study population. We used Monte Carlo maximum likelihood methods to determine the accuracy of our estimations and spatial predictions of *Pf*PR.

Chapter 5: Assessing the validity of EPI Clinic Survey data as a potential malaria M&E tool in Chikhwawa, Malawi

5.1 Introduction

As malaria transmission declines across much of sub-Saharan Africa (Nyarango et al., 2006; Bhattarai et al., 2007; Erhart et al., 2007; Sharp et al., 2007; Ceesay et al., 2008; O'Meara et al., 2008a; Rodrigues et al., 2008; Ceesay et al., 2010), there has been a call for the development of robust cost-effective approaches to measure and monitor changes in transmission. Despite increasing control efforts, malaria still remains a significant public health problem in Malawi with nearly 7 million reported suspected cases in 2010 (Ministry of Health (MoH) Malawi, 2012). Given the current levelling off of funding for malaria control (WHO, 2013a), developing complementary approaches to surveillance is becoming increasingly relevant as current methods such as large population surveys or longitudinal entomological surveillance are logistically and financially challenging (Cox et al., 2007; Satoguina et al., 2009).

Children in malaria endemic regions experience the highest rates of infection and suffer the most from clinical disease compared to adults (Greenhouse et al., 2011). In sub-Saharan Africa, clinical incidence of disease is evenly distributed across the first 10 years of life in all transmission settings, though most of the severe disease is concentrated in younger children (Carneiro et al., 2010). Thus, the surveillance focus has been in children less than five years old (O'Meara et al., 2008b; Kendjo et al., 2013) as they would be a sensitive risk strata to determine impact (MEASURE Evaluation et al., 2013a). Surveillance in children attending health facilities has some logistic advantages compared to household surveys because health facilities provide a convenient location to sample large numbers of children in a shorter time frame than in household surveys, and the collected data can easily be integrated into routine surveillance like the HMIS.

However, the representativeness of such burden estimates still depends largely on the availability of non-formal sector facilities and the pattern of health-seeking behavior, both being key factors that determine health facility utilization

rates in terms of illness (Agyepong and Kangeya-Kayonda, 2004; Erhart et al., 2007; Rowe et al., 2009). An alternative approach would be to use the United Nations International Children's Emergency Fund's (UNICEF's) Expanded Programme on Immunization (EPI) platform which has successfully been used to run well child clinics (including assessments like growth monitoring) as a source of malaria surveillance data. This surveillance will give a better estimation of asymptomatic parasitaemia than surveillance in sick children and would potentially be less susceptible to bias due to health seeking behaviour, as in developing countries, government health facilities are usually the only option for the receipt of key life-saving vaccines and this approach to surveillance has previously been explored (Delacollette C, 1990; Some et al., 1997). Because routine growth monitoring in under-fives is included as standard component of community child health services usually coupled with EPI immunization (UNICEF, 1990; Hall, 1996), well child clinics offer the potential of surveillance in under-fives. Children attending well child clinics are usually accompanied by their mothers from whom we can derive information about household uptake of control interventions, and sometimes by an older sibling who is also a source of data on burden. Immunization clinics are usually widely distributed and the determination of the origin of facility-based surveyed participants by direct questioning or observation of their clinic card would allow geospatial representation of transmission a phenomenon which has previously been explored with children hospitalized for severe malaria (Schellenberg et al., 1998; Kazembe et al., 2006). The coverage of such surveillance can easily be derived from district-level information on vaccination coverage as these children communing for immunization form the majority of children who attend well child clinics.

A potential shortcoming of this method of surveillance is the fact that children attending well child clinics may represent a biased sample of our population of interest, with better access to health facilities or come from households with higher socioeconomic status; so that derived estimates may be

inaccurate. Therefore a key consideration in this method would be the magnitude of the selection bias is significant enough to invalidate this tool, particularly in terms of its geospatial representativeness. In a study by Cibulskis et al in 2012, they attempted to explore and address the role of selection bias in average estimates of 13 health indicators (including some malaria control interventions) by comparing to those obtained from the population as a whole in 31 countries (Cibulskis et al., 2012). The study found out that average estimates of intervention coverage derived from immunized children can provide a reasonable approximation of population values if levels of immunization coverage are over 60% (Cibulskis et al., 2012). Despite the fact that other important causes of bias like information bias (Skarbinski et al., 2008) were not considered in this study, given the given the high global immunization coverage (UNICEF, 2012a), immunization clinics are a potential surveillance opportunity that needs to be validated under experimental settings.

To date, there few publications evaluating specific surveillance in children coming for well child visits to determine whether measurement of these indicators during well child visits could serve as a comparable substitute to measurement during household surveys (Cibulskis et al., 2007; Skarbinski et al., 2008; Mathanga et al., 2010). There is no publication to our knowledge that assessed the capability to measure spatial heterogeneity. In this study, we evaluated whether the estimates of coverage of control interventions and malaria transmission derived at the time of well child visits at the EPI clinic of Chikhwawa District Hospital (CDH) accurately represented population estimates and spatial heterogeneity of malaria transmission in the catchment population.

5.2 Methods

5.2.1 Study site

The study was conducted in the geographic catchment area of Chikhwawa District Hospital (CDH) in Chikhwawa District, Malawi, Southern Africa. This area

is within 15 kilometre radius from CDH, contains a catchment population of around 120,000 and is bordered in the north east by the Rift Valley escarpment, in the west by the Shire River, in the south by Nchalo sugar plantation and Lengwe National Park.

5.2.2 Study design

The study consisted of a continuous ('rolling') population-based household-level MIS (i.e. the eMIS) in 50 villages in the geographic catchment area CDH and a continuous health facility-based survey in the EPI Clinic of CDH.

5.2.3 Sampling strategy

In the eMIS, the household population in the constituent villages were first enumerated. Then households to be surveyed were selected using a two-stage sampling strategy. During each season, all 50 eMIS villages were randomly assigned to one of the 6 months (8 or 9 villages per month). A representative probability sample proportional to village size was then selected using the "spin the bottle" approach. The central point of each village was visited, and a random starting direction is chosen by spinning the bottle. If the size of the village was small (<200 households), all households in that direction were surveyed until the end of the village was reached. If the end of the village was reached without surveying enough households to satisfy the required sample size, then the bottle was spun again in front of the last household in the previous direction and the new direction taken as the new starting point for sampling. This procedure is repeated until the desired sample size is achieved. If the size of the village was large (>200 households), systematic sampling of every fourth household was done until the desired sample size was achieved. Any damaged or deserted house was not considered eligible for sampling. If the person primarily responsible for health care decision-making was not at home during the first visit, up to two revisits were made to find them to collect information for that given household, before that household was dropped i.e. random sampling without replacement.

In the EPI Clinic Survey, after the delivery of routine public health messages, the study nurse who was also part of the EPI team at CDH gave a short introduction of the study to all the mothers who had brought their children for well child visits. The assembled mothers were then informed that if they wanted to participate, they could bring their children to the study clinic, which was situated in the same MCH facility, at the end of the well child visit i.e. after receipt of vaccine or weighing. Children were then surveyed as they presented on alternate week days and no particular attempt was made to select or avoid a particular day because of case load. Their parents/guardians and any accompanying siblings (less than 15 years) were also offered participation in the study. Because of the opportunistic nature of our sampling strategy, recruitment was time limited so as not to cause undue delays to the mothers coming for well child visits. In this regard, sampling was done from when the well child clinic started to when it ended, 9:00am to 12:00 respectively. To adjust for month-to-month variations in health facility attendance, the total derived sample sized for the EPI Clinic Survey was 'rolled' over 12 months.

5.2.4 Sample size

In the eMIS, sample size was predetermined as part of ongoing rolling MIS surveillance activities (Roca-Feltrer et al., 2012b). A total number of 609 children were required in the peak season to achieve a relative 10% precision in the prevalence of Hb<8.0g/dL in children aged 6 – 59 months at an estimated baseline prevalence around 25% (wet season), and assuming a design effect of 1.35, a confidence level of 95%, and a response rate of 80%. Assuming that the low and high transmission season both last around 6 months, approximately 140 households and 100 children were surveyed each month.

To derive the sample size required to determine if there was a significant difference in estimates of our primary indicator (*Pf*PR) between the EPI Clinic Survey and the eMIS, we assumed an annual average *Pf*PR in the population of 30%

from figures for Chikhwawa District from the 2010 National MIS (Ministry of Health (MoH) Malawi, 2010) and preliminary data in the rMIS/eMIS. Then assuming a slightly lower *Pf*PR (20%) in children attending EPI clinic, to detect a significant difference in significant difference between the EAG sample and the population sample at 5% precision and 80% power, a total sample size of 588 children aged 6 to 59 months would be required (with 294 in each sample). Sample sizes were calculated using WinPepi® version 2.21 (Abramson, 2011).

5.2.5 Data collection

Interview with parent/guardian

Structured interviews were conducted with household heads or parents/guardians of all children in selected households in the household survey, and with parents/guardians of all children in the EPI Clinic Survey using a locally adapted version of the Roll Back Malaria (RBM)/ Monitoring & Evaluation Reference Group (MERG) MIS questionnaire (http://rbm.who.int/merg.html#MIS) (Annex 2). After informed consent, information was collected on ownership of household assets, household net ownership, net use and health care seeking behaviour and antimalarial treatment. The reported ITN-based household indicators were determined using the same algorithm in both surveys (Annex 3). In the eMIS, Global Positioning System (GPS) devices on PDAs were used to demarcate the village coordinates in the household survey during enumeration. In the EPI survey, the respondent was questioned about the village of origin and afterwards, the coordinates of the villages were later mapped using a Garmin eTrex® 30 (Garmin Ltd, UK) if the village was not present in the rMIS/eMIS database.

Lab procedures

Blood samples were collected from all children surveyed to prepare a Rapid Diagnostic Test (RDT) (First Response® Malaria Ag. pLDH/HRP2 Combo Card Test, Premier Medical Corporation Ltd., India), thick and thin blood film, and to

determine the child's haemoglobin concentration (HemoCue 301®, HemoCue AB, Ängelhom, Sweden). A quality control system was put in place to ensure that all study staff involved in lab procedures received regular standardized training (every 3 to 4 months) throughout the study period to conduct finger pricks for anaemia and malaria parasitaemia by RDT. The HemoCue® machines were validated every two months using low, normal and high controls for the HemoCue Hb 301 system (Eurotrol Hb 301 Control, HemoCue AB, Ängelhom, Sweden).

Clinical procedures

All parasitaemic and moderately anaemic children (Hb = 5 – 7.9g/dl) were treated as per national treatment guidelines by the research nurse in either survey. Children with severe anaemia (Hb < 5.0g/dl), and/or exhibiting and clinical signs of severe illness (including severe malaria) were assisted with transportation and referred to the nearest health facility in the household survey and referred to the paediatric ward in the EPI survey. Those who were parasitaemic by RDT and had received Coartem® in the past two weeks were referred to CDH in the household survey and to the senior clinician on-call in the EPI Clinic Survey.

Definition of indicators

Moderate-to-severe anaemia: Hb = 5 – 8 g/dl

Severe anaemia: Hb < 5g/dl

Plasmodium falciparum positive reaction: The simultaneous presence of the *P. falciparum*, *P. vivax*/other species and control bands, or the *P. falciparum* and control bands.

Other plasmodium species positive reaction: The simultaneous presence of the *P. vivax*/other species and control band.

Socioeconomic status (SES): SES was determined by means of a principal component analysis using a combination possession of key household items (e.g. a radio), access to amenities (e.g. household water supply and sanitation) and structure of

dwelling (e.g. roofing material) to derive a total score which was then aggregated into quintiles.

Reported Household ITN possession: The proportion of households with at least one ITN as elicited by direct questioning.

Confirmed household ITN possession: The proportion of households with at one ITN detected by direct observation of an ITN hanging over the sleeping place.

Reported Household ITN use:

- The proportion of children under five years old who slept under an ITN the previous night as elicited by direct questioning.
- The proportion of households with at least one ITN for every two people as elicited by direct questioning.

Confirmed U5 ITN use: The proportion of under-fives who slept under an ITN detected by direct observation of an ITN hanging over the sleeping place.

IRS coverage: The proportion of households sprayed by IRS in the past 12 months.

Households covered by vector control: The proportion of households with at least one ITN and/or sprayed with IRS in the past 12 months.

Universal coverage of vector control: The proportion of households with at least one ITN for every two people and/or sprayed by IRS in the past 12 months.

PfPR: The proportion of children aged 6-59 months with *Plasmodium falciparum* malaria infection.

APR: proportion of children aged 6-59 months with a haemoglobin measurement of less than 8 g/dL.

Data management

The study questionnaire was in English and verbally translated into the three main local dialects (Chichewa, Sena and Mang'anja). In the household survey, data was collected electronically in PDAs (Somo 650®, Socket Mobile, Newark, California) programmed in Visual CE® 11.1 language (Syware Incorporation, Cambridge, Massachusetts). In the EPI Clinic Survey, data was collected electronically in Netbooks (Toshiba NB520-A1116, Toshiba, UK) using a database in REDCap® (Vanderbilt University, Nashville, Tennessee, USA). Data analysis was done using STATA 13.1® (StataCorp, Texas, USA). Data used for comparison in this paper were restricted to children aged 6 months to 5 years, settlements within 15km radius of CDH and the first year of study, from 1st May 2011 to 30th April 2012.

Statistical analysis

Comparison of baseline characteristics

To assess the representativeness of data from children attending EPI clinic, we compared key baseline characteristics, coverage with control interventions, APR and *Pf*PR derived from this EAG sample with children in the eMIS. Data was presented as frequencies with their respective 95% confidence intervals (95% CI), and Pearson's chi squared test was used to determine whether any observed differences arose by chance. In a sub-analysis, we compared the reported vs confirmed assessment of household ITN possession and household ITN use in the eMIS with that in children attending EPI clinic to evaluate whether there was any potential bias trends in the reporting of ITN possession and use as determined by the proportion of households with at least one ITN and the proportion of under-fives who slept under an ITN the previous night respectively.

Determination of factors associated with reported household ITN possession, IRS coverage, APR and PfPR

To determine the factors associated with these key indicators, we tested this associations in univariate logistic regression analysis using Rao-Scott chi squared

values to detect associations between the outcome variable and the predictors by STATA survey procedures (StataCorp, 2013b) to account for the complex nature of the survey data. STATA survey procedures use Taylor-linearized variance estimation to estimate standard errors correcting for the increased sample-to-sample variability that results from the cluster sampling design of the population survey (StataCorp, 2013b). Weights were not required in the analysis as the comparator group (the household survey) sample was derived by proportion to size of the constituent villages. Variables that were reliably associated with reported household ITN possession, IRS coverage, APR and *Pf*PR were considered potential confounders and included in the multivariate analysis to determine if the estimates from children attending EPI clinic were significantly different from those from the same age strata in the population, even after controlling for confounders.

Determination of the difference in estimates of reported household ITN possession, IRS coverage, APR and PfPR

We first determined the unadjusted difference estimates of key indicators using both prevalence ratio and absolute difference in percentage prevalence derived from a univariate log binomial regression model in Stata using generalized linear models (GLM). To determine the significance of these differences, they were presented with their respective 95% confidence intervals, adjusted for clustering, unequal selection probabilities and potential confounders. We preferred these measures of effect as we expected the main outcome *P. falciparum* prevalence to be common and because of the nature of the population survey (Petersen and Deddens, 2008; Santos et al., 2008a).

We then determined potential confounders that should be included in a multivariate log binomial regression model using the likelihood ratio test was used to determine the significance of inclusion of confounders in the model. The final models were adjusted for age, mother's education, and socioeconomic status in the case of household ITN possession, mother's educational status in the case of IRS

coverage, distance from CDH, history of fever in the past two weeks, season and clinical malaria in the case of anaemia, and age, socioeconomic status, distance from CDH and current fever in the case of parasitaemia.

Modelling spatial variation

To model spatial variation of the underlying RDT prevalence and ITN coverage, we used geostatistical binomial models. We extended the standard geostatistical framework to allow for potential biased sampling in the EPI survey. The model corrects for spatially structured bias by assuming that the household survey delivers unbiased "gold-standard" estimates of the two outcomes of interest. To fit both models to the data, we used Monte Carlo maximum likelihood methods. The Markov Chain Monte Carlo methods are used in simulation of complex stochastic process such as the Markov random fields (Gibbs distribution) used in spatial statistics in order to calculate the integrals involved in determining statistical inferences (Metropolis et al., 1953; Hastings, 1970; Geman and Geman, 1984). The exact calculation of a maximum likelihood estimate (MLE) indicating the fit of a model using Markov Chain Monte Carlo methods is impossible, but several methods of Monte Carlo MLE (MCML) approximations have been devised. Only one of these models involving direct calculation of the MCML permits geospatial model simulation studies (Geyer and Thompson, 1992; Geyer, 1994), so this was the method employed in our study to assess the suitability of spatial prediction models. More details on our methodology of geospatial analysis are given in a separate publication (Giorgi E, 2015). The resulting contour maps were constructed using the R statistical software package (R Foundation for Statistical Computing, Vienna, Austria).

5.3 Results

A total of 50 villages were included in the household survey. Participants in the EPI Clinic Survey presented from a total of 84 villages of which 71 were within

15 km of CDH. Out of the 71 villages included in the EPI survey, 60 (84.5%) were traceable based on the reported name of the village or location (Figure 13). Forty villages were common to both surveys (i.e. an overlap of 66.7%). The majority of participants seen in the EPI survey were from Chikhwawa town and settlements on the main access road. In total of 571 households and 309 households containing children aged 6 – 59 months were surveyed in the household and the EPI survey respectively. In total, 682 and 323 children aged 6 – 59 months were surveyed from the household and EPI survey respectively. The mean age of children in the EPI survey (18 months, 95% CI 16 months, 19 months) was significantly lower than that in the eMIS (32 months, 95% CI 31 months, 33 months). The majority of children coming to the EPI Clinic (62.6%) were coming for routine growth monitoring as part of their well child clinic. Children coming for routine growth monitoring were older (mean age = 20 months, 95% CI 18, 22 months) than children coming for vaccinations (mean age = 11 months, 95% CI 9, 12 months) and the difference was statistically significant ($p < 0.001$). Slightly less than half of all children coming for vaccinations (53/114, 46.5%) were there for scheduled vaccinations. Children coming for scheduled vaccinations (mean age = 11 months, 95% CI 9, 13 months) were younger than those coming for catch-up vaccinations (mean age = 10 months, 95% CI 8, 11 months but this difference was not statistically significant ($p = 0.3918$).

Table 18 is a comparison of the background characteristics of both samples. In addition to differences in age, there were also significant differences in mother's education, socioeconomic status and travel distance to CDH. A significantly higher proportion of households in the EPI Clinic Survey reported a child with a history of fever in the past two weeks than in the eMIS (11.2% vs. 4.0% respectively, $p <0.001$). Though there was a significantly higher proportion of children presenting with fever and clinical malaria on the day of the survey in the EPI Clinic Survey compared to the eMIS (Table 18), this difference was not due to the inclusion of siblings in the EPI survey (Table 19).

5.3.1 Control intervention coverage

The estimates of control intervention coverage in the EPI Clinic Survey were all significantly higher than in the eMIS, except for the percentage of children who received any antimalarial for a febrile illness in the past two weeks and the percentage of children who received Coartem® for a febrile illness within 24 hours (Table 19).

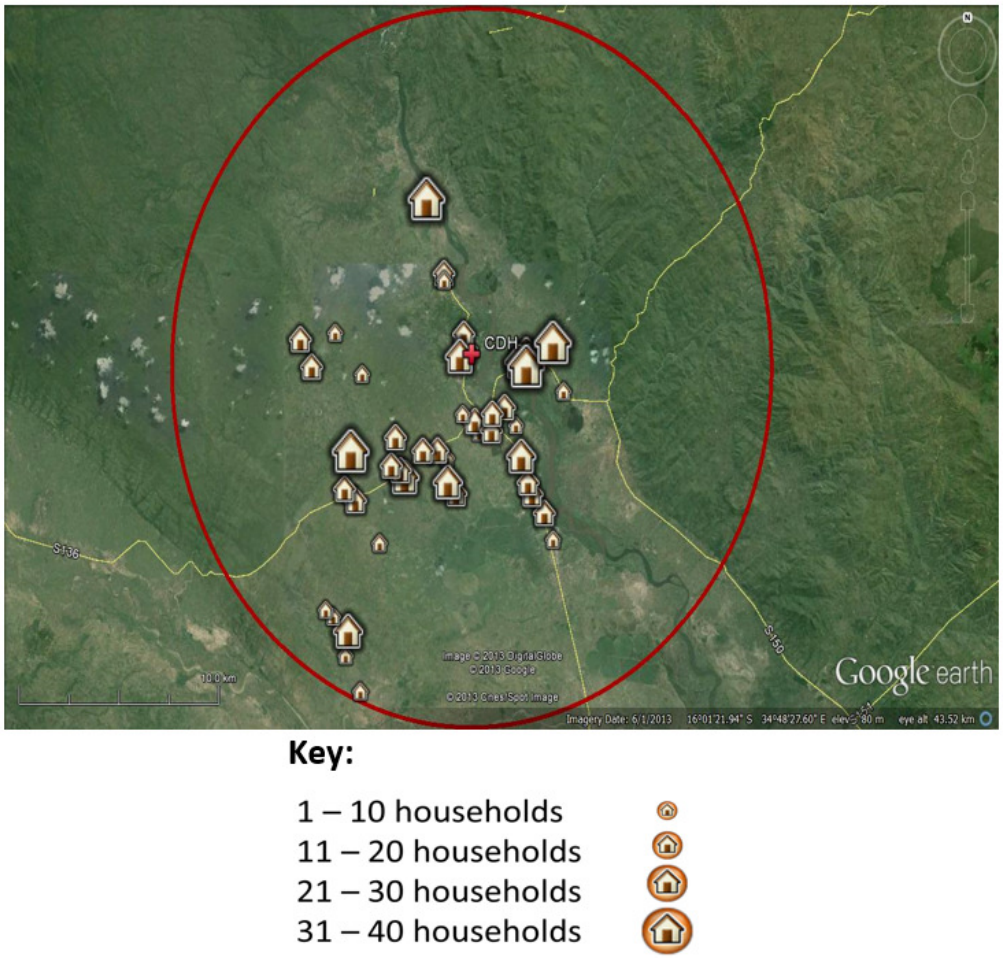
5.3.2 Reported vs. confirmed household ITN possession and use

In the household survey, average reported household ITN possession (coverage = 47.8 %, 95% CI 43.6, 52.0%) was higher compared to confirmed household ITN possession (coverage = 42.8%, 95% CI 38.4, 47.1%), but this difference was not significant (Figure 15). The average reported household ITN possession in the EPI survey (coverage = 73.9%, 95% CI 68.9, 78.9%) was significantly higher than both the reported and confirmed average household ITN possession in the household survey. A similar trend is apparent for the reported and confirmed proportion of under-fives who slept under an ITN the previous night.

5.3.3 Parasite and anaemia prevalence

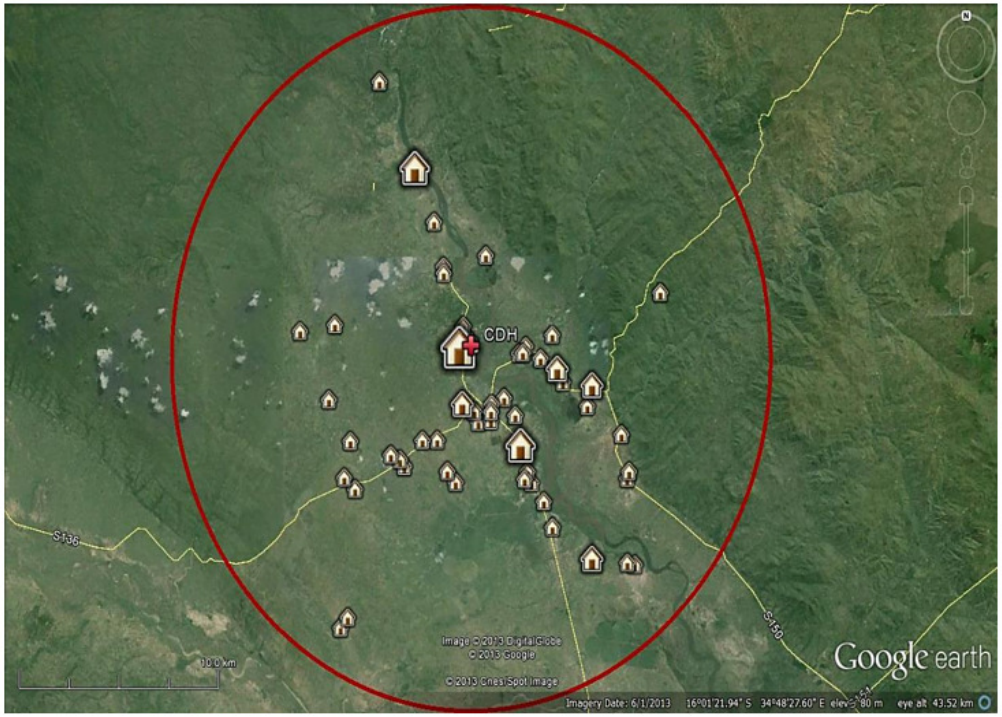
The prevalence of P. falciparum parasitaemia (by RDT) in the eMIS survey (prevalence = 23.9%, 95% CI 20.1, 27.7%) was slightly higher than that from the EPI Clinic Survey (prevalence = 20.5%, 95% CI 16.1, 24.9%) but this difference was not statistically significant (p = 0.256) (Table 20). The prevalence of other plasmodium species was alternatively slightly lower in the household survey (prevalence = 0.8%, 95% CI 0.0, 1.6%) compared to the EPI survey (prevalence = 2.2%, 95% CI 0.6, 3.8%); again the difference was not statistically significant (p = 0.096).

Figure 13: Geographic distribution of the sampling frames in the eMIS



Created using Google Earth© by Google.

Figure 14: Geographic distribution of the sampling frames in the EPI Clinic Survey



Key:

1 – 10 households

11 – 20 households

21 – 30 households

31 – 40 households

Created using Google Earth© by Google.

Table 18: Background characteristics of households with children aged 6 to 59 months in both surveys

	EPI Clinic Survey		eMIS		
	n	% (95% CI)	n	% (95% CI)	χ^2 *p-value*
Total number of households surveyed	309	-	571	-	-
Total number of under five children surveyed	323	-	682	-	-
Age group of surveyed children					
6 – 12 months	157	48.6 (43.1, 54.1)	86	12.6 (10.1, 15.1)	
12 – 23 months	73	22.6 (18.0, 27.2)	149	21.9 (18.7, 25.0)	
24 – 35 months	56	17.4 (13.2, 21.5)	149	21.9 (18.7, 25.0)	
36 – 47 months	22	6.8 (4.1, 9.6)	153	22.4 (19.3, 25.6)	
48 – 59 months	15	4.6 (2.3, 7.0)	145	21.2 (18.2, 24.3)	<0.001
Child's Sex					
Male	153	47.4 (41.9, 52.8)	317	46.5 (42.7, 50.2)	
Female	170	52.6 (47.2, 58.1)	365	53.5 (49.8, 57.3)	0.792
Mother's education					
None	61	20.1 (15.6, 24.7)	150	30.0 (26.0, 34.0)	
Primary	190	62.7 (57.2, 68.1)	291	58.2 (53.8, 62.5)	
Secondary or above	46	17.2 (13.3, 21.9)	59	11.8 (9.0, 14.6)	0.003
Households by SES					
Poorest	44	14.3 (10.4, 18.2)	182	33.2 (29.2, 37.1)	
Quintile 2	42	13.6 (9.8, 17.5)	94	17.1 (14.0, 20.3)	
Quintile 3	53	17.2 (13.0, 21.4)	139	25.3 (21.7, 29.0)	
Quintile 4	77	25.0 (20.2, 29.9)	66	12.0 (9.3, 14.8)	
Wealthiest	92	29.9 (24.7, 35.0)	68	12.4 (9.6, 15.2)	<0.001
Households with less than 5 persons	156	50.7 (45.1, 56.3)	285	51.9 (47.7, 56.1)	0.723
Distance to CDH					
0 – 5km	149	65.4 (59.2, 71.6)	312	55.5 (51.4, 59.6)	
5 – 10km	71	31.1 (25.1, 37.2)	213	37.9 (33.9, 41.9)	
10 – 15km	8	3.5 (1.1, 5.9)	37	6.6 (4.5, 8.6)	0.024
Households from hard-to-reach villages	12	5.7 (2.6, 8.8)	28	5.0 (3.2, 6.8)	0.682
Households surveyed by season					
Dry season	199	64.4 (59.1, 69.8)	338	59.2 (55.2, 63.2)	
Rainy/Post-rainy season	110	35.6 (30.2, 41.0)	233	40.8 (36.7, 44.9)	0.131
Fever in in the past two weeks	101	32.8 (27.5, 38.1)	73	15.7 (12.4, 19.0)	<0.001
Current fever	36	11.2 (7.7, 14.6)	17	4.0 (2.1, 5.9)	<0.001
Clinical malaria	23	7.1 (4.3, 10.0)	9	2.1 (0.7, 3.5)	0.001

Table 19: Coverage of control interventions in children aged 6 to 59 months in both surveys

	EPI Clinic Survey		eMIS		
	n	% (95% CI)	n	% (95% CI)	χ^2 *p-value*
Households with any bed net	241	78.3 (73.6, 82.9)	354	62.0 (58.0, 66.0)	< 0.001
Households with at least one ITN	227	73.7 (68.8, 78.6)	280	49.0 (44.9, 53.2)	< 0.001
Household with at least one ITN for any two members	3	1.7 (0.6, 4.3)	23	11.8 (8.6, 16.1)	< 0.001
Under-fives who slept under ITN the previous night	230	71.4 (66.5, 76.4)	326	47.8 (44.0, 51.6)	< 0.001
Households sprayed by IRS in the past 12 months	204	67.3 (62.0, 72.6)	300	54.7 (50.5, 58.8)	< 0.001
Households with at least one ITN and/or sprayed with IRS in past 12 months	278	90.3 (86.9, 93.6)	420	75.0 (71.4, 78.6)	< 0.001
Households with at least one ITN for every two people and/or sprayed with IRS in past 12 months	205	66.3 (60.9, 71.4)	327	57.3 (53.2, 61.3)	0.009
Under-five children with fever in past two weeks who received any antimalarial	33	30.6 (21.8 – 39.3)	21	25.0 (15.6 – 34.4)	0.396
Under-five children with fever in past two weeks who received LA within 24 hours	19	18.6 (11.0 – 26.3)	11	13.3 (5.9 – 20.6)	0.324

Figure 15: Reported vs. Observed Household ITN possession and use

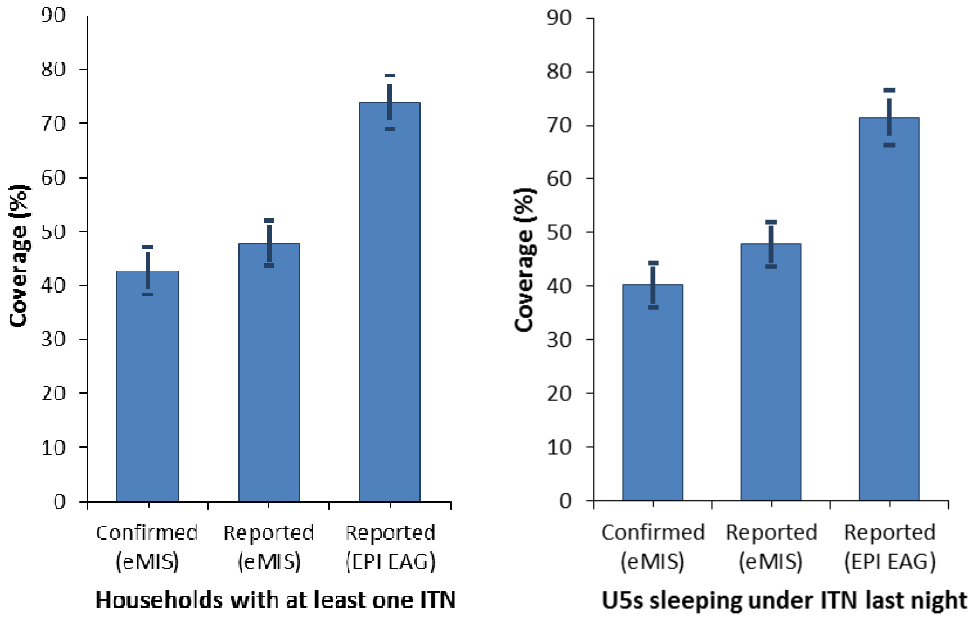


Table 20: Prevalence of *P. falciparum* parasitaemia and anaemia (Hb<8.0g/dl)

	EPI EAG		eMIS		
	n	% (95% CI)	n	% (95% CI)	χ^2 *p*-value
Prevalence of *P. falciparum* parasitaemia (RDT) in children aged 6 – 59 months					
P. falciparum parasitaemia*	66	20.5 (16.1 – 24.9)	119	23.9 (20.1 – 27.7)	0.256
Non-falciparum parasitaemia	7	2.2 (0.6 – 3.8)	4	0.8 (0.0 – 1.6)	0.096
Prevalence of anaemia in children aged 6 – 59 months					
Hb<11.0g/dl	223	69.3 (64.2 – 74.3)	303	61.3 (57.0 – 65.6)	0.021
Hb<8.0g/dl	19	5.9 (3.3 – 8.5)	22	4.5 (2.6 – 6.3)	0.355

*Includes mixed infections.

The prevalence of anaemia (Hb < 11.0g/dl) was lower in the household survey (prevalence = 61.3%, 95% CI 57.0, 65.6%) than in the EPI survey (prevalence = 69.3%, 95% CI 64.2, 74.3%) but confidence intervals overlapped (p = 0.021). There

was no significant difference between the prevalence of anaemia (Hb < 8.0g/dl) in the household survey (prevalence = 4.5%, 95% CI 2.6, 6.3%) and the EPI survey (prevalence = 5.9%, 95% CI 3.3, 8.5%)

5.3.4 Factors associated with reported ITN coverage

Table 21 shows association of reported household ITN possession and household characteristics. Insecticide treated net used significantly decreased with age in the eMIS, but though age group was significantly associated with ITN possession, no such trend was apparent in the EPI Clinic Survey. Reported ITN possession increased significantly with maternal age in the eMIS but not in the EPI Clinic Survey. Insecticide treated net possession increased with increasing SES in the eMIS and the EPI Clinic Survey, though the trend was less apparent in the latter. Smaller sized households were significantly more likely to own an ITN in the eMIS, but this trend was not apparent in the EPI Clinic Survey.

5.3.5 Factors associated with IRS coverage

Table 22 shows association of IRS in children aged 6 to 59 months with age and household characteristics. Increasing maternal education was significantly associated with a decreasing IRS in the eMIS, but this trend was not present in the EPI Clinic Survey. Coverage with IRS was higher in the dry season in both surveys but this trend was borderline. The remaining household characteristics were not significantly associated with IRS. IRS and ITN possession were correlated in the eMIS, but this trend was not apparent in the EPI Clinic Survey.

5.3.6 Factors associated with *P. falciparum* prevalence (by RDT)

Table 23 shows association of *P. falciparum* prevalence (including mixed infections) and with age, household, coverage and clinical characteristics for both surveys. The *Pf*PR increased with age group but a significant trend was only present in the eMIS. The *PfP*R decreased significantly with distance in the eMIS but

not in the EPI Clinic Survey**.** Parasite prevalence was significantly higher in the dry season compared to the rainy/post-rainy season in the eMIS (27.1% vs. 18.6% respectively, $p < 0.001$) but not in the EPI Clinic Survey (17.8% vs. 25.4% respectively, $p = 0.0052$). History of fever in the past two weeks in a child aged 6 to 59 months in the household and current fever in the surveyed child was associated with parasitaemia in both surveys. Household possession and use of ITNs did not seem to be protective against *Pf*PR in either survey. Households who have received IRS were significantly less likely to have children with *P. falciparum* in the EPI Clinic Survey (17.0% vs. 27.9% respectively, $p = 0.0290$). There was borderline protection from parasitaemia in households that had received at least one vector control option in both surveys (Table 23). The presence of a child in the household who had fever in the past two weeks and was treated with any antimalarial or Coartem® (Artemether-Lumefantrine/LA) was not associated with the presence of *P. falciparum.*

5.3.7 Factors associated with anaemia (Hb<8.0g/dl)

Table 24 shows association of anaemia with age, household, coverage and clinical characteristics for both surveys. Age group, mother's education, SES, household size, distance and whether the village was hard-to-reach or not did not appear to be significantly associated with anaemia in both surveys. The prevalence of anaemia was significantly higher in the dry season compared to the rainy/post-rainy season (6.4% vs. 0.5% respectively, $p = 0.0011$) in the eMIS but not in the EPI Clinic Survey (8.3% vs. 4.7% respectively, $p = 0.2082$). Current febrile illness and clinical malaria was associated with a significantly higher prevalence of anaemia in the EPI Clinic Survey but not the eMIS. Of all the measures of coverage of control interventions, only the proportion of households with at least one ITN appeared to be associated with a higher prevalence of anaemia in the EPI Clinic Survey. The presence of *P. falciparum* parasitaemia (by RDT) was strongly correlated with the prevalence of anaemia in both surveys.

Table 21: Factor associated with possession of at least one ITN in the household (adjusted for clustering)

Risk factor	EPI Clinic Survey		eMIS	
	n (%)	*χ^2 p value	n (%)	*χ^2 p value
Age group				
6 – 12 months	131 (83.4)		58 (67.4)	
12 – 23 months	50 (69.4)		84 (56.4)	
24 – 35 months	29 (51.8)		66 (44.3)	
36 – 47 months	14 (63.6)		61 (39.9)	
48 – 59 months	14 (93.3)	<0.0001	57 (39.3)	<0.0001
Mother's education				
None	42 (66.7)		64 (35.4)	
Primary	150 (75.4)		179 (51.3)	
Secondary and above	43 (78.2)	0.3301	39 (55.7)	0.0041
Household SES				
Poorest	30 (63.8)		96 (45.1)	
Quintile 2	29 (65.9)		43 (36.4)	
Quintile 3	36 (66.7)		80 (48.5)	
Quintile 4	65 (80.3)		43 (51.2)	
Wealthiest	78 (81.3)	0.0596	52 (66.7)	0.0054
Households with less than 5 persons				
Yes	121 (73.3)		168 (52.3)	
No	124 (75.2)	0.7163	146 (43.3)	0.0385
Households more 5km from CDH				
0 – 5km	118 (74.2)		188 (51.1)	
5 – 10km	52 (72.2)		115 (45.5)	
10 – 15km	6 (75.0)	0.9489	19 (40.4)	0.2870
Households from hard-to-reach villages				
Yes	7 (63.6)		16 (43.2)	
No	158 (75.2)	0.3915	309 (48.5)	0.6035
Season				
Dry season	153 (73.6)		201 (49.4)	
Rainy/Post-rainy season	85 (74.7)	0.8487	125 (45.5)	0.3664

*Rao-Scott chi squared p-values.

Table 22: Factors associated with IRS in households with children aged 6 months to 5 years (adjusted for clustering)

Risk factor	EPI Clinic Survey		eMIS	
	n (%)	*χ^2 p value	n (%)	*χ^2 p value
Age group				
6 – 12 months	95 (61.7)		42 (50.6)	
12 – 23 months	47 (67.4)		81 (55.1)	
24 – 35 months	41 (73.2)		82 (56.9)	
36 – 47 months	18 (81.8)		71 (49.3)	
48 – 59 months	11 (78.6)	0.2096	80 (57.1)	0.5750
Mother's education				
None	35 (55.6)		95 (54.9)	
Primary	133 (68.6)		180 (52.8)	
Secondary and above	39 (72.2)	0.1344	22 (32.8)	0.0239
Household SES				
Poorest	27 (57.5)		116 (54.5)	
Quintile 2	32 (72.7)		59 (50.0)	
Quintile 3	32 (60.4)		102 (61.8)	
Quintile 4	57 (71.3)		41 (48.8)	
Wealthiest	64 (69.6)	0.3768	38 (48.7)	0.3025
Households with less than 5 persons				
Yes	105 (66.0)		163 (50.8)	
No	107 (68.2)	0.7021	193 (57.3)	0.1523
Households more 5km from CDH				
0 – 5km	109 (70.8)		177 (50.6)	
5 – 10km	42 (58.3)		146 (59.1)	
10 – 15km	6 (85.7)	0.1115	29 (61.7)	0.1456
Households from hard-to-reach villages				
Yes	9 (90.0)		19 (63.3)	
No	141 (68.8)	0.1567	333 (53.7)	0.3868
Season				
Dry season	145 (71.1)		224 (57.4)	
Rainy/Post-rainy season	67 (59.8)	0.0518	132 (49.3)	0.0752
Households with at least one ITN				
Yes	160 (69.0)		186 (59.2)	
No	52 (61.9)	0.2600	170 (49.4)	0.0249

*Rao-Scott chi squared p-values.

Table 23: Factors associated with the presence of *P. falciparum* in households with children aged 6 months to 5 years (adjusted for clustering)

	EPI Clinic Survey		eMIS	
Risk factor	n (%)	*χ^2 *p* value	n (%)	*χ^2 *p* value
Age group				
6 – 12 months	27 (17.2)		9 (15.8)	
12 – 23 months	15 (20.8)		6 (9.1)	
24 – 35 months	11 (19.6)		29 (24.0)	
36 – 47 months	7 (31.8)		42 (31.6)	
48 – 59 months	6 (40.0)	0.1758	33 (27.3)	0.0045
Mother's education				
None	19 (30.2)		28 (22.2)	
Primary	40 (20.1)		51 (20.1)	
Secondary and above	6 (10.9)	0.0411	9 (17.3)	0.7771
Household SES				
Poorest	17 (36.2)		51 (31.1)	
Quintile 2	8 (18.2)		20 (23.0)	
Quintile 3	8 (14.8)		24 (19.1)	
Quintile 4	20 (24.7)		11 (19.0)	
Wealthiest	13 (13.5)	0.0201	9 (16.4)	0.0862
Households with less than 5 persons				
Yes	35 (21.7)		48 (20.5)	
No	31 (19.3)	0.5913	67 (26.2)	0.1593
Households more 5km from CDH				
0 – 5km	22 (13.8)		84 (31.6)	
5 – 10km	12 (16.7)		30 (16.5)	
10 – 15km	3 (37.5)	0.1943	3 (7.7)	<0.001
Households from hard-to-reach villages				
Yes	2 (18.2)		7 (24.1)	
No	37 (17.6)	0.9621	110 (23.8)	0.9724
Season				
Dry season	37 (17.8)		84 (27.1)	
Rainy/Post-rainy season	29 (25.4)	0.1123	35 (18.6)	0.0375
History of fever in the past two weeks in child aged 6 months to 5 years				
Yes	32 (29.6)		37 (47.4)	
No	34 (15.9)	0.0052	82 (19.5)	<0.001
Current fever in child aged 6 months to 5 years				
Yes	23 (63.9)		9 (52.9)	
No	43 (15.0)	<0.001	75 (18.3)	<0.001
Households with any bed net				
Yes	46 (18.3)		56 (19.1)	
No	20 (28.6)	0.0698	63 (30.9)	0.0037

Risk factor	EPI Clinic Survey		eMIS	
	n (%)	*χ^2 p value	n (%)	*χ^2 p value
Households with at least one ITN				
Yes	44 (18.5)		43 (19.6)	
No	22 (26.2)	0.1475	76 (27.3)	0.0528
Household with at least one ITN for any two members				
Yes	3 (100.0)		1 (10.0)	
No	43 (17.3)	<0.001	42 (20.0)	0.4433
Under-fives who slept under ITN previous night				
Yes	44 (19.1)		43 (19.6)	
No	22 (23.9)	0.3542	76 (27.3)	0.0528
IRS in the past 12 months				
Yes	36 (17.0)		53 (20.5)	
No	29 (27.9)	0.0290	62 (26.7)	0.1205
Households with at least one ITN and/or sprayed with IRS in past 12 months				
Yes	55 (19.0)		75 (21.1)	
No	11 (34.4)	0.0557	41 (29.5)	0.0522
Households with at least one ITN for every two people and/or sprayed with IRS in past 12 months				
Yes	36 (17.0)		57 (21.1)	
No	18 (24.0)	0.1851	21 (23.6)	0.6501
Under-five children with fever in past two weeks who received any antimalarial				
Yes	7 (21.2)		9 (56.3)	
No	25 (33.3)	0.2201	28 (45.2)	0.4357
Under-five children with fever in past two weeks who received LA within 24 hours				
Yes	3 (15.8)		6 (66.7)	
No	27 (32.5)	0.1622	31 (49.6)	0.2420
Prevalence of anaemia (Hb < 8.0g/dl) in children aged 6 – 59 months				
Yes	12 (63.2)		15 (68.2)	
No	54 (17.8)	<0.001	102 (21.6)	<0.001

*Rao-Scott chi squared p-values.

Table 24: Factors associated with anaemia (Hb < 8.0g/dl) in households with children aged 6 months to 5 years (adjusted for clustering)

Risk factor	EPI Clinic Survey		eMIS	
	n (%)	*χ^2 p value	n (%)	*χ^2 p value
Age group				
6 – 12 months	12 (7.6)		3 (5.3)	
12 – 23 months	3 (4.2)		7 (10.6)	
24 – 35 months	3 (5.4)		5 (4.2)	
36 – 47 months	1 (4.6)		4 (3.0)	
48 – 59 months	0 (0.0)	0.6872	3 (2.5)	0.0934
Mother's education				
None	3 (4.8)		0 (0.0)	
Primary	12 (6.5)		12 (4.7)	
Secondary and above	2 (3.6)	0.6779	2 (3.9)	0.0601
Household SES				
Poorest	3 (6.4)		10 (6.1)	
Quintile 2	1 (2.3)		4 (4.8)	
Quintile 3	3 (5.6)		1 (0.8)	
Quintile 4	8 (9.9)		2 (3.5)	
Wealthiest	4 (4.2)	0.4368	4 (7.3)	0.2295
Households with less than 5 persons				
Yes	12 (7.5)		10 (4.3)	
No	7 (4.4)	0.2512	11 (4.4)	0.9778
Households more 5km from CDH				
0 – 5km	5 (3.2)		17 (6.5)	
5 – 10km	5 (6.9)		4 (2.2)	
10 – 15km	0 (0.0)	0.3865	1 (2.6)	0.0921
Households from hard-to-reach villages				
Yes	1 (9.1)		1 (3.5)	
No	8 (3.8)	0.3955	21 (4.6)	0.3868
Season				
Dry season	12 (5.8)		21 (6.4)	
Rainy/Post-rainy season	7 (6.1)	0.9008	1 (0.5)	0.0011
History of fever in the past two weeks in child aged 6 months to 5 years				
Yes	9 (8.3)		8 (10.3)	
No	10 (4.7)	0.2082	14 (3.4)	0.0032
Current fever in child aged 6 months to 5 years				
Yes	5 (13.9)		0 (0.0)	
No	14 (4.9)	0.0361	15 (3.7)	0.4523
Households with any bed net				
Yes	12 (4.8)		14 (4.8)	
No	7 (10.0)	0.1118	8 (3.9)	0.6736

Risk factor	EPI Clinic Survey		eMIS	
	n (%)	*χ^2 p value	n (%)	*χ^2 p value
Households with at least one ITN				
Yes	12 (5.0)		10 (4.6)	
No	7 (8.3)	0.2866	12 (4.4)	0.9194
Household with at least one ITN for any two members				
Yes	1 (33.3)		1 (10.0)	
No	11 (4.4)	0.0211	9 (4.3)	0.4065
Under-fives who slept under ITN previous night				
Yes	12 (5.2)		10 (4.6)	
No	7 (7.6)	0.4254	12 (4.4)	0.9194
Household sprayed with IRS in the past 12 months				
Yes	12 (5.7)		12 (4.7)	
No	7 (6.7)	0.7288	9 (3.9)	0.6880
Households with at least one ITN and/or sprayed with IRS in past 12 months				
Yes	16 (5.5)		18 (5.1)	
No	3 (9.4)	0.3876	4 (2.9)	0.3715
Households with at least one ITN for every two people and/or sprayed with IRS in past 12 months				
Yes	12 (5.7)		13 (4.9)	
No	4 (5.3)	0.9276	5 (5.6)	0.7859
Under-five children with fever in past two weeks who received any antimalarial				
Yes	3 (9.1)		2 (12.5)	
No	6 (8.0)	0.8517	6 (9.7)	0.7427
Under-five children with fever in past two weeks who received LA within 24 hours				
Yes	2 (10.5)		2 (22.2)	
No	7 (8.4)	0.7752	6 (8.8)	0.2228
Prevalence of *P. falciparum* parasitaemia (RDT) in children aged 6 – 59 months				
Yes	12 (18.2)		15 (12.8)	
No	7 (2.7)	<0.001	7 (1.9)	<0.001

*Rao-Scott chi squared p-values.

5.3.8 Difference in ITN and IRS coverage between surveys

Table 25 shows results of both unadjusted and adjusted log binomial regression analyses of the difference in estimates of ITN and IRS coverage between surveys using prevalence ratios (RRs) and absolute percentage risk difference (RDs). Overall, the EPI survey significantly overestimated ITN and IRS coverage of outcome indicators in the unadjusted analysis. After adjustment for the age of the child, household ITN possession, mother's education and socioeconomic status, the EPI Clinic Survey still significantly overestimated population coverage of ITN (RD = 13.8%, 95% CI 6.8%, 20.9%, $p < 0.001$) and IRS (RD = 15.6%, 95% CI 9.0, 22.3%, $p < 0.001$).

5.3.9 Difference in the prevalence of anaemia (Hb<8.0g/dl) and *P. falciparum* (by RDT) between surveys

Table 26 shows the results of both unadjusted and adjusted log binomial regression analyses of the difference in estimates of the prevalence of anaemia (Hb<8.0g/dl) and *P. falciparum* (by RDT) between surveys using prevalence ratios and absolute percentage risk difference. In the unadjusted analysis, estimates from the EPI survey were not significantly different from population estimates. After adjusting for the effect of distance from CDH, history of fever in the past two weeks, season and clinical malaria, estimates of anaemia from the EPI Clinic Survey were not significantly different from population estimates (RD = 1.3%, 95% CI -1.6, 4.2%, $p = 0.373$). After adjusting for age, socioeconomic status, distance from CDH and current fever, estimates of *Pf*PR were not significantly different from population estimates (RD = 2.9%, 95% CI --3.8%, 9.4%, $p = 0.400$).

Table 25: Difference in ITN and IRS coverage between surveys

	Absolute percentage risk differences				Prevalence ratios			
	Crude Absolute Risk Difference (95%CI)	**p-value**	***Adjusted Risk Difference (95%CI)**	**p-value**	**Crude Prevalence Ratio (95%CI)**	**p-value**	***Adjusted Prevalence Ratio (95%CI)**	**p-value**
ITN possession (reported)	26.1 (10.0, 37.3)	<0.001	13.8 (6.8, 20.9))	<0.001	1.55 (1.40, 1.71)	<0.001	1.21 (1.07, 1.36)	0.002
IRS	13.0 (6.5, 19.4)	<0.001	15.6 (9.0, 22.3)	<0.001	1.24 (1.12, 1.38)	<0.001	1.30 (1.16, 1.46)	<0.001

*Estimates for household ITN possession adjusted for age, mother's education, and socioeconomic status.
Estimates for IRS coverage adjusted for mother's education.

Table 26: Difference in anaemia (Hb<8.0g/dl) and *P. falciparum* prevalence between surveys

	Absolute percentage risk differences				Prevalence Ratios			
	Crude Absolute Risk Difference (95%CI)	**p-value**	***Adjusted Risk Difference (95%CI)**	**p-value**	**Crude Prevalence Ratio (95%CI)**	**p-value**	***Adjusted Prevalence Ratio (95%CI)**	**p-value**
Anaemia (Hb<8.0g/dl)	1.5 (-1.7, 4.6)	0.368	1.3 (-1.6, 4.2)	0.374	1.33 (0.73, 2.41)	0.356	0.76 (0.36, 1.58)	0.456
P. falciparum parasitaemia (RDT)	-3.4 (-9.2, 2.4)	0.250	2.9 (-3.8, 9.4)	0.400	0.86 (0.66, 1.12)	0.259	1.08 (0.70, 1.65)	0.735

* Estimates for anaemia adjusted for distance from CDH, history of fever in the past two weeks and season.
Estimates for *P. falciparum* parasitaemia adjusted for age, socioeconomic status, distance from CDH and current fever.

Table 27: Log-odds estimates for the geostatistical model of ITN coverage in the combined model of the EPI survey and eMIS

Term	Estimate	p-value
Intercept	-0.737	< 0.001
SES	0.202	< 0.001

Table 28: Log-odds estimates for the geostatistical model of *P. falciparum* prevalence in the combined model of the EPI survey and eMIS

Term	Estimate	p-value
Intercept	-1.160	0.032
ITN	-0.380	< 0.001
IRS	-0.419	< 0.001
Total Rainfall (mm)	0.007	< 0.001
SES	-0.164	< 0.001

5.3.10 Geostatistical analysis

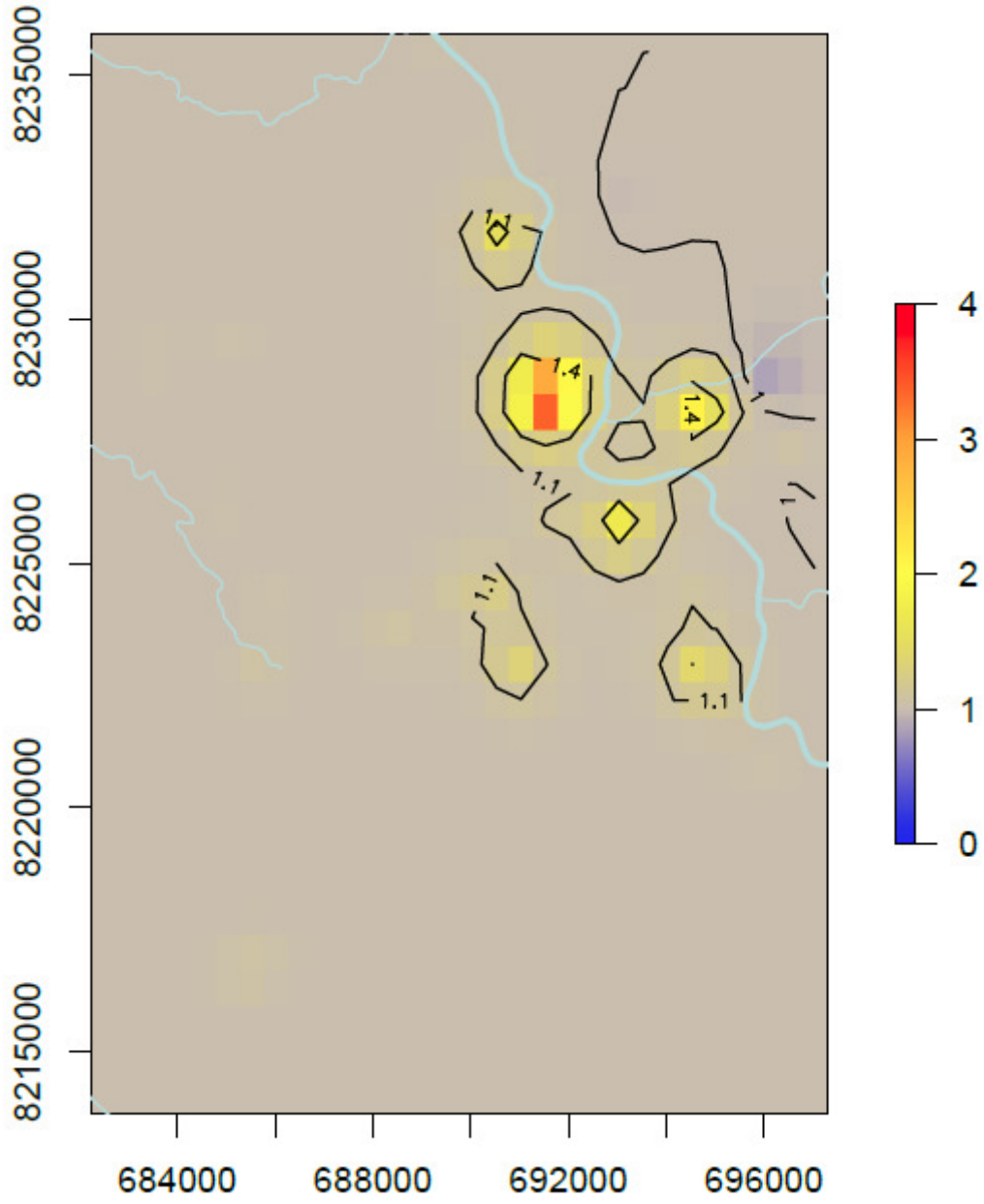
To determine the spatial heterogeneity of malaria control indicators we modelled the spatial variation in estimates in children attending EPI Clinics using geostatistical model of the combined data from both surveys. We evaluated the fit of different predictors in the model using MCML and the final model controlled for significant predictors. Household ITN possession was modelled by adjusting for socioeconomic status as this was the only significant predictor of spatial variation (Table 27). Spatial variation of IRS was modelled directly as there were no significant predictors. Spatial variation of *Pf*PR by adjusting for the effect of household ITN possession, IRS coverage, socioeconomic status and total rainfall (mm) with two months lag (Table 28), all of with were significant predictors in the model. The APR was too low to enable the assessment of its spatial variation so mean Hb was analysed as a continuous variable. Spatial predictions were then obtained over a grid of 900 pixels at spatial resolution of 700 x 400 m. At locations that were not sampled, we imputed socioeconomic status, ITN and IRS coverage by computing the respective averages of the closest village. Total rainfall was fixed at its annual average for predictions of RDT prevalence.

ITN and IRS coverage

Figures 16 and 17 are contours map of the multiplicative spatial bias of the odds ratio of a household containing at least one ITN and having received IRS respectively. The areas in the map are graduated from blue areas corresponding to areas where the EPI Clinic Survey significantly underestimated population values, to grey areas corresponding to areas where there was no bias (i.e. estimates between surveys were not significantly different), to red areas where the EPI Clinic Survey significantly overestimated population ITN coverage. The contours represent a mean estimate (odds ratio) of the area enclosed in the contour. Spatial bias for ITN coverage was highest in the areas closest to CDH where the EPI survey on the whole tended to overestimate population values. Spatial bias for IRS coverage was highest in the area closest to CDH, where again on the whole, the EPI survey tended to overestimate population values.

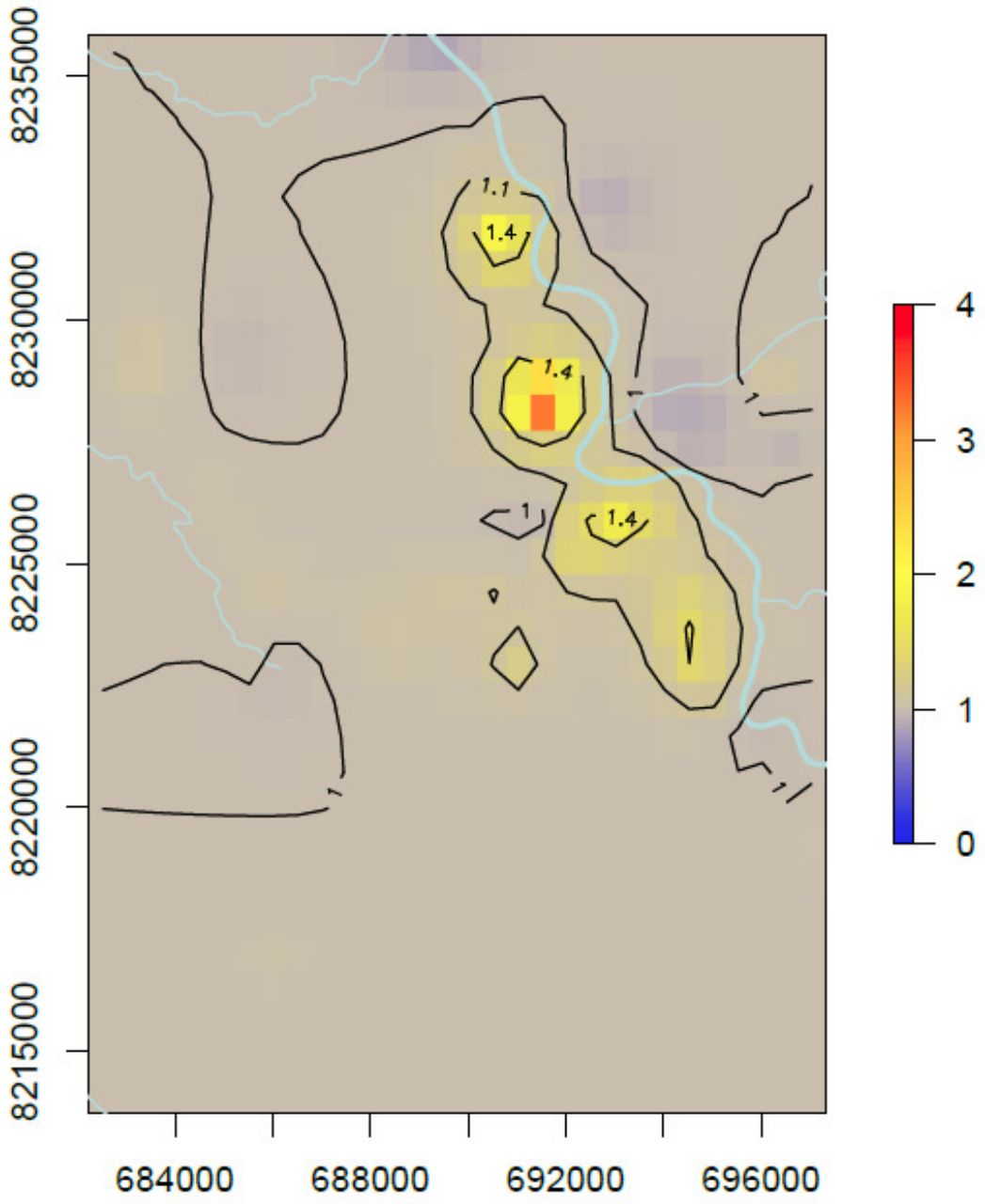
Figure 18 and Figure 19 are contour maps of the geographic distribution of coverage of ITN and IRS respectively, after removal of all spatial bias. The areas in the map are graduated from red areas correspond to areas with no coverage, to dark green areas corresponding to areas were the universal coverage target of 100% was achieved. The contours represent a mean estimate (percentage coverage) of the area enclosed in the contour. The generated map of the geospatial distribution of ITN coverage revealed that except for one area, ITN coverage was higher closer to the Shire River corresponding to the main road access in the region, though universal coverage was not achieved in any area (Figure 18). The generated map of the geospatial distribution of revealed that IRS coverage was much more varied that ITN and except for two areas, the IRS coverage was much higher in the areas closer to the Shire River and the main access roads in the region (Figure 19).

Figure 16: Multiplicative geospatial bias of the odds of ITN possession between surveys



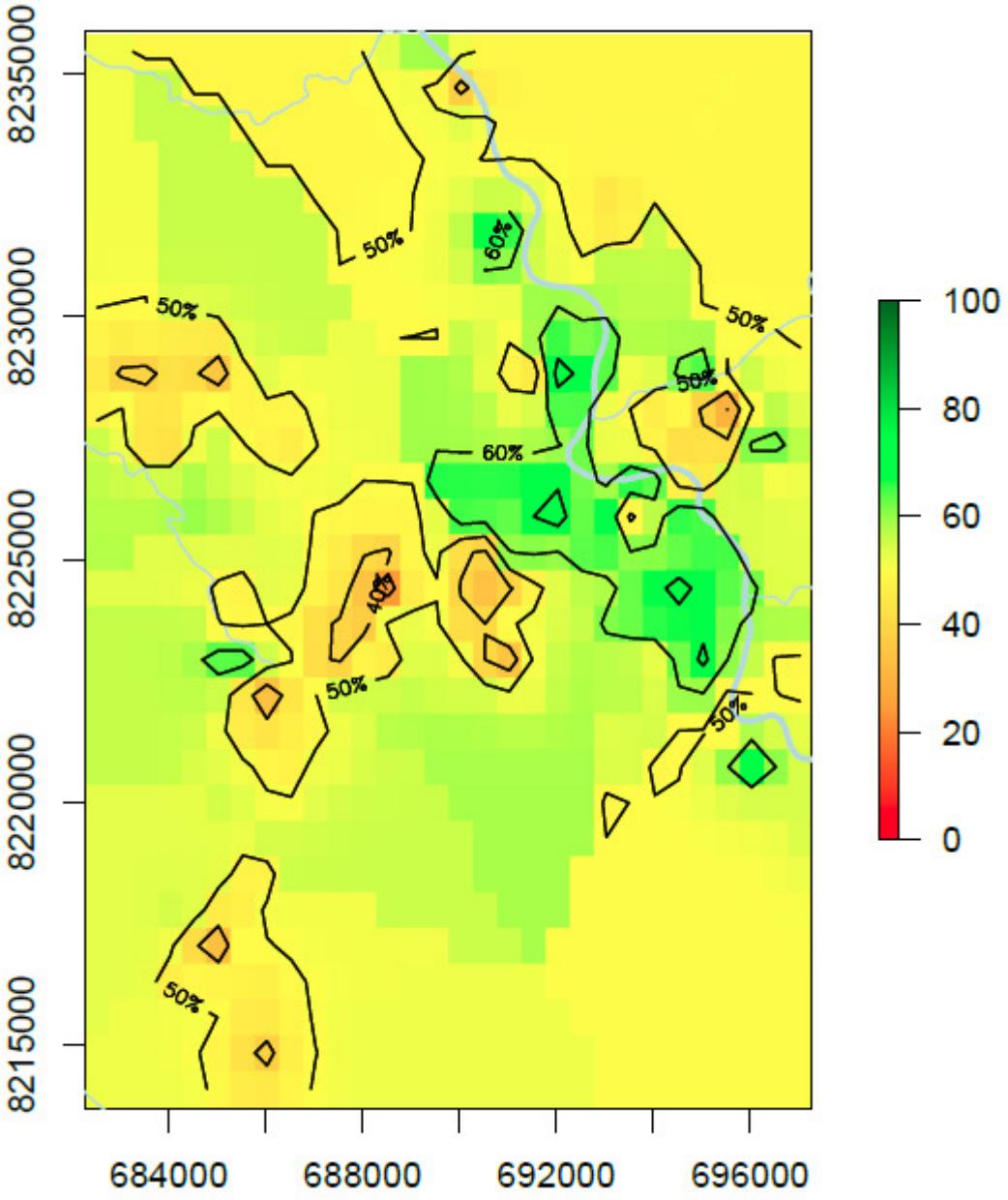
Distance between individual ticks on the x equivalent to 2km and on the and y axis equivalent to 5km.

Figure 17: Multiplicative geospatial bias of the odds of IRS coverage between surveys



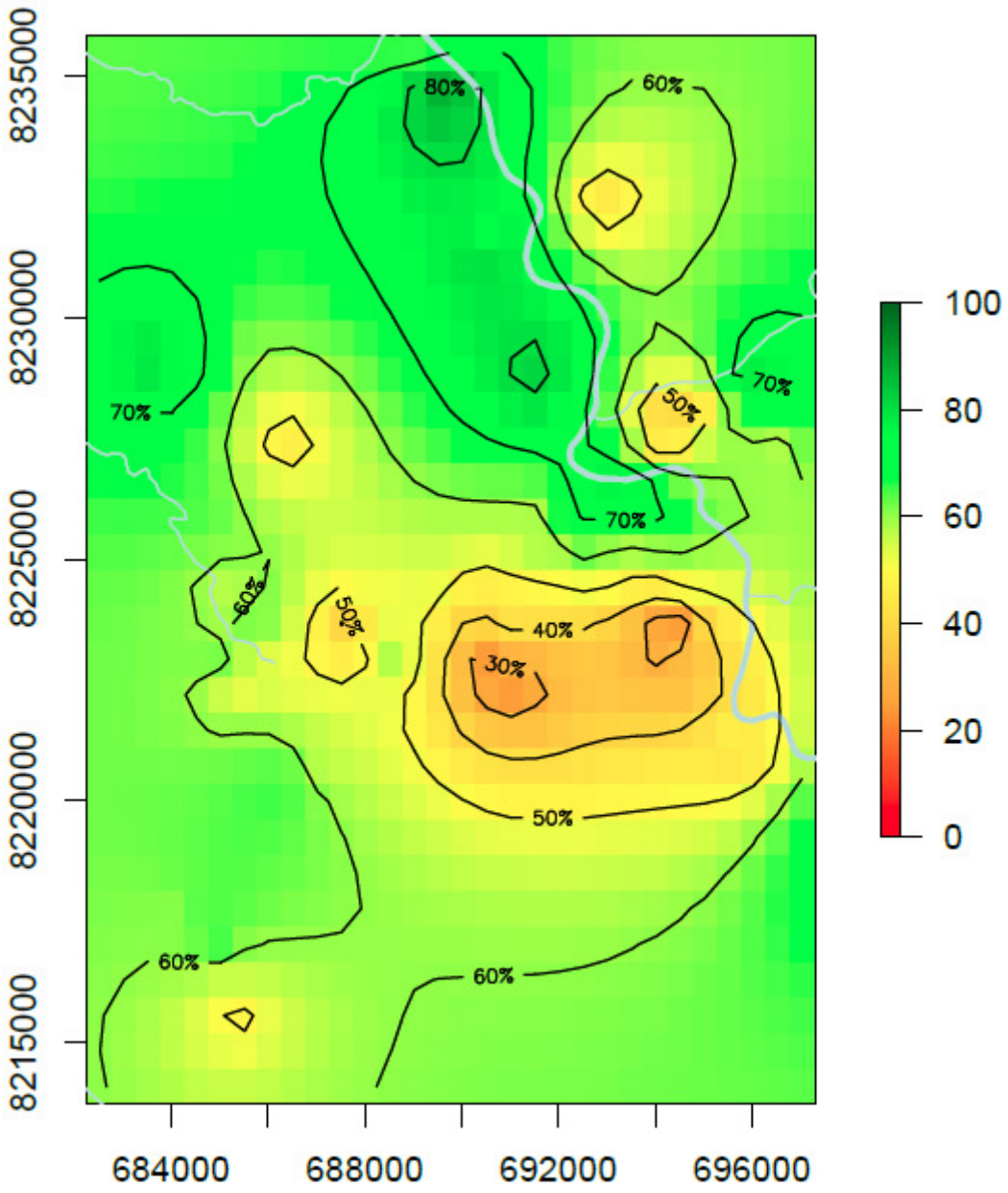
Distance between individual ticks on the x equivalent to 2km and on the and y axis equivalent to 5km.

Figure 18: Geospatial distribution of ITN possession



Distance between individual ticks on the x equivalent to 2km and on the and y axis equivalent to 5km.

Figure 19: Geospatial distribution of IRS coverage



Distance between individual ticks on the x equivalent to 2km and on the and y axis equivalent to 5km.

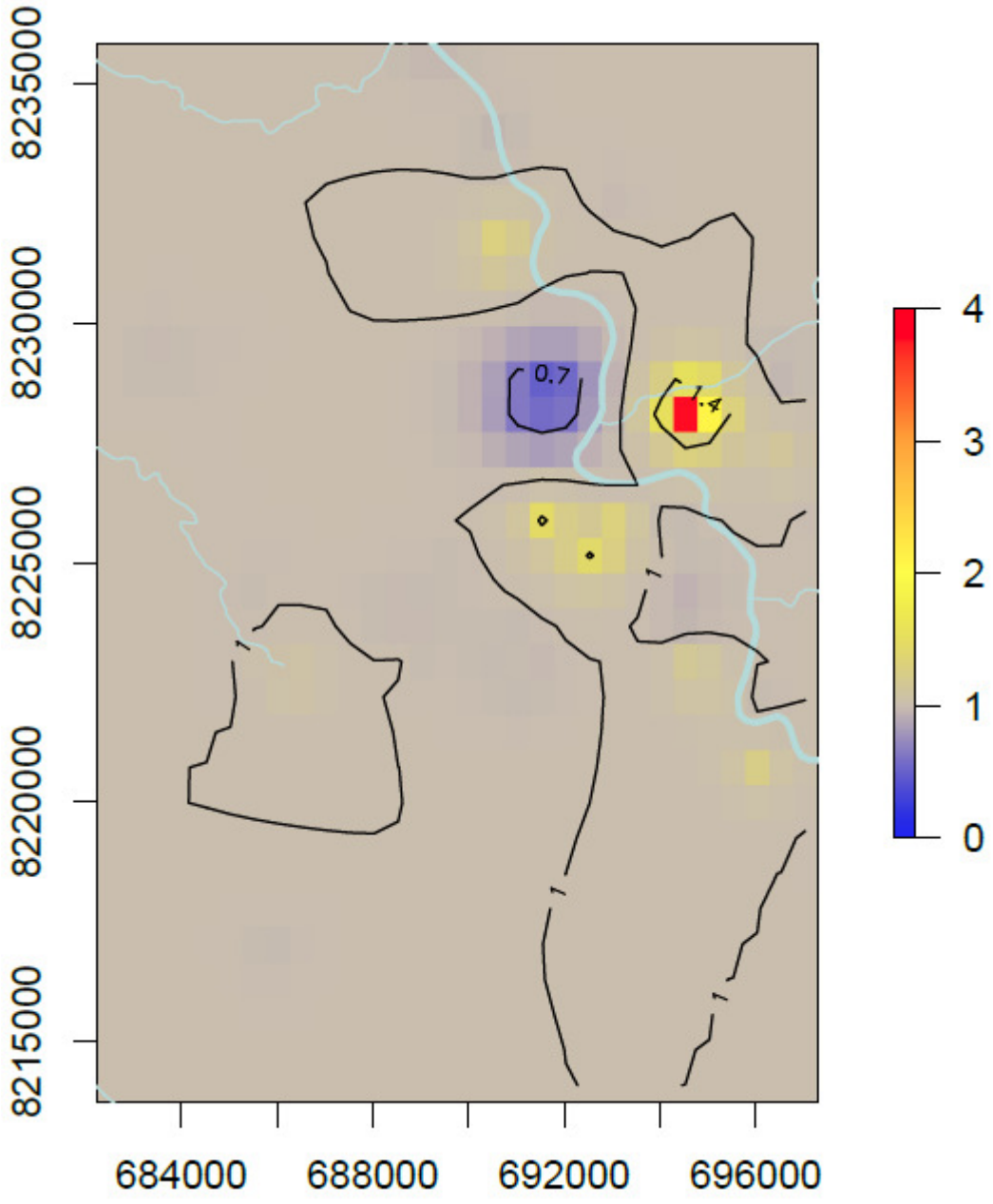
P. falciparum prevalence

Figure 20 is a contour map of the multiplicative spatial bias of the odds ratio of a household containing a child aged 6 to 59 least one ITN and having received IRS respectively. The blue areas correspond to areas where the EPI Clinic Survey underestimated population values, grey areas correspond to no bias (i.e. estimates not significantly different between surveys) and the red areas correspond to areas where the EPI Clinic Survey overestimated population values. The colour scale is the same as that for ITN and IRS coverage. Spatial bias for *P. falciparum* prevalence was highest in the areas closest to CDH (where the EPI Clinic Survey over estimated population values) and in the upper flood plain (where the EPI Clinic Survey overestimated population values). Figure 21 is the contour map of the geographic distribution of *P. falciparum* prevalence after removal of all spatial bias. The areas in the map are graduated from dark green areas where percentage prevalence is nil to red areas where prevalence is 100%. The contours represent a mean estimate (percentage prevalence) of the area enclosed in the contour. The generated map of the geospatial distribution of *Pf*PR revealed that *P. falciparum* prevalence was highest in the flood plains or the Shire River within the study area.

Distribution of mean haemoglobin values

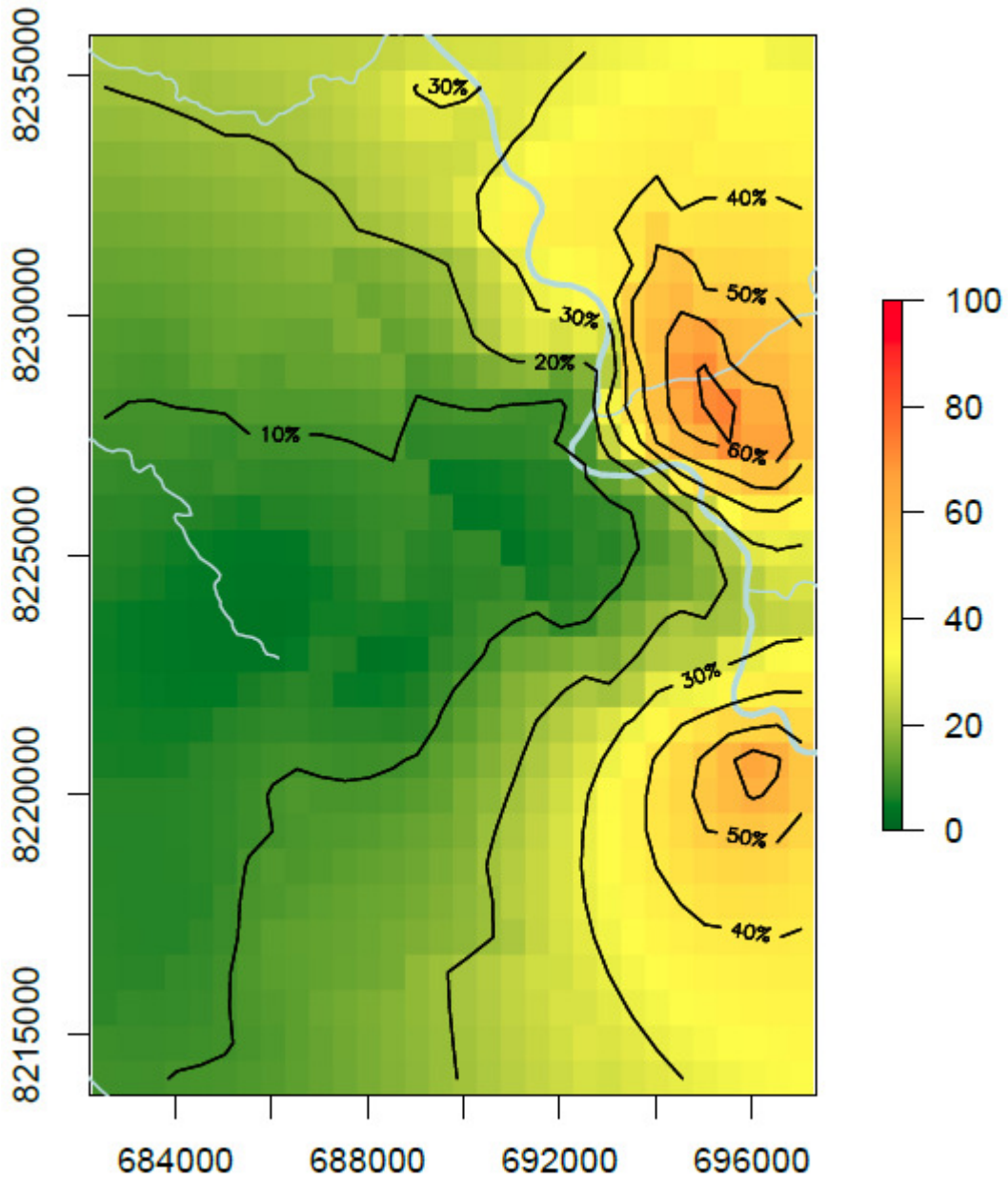
Figure 22 is a contour map of the additive spatial bias in estimates of haemoglobin modelled as a continuous variable. Blue and red areas correspond to areas of significant underestimation and overestimation respectively. Grey areas represent areas with no bias. The contours represent the difference in estimates of haemoglobin in the area enclosed in the contour. The EPI Clinic Survey appeared to significantly overestimate population values in an area not approximate to CDH and in no relation to the flood plains of the Shire River.

Figure 20: Multiplicative geospatial bias of the odds of *P. falciparum* infection between surveys



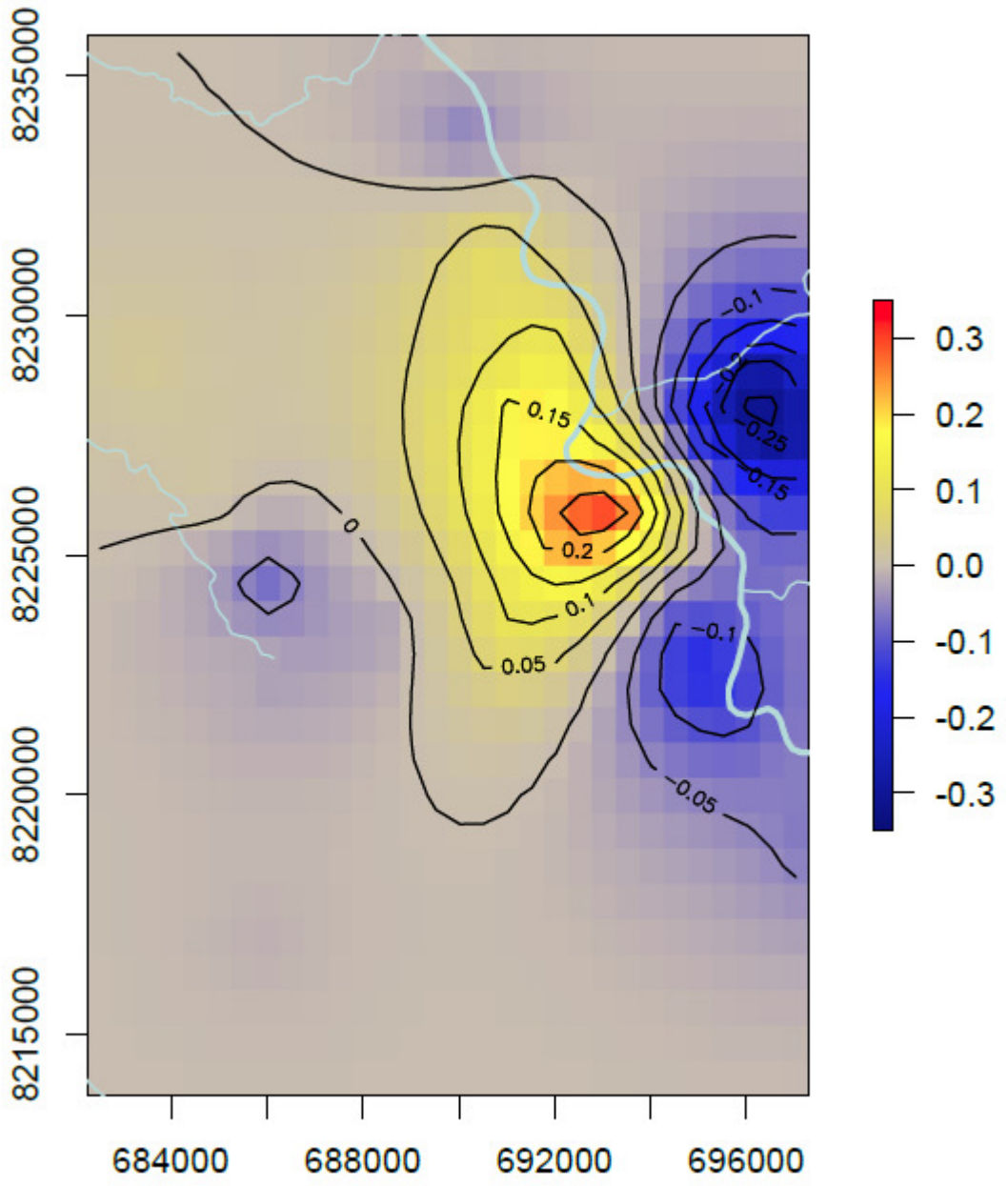
Distance between individual ticks on the x equivalent to 2km and on the and y axis equivalent to 5km.

Figure 21: Geospatial distribution of *P. falciparum* prevalence



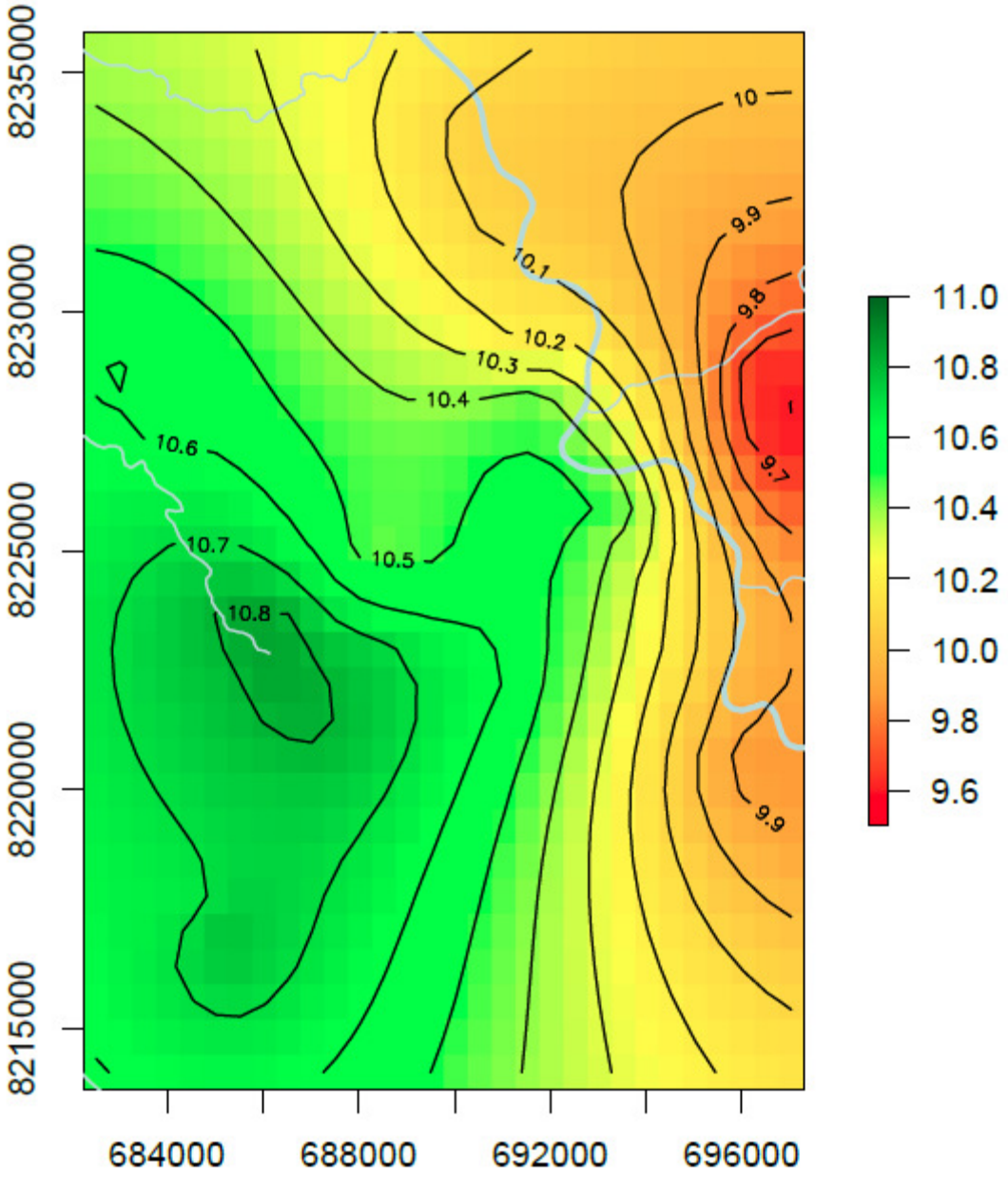
Distance between individual ticks on the x equivalent to 2km and on the and y axis equivalent to 5km.

Figure 22: Differential geospatial bias in mean haemoglobin values between surveys



Distance between individual ticks on the x equivalent to 2km and on the and y axis equivalent to 5km.

Figure 23: Geospatial bias of estimates of haemoglobin values between surveys



Distance between individual ticks on the x equivalent to 2km and on the and y axis equivalent to 5km.

The EPI Clinic survey also tended to underestimate the population haemoglobin values in the two areas in the flood plain of the Shire River. In both cases, the differences were minimal and less than 0.5g/dl. Figure 23 is the contour map of the geographic distribution of haemoglobin values after removal of all spatial bias. From Figure 23, the haemoglobin levels tended to fall as you move closer to the flood plain areas.

5.4 Discussion

In this area with high immunization coverage, the EPI Clinic Survey proved an accurate approach to assess malaria status and determine patterns of heterogeneity in transmission and intervention coverage at sub-district level, thanks to a novel geostatistical modelling method that addressed the key issue of bias seen with 'convenience' samples. This method, developed in collaboration with spatial statisticians from the University of Lancaster for the purpose of this study, allows one to control for varying residual levels of bias (both over and underestimations) of a spatial nature, by combining EPI data with an unbiased (gold standard) probability sample of the underlying population, and using this to control for bias and increase precision.

There was reasonable overlap in the geographic distribution of the sampling frames of both surveys (Figures 13 and 14), though the EPI Clinic Survey sample reflected participation of those with better road access to CDH (Figure 14). As a result, there were expected differences in baseline population characteristics and this biased the average estimates of uptake of control interventions but did not seem to significantly affect average estimates of *Pf*PR and its spatial distribution. Controlling for this difference in population characteristics in a multivariate analysis did not resolve the bias in estimates of control interventions. We posit that this residual bias was of a geospatial nature in all evaluated malaria control indicators, and argument was further strengthened when the use of previously

developed geostatistical methods (Giorgi et al., In press) to resolve the bias using a combined dataset of the EPI Clinic Survey and the eMIS where successful. Our results indicate that addition of data from a suitable probability sample of the same catchment population to form a hybrid sample is not only likely to improve the validity of average estimates from such a convenience sample as previously suggested by Hedt et al in 2011 (Hedt and Pagano, 2011), but was also likely to improve the spatial representativeness and this was a novel finding.

This geostatistical approach, which was developed after the start of the survey, helped overcome a key challenge that has deterred the use of convenience sampling in malaria M&E, and may open up surveillance opportunities. Accepted M&E practice is still largely based on probability samples to generate unbiased average estimates of (sub-) national malaria control status, or maps of confirmed probability samples. Statistically probability samples with average estimates suit a homogeneous situation or one where the underlying heterogeneity is of no interest. The increasing recognition of the importance of hotspots to fuel transmission, and expected increasing heterogeneity with reducing transmission suggests the exact opposite, and calls for more efficient sampling strategies whose sampling points and sample sizes allow more accurate descriptions and understanding of the underlying spatiotemporal patterns and bias, opening up opportunities for a range of informed convenience sampling strategies beyond those selected because they may be representative of the underlying population as with the presented EPI group.

The presented analyses on potential sources of bias illustrated this concept further as differences in baseline characteristics were explored in the multivariate analysis. Some of the potential sources of bias, like socioeconomic status, distance and education, are already known determinants of coverage of interventions (Wyss et al., 1996; Ahmed et al., 2010; Zyaambo et al., 2012). The significantly higher proportion of younger children in the EPI survey was expected, as the majority of

children coming for immunization will be infants, and the effect of the disparity in age composition between surveys was controlled for in the multivariate analysis wherever it was a significant predictor (Tables 25 and 26). The inclusion of more infants in the EPI Clinic Survey could also explain the higher socioeconomic status given the known relationship between timeliness of receipt of childhood vaccination and wealth index (Akmatov and Mikolajczyk, 2012).

The EPI Clinic Survey also included a significantly higher number of households reporting a febrile episode in a child aged 6 to 59 months in the past two weeks and children with a febrile episode on the day of the survey. Since out of pocket expenditures (e.g. due to transportation) are still a significant factor in countries that have abolished health facility user fees like Malawi (Saksena et al., 2010; Ewing et al., 2011), mothers may be more likely to come with a child that is currently febrile of has a history of fever during a well-child visits as this will represent a more efficient use of resources. These differences affect intervention coverage and impact indicators of EAG estimate. Unadjusted average estimates comparisons will thus be biased. In areas of heterogeneous delivery of control interventions (e.g. distribution of ITNs via EPI clinics) and heterogeneous transmission, adjusted average estimates for these covariates alone however, does not overcome the additional spatial bias, and geostatistical method is an essential component to enable the use of EAG data.

The need for a geostatistical approach was confirmed by the results of our 'classic' analyses which determined the adjusted average prevalence estimates of the entire study area for the key control indicators. EAGs average estimates of household ITN possession and IRS coverage were both significantly higher than population estimates even after controlling for the effect of differences in age, mother's education and socioeconomic status, indicating that there was residual bias in these estimates of control interventions. Of these only socioeconomic status was a key determinant in the geospatial model (Table 27). This suggests that one of

the reason for the geospatial bias in estimates is due to health facility utilization due to socioeconomic status, which is not surprising given what we know about our study area (Ewing et al., 2011).

ITN delivery in the period preceding the study was primarily through the ANC (Ministry of Health (MoH) Malawi, 2011; Skarbinski et al., 2011), and given the strong association between ANC and EPI attendance (Carlson et al., 2011), most of the mothers attending EPI clinic may still have their ITNs received during previous ANC visits and would thus report higher levels of ITN ownership. As the women receiving ITNs through ANC services are most likely to have good health facility access (Larson et al., 2012), this may be the reason for the EPI Clinic Survey overestimating household ITN possession in areas with good health facility access close to the main roads in our catchment area (Figure 16).

Secondly, mothers coming with their children to the EPI Clinic may falsely report a higher proportion of household ITN ownership and use due the fact that ITNs were mainly distributed initially through the ANC (Ministry of Health (MoH) Malawi, 2011; Skarbinski et al., 2011) and to social desirability bias (Skarbinski et al., 2008). Geospatial bias is also likely to explain the over-estimation of IRS coverage as Figure 17 shows a similar pattern to Figure 16 of overestimation of IRS coverage in areas with good health facility access, but with underestimation in some hard to reach villages. Since IRS is a new intervention in the study area, and public awareness of its benefits is low (NMCP (Malawi), 2012), social desirability bias would be unlikely. Also as IRS delivery is not health facility based, unlike ITNS, we also think that differential with distance from the health facility would also be unlikely. Inadequate and negative perceptions of IRS use are more prominent in rural communities and less educated individuals (Vundule and Mharakurwa, 1996; Mazigo et al., 2010; Ediau et al., 2013), and since health facility utilization is linked to education and socioeconomic status (Wyss et al., 1996; Ahmed et al., 2010;

Zyaambo et al., 2012), the women in the EPI Clinic may report higher rates of IRS coverage as they are significantly more educated and from households with higher socioeconomic status (Table 18). This may explain the pattern of bias seen in Figure 17 as it is known in our study area that women in hard to reach areas usually come from households with lower socioeconomic status and are less likely to utilize health facilities in both the rainy and dry season due to greater associated costs (Ewing et al., 2011). Though there may be differing causes of bias in estimates of ITN and IRS coverage, this bias had an obvious geospatial pattern and controlling for this pattern of geospatial bias resolved the overestimation in estimates and allowed the production of detailed maps of the geospatial heterogeneity in coverage with these control interventions (Figures 18 and 19) without the need for the exploration of the exact aetiology of the bias.

We compared our findings with the results in similar studies validating EAG estimates of uptake of control interventions with comparison with probability population samples. In a study in school children aged 10 years or older in an area with high school attendance rates in Uganda, estimates of household ITN possession derived from direct questioning of the children by school teachers were comparable with a probability sample of the same catchment population (Ndyomugyenyi and Kroeger, 2007). In another study in school children in Kenya, annual estimates of IRS coverage derived from direct questioning of the child's parent/guardian were significantly lower than estimates from the population living within 600m radius from the school, but when the estimates were restricted to children living in the same area as the community sample, the difference was not statistically significant (Stevenson et al., 2013). In both studies however, the role of geospatial bias was not evaluated and this re-enforces our point that if we do not take into account the spatial distribution, using average estimates even when controlling for potential does not overcome residual bias.

Whilst there was no significant difference in the prevalence of P. falciparum parasitaemia between the dry season and the rainy/post-rainy season in the EPI Clinic Survey (17.8% vs. 25.4% respectively, p=0.1123), *Pf*PR was significantly higher in the dry season compared to the rainy/post-rainy season in the eMIS (27.1% vs. 18.6% respectively, p=0.0375) (Table 23) and this was an unusual finding. This is likely to be due to the fact that *Anopheles funestus* is the most abundant vector in our study area with numbers peaking towards the end of the rainy season and thus becoming the predominant species throughout the dry season (Mzilahowa et al., 2012), leading to a lag period between the peak rains and peak transmission. This in turn may be due to the availability of more vector breeding sites in the latter part of the rainy season due to the seasonal changes in water flow in the Shire River flood plain (Chimatiro, 2004). This is also likely to be the same reason for the significantly higher prevalence of anaemia in dry season compared to the rainy/post-rainy season in the eMIS (6.4% vs. 0.5% respectively, p=0.0011) (Table 24).

Our analysis on key impact indictors showed that geospatial bias was minimal in both estimates of *Pf*PR and mean Hb levels (Figures 20 and 21). This could be due to the fact that these indicators depend on exposure to different transmission ecologies and are thus not necessarily affected by risk factors for health facility utilization (like socioeconomic status or distance) that also affected uptake of control interventions, but rather depend on the inclusion of enough individuals from all areas of differing transmission ecologies to make the average estimates representative, and accurately reflect the existing variation and thus spatially representative. Whilst the wealth of evidence suggests a strong link between uptake of control measures and malaria infection, the picture is not so clear with susceptibility to infection (Worrall et al., 2005). Rather the emerging literature is suggesting that malaria is a cause rather than a consequence of poverty (de Castro and Fisher, 2012). The overestimation of *Pf*PR from the most prominent hotspot in our study area which is also includes hard to reach villages (Figure 20),

may be due to the fact children from this areas may be more likely to be brought to hospital if sick due to the impact of the indirect costs of health facility utilization (Ewing et al., 2011).This may account for the significantly higher the rates of pyrexia in the EAG sample (Table 18). The underestimation of *Pf*PR in the district headquarter town of Chikhwawa could be due to the fact that there are other options for healthcare including private facilities and so children with fever may be taken to private health care providers (Wiseman et al., 2008; Okeke and Okeibunor, 2010). The overall effect in our study was that of minimal geospatial bias in estimates of *Pf*PR.

There have been similar studies validating EAG estimates of impact indicators with comparison with probability population samples, but all have focused their comparisons on average estimates. In a similar transmission setting in Rwanda involving sick child visits where *Pf*PR was determined by PCR, EAG estimates were similar to population estimates (Gahutu et al., 2011). Another study by Mathanga et al 2010 in Malawi where *Pf*PR was determined by microscopy in children aged 6 to 30 months attending EPI clinics for well child visits, the EAG sample over-estimated *Pf*PR in 2005 whilst in the consequent survey in 2008, the difference between the EAG sample and the population sample was not statistically significant (Mathanga et al., 2010). This is probably due to the difference in the sampling methodology used to select the population sample in the different survey years rather than an improvement in accuracy. In the Gambia where malaria transmission is intensely seasonal, the *Pf*PR by microscopy in all patients attending health facilities (regardless of diagnosis) was significantly higher than that of the population in the rainy season and slightly lower in the dry season (Oduro et al., 2011a). In the rainy season, the increased *Pf*PR was due to higher parasitaemia in children less than 15 years, suggesting that most children brought to hospital were likely to be sick and not representative of the underlying population. The evidence from these studies suggest that the pattern of health facility utilization and its consequent effect of over or under representing certain areas of the population is

more likely to lead to biased estimates where malaria transmission is more heterogeneous.

We explored the validity of estimates of APR from children attending EPI Clinic by comparing to population estimates and from our results also indicate that the average annual APR was comparable between surveys. This was supported by the study in Malawi by Mathanga et al 2010 in which annual APR measured from children coming for well child visits was not only accurate but was able to detect a change in transmission (Mathanga et al., 2010). In the study in the Gambia, the EAG overestimated APR in the population in both the rainy season and dry season (Oduro et al., 2011a). Again, this could be due to sick children presenting to health facilities being more likely to have significant anaemia (Kiggundu et al., 2013). , The APR in the EPI EAG and the population sample was a little lower than expected, 5.9% and 4.5% respectively, given the figures for the Southern Region from the 2010 and 2012 nationwide MIS (i.e. 13.6% and 8.5% respectively) (Ministry of Health (MoH) Malawi, 2010; NMCP (Malawi) and ICF International, 2012). We believe our finding is not unusual because in a study evaluating the aetiology of severe anaemia in the same hospital as our EPI survey, severe anaemia was more strongly associated with hookworm infestation, nutritional deficiencies and G6PD but not associated with *P. falciparum* parasitaemia (Calis et al., 2008). Given the fact that APR was assessed as a metric when malaria epidemiology was different from what is it today (Korenromp et al., 2004), and the increase in coverage of micronutrient supplementation, vitamin A administration and deworming programmes, we believe that validity of APR as a malariometric should be re-evaluated.

We were not powered enough to carry out a geostatistical analysis on APR, and evaluated the geospatial distribution of mean haemoglobin values instead. From our results, mean Hb results were higher in the EAG than the population closest to CDH and lower in the two known hotspots in the study area (Figure 21). We believe that is a direct reflection of the effect socioeconomic status on nutrition,

with children from further away being more likely to be less well-nourished and brought to hospital if sick (Ewing et al., 2011). Again correcting for this geospatial bias improved the accuracy of estimates of mean Hb in the EAG and we were able to demarcate similar hotspots. Our experience with this indicator suggests that were APR is low, mean Hb can be used to accurately demarcate hotspots and this is a novel finding.

In summary, the relatively high transmission in our study area geospatial bias seemed to exert a lesser effect on impact indicators compared to those measuring uptake of control interventions. In all cases, controlling for geospatial (regardless of the aetiology) not only improved the accuracy of average estimates but also allowed the construction of high resolution contours maps displaying geospatial heterogeneity.

5.5 Conclusions

The results of the study suggest that in moderate to high transmission settings, EPI Clinic Surveys have great potential in providing timely population estimates of geospatial heterogeneity in *Pf*PR, and could be used for M&E and surveillance of the malaria transmission. EPI Clinic Surveys however tend to significantly overestimate average estimates of coverage of control interventions. Our results indicate that this is likely to be due to geospatial bias which can be corrected using a probability sample of the population, resulting in accurate representations of the geospatial pattern of intervention coverage. Our results also indicate that geospatial bias for estimates of *P. falciparum* prevalence and average haemoglobin values can also be corrected using this method, resulting in accurate representations of the geospatial pattern of malaria morbidity. Our results suggest that in areas where APR is low, mean Hb values are a good metric to delineate geospatial heterogeneity in transmission and we recommend that this metric be evaluated. This approach is promising and the need for a probability population

sample to validate results from such and easy access sample could be satisfied by using a hybrid sampling approach as suggested by Hedt et al 2011. This approach could be used to target malaria control interventions and needs to be validated in other transmission settings.

Chapter 6: EPI Clinic Survey data as a potential tool for monitoring short-term temporal trends in malaria control progress in Chikhwawa, Malawi

6.1 Introduction

Timely accurate estimates of malaria transmission intensity and coverage of control interventions are needed to evaluate control progress and guide malaria program strategy, but this can be a logistically and financially demanding, especially where there is low malaria transmission intensity (Hay et al., 2008). Children coming to health facilities for well child visits are one such EAG that could measure temporal trends in uptake of control intervention and malaria transmission intensity (Cibulskis et al., 2007; Skarbinski et al., 2008; Mathanga et al., 2010). Among those coming to health facilities, continuous surveillance in children coming for well-visits such as vaccinations may provide a suitable easy access group (EAG) and a potential M&E tool that may be a cost effective approach to monitor (sub) district level control progress and guide more targeted control efforts.

Continuous surveillance in children attending EPI clinics is logistically attractive because it provides an easily accessible location to determine burden in a high-risk group young, healthy children that could provide the 'force of infection' in moderate to high transmission areas, and offers the potential of continuous evaluation of the population that can be integrated into district level malaria control activities (Rowe, 2009b). In chapter 4 we assessed the use of EPI data to determine spatial heterogeneity of malaria burden and intervention coverage indicators using geostatistical methods and showed how the used of mixed survey data from an EPI and household survey can be used to overcome the inherent selection bias. Selection bias could also obscure the level and temporal trend in control progress particularly in areas with low health facility utilization (Cibulskis et al., 2012). Determining whether surveillance in this EAG could provide an accurate reflection of temporal trends in control progress in the proposed risk strata in the population requires direct comparison to a contemporaneous probability sample of the population from the same geographic area.

While timely local estimates may save costs by guiding more targeted efforts, the precision needed to inform decision-making from population surveys drive up the sample size and costs of surveillance. The minimum level of information and associated precision needed to support pragmatic decisions by control programmes may differ considerably between settings, depending on the local heterogeneity of malaria, targeting and timing of control efforts, and the coverage of the health care system. How to identify the spatiotemporal sample size need for a certain situation and time period may need to become a key part of any new surveillance tool in order to ensure efficiency and convince policy makers and programme managers. A sampling strategy to determine short-term change may further differ from one aiming to identify transmission hotspots, which tend to be stable over time.

Cognizant of these challenges and our relatively monthly small sample sizes, we evaluated whether estimates of the trend in coverage of control interventions and burden derived from continuous surveillance in children attending the EPI clinics of Chikhwawa District Hospital (CDH) for well child visits accurately reflected temporal trends in the population in its geographic catchment area (independent of potential over or underestimates of individual indicators in the EPI EAG), by comparing these to estimates from a concurrent continuous MIS in the same catchment population.

6.2 Methods

The study site and study procedures, including study design, sampling strategy, recruitment, data collection, clinical, laboratory, and data management procedures have been described in detail in chapter 3 and 4. In contrast to chapter 4, the current analyses cover a 2 year period to explore temporal trends. Data for the

eMIS was not collected in April 2012, during a period of political uncertainty after the Malawi president died in office.

Control efforts

In our study area, the delivery of ITNs was initially via MCH services with distribution via ANC and EPI clinic visits. Women would be eligible to receive 2 ITNs (on during their pregnancy, and one during infancy of their newborn) (Ministry of Health (MoH) Malawi, 2011; Skarbinski et al., 2011), and later supplemented by a population distribution campaign initiated in July 2012. This campaign aimed to achieve the latest RBM ITN coverage target of 1 ITN for every 2 individuals in a household. The initial district IRS round was in February to March 2011 followed by an catch-up round of selected villages in November to December 2011, and a third full district round in November to December 2012(NMCP (Malawi), 2012).

Sampling strategy

The sampling strategy for both groups has been described in detail in Chapter 4. In brief, and of relevance to the conducted temporal analyses: the household survey was designed to provide a probability sample over a 6-month period to capture any seasonality (Roca-Feltrer et al., 2012b). To improve the representativeness of the sample, villages where stratified by distance and the rolling methodology ensured that each village would not be revisited within a four month interval and once surveyed in the rainy season would only be surveyed again in the dry season.

Climatic data

Data on daily temperature and rainfall were obtained from the Kasinthula irrigation project (16° 5' S, 34° 49' E; the nearest weather station to the study site and used to compile mean monthly temperatures and total monthly rainfall. Data were

obtained with the kind permission of the regional Malawian Meteorological Service in Blantyre.

Statistical analysis

The analysis only included children aged 6 to 59 months whose home location was within the catchment area of CDH (i.e. 15km radius) in both the EPI Clinic Survey and eMIS, collected between May 2011 and April 2013. Statistical analyses were performed in Stata 13.1 unless otherwise stated. Baseline data was presented as proportions with their respective 95% confidence interval. The Chi-squared test was used to compare categorical data and the Wilcoxon rank-sum test (also known as the Mann-Whitney two-sample statistic) was used to compare continuous data that was not normally distributed (Wilcoxon, 1945; Mann and Whitney, 1947).

*Pf*PR and APR were considered the main outcome variables and were presented as monthly percentages with their respective 95% confidence intervals. Household level ITN ownership and IRS coverage (IRS in the past 12 months) were considered as the main control intervention variables and were also presented as monthly percentages with respective 95% confidence intervals. Other exposure variables were either presented as categorical variables (e.g. season), monthly averages (e.g. temperature) or monthly total (e.g. rainfall).

To assess seasonality in *Pf*PR and APR, autocorrelation and partial autocorrelation coefficients were calculated using the monthly percentage prevalence to determine the correlation between *Pf*PR at different monthly lags using Stata's CORRGRAM command (Stata-Press, 2013a). Correlograms can be used to examine seasonal patterns in time series. The correlogram displays graphically and numerically the autocorrelation function, that is, serial correlation coefficients (and their standard errors) for consecutive lags in a specified range of

lags (e.g. 1 through 12) (McDowall et al., 1980). In correlograms the consecutive lags are dependent, so it is usually required to examine the partial autocorrelation function via a partial correlogram were lags are not serially dependent thus providing a "cleaner" picture of serial dependencies for individual lags (not confounded by other serial dependencies)(McDowall et al., 1980). The results were plotted on correlogram and partial correlograms graphs of correlation versus lag to allow visualization of any seasonal trend. The significance of any lag was determined using the Portmanteau (Q) test for white noise. A p-value of < 0.05 was considered to be statistically significant. A significant lag at the seasonal lag point of 12 months was considered as conclusive evidence of seasonality.

To extract the general trend over the two years of concurrent surveys from the data, we used Locally Weighted Scatterplot Smoothing (LOWESS) which is robust to aberrant behaviour in the time series (StataCorp, 2013a). LOWESS divides the data into two parts: the smoothed data and a rough part left over after subtracting the smoothed data from the overall data. The smoothed data was derived by running a regression of survey month on key variables (e.g. monthly *Pf*PR), by using data from each central point (x_i; y_i) and nearby data points. The regression is then weighted so that the central point (x_i; y_i) gets the highest weight and points that are farther away (based on the distance $|x_j \circledcirc x_i|$) receive less weight. The estimated regression line is then used to predict the smoothed value $\hat{y}_i$ for y_i only. Separate weighted regression is performed for every point in the data to obtain the remaining smoothed values. Centred subsets of approximately bandwidth x (n nearby observations) are used for smoothing except at endpoints were uncentered bands are used. To display the smoothed trend, we used a bandwidth of 0.8 i.e. 80% of nearby observations were used for smoothing.

6.3 Results

Between the 1st of May 2011 and the 31th of April 2013, a total of 1302 and 575 children aged 6 to 59 months were surveyed in the eMIS and EPI Clinic Survey respectively. Table 29 presents the background characteristics of the children in both surveys. Overall, pooling the data over these 2 years, children in the EPI Clinic Survey were significantly younger, differed in SES, reported high ITN ownership, and had a lower parasite prevalence compared to children from the household MIS survey

6.3.1 Temporal trends in monthly ITN possession, IRS coverage, *Pf*PR and APR in both surveys in relation to rainfall

Figure 24 illustrates the trends in the percentage of household ITN possession per month in both surveys over the study period. In the eMIS, monthly household ITN possession tended to increase with time from the beginning of the study and levelled off around the middle of the second year of the study. The data from the EPI Clinic Survey showed an overall slight increase in household ITN possession over time. Before the community distribution of ITNs when they were still distributed through the ANC, the EPI Clinic Survey consistently overestimated coverage with ITNs. The population survey correctly picked up the increase in ITN coverage after the community distribution exercise.

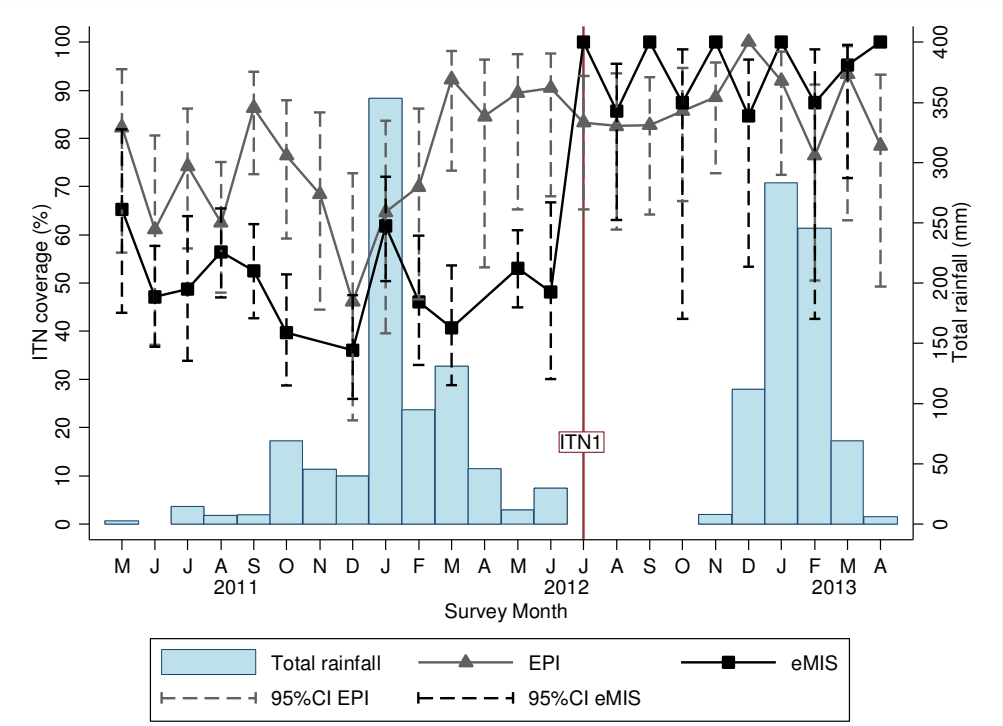
Figure 25 illustrates the trends in percentage IRS coverage by month between surveys. The data from the EPI Clinic Survey shows a decrease in monthly IRS coverage after March 2012 that started to rise again after the third IRS round in 2013. The eMIS showed considerable monthly variation in IRS coverage but with no clear trend. Both monthly household ITN possession and IRS coverage did not seem to have been affected by rainfall (Figures 24 and 25).

Table 29: Background characteristics of children aged 6 – 59 months in both surveys

	EPI Survey		eMIS		
	n	% (95% CI)	n	% (95% CI)	χ^2 *p-value*
No. of under five children surveyed	575	-	1302	-	-
Median age in months (IQR)		10 (8, 17)		35 (20, 47)	<0.001*
Household SES					
Poorest	100	17.4 (14.4, 20.7)	410	32.0 (29.5, 34.6)	
Quintile 2	75	13.0 (10.5, 16.1)	242	18.9 (16.8, 21.1)	
Quintile 3	113	19.7 (16.6, 23.1)	289	22.5 (20.3, 24.9)	
Quintile 4	126	21.9 (18.7, 25.5)	214	16.7 (14.7, 18.8)	
Wealthiest	161	28.0 (24.5, 31.8)	128	10.0 (8.5, 11.7)	<0.001
HH owns ITN	458	79.8 (76.3, 82.9)	526	54.3 (51.2, 57.5)	<0.001
HH IRS	298	52.8 (48.7, 56.9)	618	48.2 (45.4, 50.9)	0.065
***P. falciparum* parasitaemia (RDT)**	114	19.8 (16.8, 23.3)	359	27.6 (25.2, 30.1)	<0.001
Anaemia (Hb < 8.0g/dl)	43	7.5 (5.6, 9.9)	68	5.2 (4.1, 6.6)	0.056

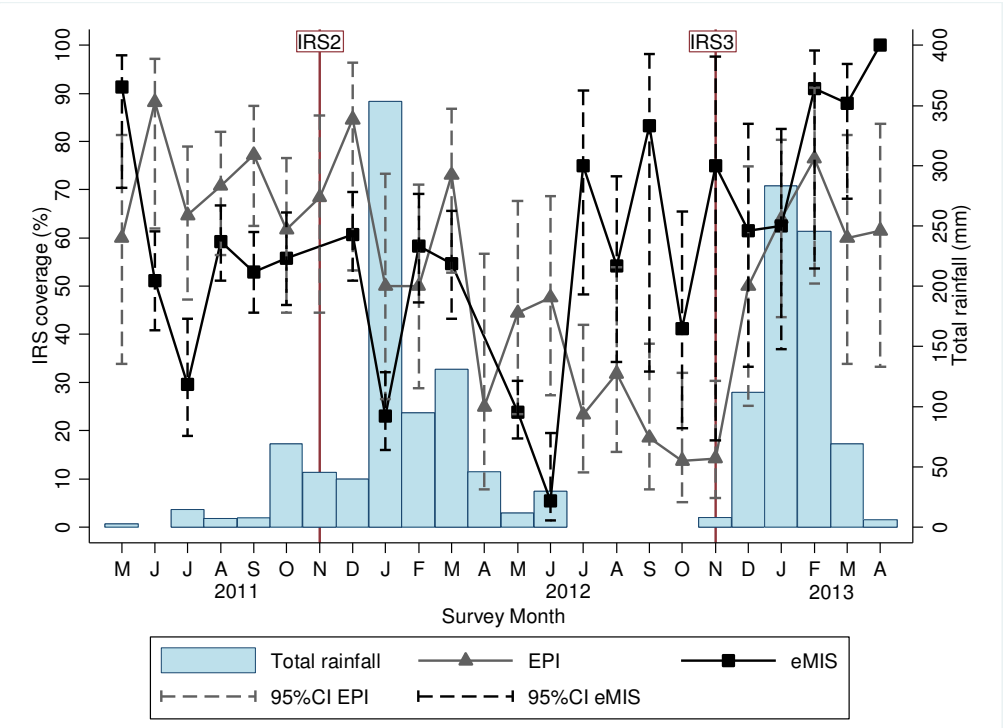
*Wilcoxon rank sum (Mann-Whitney) test X^2 p-value. IRS: IRS in the past 12 months.

Figure 24: Monthly household ITN possession by survey over the study period



ITN1 = start of ITN community distribution campaign. Before this campaign ITNs were distributed via MCH services, via ANC clinics and EPI clinics.

Figure 25: Trends in monthly IRS coverage per survey over the study period



IRS2 = IRS update round in selected villages, IRS3 = Third IRS round. IRS1 was conducted in Feb-Mar 2011.

Figure 26: Trends in monthly *Pf*PR per survey over the study period

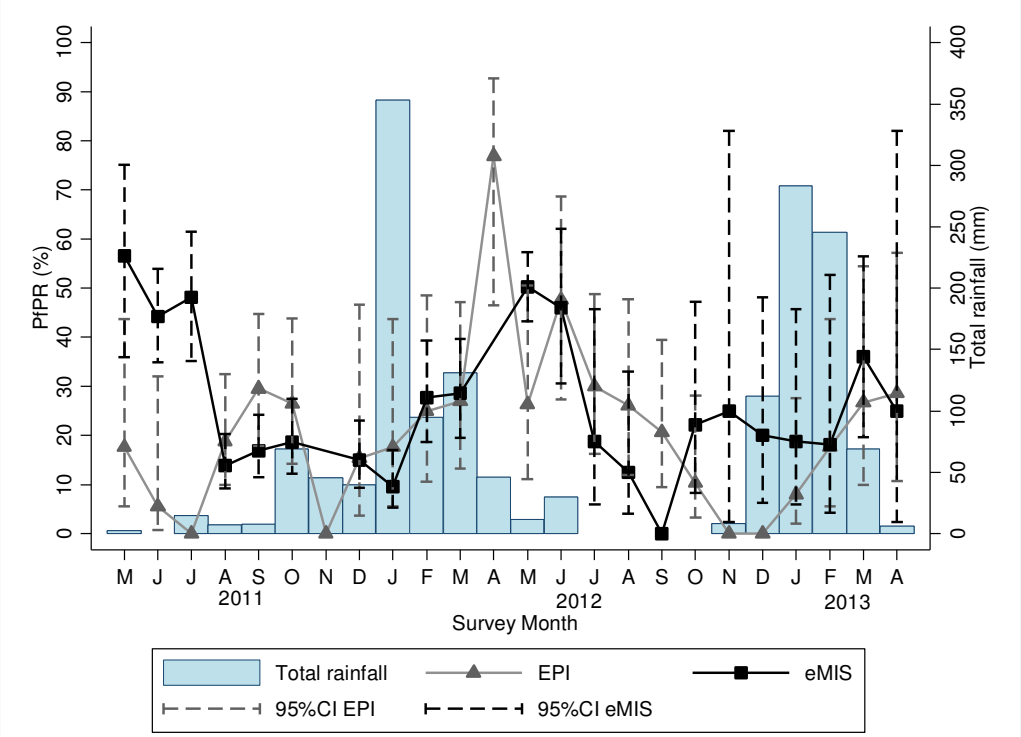


Figure 27: Trends in monthly APR per survey over the study period

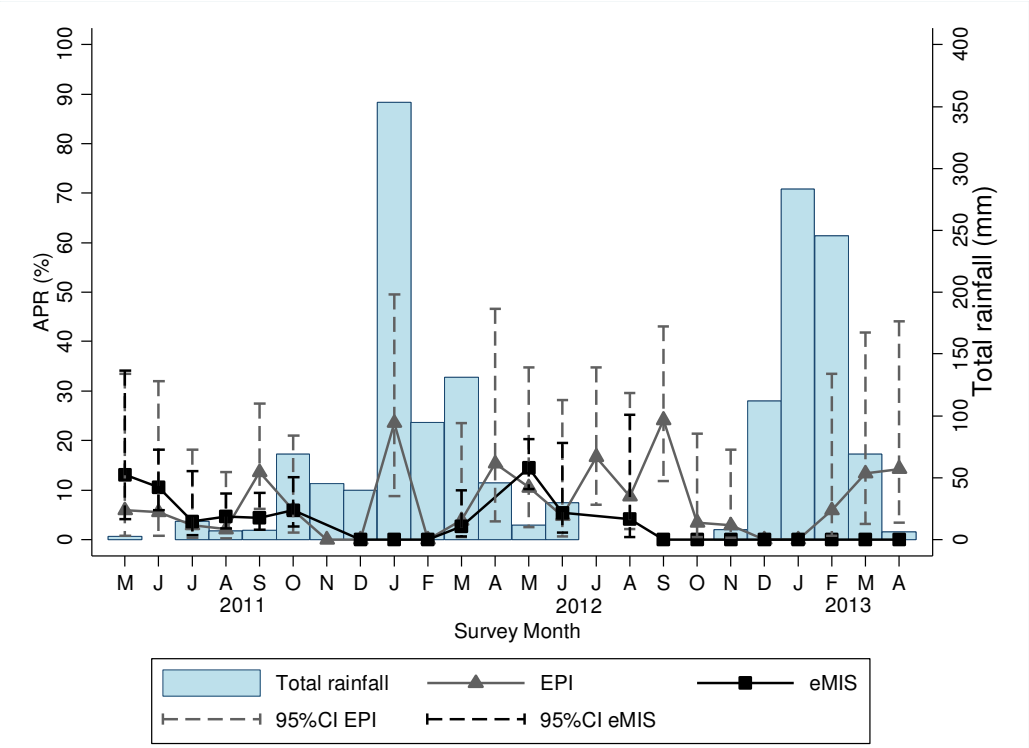
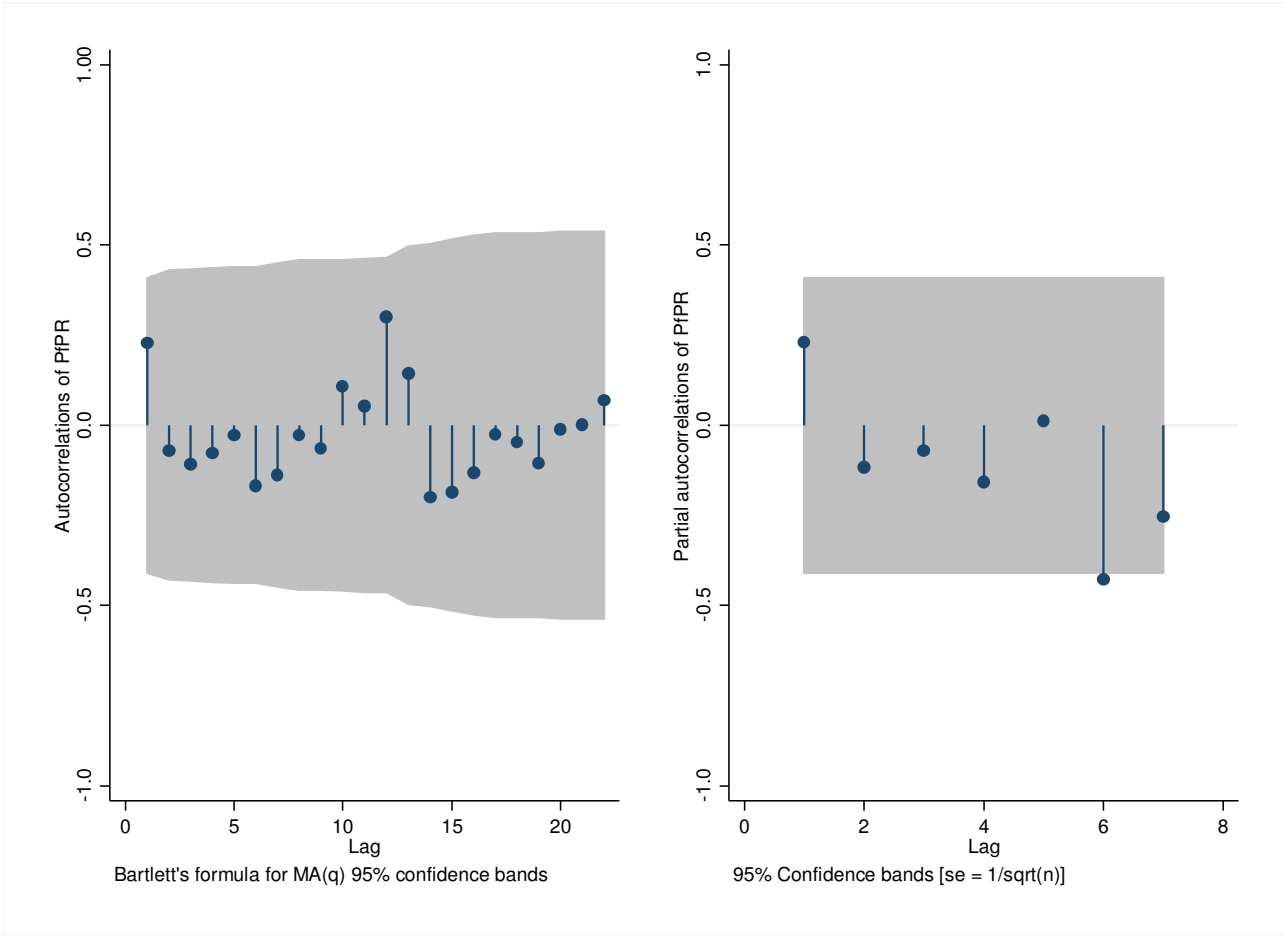


Figure 26 presents the monthly prevalence in *Pf*PR (by RDT) in both surveys. The eMIS data show peaks in May to July yearly, with a lag (of approximately 3 months) between peak rainfall and peak *Pf*PR. There was a peak in *Pf*PR occurring in March to June 2012 in the EPI Clinic Survey. Figure 27 presents the monthly trend in the prevalence of anaemia (Hb<8.0g/dl) in both surveys. The eMIS data show a peak at the tail end of the rainy season and there were no cases of anaemia (Hb < 8.0g/dl) in the eMIS after September 2012. The EPI Clinic Survey data showed occasional peaks but no obvious relation to rainfall.

6.3.2 Investigation of seasonality in temporal trends of *Pf*PR and APR

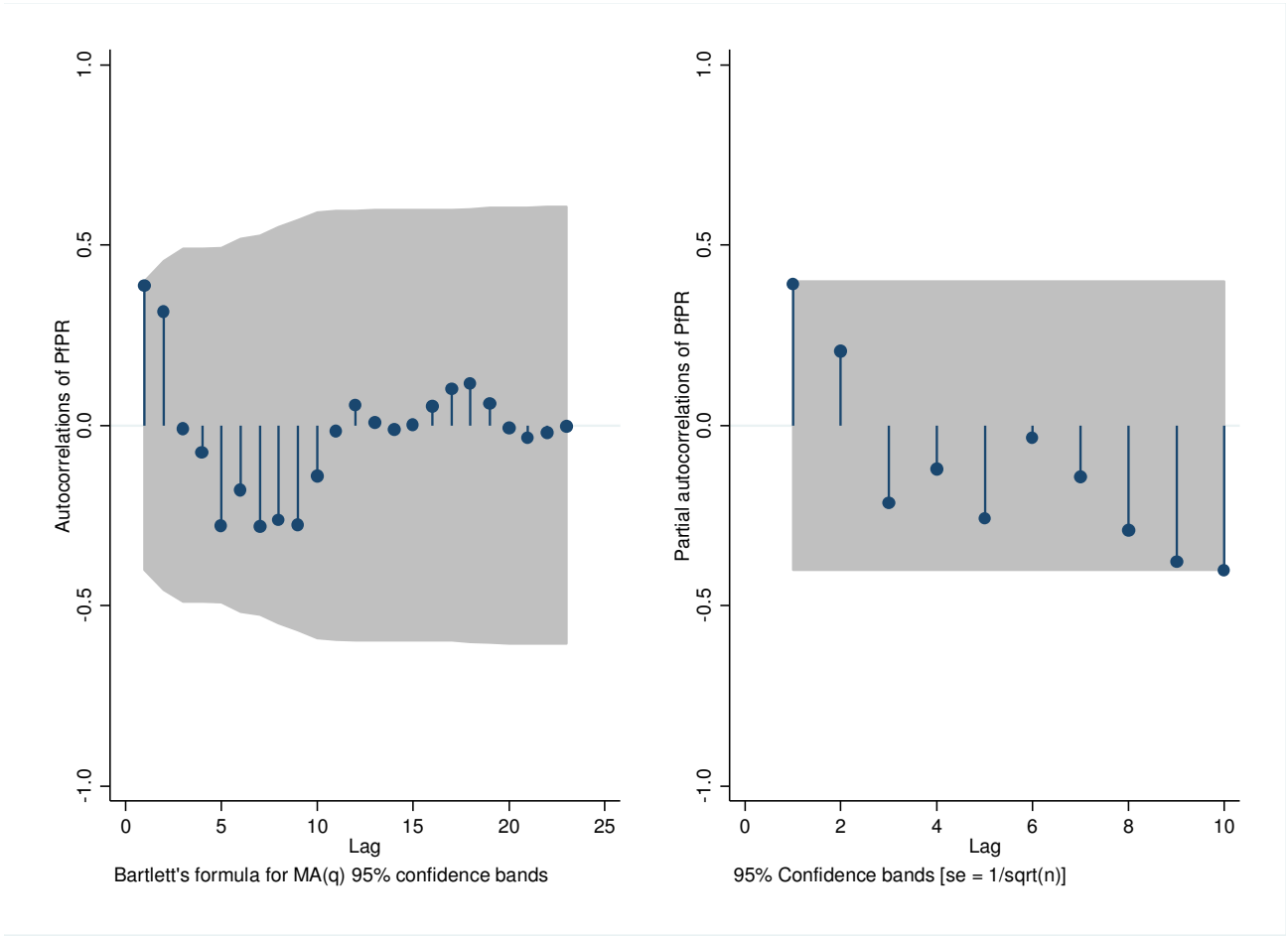
To evaluate seasonality in *Pf*PR, the monthly data was assessed using correlograms. Figure 28 and 29 are correlograms of the autocorrelation and partial autocorrelation of *Pf*PR in the eMIS and EPI survey respectively versus lag in months. The shaded area corresponds to the pointwise 95% confidence intervals and correlations outside this intervals are statistically significant. The graphs are extended to the maximum lag allowed per series. From the resulting correlogram for monthly *Pf*PR in the eMIS (Figure 28), there was no significant autocorrelation or partial autocorrelation at the seasonal lag of 12. This patterns means that the pattern of monthly *Pf*PR seen in the eMIS does not represent a true seasonal trend based on the data available. From the resulting correlogram for monthly *Pf*PR in the EPI survey, there was no significant autocorrelation or partial autocorrelation at the seasonal lag of 12. Again, this pattern means that there was no seasonality in *Pf*PR based on the data from the EPI Clinic Survey. Figure 29 and 30 are correlograms of the autocorrelation and partial autocorrelation of anaemia prevalence in the eMIS and EPI Clinic Survey respectively versus lag in months. From the resulting correlogram for monthly APR in the eMIS (Figure 29), there was no significant autocorrelation or partial autocorrelation at the seasonal lag of 12. Similarly from the resulting correlogram from monthly APR in the EPI Clinic Survey (Figure 30), there is no significant evidence of seasonality from the available data.

Figure 28: Graph of autocorrelations and partial autocorrelations of *Pf*PR by lag in months in the eMIS



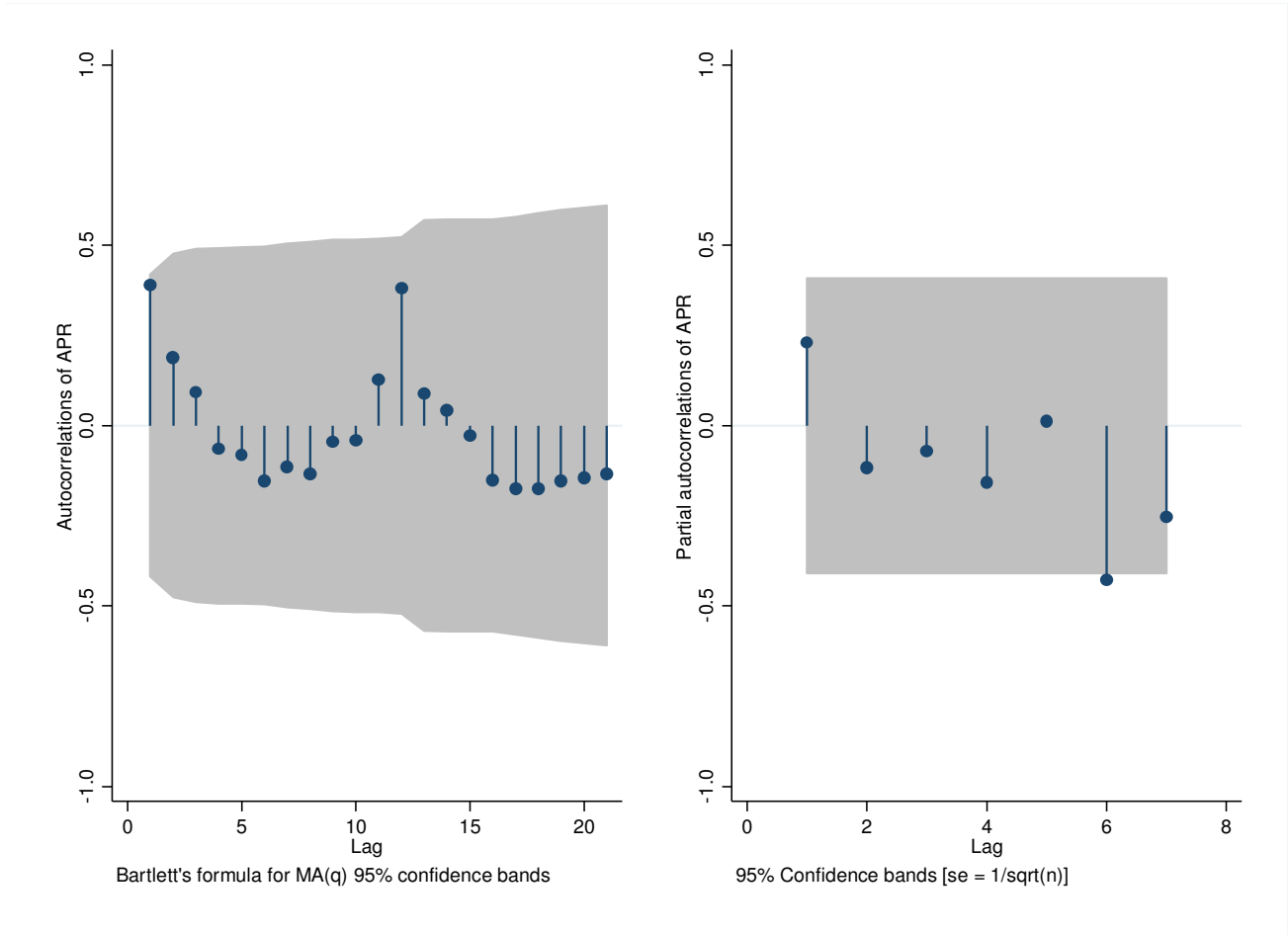
*Confidence intervals in graph of partial autocorrelation based on standard error estimates of $1/\sqrt{n}$

Figure 29: Graph of autocorrelations and partial autocorrelations of *Pf*PR by lag in the EPI survey



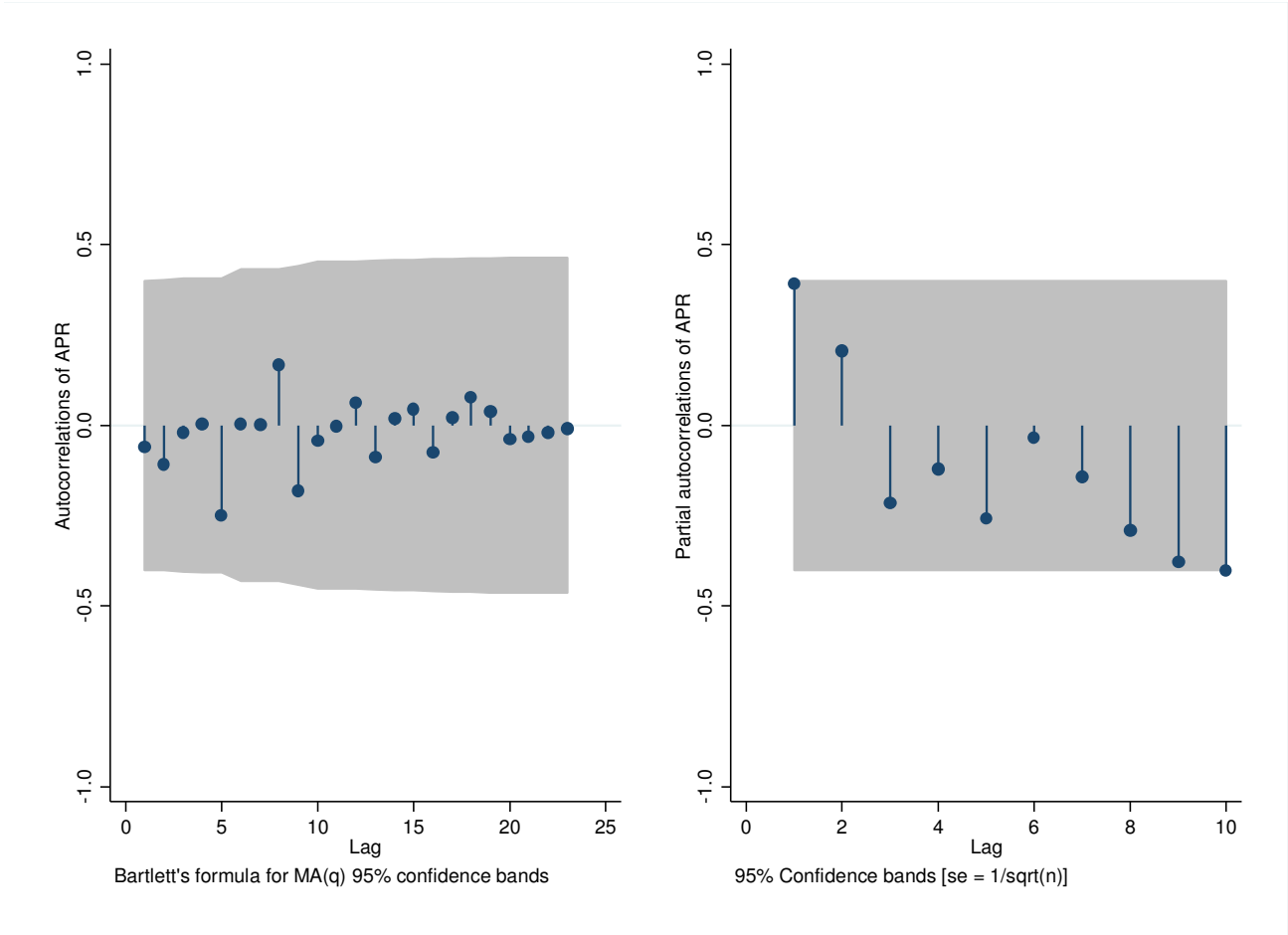
*Confidence intervals in graph of partial autocorrelation based on standard error estimates of $1/\sqrt{n}$

Figure 30: Graph of autocorrelations and partial autocorrelations of APR by lag in months in the eMIS



*Confidence intervals in graph of partial autocorrelation based on standard error estimates of $1/\sqrt{n}$

Figure 31: Graph of autocorrelations and partial autocorrelations of APR by lag in months in the EPI survey



*Confidence intervals in graph of partial autocorrelation based on standard error estimates of $1/\sqrt{n}$

Figure 32: Smoothed trends in monthly ITN possession in both surveys

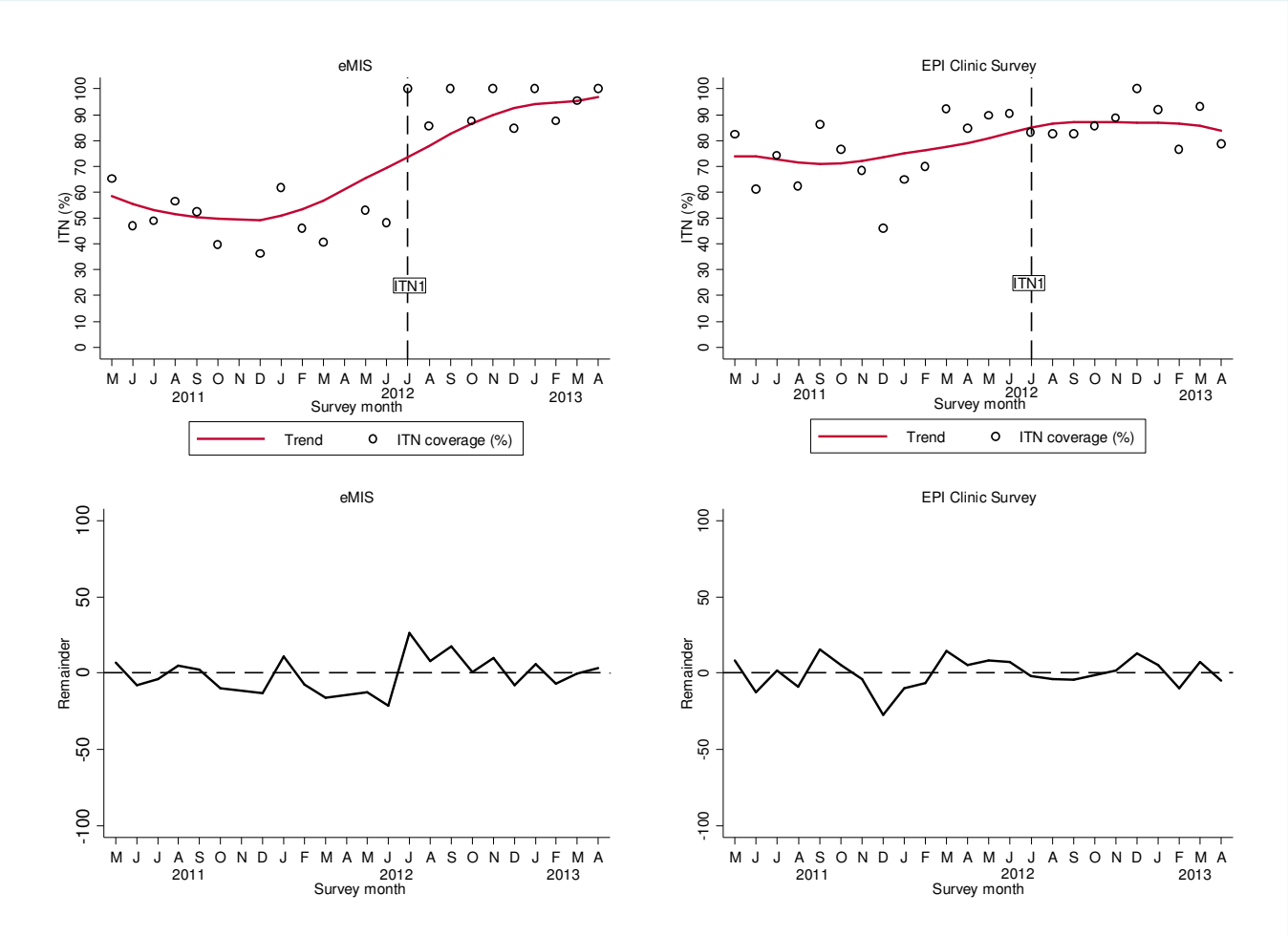


Figure 33: Smoothed trends in monthly IRS coverage in both surveys

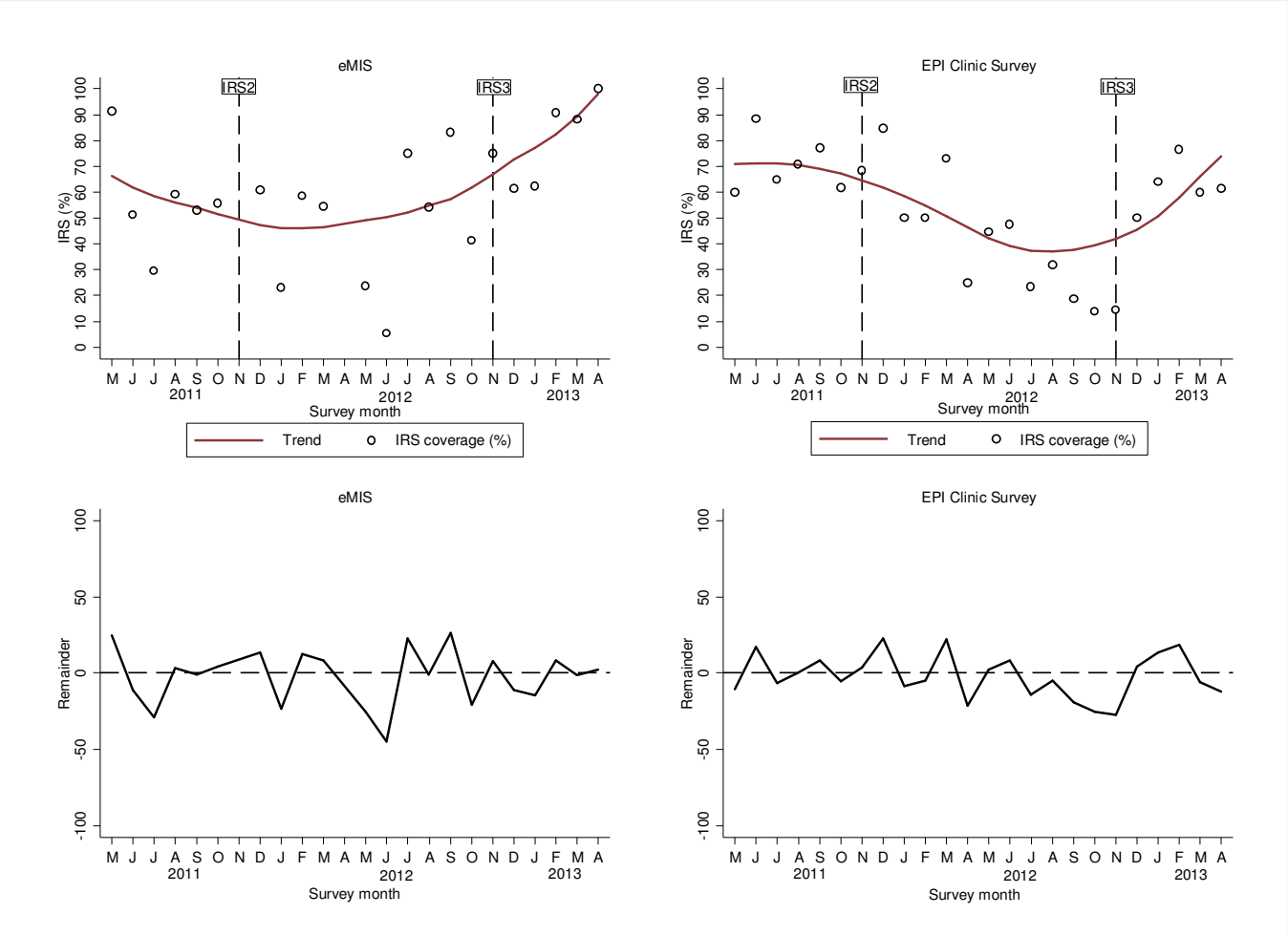


Figure 34: Smoothed trends in monthly *Pf*PR in both surveys

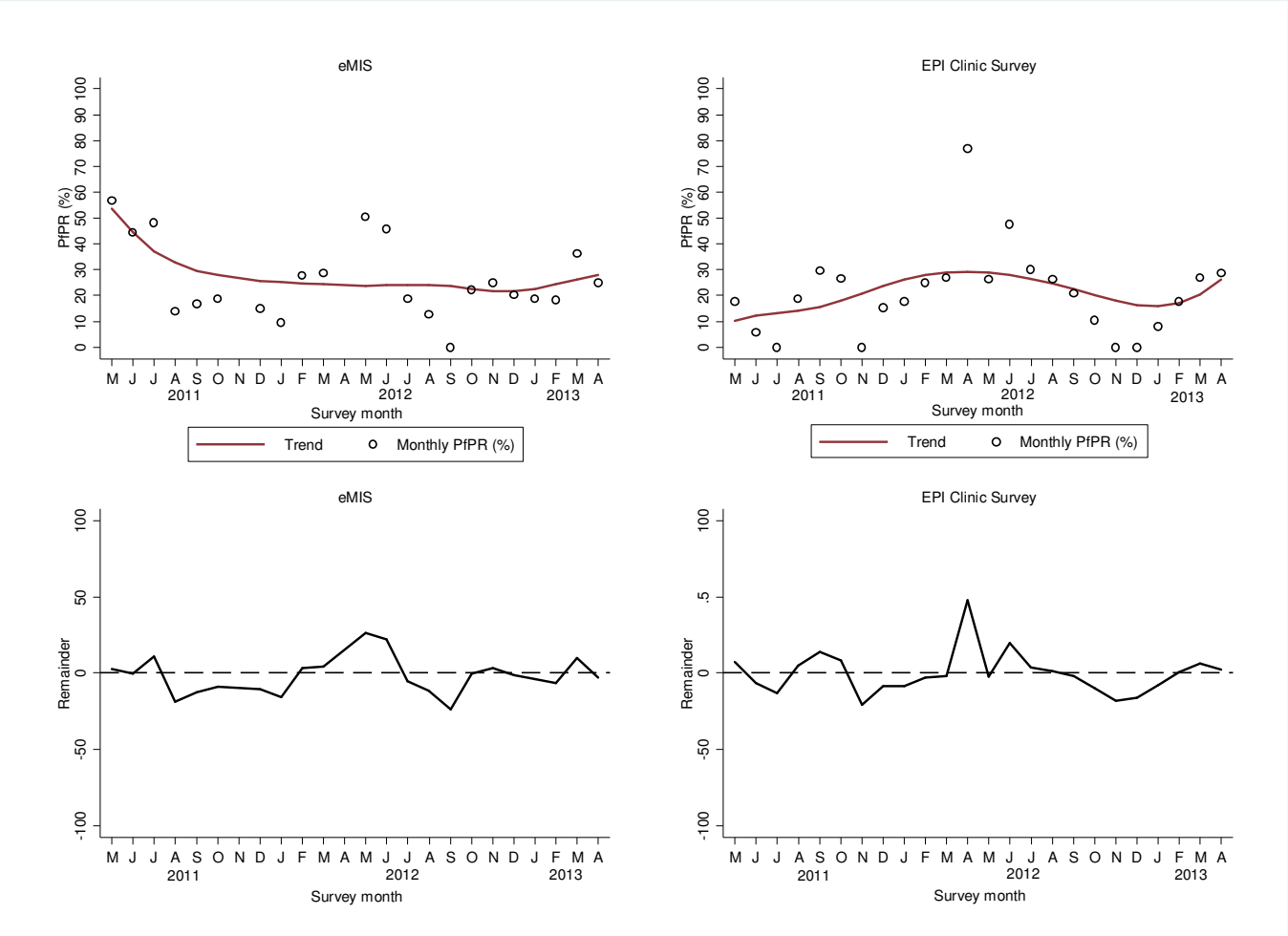
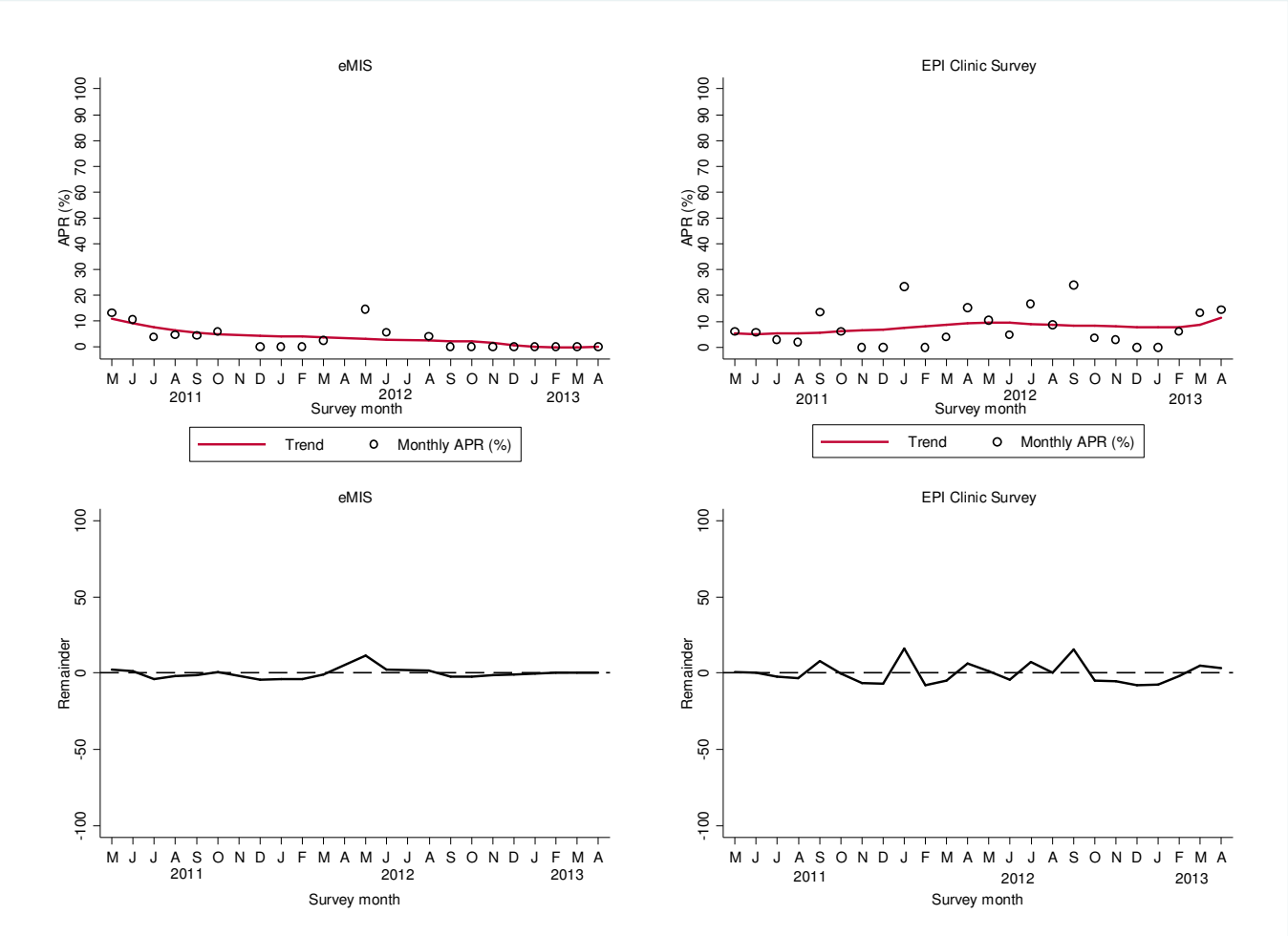


Figure 35: Smoothed trends in monthly APR in both surveys



6.3.3 Smoothed trends in monthly ITN possession, IRS coverage, *Pf*PR and APR

Figures 32 to 35 represent the smoothed trends in household ITN possession, IRS coverage *Pf*PR and APR using Locally Weighted Scatterplot Smoothing (LOWESS). This was plotted with the remainder which is the component that remains after the trend has been removed from the series, so that we could detect if all that remains does not follow a particular pattern. Figure 31 illustrates the trend in monthly percentage household ITN possession between surveys. The trend line for ITN possession in the eMIS indicated a gradual increase in monthly percentage household ITN possession over the study duration. In the residual series, there was no clear repeating pattern of deviation indicating that this residual series was white noise. The trend line for ITN possession in the EPI survey showed a less prominent increase and the residual series also indicated white noise.

Figure 33 illustrates the smoothed trends in monthly percentage IRS coverage between surveys, with the area between the dotted black lines representing the second round of IRS in the study area which was carried out during the survey. IRS coverage in the eMIS started rising from just above 50% in February 2012 to 100% coverage at the end of the survey indicating a lag of one month between the IRS round and perceived increase in coverage. The residual series indicated white noise. The smoothed trend line for IRS coverage in the EPI survey showed a drop in IRS coverage and then a sharp increase. The residual series again, was white noise.

Figure 34 illustrates the smoothed trends in *Pf*PR coverage between surveys. From the smoothed trends for *Pf*PR in the eMIS fell early in the survey and then levelled out for most survey. The trend line for the EPI survey showed a rise in the peaking in mid-2012, followed by a fall an then a peak toward early 2013. In both curves the residual series did not exhibit a significant pattern.

Figure 35 illustrates the smoothed trends in APR coverage in both surveys. From the eMIS, APR fell from just above 10% at the start of the survey to 0% around November 2012. The trend line for APR in the EPI survey showed a slight rise over the study period. In both residual series, there was not significant pattern.

6.4 Discussion

This is the first time that monthly estimates of control progress derived from children attending EPI clinic for "well child" visits have been directly compared to those from a MIS in the same catchment population to determine their accuracy in providing short-term trends of control progress. While based on small monthly sample sizes, the results suggest that monthly estimates from children attending EPI can detect short-term changes in household ITN possession, IRS coverage, *Pf*PR and APR, and thus could potentially measure short to medium term control progress.

The EPI Clinic Survey was able to pick a short-term increase in ITN ownership around July 2012 to a consistent high HH ITN coverage >80% following a district wide community-ITN distribution in July 2012, with wide confidence intervals. Similarly the EPI survey picked up a sudden strong increase in IRS coverage following a district wide IRS campaign in November 2012. In terms of burden indicators, EPI survey also showed crude parasite prevalence estimates with a strongly seasonal pattern and a peak prevalence that followed the expected seasonality based on the district rainfall pattern.

While the observed short-term changes in reported intervention coverage indicators matches known timelines of control activities, there were clear differences with the eMIS. Although some of this difference may have been due to random sampling variation with the small sample sizes, the differences are

explained by several factors. At a monthly level the household sample no longer represent a probability sample. The sampling strategy used a standard 2-step sampling strategy, selecting villages, followed by HH within those selected villages. This strategy was designed to generate a probability sample over a period of 6 months as all 50 villages were sampled over that period, with 8 villages sampled per month. While villages were stratified into two groups by distance to the CDH, samples would have been clustered. The EPI sample however, while biased, would have sampled from a wider range of locations each month. Thus, despite the overall 'gold standard' probability sample of the household survey, the monthly estimates do not reflect a pure probability sample and can be biased themselves by spatially targeted control efforts or burden variations. This situation is not unlike other settings that lack gold standards. An alternative more positive response to residual 'bias' in this situation may be to view it as a sign of relevant underlying spatial and temporal trends which one needs to understand in order to successfully interpret malaria control data. Among policy makers and programme managers there is an increasing call to move away from classic average estimates towards ways to capture, describe and interpret this variation.

We captured a variety of differences that could explain some of the observed differences and patterns. There were significant differences in baseline characteristics between the children in both surveys. Children in the eMIS were significantly older than children in the EPI Clinic Survey, due to inclusion of a higher proportion if infants in the latter. Children in the EPI Clinic Survey tended to come from households with higher socioeconomic status and this was expected given the known relationship between socioeconomic status and health facility attendance (Wyss et al., 1996; Ahmed et al., 2010; Zyaambo et al., 2012). Household ITN possession was estimated to be significantly higher in the EPI Clinic Survey compared to the eMIS. *Pf*PR (detected by RDT) was on the whole significantly lower in the EPI Clinic Survey.

When we explored the trends for monthly household ITN possession, both the crude and smoothed trends in the EPI Clinic Survey were consistently higher than that in the eMIS before the community distribution campaign. There may be three plausible reasons for the significantly higher reported ITN possession in the EPI Clinic Survey.

Firstly, between 2007 and 2009, most of the ITN distribution in Malawi was through health facilities to pregnant women and children <5 years old (President's Malaria Initiative, 2010), and this continued till the latter half of 2011. This ITN delivery strategy was affected by health facility utilization and access (Larson et al., 2012). Mothers of EPI children thus represented targeted households for ITN delivery, whereas the HH in the MIS survey represented all households, including those without young children and those not attending ANC or EPI facilities.

Secondly, reported ITN ownership by women attending health facilities may be more prone to information bias, such as social desirability bias as they know the public health value of ITNs and may falsely report higher level of possession in an EPI setting where this cannot be confirmed (Skarbinski et al., 2006). Since IRS is a new phenomenon in the study area, and the public health value is not widely known, as confirmed by refusal of some residents to be included in any IRS activities (NMCP (Malawi), 2012), social desirability bias would unlikely affect the reporting of IRS coverage. This is further supported by the fact that the difference in IRS coverage between surveys was not significant. Malawi's ITN policy was changed in 2007 focusing on the delivery of LLINS by multiple approaches including routine distribution through ANC clinics for pregnant women, EPI clinics for children and periodic catch-up campaigns targeting rural areas every two to three years (Ministry of Health (MoH) Malawi, 2011; Skarbinski et al., 2011).

The third potential reason for the observed difference is that there is reliable evidence that household ITN possession (and to some extent its use) in children less than 5 years old is more likely in infants (Eisele et al., 2009; Hanson et al., 2009). This could explain why the EPI Clinic Survey consistently overestimated monthly levels of household ITN possession before the community distribution campaign. This effect is likely to be absent where ITNs are not delivered through MCH facilities.

In terms of the measurement of trends in IRS coverage, the EPI Clinic Survey correctly showed a decrease after February 2012 which was expected because the definition of the indicators states IRS over the duration of one year and if there is no spraying after one year (MEASURE Evaluation et al., 2013a), the levels of this indicator will drop rapidly, unless there was a catch-up round like in our study area. Coverage rose again immediately after the third IRS round. This trend was not apparent in the eMIS data and we think this is due to its sampling methodology. In the eMIS, clusters of villages are sampled monthly (up to 8) (Roca-Feltrer et al., 2012b), and given the differential uptake of the earlier round of IRS with sometimes whole villages refusing to be included (NMCP (Malawi), 2012), there would be significant month to month variation in estimates depending on which villages were included. The EPI survey was thus much more effective in demarcating a trend in this situation.

We then compared monthly trends in *Pf*PR and APR between surveys. There was a 3 to 4 month lag between peak rainfall and peak *Pf*PR in both surveys demonstrated (Figure 26) This was expected given the predominance of *Anopheles funestus* in our study area and water flow patterns in the Shire River flood (Chimatiro, 2004; Mzilahowa et al., 2012). A similar trend wasn't seen in monthly APR (Figure 27) and this is likely to be due to the low monthly anaemia prevalence, though the smoothed trends from the eMIS suggested a gradual decline till September 2012 and then no more cases of anaemia were seen till the end of the study (Figure 35). We further investigated for the presence of seasonality in

monthly *Pf*PR and APR data using autocorrelation and partial autocorrelation. This method evaluated for the presence of seasonality regardless of the conventional climatic seasons, and for both indicators there wasn't convincing evidence of seasonality. There may be two possible reasons for this finding. Firstly, the water flow pattern in the Shire River flood plains and farming activities produce (Kalowekamo, 2000; Chimatiro, 2004) create perennial breeding sites for vectors independent of rainfall, hence the preponderance of vectors throughout the year and the high EIR of 183 per person per year (Mzilahowa et al., 2012). The geographic restriction of our study area could have included a disproportionate number of village in the Shire River flood plain and this could have masked any seasonal trends. Secondly, we only had two years' worth of monthly data and this could have been too little information for our seasonality analysis to be robust.

Despite the significantly increased ITN and maintained IRS coverage over the study period, neither survey suggested a significant decline in monthly *Pf*PR. This lack of a significant decline has been noted in previous publications in Malawi from 2000 to 2010 (Roca-Feltrer et al., 2012a; Okiro et al., 2013). Though there is significant background pyrethroid resistance (Hunt et al., 2010; Skarbinski et al., 2012), a more likely explanation of the lack of a significant decline is the previously postulated time lag between achieving high coverage and having the population experience the intervention benefit (Steketee and Campbell, 2010) especially if transmission intensity was initially high.

In summary, given the multifactorial aetiology of health facility utilization (Wyss et al., 1996; Asenso-Okyere et al., 1998; Nyamongo, 2002; Baker and Liu, 2006; Ewing et al., 2011; Zyaambo et al., 2012), monthly data from children in the EPI Clinic Survey is likely to be biased. The difference in trends between surveys in our study may not be marked given the high vaccine uptake in our study area (Malawi National Statistical Office and ICF Macro, 2011), and we recommend that

data from this EAG be interpreted using monthly data on immunization rates whenever available. The use of a hybrid sampling methodology involving selecting additional small, continuous, temporal-spatial probability samples of the catchment population (e.g. every two months) could improve the accuracy of estimates of malaria control indicators (Hedt and Pagano, 2011).

As a next step, our collaborators in Lancaster are developing an extension of their spatial geostatistical model to include temporal trends. Based on these findings, a model based spatiotemporal approach would help overcome some of the presented challenges.

6.5 Conclusions

Data from children attending EPI clinic could be a useful potentially low-cost tool to assess short- to medium-term impact of scaling up of malaria control interventions. This data must however be interpreted taking into consideration that such health facility based surveys may only be representative of those with good health facility access and may not be representative of the population. Data on immunization rates if available would be useful in interpreting trends, and small additional small temporal-spatial probability samples could improve the accuracy of estimates. This method urgently needs to be validated in other transmission settings.

Chapter 7: Assessing the validity of Antenatal Clinic Survey data as a potential Monitoring and Evaluation tool for malaria

7.1 Introduction

Malaria in pregnancy (MIP) is an important public health problem with at least 125 million pregnancies occurring in areas with active malaria transmission (Dellicour et al., 2010). In high transmission settings, there is a higher risk of *P. falciparum* parasitaemia during pregnancy compared to non-pregnant women, and parasites can be detected in the placenta; prevalence is typically higher in the first compared to subsequent pregnancies (Gilles et al., 1969; Brabin, 1983; McGregor et al., 1983; Desai et al., 2007) due to the development of parity specific immunity (Fried and Duffy, 1996). In stable high transmission settings for *P. falciparum* infection, there is a higher prevalence of parasitaemia in early pregnancy, which peaks in the second trimester (Gilles et al., 1969; Brabin, 1983; McGregor et al., 1983; Desai et al., 2007). In stable high transmission settings infection is often asymptomatic, and the main clinical effect in the mother is usually anaemia (Gilles et al., 1969; Fleming, 1989; Shulman and Dorman, 2003). Maternal HIV infection is known to modify this parity-specific pattern of malaria risk by increasing the frequency and density of malaria infections (Steketee et al., 1996; van Eijk et al., 2003; ter Kuile et al., 2004).

Because of the increased malaria risk in pregnant women, various malaria control strategies focus specifically on malaria in pregnancy (MIP). In areas with stable high transmission, WHO recommends the use of ITNs, intermittent preventive treatment (IPTp) with sulfadoxine–pyrimethamine (SP) and effective case management of malaria and anaemia, whilst in low transmission settings, the focus is on prompt and effective case management (WHO/AFRO, 2004). Though a number of core indicators have been identified to evaluate control of malaria in pregnancy (WHO, 2007a), there have been recent suggestions that these be updated (Brabin et al., 2008). The currently advocated indicators are divided into those that need to be measured at the health facility level (e.g. percentage of pregnant women attending antenatal care who receive a second dose of IPTp under direct observation) and those that need to be measured at the population level through

nationally representative household surveys (e.g. percentage of pregnant women who report having slept under an ITN the previous night) (WHO, 2007a).

Monitoring and evaluation of malaria control in pregnancy is essential in assessing the efficacy and effectiveness of health interventions aimed at burden reduction in pregnant women living in endemic areas. However, because of their increased malaria susceptibility pregnant women could potentially act also as a sentinel group to monitor spatiotemporal trends and control progress in malaria prevalence in general at population level. Moreover, over the past few years malaria control guidelines have moved from ITN scale-up efforts targeted at young children and pregnant women as high burden groups to target the whole population in an effort to reduce transmission.

To survey a representative sample of pregnant women from the population however, requires a much larger sample size than those assessed in a conventional MIS (WHO, 2007a) which would be logistically and financially demanding. Facility-based surveillance of pregnant women during gestation and at delivery offers an opportunistic low-cost strategy to measure spatiotemporal trends in the population. The relatively higher burden in pregnancy peaking in the second trimester, the high antenatal attendance (UNICEF, 2013) compared to delivery rates in facilities (Singh et al., 2013) and wide geographic distribution of antenatal clinics all suggests that surveillance in women attending ANC offers a strategic opportunity to estimate population parasite prevalence and its geospatial heterogeneity, and would be more suitable than assessment in other pregnancy related services such as delivery wards.

The aim of this study was to determine whether women attending ANC are a potential source of representative data on the geospatial distribution of the prevalence of *P. falciparum* parasitaemia in the population, by assessing the spatial pattern of *P. falciparum* prevalence between different risk categories in pregnant

women visiting the ANC as a comparison to the pattern seen in young children (Chapter 5).

7.2 Methods

7.2.1 Study site and population

This EAG data for women attending ANC came from a screening and enrolment log of a non-inferiority, multi-centre, randomized, open label trial of different fixed-dose artemisinin combination therapies (ACT) for the treatment of malaria in pregnancy the PREGACT (NCT00852423) (ClinicalTrials.gov, 2014), based in the antenatal clinic of Chikhwawa District Hospital (CDH) (i.e. the ANC Survey) in Chikhwawa, Malawi. The screening log was kept between November 2010 and April 2012. This government run hospital is the main referral hospital in Chikhwawa District and offers free ANC services. According to the latest DHS for Malawi , 98% of women aged 15 to 49 years in rural areas had attended ANC at least once with a median of 5.5 months pregnancy at the first ANC visit (Malawi National Statistical Office and ICF Macro, 2011). Chikhwawa district also has 14 health centres serving a population of 450,000. Chikhwawa District Hospital has a total capacity of 200 beds of which 30 are in the maternity ward. The hospital is staffed by 1 medical doctor, 15 clinical officers and 30 nurses. On average there are 300-450 ANC attendees and 100-150 deliveries per month. Previous studies in CDH conducted in the 1990s found a parasitaemia prevalence of 35.3% in primigravidae and 13.6% in multigravidae (Verhoeff et al., 1998). Malaria transmission is perennial in the study area transmission with some intensification during the rainy season from December to April. The estimated annual average EIR in the Chikhwawa field site is 50 infectious bites per year based on estimates from two villages just outside our assessed area (Mzilahowa et al., 2012).

7.2.2 Study design

This study used a continuous cross-sectional screening and enrolment log as the EAG surveillance. The study was conducted concurrently with a continuous ('rolling') population-based household-level MIS (i.e. the eMIS) in 50 villages in the geographic catchment area of CDH (i.e. within 15 km radius of CDH).

7.2.3 Sampling strategy

All pregnant women presenting for their first ANC visit at CDH regardless of age were screened for *P. falciparum* infection by RDT as part of the screening process of the PREGACT trial. After consent, demographic data were collected and recorded in the screening and enrolment log. This included age, gravidity and gestation as estimated from the health passport. In all patients with a positive malaria rapid diagnostic test, a haemoglobin assessment was done on a finger prick specimen with HemoCue to determine eligibility for inclusion in the trial.

In the household survey (i.e. the eMIS), conducted between May 2011 and June 2013, after enumeration of constituent 50 villages, a representative probability sample of households was derived to produce estimates for the study area as a whole and each season separately. Within each village, households were randomly selected from a list of households. In each household, all children aged 6 to 59 months (described in chapter 3) and one randomly selected woman of childbearing age (15 to 49 years) regardless of pregnancy status who was present on the day of the survey were selected for inclusion.

7.2.4 Data collection

ANC EAG group

With screening consent, data on age, parity, gravidity, gestational age of current pregnancy, village and traditional area of origin where extracted from the health passport of the participant. Where this data was not available, it was extracted by direct questioning. This data was recorded in the trial screening and

enrolment log. The coordinates of the village of origin were later determined using the most recent Global Positioning System (GPS) database for Malawi (http://www.geonames.org/about.html).

Population level data from women in the household survey

Structured interviews were conducted with household heads or parents/guardians of all children in selected households in the household survey using a locally adapted version of RBM/MERG MIS questionnaire (http://rbm.who.int/merg.html#MIS). After informed consent, in households containing women of childbearing age, information was collected on pregnancy status by direct questioning and inspection of the participant's health passport. Data was recorded in electronic questionnaires on PDAs which also had GPS devices to record the household and village coordinates.

Laboratory procedures

Among women attending ANC, finger-prick blood samples were taken for a malaria rapid diagnostic test (RDT) (First Response® Malaria Ag. pLDH/HRP2 Combo Card Test, Premier Medical Corporation Ltd., India), and thick blood film. All women with a positive RDT also had their haemoglobin concentrations measured using a HemoCue® haemoglobinometer (HemoCue AB, Angelholm, Sweden). Blood films from all attendees with a positive malaria RDT result were dried, stained with Field's stain and read on site. In the household survey, blood samples were collected from all women of childbearing age surveyed to prepare an RDT (First Response® Malaria Ag. pLDH/HRP2 Combo Card Test, Premier Medical Corporation Ltd., India), thick and thin blood film, and to determine the woman's haemoglobin concentration (HemoCue 301®, HemoCue AB, Ängelhom, Sweden).

Clinical procedures

All women attending ANC who were parasitaemic but were not severely anaemic and satisfied other enrolment criteria, were included into the trial and randomised into treatment arms and treated for their malaria infection as per protocol. Women with other illnesses were referred to the ANC for treatment. All women who were parasitaemic and/or had moderate anaemia (Hb < 11.0 g/dl) in the household survey (i.e. the eMIS) were treated as per national treatment guidelines at the time of the study by the study research nurse. Women with severe anaemia (Hb < 7.0 g/dl), and/or exhibiting clinical signs of severe illness (including severe malaria) in the household survey were assisted with transportation and referred to the nearest health facility.

Definition of terms

Hot/Cold dry season: May to October.

Rainy/post-rainy season: November to April.

First trimester: 0 to 12 weeks gestation.

Second trimester: 13 to 26 weeks gestation.

Third trimester: $\geq$ 27 weeks gestation.

Primigravidae: Women in their first pregnancy.

Secundigravidae: Women in their second pregnancy.

Multigravidae: Women with $\geq$ 3 pregnancies.

Adolescence: Age 15 to 19 years.

Child-bearing age: Age 15 to 49 years.

Plasmodium falciparum positive: The simultaneous presence of the *P. falciparum*, *P. vivax*/other species and control bands, or the *P. falciparum* and control bands in the rapid diagnostic test.

Data management and Statistical analysis

Data from the screening and enrolment log of the PREGACT trial was double-entered in two separate databases in REDCap® (Vanderbilt University, Texas, USA), reconciled and cleaned with errors amended. Data from the eMIS was

entered into in PDAs (Somo 650®, Socket Mobile, Newark, California) programmed in Visual CE® 11.1 language (Syware Incorporation, Cambridge, Massachusetts). Data was analysed using Stata version 13.1 (Stata Corporation, College Station, Texas, USA). The data for this analysis was restricted to the first overlapping year of both surveys i.e. 14th June 2011 to 13th June 2012, to study subjects resident in the geographic catchment area of CDH, women of childbearing age (i.e. 15 to 49 years) attending ANC and the eMIS. In women attending ANC, data was restricted to women with accurate information on gravidity. The prevalence of *P. falciparum* parasitaemia (*Pf*PR) was calculated as a percentage with the respective 95% confidence interval and compared between surveys and sub-groups, to assess the varying risks of exposure.

Independent determinants of *Pf*PR were explored using logistic regression. Univariate logistic regression was used to identify possible predictors on *Pf*PR in each survey. Factors exhibiting a significant relationship with *Pf*PR (defined as $p < 0.10$) or those previously described as determinants were further explored using multivariate logistic regression. Likelihood ratio tests were used to determine the effect of predictors in the model as odds ratios and their 95%CI, and significant predictors were included stepwise in the multivariate analysis by forward selection.

Determining the different at-risk categories for P. falciparum infection in women attending ANC

To determine the different at-risk category for *P. falciparum* infection in women attending ANC, we used a "probit" regression model to study the interaction between two variables, age and gravidity, that exhibited a strong inverse relationship with the risk of *P. falciparum* infection (detected by RDT) in both the univariate and multivariate logistic regression model. To assess the interaction between the effects of age (in years) and gravidity on with the probability of *P. falciparum* infection, we included an interaction term (age in five year categories x gravidity) in the probit regression model. We preferred the probit

to the logit model because we wanted to present the probability of *P. falciparum* infection with age which is more easily interpretable with respect to *Pf*PR. The product term of such a model is given by:

$$\Pr(Y) = \Phi\left[\beta_0 + \beta_1 age + \beta_2 gravidity + \beta_3 trimester + \beta_4 season + \beta_{ag}(age\ x\ gravidity)\right] \quad (16)$$

where Φ is the probit link function.

We then predicted the change in the probability of P. falciparum infection with increasing age for different categories of gravity, modelling age as a continuous variable with a unit increase every five years. We displayed our results using the Stata "MARGINSPLOT" command (Stata-Press, 2013b), to observe the difference in probability of infection between the different categories of gravidity with increasing age. We then used the different at-risk categories in a geostatistical model to develop contour maps of spatial heterogeneity in *Pf*PR.

Developing spatial maps of PfPR in women attending ANC

In order to account for potential bias in the data derived from women attending ANC, we used a previously developed geostatistical model (Giorgi et al., In press) combining the information on the prevalence of P. falciparum infection from the ANC sample with that from a probability sample of women of childbearing age from the same catchment population during the eMIS. Due to the opportunistic nature of the survey in women attending ANC, we were not able to collect data on potential confounders like socioeconomic status so we used data from the population sample as a reference group to estimate and correct for spatial bias in data from the ANC Survey.

In the eMIS data, only information on the pregnancy status was available whilst information on gravidity and trimester were not collected. The likely

gravidity of women in the eMIS was imputed from age using the available information from women attending ANC as follows. First we fitted a multinominal regression model for the three categories of gravidity, primigravidae, secundigravidae and three or more pregnancies with the quadratic effect of age. Then we used the available information on the age of pregnant women in the eMIS to predict their most likely gravidity.

We then used the following methods for parameter and standard errors estimation. Firstly, we simulated the trimester status or each pregnant in the eMIS with a probability of 1/3 for each of the three categories. Secondly, we estimated the parameters of age, season indicator, pregnancy status, gravidity and trimester using the geostatistical model detailed in a separate publication (Giorgi et al., In press) to the corresponding standard errors. Finally we repeated the preceding two steps 200 times; the output of the *i*-th iteration is an estimate of the regression coefficients ($\widehat{\beta}_i$), and the corresponding standard errors ($\widehat{v}_i$). The final estimate of the regression coefficients is obtained by averaging over each estimate, hence $\bar{\beta} = \sum_{i=1}^{200} \hat{\beta}\,/200$, and the respective standard errors (to account for additional uncertainty introduced by the imputation) are given by:

$$\sqrt{\left(\frac{1}{200}\sum_{i=1}^{200}\left(\widehat{\beta}_i - \bar{\beta}\right)^2 + \frac{1}{200}\sum_{i=1}^{200}\hat{v}_i^2\right)} \qquad (17)$$

The contours maps were all constructed for women attending ANC for all trimesters and in the dry season. We used the dry season because given what we know about transmission in our study area (Mzilahowa et al., 2012), as we expected *Pf*PR to be higher in this season when the effect of temporary breeding site will be relatively absent and hotspots are more prominent.

7.2.5 Ethical approval

This study was approved by the College of Medicine (Malawi) Research and Ethics Committee (COMREC) and the Liverpool School of Tropical Medicine Research and Ethics Committee (LSTMREC) as an amendment of the main EvalMal proposal (COMREC P08/10/971 and LSTMREC 10.79).

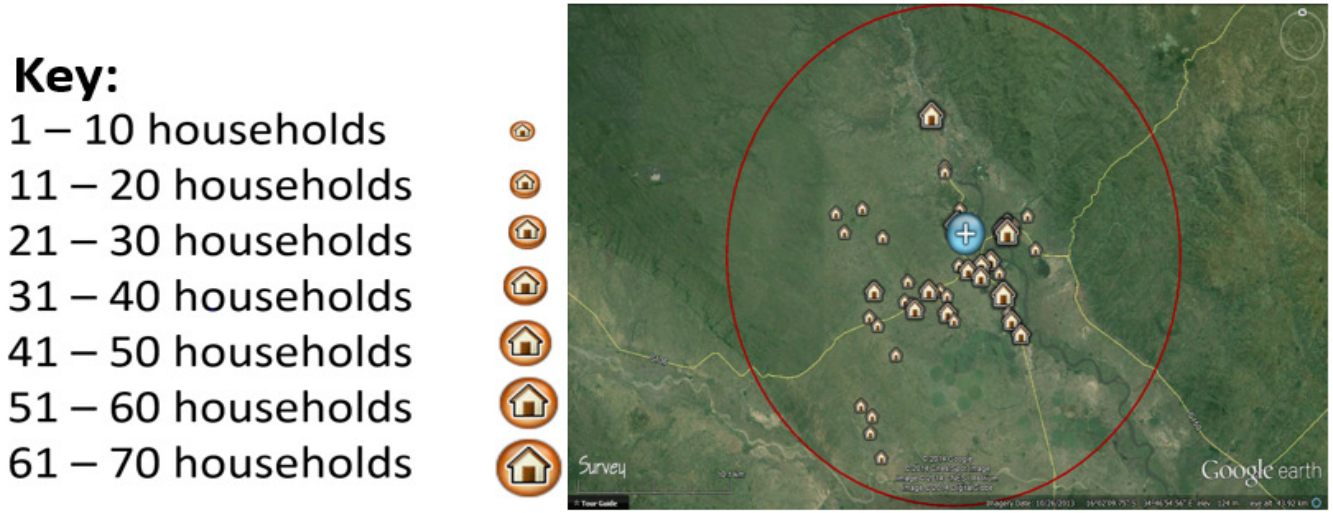
7.3 Results

7.3.1 Study population characteristics

A total of 50 villages were included in the household survey. Participants in the ANC Survey presented from a total of 143 villages of which 130 were within 15 km of CDH. Forty villages were common to both surveys (i.e. an overlap of 30.8%) (Figures 36 and 37) and there was no predilection for the villages close to the main roads in Chikhwawa in the ANC Survey (Figure 37). Between 14th June 2011 and 13th June 2012, 1828 pregnant women aged 15 to 49 years were included in the ANC EAG group. Information on gravidity and trimester was not recorded in 4/1828 (0.2%) and 6/1828 (0.3%) of surveyed women respectively. A total of 582 women aged 15 to 49 years were surveyed in the household survey (i.e. eMIS) in the same study period, of which 8% (48/582) were pregnant.

The characteristics of the women of child bearing age in both the ANC Survey and the eMIS are compared in Table 30. The mean age of all pregnant women of childbearing age in the ANC Survey (mean age = 23.9 years, 95% CI 23.7, 24.2 years) was similar to that in pregnant women in the eMIS (mean age = 25.5 years, 95% CI 23.6, 27.5 years); and both were significantly lower than non-pregnant women in the eMIS (mean age = 28.9, 95% CI 28.3, 29.6 years) due to a significantly higher proportion of non-pregnant women aged 35 years and older surveyed in the eMIS than pregnant women in the eMIS and ANC Survey (22.1% vs. 10.4% vs 6.2% respectively, $p < 0.001$). A significantly higher proportion of non-pregnant women in the eMIS were surveyed in the dry season compared to the pregnant women in the eMIS and ANC Survey (67% vs. 56% vs. 55% respectively, $p < 0.001$).

Figure 36: Geographic distribution of the sampling frame of pregnant women in the eMIS



Created using Google Earth® by Google.

Figure 37: Geographic distribution of the sampling frame of ANC Survey

Created using Google Earth® by Google.

Table 30: Background characteristics of women of childbearing age in the ANC Survey and eMIS

	ANC ***N* = 1824** ***n* (%)**	**eMIS preg** **N = 44** **n (%)**	**eMIS not-preg** **N = 462** **n (%)**	***p-value****
Age (years)				
15 to 19	479 (26.3)	14 (29.2)	59 (11.1)	
20 to 34	1232 (67.5)	29 (60.4)	357 (66.9)	
≥ 35	113 (6.2)	5 (10.4)	118 (22.1)	< 0.001
Mean age in years	23.9	25.5	28.9	
(95% CI)	(23.7, 24.2)	(23.6, 27.5)	(28.3, 29.6)	
Season				
Dry season	1003 (55.0)	27 (56.3)	358 (67.0)	
Rainy/Post-rainy season	821 (45.0)	21 (43.7)	176 (33.0)	< 0.001

*X^2 p values.
All data presented as numbers and percentages unless indicated otherwise.

Table 31: Background characteristics of pregnant women in the ANC Survey

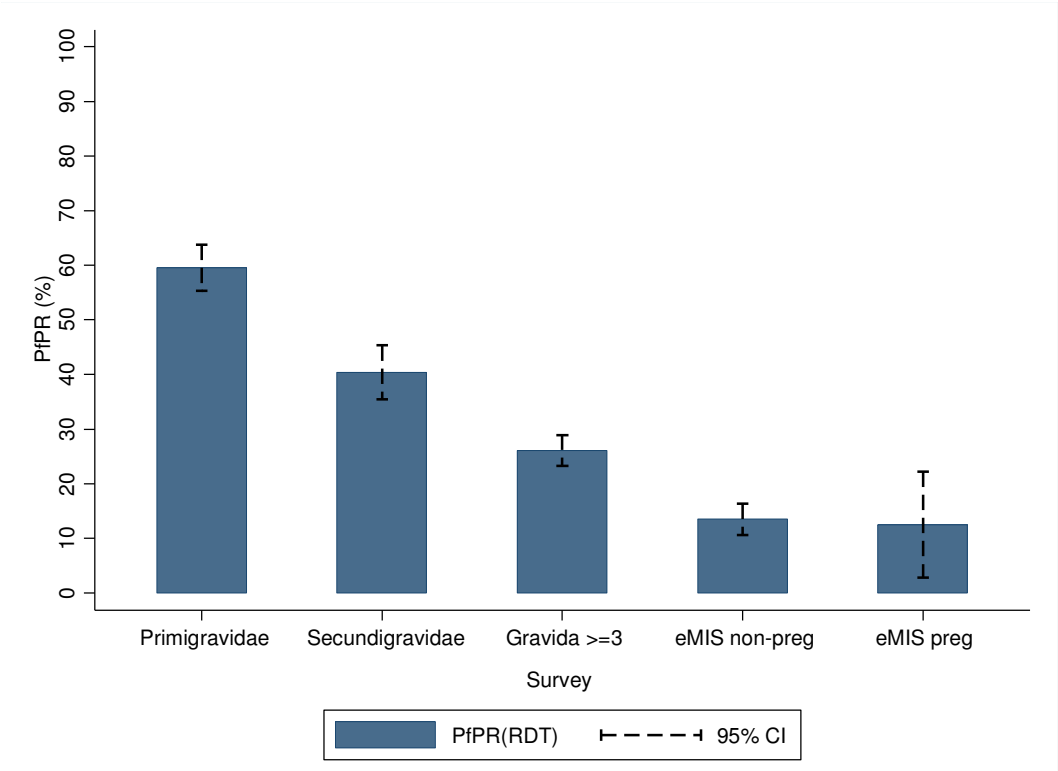
	Primi (G_1) ***N* = 514** ***n* (%)**	**Secundi (G_2)** ***N* = 391** ***n* (%)**	**≥ 3 preg (G_{3+})** ***N* = 919** ***n* (%)**	***X^2 p-value***
Age (years)				
15 to 19	394 (76.7)	79 (20.2)	6 (0.7)	
20 to 34	119 (23.2)	310 (79.3)	803 (87.4)	
≥ 35	1 (0.2)	2 (0.5)	110 (12.0)	< 0.001
Mean age in years	18.4	21.7	28.0	
(95% CI)	(18.2, 18.6)	(21.4, 22.0)	(27.7, 28.3)	
Gestation				
1st trimester	86 (16.8)	53 (13.6)	111 (12.1)	
2nd trimester	382 (74.5)	293 (74.9)	675 (73.7)	
3rd trimester	45 (8.8)	45 (11.5)	130 (14.2)	0.010
Gestational age in weeks	18.6	19.3	20.1	
(95% CI)	(18.1, 19.1)	(18.7, 19.8)	(19.7, 20.4)	
Season				
Dry season	275 (53.5)	200 (51.2)	528 (57.5)	
Rainy/Post-rainy season	239 (46.5)	191 (48.9)	391 (42.6)	0.080

All data presented as numbers and percentages unless indicated otherwise.

The characteristics of the pregnant women presenting to the ANC for their first antenatal visits are summarized in Table 30. The majority (76.7%) of primigravidae were less than 20 years old, whilst the majority of secundigravidae and women with three or more pregnancies were aged 20 to 34 years (79.3% and 87.4% respectively, $p < 0.001$). As a result, the mean age of primigravidae was

significantly lower than that for secundigravidae, which was in turn significantly lower than women with three or more pregnancies. The majority of pregnant women in the ANC Survey were in the 2nd trimester for all categories of gravidity and women with three or more pregnancies were less likely to present in the first trimester and more likely to present in the third trimester than primi- or secundigravidae and this trend was significant (p = 0.010) . In the ANC Survey, the difference in the proportion of women surveyed by season was not statistically significant (0.068).

Figure 38: *Pf*PR between gravidity in the ANC Survey and eMIS



Primigravidae – primigravidae in the ANC Survey; Secundigravidae – secundigravidae in the ANC Survey; Gravida>= 3 - women with three or more pregnancies in the ANC Survey; eMIS non-preg – non-pregnant women in the eMIS; eMIS preg. = pregnant women in the eMIS

Table 32: Factors associated with *P. falciparum* parasitaemia (by RDT) in pregnant women in the ANC survey

	Crude analysis			Adjusted analysis		
Risk factor	**Odds ratio**	**95% CI**	***p*-value**	**Odds ratio***	**95% CI**	***p*-value**
Age						
15 to 19	1.00			1.00		
20 to 34	0.33	0.27, 0.41		0.70	0.51, 0.95	
35 to 49	0.20	0.12, 0.32	< 0.001	0.55	0.31, 0.96	0.013
Trimester						
1st trimester	1.00			1.00		
2nd trimester	0.99	0.75, 1.30		1.09	0.81, 1.45	
3rd trimester	0.56	0.38, 0.83	0.007	0.66	0.44, 0.99	0.095
Gravidity						
Primigravidae	1.00			1.00		
Secundigravidae	0.46	0.35, 0.60		0.57	0.41, 0.78	
≥ 3 pregnancies	0.24	0.19, 0.30	< 0.001	0.33	0.24, 0.46	< 0.001
Season						
Dry season	1.00			1.00		
Rainy/Post-rainy season	1.22	1.01, 1.47	0.041	1.17	0.96, 1.42	0.133

*Adjusted for age, trimester, gravidity and season.

7.3.2 Prevalence of *P. falciparum* infection (by RDT) between gravidity groups and surveys

Figure 38 shows a comparison of *Pf*PR between the ANC group and the women in the eMIS. The prevalence of *P. falciparum* infection was highest in primigravidae in the ANC Survey (*Pf*PR = 59.5%, 95% CI 55.3%, 63.8%), followed by secundigravidae (*Pf*PR = 40.4%, 95% CI 35.5%, 45.3%), followed by women with three or more pregnancies (*Pf*PR = 26.1%, 95% CI 23.3%, 29.0%), and this trend was significant from the 95% confidence intervals. The *Pf*PR in pregnant women in the eMIS (*Pf*PR = 12.5%, 95% CI 2.8%, 22.2%) was lower than that in non-pregnant women (*Pf*PR = 13.5%, 95% CI 10.6%, 16.4%) in the eMIS, but from the overlapping confidence interval, this difference was not statistically significant. This suggested that the risk of infection primigravidae (attending ANC) was significantly higher than that in other gravidities and both pregnant and non-pregnant women in the eMIS.

7.3.3 Identifying the subgroup with the highest risk of *P. falciparum* prevalence (by RDT) in women in the ANC Survey

In order to identify the subgroup with the highest risk of *P. falciparum* infection (detected by RDT) amongst pregnant women attending ANC that may be most suitable for M&E purposes, we assessed the role of age, trimester, gravidity and season in a univariate and multivariate logistic regression model. Table 32 illustrates the factors associated with *P. falciparum* infection in pregnant women in the ANC survey. Compared to women aged 15 to 19 years, in the univariate analysis, *P. falciparum* infection was significantly less likely in women aged 30 to 34 years or peak child-bearing age and in older women or women aged 35 to 49 years in the ANC survey. *P. falciparum* infection was less likely to occur in the 3rd trimester of pregnancy (OR = 0.56) compared to the first or second trimester. Compared to primigravidae, *P. falciparum* infection was significantly less likely in secundigravidae (OR = 0.46, 95% CI, 0.35, 0.60, $p < 0.001$) and women with three or more pregnancies (OR = 0.24, 95% CI, 0.19, 0.30, $p < 0.001$). *P. falciparum* infection

was significantly higher in the rainy/post-rainy season (OR = 1.22, 95% CI, 1.01, 1.48, p = 0.040).

In the multivariate analysis, after adjusting for trimester and gravidity, the risk of *P. falciparum* infection still decreased significantly with increasing age, with the risk being highest in the reference category (i.e. pregnant women attending ANC aged 15 to 19 years). After adjusting for age and gravidity in the multivariate model, the third trimester was still associated with a lower risk of *P. falciparum* infection but this was borderline statistically significant as the upper limit is close to one or no effect (AOR = 0.66, 95% CI, 0.44, 0.99, p = 0.044). After adjusting for age and trimester, the risk of *P. falciparum* infection still decreased significantly with increasing gravidity. In the multivariate analysis, season did not significantly influence the fit of the multivariate model and was thus not included in the final model. From our analyses, age, trimester and gravidity appear to be significant predictors of *P. falciparum* infection and need taken into account in the geostatistical model.

7.3.4 Interaction between the effects of age and gravidity on *P. falciparum* parasitaemia in women attending ANC

Using the risk factors for *P. falciparum* infection in pregnant women attending ANC, as determined from the earlier multiple logistic regression model, we examined the two risk factors that exhibited a strong inverse relationship with *Pf*PR for any interaction (i.e. age and gravidity). Table 33 presents the probit models for the probability of *P. falciparum* infection both with and without the inclusion of an interaction term. When the term is included the association between age and P. falciparum infection is now limited to women less than 25 years.

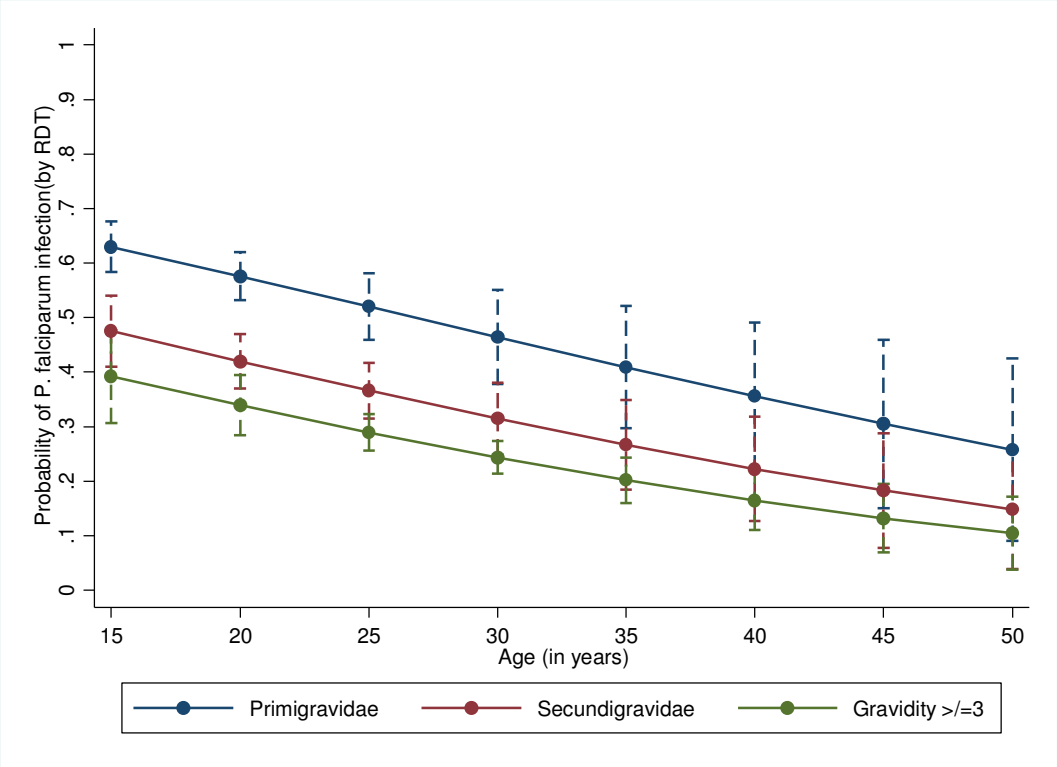
Table 33: Probit models of the probability of *P. falciparum infection* and predictors in women attending ANC

Term	Model with interaction term			Model without interaction term		
	Coefficient	*95% CI*	*p*-value	Coefficient	*95% CI*	*p*-value
Intercept	0.244	0.045, 0.442	0.016	0.241	0.045, 0.438	0.016
Age 20 to 24	-0.206	-0.411, -0.002	0.048	-0.202	-0.399, -0.005	0.044
Age 25 to 29	-0.364	-0.796, 0.068	0.099	-0.337	-0.593, -0.081	0.010
Age 30 to 34	-0.497	-1.262, 0.267	0.203	-0.444	-0.738, -0.149	0.003
Age 35 to 39	-0.471	-1.594, 0.652	0.411	-0.390	-0.754, -0.027	0.035
Age 40 to 44	-0.952	-2.426, 0.512	0.203	-0.862	-1.721, -0.002	0.049
Age 45 to 49*	-	-	-	-		-
2nd trimester	0.052	-0.125, 0.229	0.562	0.053	-0.124, 0.230	0.556
3rd trimester	-0.226	-0.471, 0.018	0.070	-0.226	-0.470, 0.019	0.071
Secundigravidae	-0.362	-0.583, -0.141	0.001	-0.355	-0.555, -0.155	<0.001
Three or more pregnancies	-0.614	-1.036, -0.191	0.004	-0.587	-0.816, -0.357	<0.001
Rainy season	0.077	-0.046, 0.199	0.220	0.077	-0.045, 0.199	0.217
Age x gravidity	0.013	-0.162, 0.189	0.882			

*No individual in this age category with *P. falciparum* infection.

Marginsplot syntax was used to plot the graph after using a "probit" logistic regression model, adjusting for the effect of trimester. The values in the graph represent the adjusted probabilities of *P. falciparum* infection (detected by RDT) with their respective 95% confidence intervals by age for the different categories of gravidity. From the graph (Figure 39), there is a clear linear trend of decreasing probability of *P. falciparum* infection with increasing age in all gravidity categories, and a stable difference in risk between gravidity groups. From 15 to 25 years of age, the adjusted prevalence of *P. falciparum* infection in primigravidae was significantly higher compared to secundi and multi gravidae.

Figure 39: Probability of *P. falciparum* infection (detected by RDT) with age stratified by gravidity in women attending ANC



7.3.5 Geostatistical analysis

The findings on determinants and epidemiology were used to inform the geostatistical analyses. The maps were all constructed for women attending ANC for all trimesters and in the dry season.

Table 34: Log-odds estimates for the geostatistical model of *P. falciparum* prevalence in combined model of the ANC Survey and eMIS

Term*	**Estimate**	**p-value**
Intercept	-0.650	0.296
eMIS=Yes	-1.514	0.009
Age ≥ 20yrs	-0.435	0.011
Rainy season	0.212	0.053
Woman pregnant	1.150	0.061
Secundigravidae	-0.809	<0.001
Three or more pregnancies	-1.486	<0.001
2nd trimester	0.148	0.384
3rd trimester	-0.413	0.083

*Dry season, primigravidae and 1st trimester as the reference groups for season, gravidity and trimester respectively.

Table 34 is a representation of the geostatistical model of the combined data set. From the results in the table, all women of childbearing age in the eMIS (regardless of pregnancy status) had a significantly lower risk of *P. falciparum* infection than women in ANC Survey. Women aged 20 years and older in the whole data set had a significantly lower risk of *P. falciparum* infection by RDT compared to women aged 15-19 years, indicating and overall age effect in our sample. The lack of pregnancy status being associated with a higher risk of *P. falciparum* infection in the population sample is probably due to the small sample of pregnant women. The rainy season was associated with a borderline significant increase in *Pf*PR. Secundigravidae and women with three or more pregnancies were associated with a significantly lower risk of *P. falciparum* infection compared to primigravidae. Unlike in the multivariate logistic regression model, the 3rd trimester of pregnancy was not associated with a significantly lower risk of *P. falciparum* infection compared to the first trimester.

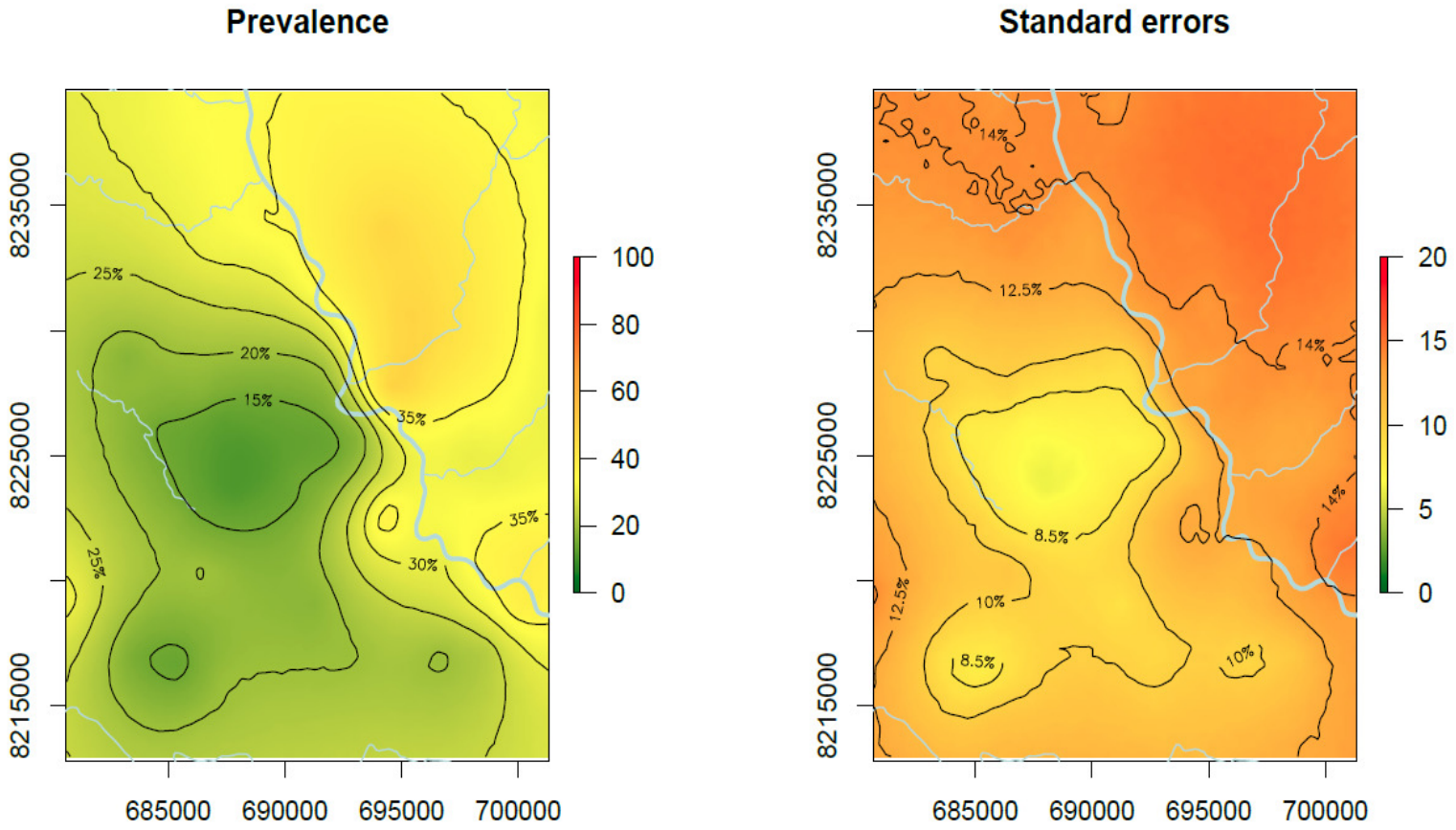
Based on the results of the geostatistical model and historical evidence, we selected primigravidae aged 15 to 19 years, secundigravidae aged 20 years or more

and women with three or more pregnancies ages 20 years or more as three potential different ANC sub-groups to assess the geospatial heterogeneity of *Pf*PR. The risk maps resulting from the geostatistical analyses are presented in Figures 40 to 42.

Figure 40 is a contour map of the geographic distribution of *Pf*PR in primigravidae less than 20 years old (in all trimesters) in the dry season with accompanying standard errors. The areas in the prevalence map are graduated from dark green areas where percentage prevalence is nil to red areas where prevalence is 100%. The contours represent a mean estimate (percentage prevalence) of the area enclosed in the contour. The contours in the standard error maps represent the standard error of our estimates from the prevalence map based on the corrected geospatial model and the areas in the map are graduated from dark green where the standard errors are small and to red where the standard errors are large. The generated map of the geospatial distribution of *Pf*PR revealed that it is highest in the floodplains of the Shire River within the study area. The highest prevalence of *P. falciparum* infection (by RDT) (*Pf*PR = 35%) was seen in the floodplains of the Shire River Valley but the contours did not seem to detect sufficient small scale variations in *Pf*PR.

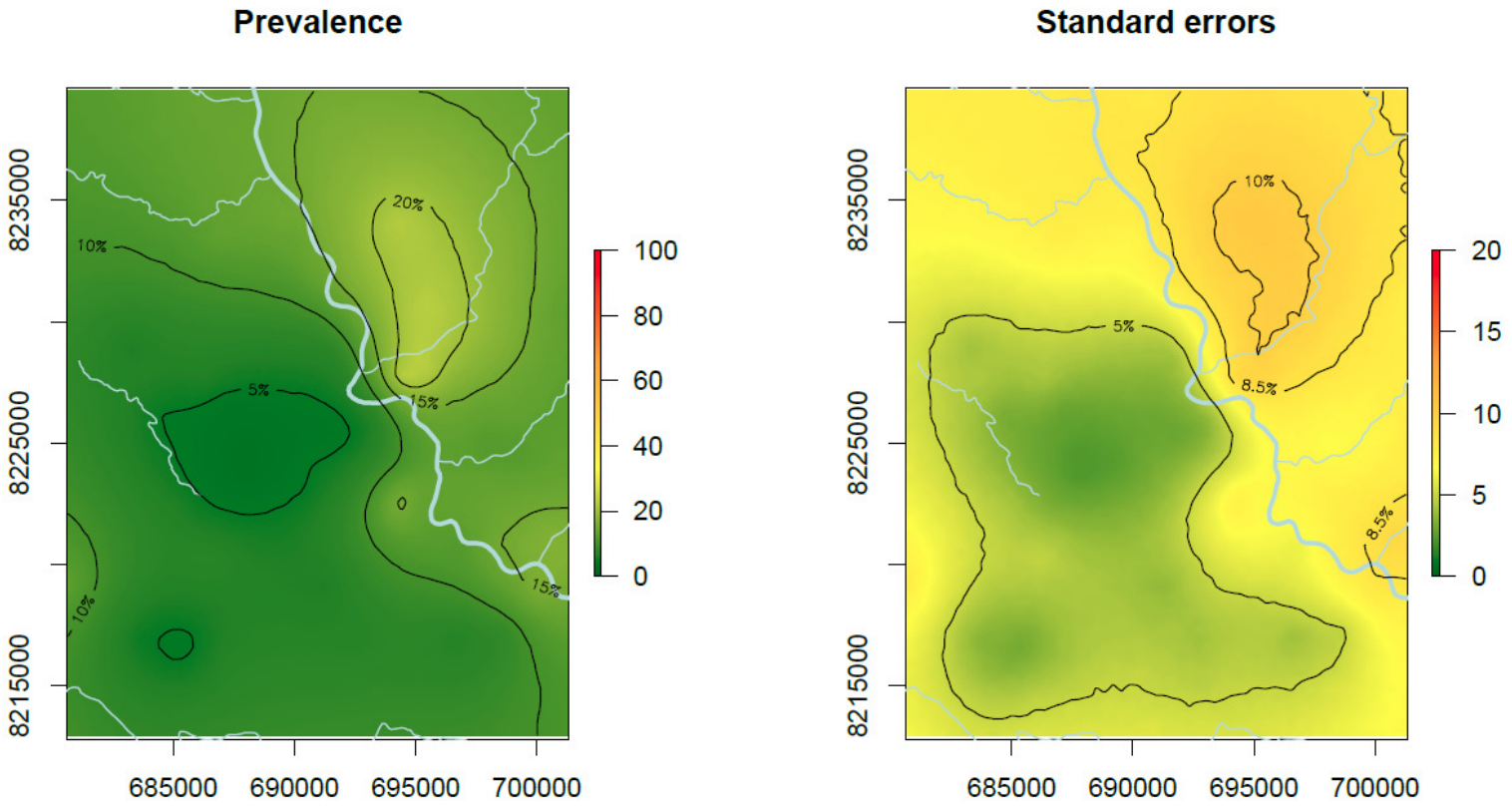
Figure 41 is a contour map of the geographic distribution of *Pf*PR in secundigravidae aged 20 years or more in the dry season with accompanying standard errors. The generated map reveals lower overall prevalence than in primigravidae with smaller standard errors around estimates from the Shire River flood plains. Again the *Pf*PR was highest in the floodplains of the Shire River valley but the contours do not seem to detect sufficient small scale variations in *Pf*PR and performed worse than the younger primigravidae subgroup.

Figure 40: Geographic distribution of the population prevalence *P. falciparum* infection (by RDT) in primigravidae aged 15 to 19 years in all trimesters in the dry season with standard errors



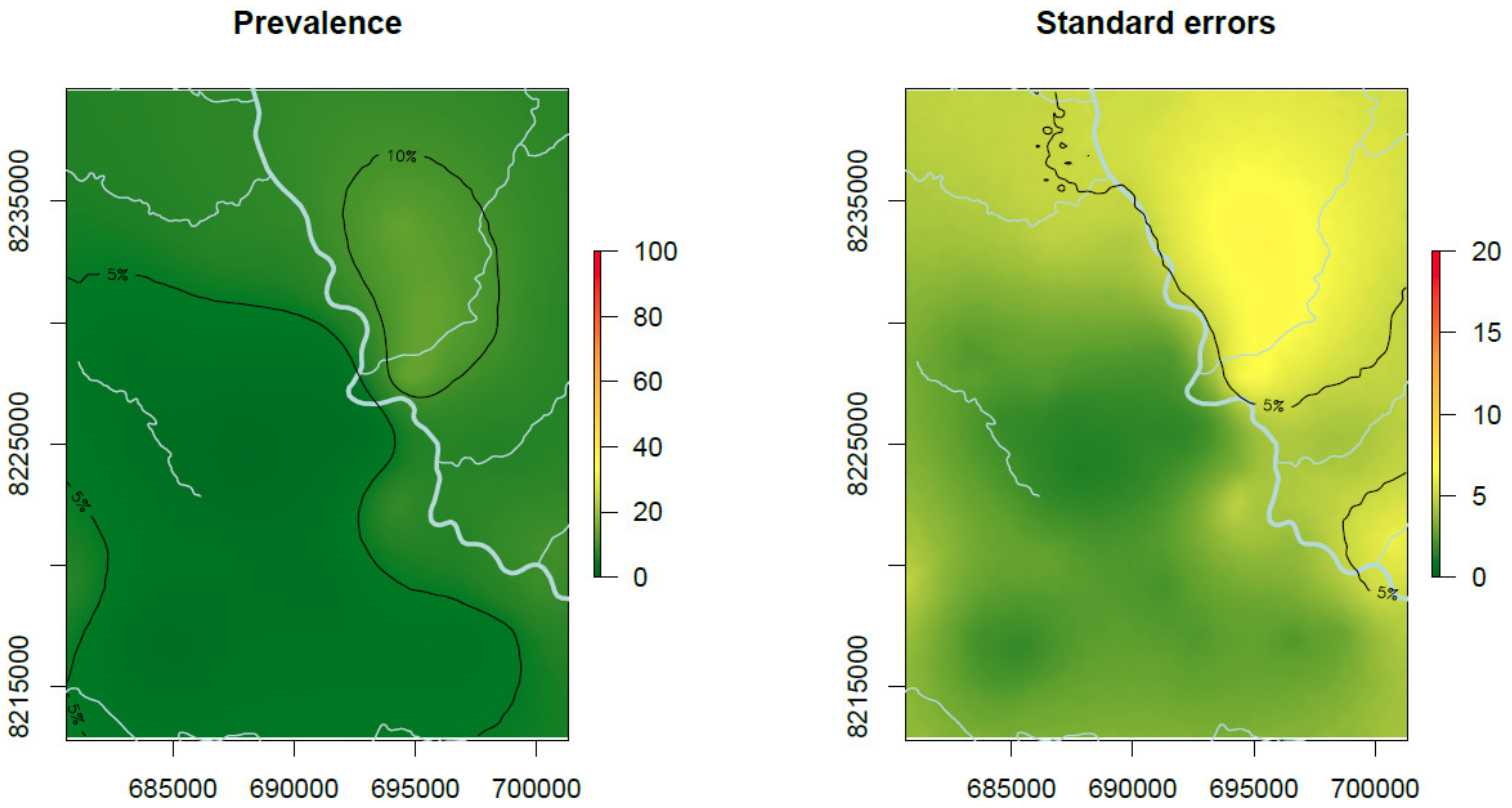
Distance between individual ticks on the x and y axis equivalent to 5km.

Figure 41: Geographic distribution of the population prevalence *P. falciparum* infection (by RDT) secundigravidae aged 20 years or more in all trimesters in the dry season with standard errors



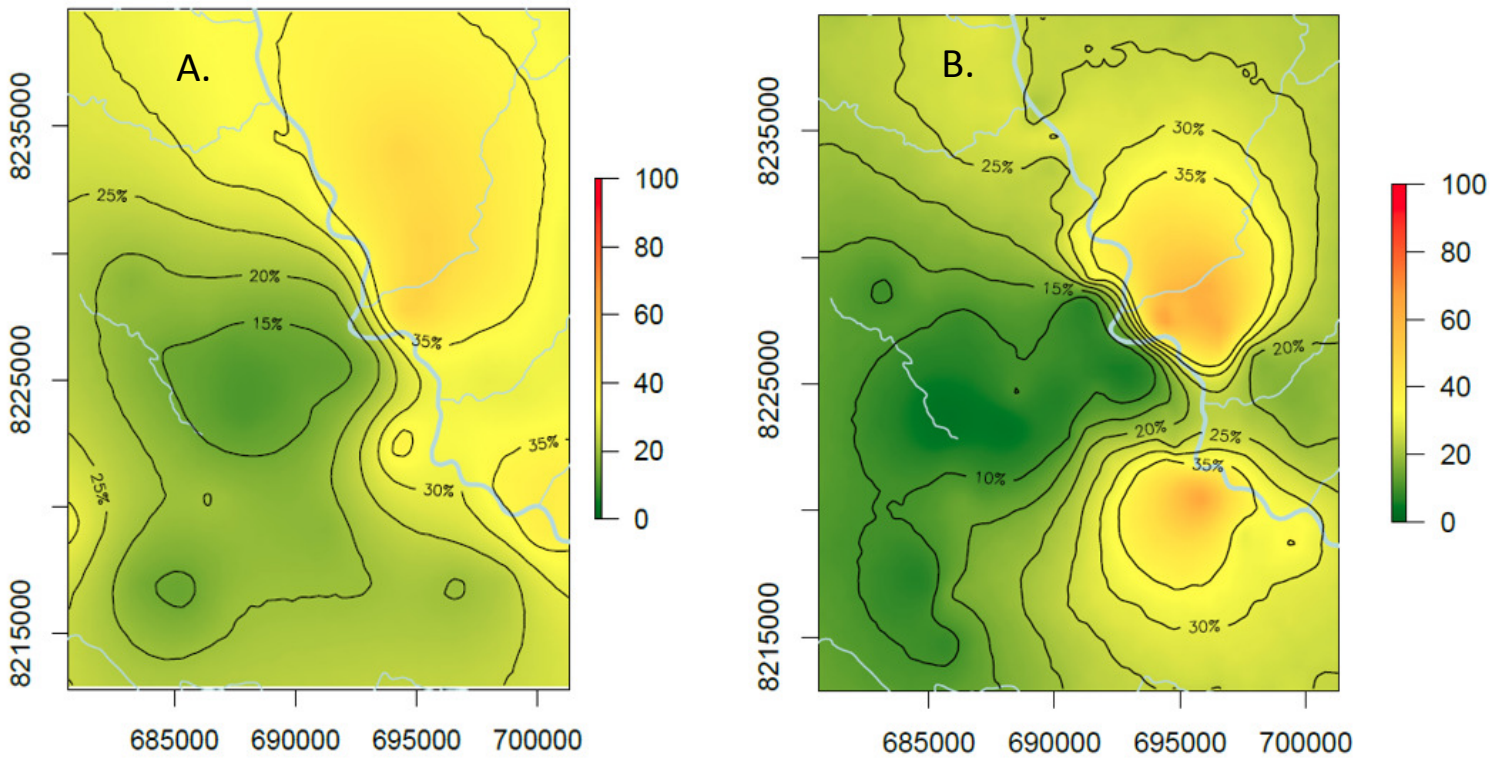
Distance between individual ticks on the x and y axis equivalent to 5km

Figure 42: Geographic distribution of the population prevalence *P. falciparum* infection (by RDT) multigravidae aged 20 years or more in all trimesters in the dry season with standard errors



Distance between individual ticks on the x and y axis equivalent to 5km

Figure 43: Geographic distribution of the population prevalence *P. falciparum* infection (by RDT) in (A.) primigravidae aged 15 to 19 years and (B.) children aged 6-59 months (corrected for bias)



Distance between individual ticks on the x and y axis equivalent to 5km in (A.) and 2km in (B.)

Figure 42 is a contour map of the geographic distribution of *Pf*PR in secundigravidae aged 20 years or more in the dry season with accompanying standard errors. The generated map reveals lower overall prevalence than in primigravidae with smaller standard errors around estimates from the Shire River flood plains. Again the *Pf*PR was highest in the floodplains of the Shire River valley but the contours do not seem to detect sufficient small scale variations in *Pf*PR and performed worse than the younger primigravidae subgroup.

Figure 43 compares the geospatial heterogeneity displayed by women aged less than 20 years in the ANC Survey and children aged 6 to 59 months in the EPI Clinic Survey after corrected for geospatial bias. On the whole, the prevalences are lower in the ANC Survey compared to the EAG Clinic Survey, and the latter was able to detect a finer scale of geospatial heterogeneity in PfPR. The geo-referenced data from primigravidae aged less than 20 years detected hotspots but to a lesser degree of accuracy than children aged 6 to 59 months.

7.4 Discussion

Our findings confirm that ANC surveys of pregnant women can provide fairly accurate estimates of geographical heterogeneity in *Pf*PR of the underlying population. In line with the known epidemiology of malaria in pregnancy, adolescent primigravidae were associated with the highest risk of infection, and showed more detail in terms of heterogeneity of the spatial prevalence pattern. While our findings suggest that ANC surveys of primigravidae, and other ANC subgroups, may not be able to identify small hotspots as well as EPI based surveys in young children, the broad similarity between spatial parasitaemia prevalence patterns based on primigravidae and those based on children in the adjusted EPI analyses, confirms the validity of ANC surveys as an M&E tool to monitor (sub-) district level malaria heterogeneity.

The use of ANC surveys may be a surprisingly simple M&E tool to guide local malaria control efforts. The presented example involves only a few key data points. Apart from 4 variables already collected as standard ANC practice (visit date, gravidity, age, gestational age/trimester), only a malaria RDT was added to routine practice. The associated finger prick blood sampling was already conducted as part of routine practice to determine anaemia (although not used for our analyses). Adding RDTs for M&E purposes is not a minor undertaking, but these are tests that are already provided to small clinics and would not require separate procurement or delivery chains. As increasing levels of drug resistance are reported for SP given for IPTp, alternatives using intermittent screening and treatment are being considered. If implemented, the involved screening with RDTs would become programmatic diagnostic practice and could simultaneously act as an M&E tool. As the high overall ANC attendance in many countries, including Malawi (Malawi National Statistical Office and ICF Macro, 2011), confirms that surveillance across ANC clinics would provide good spatial coverage of the underlying population, but there are two key features of ANC EAG surveillance that need to be taken into account; firstly, the absence of an ideal probability sample comparator group, and secondly the considerable variability in malaria susceptibility seen among pregnant women, associated with gravidity, age, and gestational age.

Unlike the situation presented with the EPI EAG surveillance, we did not have the ideal comparator group to validate the ANC data against: a probability sample of a sufficient sample size of pregnant women at population level. Collecting this would have been too costly for the project. Despite this we am confident that the presented findings convincingly show this EAG group accurately show spatial transmission patterns because: 1. ANC attendance is high in Malawi (Malawi National Statistical Office and ICF Macro, 2011). Indeed, the ANC survey provided a large representative sample of the study area; women attending ANC population came from all 50 villages in the study area with numbers representative of the underlying village sizes. 2. The mapped spatial pattern of malaria

heterogeneity and hotspots seen in the women was comparable to the pattern seen in young children. While the underlying susceptibility may be different between groups and levels of parasitaemia prevalence between children and pregnant women may differ, the spatial patterns and location of hotspots should be similar.

Unlike young children, pregnant women represent a relatively broader group with varying levels of susceptibility, age and pregnancy related acquired malaria immunity, which has been a well-described part of the epidemiology of malaria in pregnancy. To review the effect of these differences on the malaria risk maps, confirm the quality of the ANC data, and determine the optimal subgroup and 'scenario' to model in the geostatistical analyses, we assessed the determinants of malaria in the ANC survey in both standard statistical models and geostatistical models. From our multiple logistic regression models younger age (15 to 19 years) and primigravidae status was associated with significantly higher risks of infection in pregnant women attending ANC. This is agreement with most publication on the subject (Rogerson et al., 2000; Leenstra et al., 2003; Marques et al., 2005; Walker-Abbey et al., 2005; Ouma et al., 2007). Our probit model suggested that this effect occurs up to 25 years, which is not unusual as some studies suggest a higher cut-off age (Clerk et al., 2009; Taylor et al., 2011). From 25 years onwards, primigravidae do not appear to be at a significantly higher risk of infection, but the precision of our estimates is affected by the small numbers of primigravidae in this older age group resulting in wider confidence intervals. Based on this, we opted to use the standard cut-off of 20 years and this was found to be significant in the geostatistical model ($p = 0.011$) (Table 41). As a result we explored the following risk strata in our geospatial model: primigravidae less than 20 years, secundigravidae 20 years and older, and women with three of more pregnancies aged 20 years or more. The first risk strata represents the most susceptible subgroup. All explored risk strata accurately delineated the same geographic region with the highest transmission risk as the estimates in children aged 6 to 59 months in the same study area (Chapter 5), but with varying levels of detail.

The risk of malaria infection is thought to be highest in the second trimester (Desai et al., 2007), however in our study there was no difference in risk between trimesters after controlling for potential confounders. Since most women present late for their first antenatal visit, it is likely that that the women in the first trimester present late that their risk effect overlaps with that in the second trimester. There was an inverse relationship between gravidity and the risk of *P. falciparum* infections as has been detected in other studies (Walker-Abbey et al., 2005).

The risk of infection with *P. falciparum* was significantly higher in pregnant women of all gravidities than pregnant and non-pregnant women in the household survey. The similar risk of infection between pregnant and non-pregnant women in the household survey is an unusual finding given all the evidence (Mvondo et al., 1992; Parekh et al., 2007; Almeida et al., 2010; Taylor et al., 2011) but was likely due to the small sample size of pregnant women in the household survey. Given that ages of pregnant women in the ANC and household survey were similar, we believe that the significantly higher risk of infection seen in the former may be due to two reasons. Firstly we could have captured women in the earlier stages of pregnancy in the ANC survey than in the eMIS as women in the household survey may not have disclosed their early pregnancy status or were not aware of its existence; and since women are more likely to be parasitaemic earlier in the pregnancy (Desai et al., 2007), this may be one reason for the higher risk of infection in the ANC survey. Secondly, women may be more likely to attend ANC clinic if parasitaemic and ill and since we did not differentiate these women from the rest of the sample of women attending ANC, this may also account for increased risk.

The above findings may suggest that young primigravidae < 25 years are the potential subgroup to focus on with ANC surveillance. However, the need to capture a representative sample of EAG data points across the area of interest in order to pick up fine-scale heterogeneity suggests that ANC surveillance should include data from all gravidities and age group. While the patterns were less

defined, all gravidity risk maps showed the same underlying parasite prevalence pattern, and would contribute to improved precision of the modelled risk map. Also, primigravidae only comprise around 25% of pregnancies in this area, the number of pregnancies may not provide enough spatial representation.

This survey is the first to provide a proof-of-concept for ANC surveys, but the opportunistic nature of the study led to two important limitations; the restricted size of the study area and the limited number of indicators assessed. The comparison with household data from women of childbearing age and EPI data meant that the comparison was conducted in an area of 50 villages, rather than the full ANC catchment area, approximately double the size of the area currently assessed. Women living on the edges of a catchment are furthest away from the ANC in hard-to-reach areas may differ in characteristics. The opportunistic nature of the study also meant that we didn't measure other standard MIS indicators, or data of potential confounders including ITN ownership and SES. Future surveys should ideally involve the standard MIS methodology and measure these confounders in a small random subset (because of the time taken to administer the questionnaire) or use key proxy variables like educational status to adjust for social determinants that may affect ANC attendance or malaria infection; as these may improve prediction of estimates of control progress. Indicators measuring the uptake of control interventions could easily be included as part of the ANC visit. Because the geolocation of women attending ANC was only possible at the village level, we included a probability sample of women of childbearing age from the population to improve our spatial predictions. A suitable probability sample of pregnant women in the population would be the ideal strategy but a survey of such a sample would be logistically challenging. The use of an alternative method of geolocation of the household like map books may be a logical next step (MacPherson et al., 2013). Lastly, time restrictions stopped us from assessing the use of ANC survey data to capture temporal patterns of parasitaemia prevalence in this area.

With this proof of concept from a single site, the next step is to evaluate this approach at a larger scale in studies with multiple ANC clinics to capture larger (sub)district areas, in other transmission settings and in areas with varying ANC attendance. Since our study did not measure other malaria control indicators like anaemia prevalence, ITN uptake and IRS coverage; we suggest that estimates of these indicators from women attending ANC are assessed. Methods of improving the precision and controlling for bias could include the use of a designed hybrid sampling approach as suggested by Hedt et al 2011, using a probability sample of women of childbearing age (regardless of pregnancy status) to improve the spatial prediction. In practice, the sampling strategy employed with a hybrid sample, will depend on a trade-off between the desired accuracy, the feasibility and the logistics available.

7.5 Conclusions

This study is the first to provide evidence that ANC surveys are able to generally inform malaria control strategies (and not only that for MIP), and could be used to measure geospatial heterogeneity in *Pf*PR, and thus inform more targeted malaria control efforts. Our results suggest that using a small probability sample of women of child bearing age in the population improves the spatial prediction of our estimates. Younger primigravidae are the risk strata with the most potential in detecting geographic variation in *Pf*PR given their lower pregnancy-specific immunity, and could demarcate a finer scale of hotspots to guide targeting of interventions. As National Malaria Control Programmes continue to scale up control efforts, the ability to obtain timely information on geospatial distribution of PfPR will be essential in strategizing control efforts as transmission falls and the distribution of transmission becomes more heterogeneous.

Chapter 8: Discussion and conclusions

8.1 Two novel health facility-based EAGs for monitoring malaria control progress

In this thesis we showed from a comprehensive review of the validation of estimates of malaria control progress indicator from multiple EAGs that previous efforts focused on comparing average estimates with contemporaneous data from a probability sample from the population (Rodrigues et al., 2008; Skarbinski et al., 2008; Mathanga et al., 2010; Gahutu et al., 2011; Oduro et al., 2011b; Stevenson et al., 2013). Apart from a recent evaluation of school surveys (Stevenson et al., 2013), none of these studies attempted to address or control for inherent bias. None of these studies attempted to examine the EAGs potential to adequately measure geospatial heterogeneity in malaria transmission which is a key omission based on current knowledge of spatial patterns of transmission (Carter et al., 2000; Bousema et al., 2012). Not surprisingly, there was great variability in the accuracy of average estimates from different EAGs previously evaluated, and the overall outcome was that these average estimates were usually biased. This has been a major reason that has held back the use of EAGs, but the advent of new statistical methods especially in dealing with geospatial bias (Giorgi et al., In press), has opened up an exciting opportunity that warrants a revisiting of EAG monitoring as this approach is logistically less demanding than population surveys. The main rationale for the presented studies was to determine whether surveillance in EAGs is a reliable malaria M&E approach. We focused our approach on children attending EPI clinics for well child visits and women attending ANC as these were the most promising novel EAGs.

Children coming for well child visits could potentially be sampled to assess the *Pf*PR in children aged 6 to 59 months (Some et al., 1997), the main risk strata suggested as a sensitive group to monitor changes in malaria transmission (O'Meara et al., 2008b; Kendjo et al., 2013; MEASURE Evaluation et al., 2013a). There is information available on the feasibility of this approach to malaria surveillance (Delacollette C, 1990; Some et al., 1997), and attempts have been made to validate estimates from this EAG (Mathanga et al., 2010; Cibulskis et al., 2012).

Given the high immunization uptake in the study area (Malawi National Statistical Office and ICF Macro, 2011), we expected the estimates to be reasonably representative of that in the catchment population (Cibulskis et al., 2012).

Women attending ANC are another potential EAG in whom currently M&E is focused on detecting the effects of specific interventions for malaria in pregnancy (WHO, 2007a). Pregnant women represent another key risk strata for *P. falciparum* malaria infection (Duffy and Fried, 2005), particularly in high transmission settings (Gilles et al., 1969; Brabin, 1983; McGregor et al., 1983; Desai et al., 2007). The currently recommended impact indicators for malaria in pregnancy focus on parity-specific low birth weight rates and the gravidity specific prevalence rates of anaemia (WHO, 2007a), and it is not yet clear how these indicators will be integrated with other malaria control efforts and indicators. With such impact indicators meant to be measured through population surveys like MISs, this will make an already logistically and financial challenging process more complex by the requirement of a large sample size to survey an appropriate number of pregnant women (WHO, 2007a; MEASURE DHS, 2013b). The feasibility of such an approach as an M&E tool has been explored (Parise et al., 2003), and given the ubiquitous nature of the *Pf*PR metric (Hay et al., 2009; Gething et al., 2011), the rates of maternal *P. falciparum* infection could potentially be used to measure geospatial heterogeneity in malaria transmission. Given the high ANC attendance in our study area (Malawi National Statistical Office and ICF Macro, 2011), we again expect our results to be reasonably representative of the study area.

These two novel EAGs, being key risk strata for malaria infection, offer the potential of measuring detailed small area estimates of geospatial heterogeneity in transmission. How accurate these estimates are and whether any inherent bias in EAG estimates can be resolved by statistical techniques is the main approach in this thesis, though we also evaluated the potential of these EAGs to provide short-term trends of control progress.

8.1.1 Measuring malaria control indicators by surveillance in children coming for well child visits

We approached the evaluation of this EAG by firstly determining if average annual estimates of malaria control indicators derived from children coming to EPI clinics for well child visits were comparable to a probability sample of the population in the same catchment area. Since we were mainly interested in the measurement of the heterogeneity of malaria transmission, our main indicator in the comparison was the geospatial distribution *Pf*PR (assessed by RDT) in the children aged 6 to 59 months, a key risk strata for measuring impact of malaria control interventions (O'Meara et al., 2008b; Kendjo et al., 2013; MEASURE Evaluation et al., 2013a). Geospatial heterogeneity in APR was also included in the comparison as moderate to severe anaemia (Hb < 8.0g/dl) has been previously shown to be a reliable indicator of malaria morbidity and impact of control interventions (Korenromp et al., 2004; RBM et al., 2009), and is a recommended malaria M&E indicator (MEASURE Evaluation et al., 2013a).

In our study, the APR in both the EAG and the population sample were low, 5.9% and 4.5% respectively, given the malaria transmission in our study area (Skarbinski et al., 2011; Mzilahowa et al., 2012). A study in the same catchment population revealed hookworm infestation, nutritional deficiencies and G6PD as more important causes of severe anaemia (Calis et al., 2008). Caution is already advised on the interpretation of APR in the current malaria indicator guidelines, taking cognisance of the multifactorial nature of the aetiology anaemia (MEASURE Evaluation et al., 2013a). Given the proliferation of micronutrient supplementation, vitamin A administration and deworming programmes, and the fact that anaemia was assessed as a metric when malaria epidemiology was different from what is it today (Korenromp et al., 2004), we suggest the current validity of APR as a malariometric needs to be re-evaluated. Since we were obviously underpowered for geostatistical analysis using APR, we utilized mean haemoglobin values instead in our geospatial analysis.

Our main findings were that estimates of malaria control indicators were subject to geospatial bias, though estimates of impact indicators like *Pf*PR and APR were less subject to this bias than estimates of coverage of control intervention like ITN and IRS coverage. This was probably due to the fact accuracy of estimates of impact indicators depended on the inclusion of a sample that included enough individuals from the differing transmission ecologies within the study area, whilst the of impact indicators depended on risk factors of health facility utilization like socioeconomic status. Though the geospatial bias was due to different aetiologies, adjusting for this bias resolved any problems of geospatial bias allowing the development of fine detail contour maps displaying the spatial heterogeneity in malaria control indicators.

Geographic patterns of health facility utilization have long since been recognised (Shannon et al., 1973; Guagliardo, 2004; Alegana et al., 2012; Delamater et al., 2012), and our understanding of the aetiology of these patterns have since improved, implying the interaction of several factors including the availability of medical services, cost of treatment, distance, level of education and socioeconomic status (Wyss et al., 1996; Asenso-Okyere et al., 1998; Nyamongo, 2002; Baker and Liu, 2006; Ewing et al., 2011; Zyaambo et al., 2012). The geospatial bias in estimates of malaria control indicators derived from health facility-based EAGs are probably a proxy measure of geographic patterns of health facility utilization rates which a result of multifactorial aetiologies affecting malaria control indicators in different ways. Controlling for geospatial bias in estimates of malaria control indicators derived from health facility-based improved the accuracy of the measurement of spatial heterogeneity in these indicators regardless of the aetiology. It is highly likely that other EAGs that depend on natural systems of selection outside the control of the researcher that similarly have a multifactorial aetiology, are subject to similar geographic restrictions in the sampling frame which is amendable to correction of geospatial bias by geostatistical methods relying on the inclusion of a probability sample of the population and this has important public health implications given the logistical attractiveness of EAG surveillance.

8.1.2 Measuring short-term trends in malaria control indicators using the EPI EAG

We assessed the ability of this EAG to measure short-term changes in control progress, by comparing monthly trends in malaria control indicators in children aged 6 to 59 months to the same age strata of a probability sample of the population. Again, we were mainly interested in the measurement of trends in malaria transmission intensity so we focused on *Pf*PR. From our results monthly data from the EAGs correctly reflected that despite the significant increase in ITN coverage in the study from May 2011 to April 2013, there was no significant change in *Pf*PR. This lack of decline of malaria in Malawi has been noted in preceding publications (Roca-Feltrer et al., 2012a; Okiro et al., 2013).

There were differences in the crude and smoothed trends between surveys probably due to months where the pattern of health facility utilization in the EAG sample led to significantly biased monthly estimates. An exploration of the role of the bias in the linear trends revealed that the role of bias in the overall trend was not statistically significant even after controlling for potential confounders, probably due to the high immunization rates in our study area (Malawi National Statistical Office and ICF Macro, 2011). The effect of month to month variation in health facility utilization rates on the estimates of malaria control indicators is a clear indicator that the commonly held suggestion that bias in such health facility-based samples remains reasonably constant enough to enable the accurate detection of population trends (Saphonn et al., 2002). Trends in malaria control interventions from this EAG must be interpreted with this in mind and the accuracy estimates could potentially be improved by small additional temporal-spatial probability samples of the population (Hedt and Pagano, 2011), which will still be less financially demanded than using continuous district level household surveys. Again, this has important public health implications as measurement of short-term trends can help guide the efficiency of control programme resource mobilization the interval between serial MISs.

8.1.3 Measuring geospatial heterogeneity by surveillance in women attending ANC

In women attending ANC, we compared retrospective screening data from a antimalarial efficacy trial to a synchronous probability sample of women of childbearing age (i.e. 15 to 49 years) in the population to determine the excess risk of *P. falciparum* infection (detected by RDT) in pregnant and to delineate the most sensitive risk strata in that EAG to measure geospatial heterogeneity in *Pf*PR in the catchment population. From our results, pregnant women aged less than 25 years were at a significantly higher risk of *P. falciparum* parasitaemia compared to other parities and ages. Most of the literature from similar transmission settings (Rogerson et al., 2000; Leenstra et al., 2003; Marques et al., 2005; Walker-Abbey et al., 2005; Ouma et al., 2007) suggest less than 20 years is the group with high risk but there are studies in support of our findings (Clerk et al., 2009; Taylor et al., 2011).

In our study, we explored the potential of primigravidae aged 15 to 19 years in detecting geographic variation in *Pf*PR, as previous literature supports this as the highest risk strata in pregnant women in similar transmission settings (Rogerson et al., 2000; Leenstra et al., 2003; Marques et al., 2005; Walker-Abbey et al., 2005; Ouma et al., 2007), due to the combined effects of parity specific risk and age specific risk. We compared the ability of this risk strata to detect small scale variations in *Pf*PR by comparing contour maps derived from this risk strata with older secundigravidae and women with three or more children (aged 20 years or more) to reduce overlap in the parity- and age-specific effects. The data from primigravidae aged 16 to 19 years allowed us to detect the geospatial heterogeneity in *Pf*PR in our study area, correctly detecting known hotspots, but this group seemed less sensitive to small scale variation in transmission compared to children aged 6 to 59 months (Figure 20), probably due to their higher age specific immunity. The ability to detect geospatial heterogeneity decreased with increasing parity probably due to the additional effect of parity specific immunity (Fried and Duffy, 1996). Primigravidae aged 15 to 19 years were the risk strata with the most potential for measuring

geospatial heterogeneity in our transmission setting due to the lower pregnancy and age specific immunity, and we advise that potential of different risk strata be evaluated for this potential in different transmission settings, especially in the presence of significant rates of maternal HIV infection (Steketee et al., 1996; van Eijk et al., 2003; ter Kuile et al., 2004). In low transmission settings were the age and parity-specific effect is less marked, it is likely that surveillance in all women attending ANC would provide accurate information of geospatial heterogeneity in *Pf*PR (Duffy and Fried, 2005; Desai et al., 2007). The inclusion of a small probability sample of women of childbearing age from the catchment population improved the spatial precision of our estimates of *Pf*PR and we recommend this approach to increase the representativeness of this EAG.

8.2 The attractiveness of surveillance in EAGs

In a time when we are facing considerable potential changes in malaria epidemiology, with the introduction of new control measures and indicators, a key element in focusing malaria control and elimination efforts will be the availability of low-cost surveillance strategies that can provide timely accurate average estimates of control progress and can easily be integrated into district malaria control activities (Rowe, 2009b; The malERA Consultative Group on Monitoring, 2011). These surveillance strategies must also be capable of capturing the effects of transmission reduction, including a shift in burden to older children (Schellenberg et al., 2004; Ceesay et al., 2008; O'Meara et al., 2008a), and increasingly localised areas of transmission or hotspots as transmission falls (Bousema et al., 2012). The appeal of EAG surveillance is due to its low cost (due to a lower logistical requirement than household surveys), ability to provide timely estimates of malaria control indicators from small catchment areas and the measure geospatial heterogeneity in malaria transmission and coverage of control interventions. We expound on this in the following sections.

8.2.1 Comparing the cost of surveillance in EAGs to population surveys

Surveillance in population subgroups that are readily available and routinely aggregate in a convenient location of relatively small geographic size (e.g. children attending EPI clinic), offers the opportunity to sample a large number of that population subgroup or a specific risk strata in a shorter timeframe than would be required for a household survey, representing significant cost savings. For example, in a detailed cost comparison between school surveys and a standard MIS both implemented at the national level in Kenya, the national MIS cost twice as much per cluster as school surveys, with the extra cost being due to higher personnel, transportation and communication costs (Brooker et al., 2009). Opportunistic low-cost surveillance of the whole population or specific risk strata is also possible through integration with other public health initiatives like NIDs and MDA (Santos et al., 2008b) enabling cost sharing between the public health campaign and surveillance. The main benefit of using an EAG sample for malaria M&E is that it will require fewer resources that that required in a standard population-based survey. It is also very easy to implement with few rules governing how the sample should be collected.

8.2.2 The provision of timely small area data from EAGs

Malaria control programmes should have the ability to modify their control strategies and M&E strategy of MTI decreases (Yekutiel, 1960) using average estimates of key population indicators to determine when a reorientation in programme strategy is required (Hay et al., 2008). Continuous or more frequent serial surveys would provide early evidence of transmission reduction by illustrating a decreasing trend impact indicators like *Pf*PR and APR in the general population or key risk strata. The financial and logistic requirement of a standard MIS makes it unlikely to allow small enough intervals between surveys for the survey to be considered as continuous. Whilst rolling MIS partly answer this question, the complex sampling routine required and the fact that is still a household level survey requiring mobile field teams means it is likely more difficult

to implement and more expensive than EAG surveillance (Roca-Feltrer et al., 2012b).

The EAGs that offer the potential for continuous surveillance evaluated in this thesis, like children attending EPI immunization clinics and women attending ANC are relatively inexpensive and easy to implement. The figures from each catchment area may provide average estimates that can be pooled to generate average estimates for much larger areas like sub-district divisions (Rowe, 2009b). Whilst for household surveys the primary sampling unit or clusters are villages, in such health facility-based EAGs, the primary sampling unit or cluster will be the health facility. Within the clusters in the household surveys, households are randomly sampled; and within the clusters in the facility-based surveys, all children attending well child clinics and women attending ANC should be sampled. The availability of timely data on average estimates of malaria control indicators can help motivate district health management teams in improving performance and achieving control targets through the Hawthorne effect (Mayo, 1945).

Unlike MISs which are a standalone M&E tool, continuous surveillance in these EAGs can easily be integrated into district programmatic activities to support the scaling up of malaria control interventions (Rowe, 2009b). Such continuous surveillance will encourage a dynamic programme response, where timely estimates of MTI facilitate a reaction to emerging transmission changes, compared to serial MISs done every three to five years which result in timed simultaneous static measurements of malaria transmission intensity and uptake of control interventions, resulting in a static programmatic response. In a static programme response, control efforts are guided by data collected at one time point; and the effects of interventions can only be assessed at the next assessment time point. It then becomes arduous to demonstrate clearly whether the up-scaling of interventions actually resulted in the in a perceived reduction in malaria transmission intensity. The interim period between the timed assessments becomes

a "blind spot" in which interventions are rolled out with little information about their effectiveness or whether there are any emerging transmission changes.

8.2.3 The provision of data on geospatial heterogeneity in malaria transmission from EAGs

Given the known heterogeneity in malaria transmission within countries (Carter et al., 2000), it is unlikely that different regions in the same country would be at the same level in the transmission spectrum even as malaria transmission intensity falls. National level MISs provide single cross-sectional assessments of national disease burden and are not representative at the district level; because the two-stage cluster sampling technique does not include all districts and the number of clusters and sample size within a district is small (MEASURE DHS, 2013b). Whilst the stratification by transmission intensity as recommended by the new sampling guidelines will improve the accuracy of national estimates (MEASURE DHS, 2013b), it will not enable direct measurement of heterogeneity in transmission and requires foreknowledge of the different transmission patterns within a country, a situation that is not always possible. MISs therefore cannot not accurately reflect the variability of malaria transmission at a sub-national level, a potential shortcoming that becomes increasingly important as malaria transmission falls and distribution becomes more heterogeneous when targeting hotspots may be a much more efficient use of resources (Bousema et al., 2012). EAGs are likely to produce data on malaria control indicators that are more likely to be accurate over small catchment areas (Stevenson et al., 2013). Pooling the results from several EAGs may allow the development of maps of the distribution of malaria control indicators over a much wider area like a district (Rowe, 2009b).

8.3 Addressing lack of representativeness in EAGS

The main issue with using EAG samples is the potential lack of representativeness when compared to population samples. Lack of representativeness in EAG samples could be due to selection bias (an absence of

comparability between the EAG and the population) and/or information bias (incorrect determination of malaria control indicators due to misinformation). This is because unlike probability samples where there is an equal chance of selection of a participant (International Epidemiological Association, 2008), and this usually involves a process of randomization carried out by the investigator, non-probability samples depend on natural systems to do the selection for the investigator (Law and Pascoe, 2013) making the sample logistically appealing especially since details of the sampling frame are not a prerequisite to sampling like in the randomised approach. The natural systems that make the sample easy to select and survey are also the main potential causes of bias.

8.3.1 Dealing with selection bias

Selection bias in EAGs mainly results from low or differential coverage when it is likely some individuals in the population are poorly represented in the EAG and these individuals possess a certain attribute that significantly affects the indicator we are measuring. For example if our EAG households with higher socioeconomic status than the population, given the known association between socioeconomic status and household ITN possession (Garcia-Basteiro et al., 2011; Larson et al., 2012), we are likely to overestimate the level of this malaria control indicator in the population. Where there is a high probability of inclusion and the difference in the estimates of an indicator measured from individuals who are and are not included in the EAG sample is not statistically significant; the EAG is likely to be representative of the situation in the population. For example, coverage rates of public health interventions were similar between vaccinated and unvaccinated children if population vaccine coverage is over 60% (Cibulskis et al., 2012). Any other situation will lead to varying magnitude and direction of selection bias and a sample that will not be representative.

Recent advances in statistical techniques in dealing with selection bias in surveys particularly the ability to combine the data from multiple surveys into one multivariate generalized linear geostatistical model (Giorgi et al., In press),allows

us to correct for some of these natural systems of selection especially when they follow a geographic pattern. Central to the methodology of this approach is a probability sample of the target population which is used to detect geospatial by combining with EAG data in a geostatistical binomial models, therein correcting for this bias improves the estimates from the EAG sample. For example, it is known that despite the aetiology of health facility utilization being multifactorial (Wyss et al., 1996; Asenso-Okyere et al., 1998; Nyamongo, 2002; Baker and Liu, 2006; Ewing et al., 2011; Zyaambo et al., 2012), the resultant patterns of health facility utilization are geographic (Shannon et al., 1973; Guagliardo, 2004; Alegana et al., 2012; Delamater et al., 2012). Geospatial bias in estimates thus represent a proxy measure of all these risk factors, and controlling for the effect of this bias improves the accuracy of measurement of geospatial heterogeneity (Giorgi et al., In press) without the need to measure all potential factors of responsible for patterns of health facility utilization which may not always be possible. Ideally, selection bias in EAGs should be dealt with at the sampling stage and improvement in computer technology and statistical programmes have improved the feasibility of hybrid sampling (Hedt and Pagano, 2011), lot quality assurance sampling (LQAS) (Dodge and Romig, 1929; Shewhart, 1931) and geo-spatial sampling (Ripley, 2004). Of these only LQAS has been assessed at the district level (Dias et al.; Okoh et al., 2006; Ministry of Health of Eritrea, 2008; Laly et al., 2009) and national level (Biedron et al., 2010).

8.3.2 Dealing with information bias

Information bias in our case could occur if there is incorrect determination of estimates of malaria control indicators. The information bias could lead to differential misclassification due incorrect reporting of outcome indicators like household ITN possession in the EAG survey due to social desirability bias (Skarbinski et al., 2006). By virtue of the fact that most EAGs are selected by natural systems, it may not be possible to validate household-level indicators like ITN possession by direct inspection as recommended in a standard MIS (MEASURE Evaluation et al., 2013a).This is a potential shortcoming of this approach.

Information bias could also result if information on indicators is gathered incorrectly in both the EAG and the general population. Information bias may be minimized by the use of a standard questionnaire tool like the MIS questionnaire (http://rbm.who.int/merg.html#MIS) or use of an algorithm to determine key household indicators like we did with ITNs in our study (Annex 3).

8.4 Conclusions

Our results provide evidence that surveillance in these two EAGs can inform malaria control strategies and can be used to measure short-term changes in control progress. Natural systems of selection that determine the sampling frame of these health facility-based EAG samples available for survey appear to follow a geographic pattern, and controlling for this geospatial bias improves the validity of EAG estimates. Geospatial bias seems to be a proxy measure of the effect of these natural systems on the sampling frame and it is likely that other EAGs may be subject to the same phenomenon. This has important policy implications given the low cost of this method of surveillance. EAGs that are representative of key population risk strata can be used for malaria surveillance at different parts of the transmission spectrum. For example, in moderate to high transmission settings where the burden of disease is in younger children and pregnant women, the ANC and the EPI EAG could be used as an M&E tool. Where transmission pattern is changing and the age shift to older children is suspected, school surveys for example would be a more appropriate EAG. At the elimination threshold where the sample size required to adequately measure transmission is prohibitive, opportunistic surveillance during large population-based public health campaigns like MDA are a suitable M&E tool. Given the heterogeneity in transmission, it is likely that countries might use combination of different EAGs in different settings to provide estimates of control progress complementary to nationwide MISs, especially in the interval between MISs or in problem district where a more intense examination of control progress may be required.

However, this tool is not ready for widespread application to guide control program strategy. More needs to be done to understand natural systems (like health facility utilization) that determine how representative the sampling frame of different EAGs are compared to key risk strata or the general population, as they are likely to be different in various settings and transmission ecologies. Constant correction for geospatial bias using a representative probability sample is not a sustainable option. Instead, research should focus on how to improve the accuracy of EAG estimates through improved sampling strategies like hybrid sampling. The effects of different natural systems and which sampling strategy might be most appropriate could be explored in statistical simulation models. The effect of different sampling strategies on the validity of EAG estimates could be explored through statistical simulation models to advice on the most appropriate strategy for different settings. Most malaria endemic countries like Malawi are currently scaling up proven control interventions and there is an increasing requirement for continuous sub-national malaria surveillance and M&E to effectively target malaria control interventions at the district level and guide programme implementation in-between nationwide surveys. As NMCPs continue to take increasing responsibility in the operational and financial aspects of malaria control and elimination, the capacity to accurately measure malaria transmission in an efficient way will be key to targeting malaria control and long term sustainability. If our findings are replicated in other transmission settings, surveillance in EAGs like those evaluated in our study could provide useful and operationally attractive approach of measuring malaria transmission at the district level.

References

Abba, K., Deeks, J. J., Olliaro, P., Naing, C. M., Jackson, S. M., Takwoingi, Y., Donegan, S. & Garner, P. (2011). Rapid diagnostic tests for diagnosing uncomplicated P. falciparum malaria in endemic countries. *Cochrane Database Syst Rev*, Cd008122.

Abramson, J. H. (2011). WINPEPI updated: computer programs for epidemiologists, and their teaching potential. *Epidemiol Perspect Innov,* **8**, 1.

ACT Consortium. (2014). *The ACTia trial: Safety of repeated drug use in children*. URL: http://www.actconsortium.org/projects/18/the-actia-trial-safety-of-repeated-drug-use-in-children [19th February, 2014].

Afrane, Y. A., Zhou, G., Githeko, A. K. & Yan, G. (2013). Utility of health facility-based malaria data for malaria surveillance. *PLoS One,* **8**, e54305.

Agyepong, I. A. & Kangeya-Kayonda, J. (2004). Providing practical estimates of malaria burden for health planners in resource-poor countries. *Am J Trop Med Hyg,* **71**, 162-7.

Ahmed, S., Creanga, A. A., Gillespie, D. G. & Tsui, A. O. (2010). Economic status, education and empowerment: implications for maternal health service utilization in developing countries. *PLoS One,* **5**, e11190.

Akmatov, M. K. & Mikolajczyk, R. T. (2012). Timeliness of childhood vaccinations in 31 low and middle-income countries. *J Epidemiol Community Health,* **66**, e14.

Alba, S., Hetzel, M. W., Nathan, R., Alexander, M. & Lengeler, C. (2011). Assessing the impact of malaria interventions on morbidity through a community-based surveillance system. *International Journal of Epidemiology,* **40**, 405-416.

Alegana, V. A., Atkinson, P. M., Wright, J. A., Kamwi, R., Uusiku, P., Katokele, S., Snow, R. W. & Noor, A. M. (2013). Estimation of malaria incidence in northern Namibia in 2009 using Bayesian conditional-autoregressive spatial-temporal models. *Spat Spatiotemporal Epidemiol,* **7**, 25-36.

Alegana, V. A., Wright, J. A., Pentrina, U., Noor, A. M., Snow, R. W. & Atkinson, P. M. (2012). Spatial modelling of healthcare utilisation for treatment of fever in Namibia. *Int J Health Geogr,* **11**, 6.

Aliaga, A. & Ren, R. (2006). *Optimal sample sizes for two-stage cluster sampling in Demographic and Health Surveys.* Calverton, Maryland: MEASURE DHS.

Almeida, L. B., Barbosa, M. & Martinez-Espinosa, F. E. (2010). [Malaria among women aged 10 to 49 years, according to SIVEP-Malaria, Manaus, State of Amazonas, 2003-2006]. *Rev Soc Bras Med Trop,* **43**, 304-8.

Alves, F. P., Durlacher, R. R., Menezes, M. J., Krieger, H., Silva, L. H. & Camargo, E. P. (2002). High prevalence of asymptomatic Plasmodium vivax and Plasmodium falciparum infections in native Amazonian populations. *Am J Trop Med Hyg,* **66**, 641-8.

Ansah, E. K., Narh-Bana, S., Epokor, M., Akanpigbiam, S., Quartey, A. A., Gyapong, J. & Whitty, C. J. (2010). Rapid testing for malaria in settings where microscopy is available and peripheral clinics where only presumptive treatment is available: a randomised controlled trial in Ghana. *Bmj,* **340**, c930.

Antinori, S., Galimberti, L., Milazzo, L. & Corbellino, M. (2013). Plasmodium knowlesi: the emerging zoonotic malaria parasite. *Acta Trop,* **125**, 191-201.

Aponte, J. J., Schellenberg, D., Egan, A., Breckenridge, A., Carneiro, I., Critchley, J., Danquah, I., Dodoo, A., Kobbe, R., Lell, B., May, J., Premji, Z., Sanz, S., Sevene, E., Soulaymani-Becheikh, R., Winstanley, P., Adjei, S., Anemana, S., Chandramohan, D., Issifou, S., Mockenhaupt, F., Owusu-Agyei, S., Greenwood, B., Grobusch, M. P., Kremsner, P. G., Macete, E., Mshinda, H., Newman, R. D., Slutsker, L., Tanner, M., Alonso, P. & Menendez, C. (2009). Efficacy and safety of intermittent preventive treatment with sulfadoxine-pyrimethamine for malaria in African infants: a pooled analysis of six randomised, placebo-controlled trials. *Lancet,* **374**, 1533-42.

Aron, J. L. (1988). Mathematical modeling of immunity to malaria. *Mathematical Biosciences,* **50**, 347-357.

Asante, K. P., Abdulla, S., Agnandji, S., Lyimo, J., Vekemans, J., Soulanoudjingar, S., Owusu, R., Shomari, M., Leach, A., Jongert, E., Salim, N., Fernandes, J. F., Dosoo, D., Chikawe, M., Issifou, S., Osei-Kwakye, K., Lievens, M., Paricek, M., Moller, T., Apanga, S., Mwangoka, G., Dubois, M. C., Madi, T., Kwara, E., Minja, R., Hounkpatin, A. B., Boahen, O., Kayan, K., Adjei, G., Chandramohan, D., Carter, T., Vansadia, P., Sillman, M., Savarese, B., Loucq, C., Lapierre, D., Greenwood, B., Cohen, J., Kremsner, P., Owusu-Agyei, S., Tanner, M. & Lell, B. (2011). Safety and efficacy of the RTS,S/AS01E candidate malaria vaccine given with expanded-programme-on-immunisation vaccines: 19 month follow-up of a randomised, open-label, phase 2 trial. *Lancet Infect Dis,* **11**, 741-9.

Asenso-Okyere, W. K., Anum, A., Osei-Akoto, I. & Adukonu, A. (1998). Cost recovery in Ghana: are there any changes in health care seeking behaviour? *Health Policy Plan,* **13**, 181-8.

Ashton, R. A., Kefyalew, T., Tesfaye, G., Pullan, R. L., Yadeta, D., Reithinger, R., Kolaczinski, J. H. & Brooker, S. (2011). School-based surveys of malaria in Oromia Regional State, Ethiopia: a rapid survey method for malaria in low transmission settings. *Malar J,* **10**, 25.

Asih, P. B., Rozi, I. E., Herdiana, Pratama, N. R., Hidayati, A. P., Marantina, S. S., Kosasih, S., Chand, K., Wangsamuda, S., Rusdjy, F. A., Sumiwi, M. E., Imran, A., Yuniarti, T., Sianturi, T., Nur, J., Asnita, Bukhari, Barussanah, C., Yani, M., Ainun, C., Jamil, K., Mariam, C., Sengkerij, S. P., Laihad, F. J., Hawley, W. & Syafruddin, D. (2012). The baseline distribution of malaria in the initial phase of elimination in Sabang Municipality, Aceh Province, Indonesia. *Malar J,* **11**, 291.

Atieli, H., Menya, D., Githeko, A. & Scott, T. (2009). House design modifications reduce indoor resting malaria vector densities in rice irrigation scheme area in western Kenya. *Malar J,* **8**, 108.

Ayoya, M. A., Bendech, M. A., Zagre, N. M. & Tchibindat, F. (2012). Maternal anaemia in West and Central Africa: time for urgent action. *Public Health Nutr,* **15**, 916-27.

Baird, J. K. (1995). Host age as a determinant of naturally acquired immunity to Plasmodium falciparum. *Parasitol Today,* **11**, 105-11.

Baird, J. K., Purnomo, Basri, H., Bangs, M. J., Andersen, E. M., Jones, T. R., Masbar, S., Harjosuwarno, S., Subianto, B. & Arbani, P. R. (1993). Age-specific prevalence of Plasmodium falciparum among six populations with limited histories of exposure to endemic malaria. *Am J Trop Med Hyg,* **49**, 707-19.

Baker, J. & Liu, L. (2006). The determinants of primary health care utilization: a comparison of three rural clinics in Southern Honduras. *GeoJournal,* **66**, 295-310.

Bastiaens, G. J., Bousema, T. & Leslie, T. (2014). Scale-up of malaria rapid diagnostic tests and artemisinin-based combination therapy: challenges and perspectives in sub-Saharan Africa. *PLoS Med,* **11**, e1001590.

Bastiaens, G. J., Schaftenaar, E., Ndaro, A., Keuter, M., Bousema, T. & Shekalaghe, S. A. (2011). Malaria diagnostic testing and treatment practices in three different Plasmodium falciparum transmission settings in Tanzania: before and after a government policy change. *Malar J,* **10**, 76.

Baughman, A. L., Bisgard, K. M., Lynn, F. & Meade, B. D. (2006). Mixture model analysis for establishing a diagnostic cut-off point for pertussis antibody levels. *Stat Med,* **25**, 2994-3010.

Becher, H., Kynast-Wolf, G., Sie, A., Ndugwa, R., Ramroth, H., Kouyate, B. & Muller, O. (2008). Patterns of malaria: cause-specific and all-cause mortality in a malaria-endemic area of west Africa. *Am J Trop Med Hyg,* **78**, 106-13.

Bejon, P., Williams, T., Liljander, A., Noor, A., Wambua, J., Ogada, E., Olotu, A., Osier, F., Hay, S. & Farnert, A. (2010). Stable and unstable malaria hotspots in longitudinal cohort studies in Kenya. *PLoS Med,* **7**, e1000304.

Bennett, A., Kazembe, L., Mathanga, D. P., Kinyoki, D., Ali, D., Snow, R. W. & Noor, A. M. (2013). Mapping malaria transmission intensity in Malawi, 2000-2010. *Am J Trop Med Hyg,* **89**, 840-9.

Bhattarai, A., Ali, A. S., Kachur, S. P., Martensson, A., Abbas, A. K., Khatib, R., Al-Mafazy, A. W., Ramsan, M., Rotllant, G., Gerstenmaier, J. F., Molteni, F., Abdulla, S., Montgomery, S. M., Kaneko, A. & Bjorkman, A. (2007). Impact of artemisinin-based combination therapy and insecticide-treated nets on malaria burden in Zanzibar. *PLoS Med,* **4**, e309.

Biedron, C., Pagano, M., Hedt, B. L., Kilian, A., Ratcliffe, A., Mabunda, S. & Valadez, J. J. (2010). An assessment of Lot Quality Assurance Sampling to evaluate malaria outcome indicators: extending malaria indicator surveys. *Int J Epidemiol,* **39**, 72-9.

Birmingham, M. E., Aylward, R. B., Cochi, S. L. & Hull, H. F. (1997). National immunization days: state of the art. *J Infect Dis,* **175 Suppl 1**, S183-8.

Bisoffi, Z., Sirima, B. S., Angheben, A., Lodesani, C., Gobbi, F., Tinto, H. & Van den Ende, J. (2009). Rapid malaria diagnostic tests vs. clinical management of malaria in rural Burkina Faso: safety and effect on clinical decisions. A randomized trial. *Trop Med Int Health,* **14**, 491-8.

Biswas, S. (2004). Inter-test comparison between filter paper absorbed blood eluate and serum for malaria serology by enzyme immunoassay: an operational feasibility. *J Immunoassay Immunochem,* **25**, 399-410.

Black, R. H. (1968). *Manual of epidemiology and epidemiological services in malaria programmes.* Geneva: WHO.

Bouma, M. J., Parvez, S. K., Nesbit, R. & Winkler, A. M. F. (1996). Malaria control using permethrin applied to tents of nomadic Afghan refugees in northern Pakistan. *Bulletin of the World Health Organization,* **74**, 413-421.

Bousema, J. T., Gouagna, L. C., Drakeley, C. J., Meutstege, A. M., Okech, B. A., Akim, I. N., Beier, J. C., Githure, J. I. & Sauerwein, R. W. (2004). Plasmodium falciparum gametocyte carriage in asymptomatic children in western Kenya. *Malar J,* **3**, 18.

Bousema, T., Griffin, J. T., Sauerwein, R. W., Smith, D. L., Churcher, T. S., Takken, W., Ghani, A., Drakeley, C. & Gosling, R. (2012). Hitting hotspots: spatial targeting of malaria for control and elimination. *PLoS Med,* **9**, e1001165.

Bouvier, P., Rougemont, A., Breslow, N., Doumbo, O., Delley, V., Dicko, A., Diakite, M., Mauris, A. & Robert, C. F. (1997). Seasonality and malaria in a west African village: does high parasite density predict fever incidence? *Am J Epidemiol,* **145**, 850-7.

Boyd MF, P. P., Christophers R (1949). *Malariology A comprehensive survey of all aspects of this group of diseases from a global standpoint.* Philadelphia and London: W.B. Saunders.

Brabin, B. J. (1983). An analysis of malaria in pregnancy in Africa. *Bull World Health Organ,* **61**, 1005-16.

Brabin, B. J. (1991). The risks and severity of malaria in pregnant women. Applied Field Research in Malaria, Report No. 1. UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

Brabin, B. J., Warsame, M., Uddenfeldt-Wort, U., Dellicour, S., Hill, J. & Gies, S. (2008). Monitoring and evaluation of malaria in pregnancy - developing a rational basis for control. *Malar J,* **7 Suppl 1**, S6.

Brass, W. & Coale, A. J. (1968). Method of Analysis and estimation. *In:* Brass, W., Coale, A. J., Demeny, P., Heisel, D. F., Lorimer, F., Romanuik, A. & van der Walle, E. (eds.) *The Demography of Tropical Africa.* Princeton: Princeton University Press.

Brooker, S., Clarke, S., Snow, R. W. & Bundy, D. A. (2008a). Malaria in African schoolchildren: options for control. *Trans R Soc Trop Med Hyg,* **102**, 304-5.

Brooker, S., Hotez, P. J. & Bundy, D. A. (2008b). Hookworm-related anaemia among pregnant women: a systematic review. *PLoS Negl Trop Dis,* **2**, e291.

Brooker, S., Kolaczinski, J. H., Gitonga, C. W., Noor, A. M. & Snow, R. W. (2009). The use of schools for malaria surveillance and programme evaluation in Africa. *Malar J,* **8**, 231.

Bruce-Chwatt, L. J., Draper, C. C. & Konfortion, P. (1973). Seroepidemiological evidence of eradication of malaria from Mauritius. *Lancet,* **2**, 547-51.

Bryce, J., Boschi-Pinto, C., Shibuya, K. & Black, R. E. (2005). WHO estimates of the causes of death in children. *Lancet,* **365**, 1147-52.

Burkot, T. R. & Graves, P. M. (1995). The value of vector-based estimates of malaria transmission. *Ann Trop Med Parasitol,* **89**, 125-34.

Burkot, T. R., Williams, J. L. & Schneider, I. (1984). Identification of Plasmodium falciparum-infected mosquitoes by a double antibody enzyme-linked immunosorbent assay. *Am J Trop Med Hyg,* **33**, 783-8.

Cairns, M., Roca-Feltrer, A., Garske, T., Wilson, A. L., Diallo, D., Milligan, P. J., Ghani, A. C. & Greenwood, B. M. (2012). Estimating the potential public

health impact of seasonal malaria chemoprevention in African children. *Nat Commun,* **3**, 881.

Calis, J. C. J., Phiri, K. S., Faragher, E. B., Brabin, B. J., Bates, I., Cuevas, L. E., de Haan, R. J., Phiri, A. I., Malange, P., Khoka, M., Hulshof, P. J. M., van Lieshout, L., Beld, M. G. H. M., Teo, Y. Y., Rockett, K. A., Richardson, A., Kwiatkowski, D. P., Molyneux, M. E. & van Hensbroek, M. B. (2008). Severe Anemia in Malawian Children. *New England Journal of Medicine,* **358**, 888-899.

Carlson, M., Paintain, L. S., Bruce, J., Webster, J. & Lines, J. (2011). Who attends antenatal care and expanded programme on immunization services in Chad, Mali and Niger? the implications for insecticide-treated net delivery. *Malar J,* **10**.

Carneiro, I., Roca-Feltrer, A., Griffin, J. T., Smith, L., Tanner, M., Schellenberg, J. A., Greenwood, B. & Schellenberg, D. (2010). Age-patterns of malaria vary with severity, transmission intensity and seasonality in sub-Saharan Africa: a systematic review and pooled analysis. *PLoS One,* **5**, e8988.

Carter, R., Mendis, K. N. & Roberts, D. (2000). Spatial targeting of interventions against malaria. *Bull World Health Organ,* **78**, 1401-11.

CDC (1998). Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. *MMWR Recomm Rep,* **47**, 1-29.

Ceesay, S. J., Casals-Pascual, C., Erskine, J., Anya, S. E., Duah, N. O., Fulford, A. J., Sesay, S. S., Abubakar, I., Dunyo, S., Sey, O., Palmer, A., Fofana, M., Corrah, T., Bojang, K. A., Whittle, H. C., Greenwood, B. M. & Conway, D. J. (2008). Changes in malaria indices between 1999 and 2007 in The Gambia: a retrospective analysis. *Lancet,* **372**, 1545-54.

Ceesay, S. J., Casals-Pascual, C., Nwakanma, D. C., Walther, M., Gomez-Escobar, N., Fulford, A. J., Takem, E. N., Nogaro, S., Bojang, K. A., Corrah, T., Jaye, M. C., Taal, M. A., Sonko, A. A. & Conway, D. J. (2010). Continued decline of malaria in The Gambia with implications for elimination. *PLoS One,* **5**, e12242.

Chanda, P., Hamainza, B., Mulenga, S., Chalwe, V., Msiska, C. & Chizema-Kawesha, E. (2009). Early results of integrated malaria control and implications for the management of fever in under-five children at a peripheral health facility: a case study of Chongwe rural health centre in Zambia. *Malar J,* **8**, 49.

Child Info. (2012). *Multiple Indicator Cluster Surveys - Round 4 Manual*. URL: http://www.childinfo.org/mics4_manual.html.

Chimatiro, S. K. (2004). *The Biophysical dynamics of the Lower Shire River floodplain fisheries in Malawi.* PhD, Rhodes University.

Cibulskis, R. E., Aregawi, M., Williams, R., Otten, M. & Dye, C. (2011). Worldwide incidence of malaria in 2009: estimates, time trends, and a critique of methods. *PLoS Med,* **8**, e1001142.

Cibulskis, R. E., Bell, D., Christophel, E. M., Hii, J., Delacollette, C., Bakyaita, N. & Aregawi, M. W. (2007). Estimating trends in the burden of malaria at country level. *Am J Trop Med Hyg,* **77**, 133-7.

Cibulskis, R. E., Pujari, S. & Otten, M. W. (2012). Do estimates of intervention coverage obtained from children at immunization clinics provide a reasonable approximation to population values? *J Infect Dis,* **205 Suppl 1**, S91-102.

Clements, A. C., Reid, H. L., Kelly, G. C. & Hay, S. I. (2013). Further shrinking the malaria map: how can geospatial science help to achieve malaria elimination? *Lancet Infect Dis,* **13**, 709-18.

Clerk, C. A., Bruce, J., Greenwood, B. & Chandramohan, D. (2009). The epidemiology of malaria among pregnant women attending antenatal clinics in an area with intense and highly seasonal malaria transmission in northern Ghana. *Trop Med Int Health,* **14**, 688-95.

ClinicalTrials.gov. (2014). *Safe and Efficacious Artemisinin-based Combination Treatments for African Pregnant Women With Malaria (PREGACT).* URL: http://clinicaltrials.gov/ct2/show/NCT00852423?term=the+PREGACT+trial&rank=1 [19th February, 2014].

Collins, W. E., Skinner, J. C. & Jeffery, G. M. (1968). Studies on the persistence of malarial antibody response. *Am J Epidemiol,* **87**, 592-8.

Coosemans, M., Wery, M., Mouchet, J. & Carnevale, P. (1992). Transmission factors in malaria epidemiology and control in Africa. *Mem Inst Oswaldo Cruz,* **87 Suppl 3**, 385-91.

Corran, P., Coleman, P., Riley, E. & Drakeley, C. (2007). Serology: a robust indicator of malaria transmission intensity? *Trends Parasitol,* **23**, 575-82.

Corran, P. H., Cook, J., Lynch, C., Leendertse, H., Manjurano, A., Griffin, J., Cox, J., Abeku, T., Bousema, T., Ghani, A. C., Drakeley, C. & Riley, E. (2008). Dried blood spots as a source of anti-malarial antibodies for epidemiological studies. *Malar J,* **7**, 195.

Cox-Singh, J., Davis, T. M., Lee, K. S., Shamsul, S. S., Matusop, A., Ratnam, S., Rahman, H. A., Conway, D. J. & Singh, B. (2008). Plasmodium knowlesi malaria in humans is widely distributed and potentially life threatening. *Clin Infect Dis,* **46**, 165-71.

Cox, J., Hay, S. I., Abeku, T. A., Checchi, F. & Snow, R. W. (2007). The uncertain burden of Plasmodium falciparum epidemics in Africa. *Trends Parasitol,* **23**, 142-148.

Cressie, N. (1993). *Statistics for Spatial Data, Revised Edition.* New York: John Wiley & Sons, Inc.

Davis, J. R., Hall, T., Chee, E. M., Majala, A., Minjas, J. & Shiff, C. J. (1995). Comparison of sampling anopheline mosquitoes by light-trap and human-bait collections indoors at Bagamoyo, Tanzania. *Med Vet Entomol,* **9**, 249-55.

de Castro, M. C. & Fisher, M. G. (2012). Is malaria illness among young children a cause or a consequence of low socioeconomic status? evidence from the united Republic of Tanzania. *Malar J,* **11**, 161.

Delacollette C, B. M., Mpitabakana P. (1990). Epidemiologie du paludisme au Burundi: observations preliminaires. *Med Afr Noire* **37**, 718–721.

Delamater, P. L., Messina, J. P., Shortridge, A. M. & Grady, S. C. (2012). Measuring geographic access to health care: raster and network-based methods. *Int J Health Geogr,* **11**, 15.

Dellicour, S., Tatem, A. J., Guerra, C. A., Snow, R. W. & ter Kuile, F. O. (2010). Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. *PLoS Med,* **7**, e1000221.

DeMaeyer, E. M. & Joint WHO/UNICEF Nutrition Support Programme (1989). *Preventing and controlling iron deficiency anaemia through primary health care: a guide for health administrators and programme managers.* Geneva: WHO.

Deressa, W., Fantahun, M. & Ali, A. (2007). Malaria-related mortality based on verbal autopsy in an area of low endemicity in a predominantly rural population in Ethiopia. *Malar J,* **6**, 128.

Desai, M., ter Kuile, F. O., Nosten, F., McGready, R., Asamoa, K., Brabin, B. & Newman, R. D. (2007). Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis,* **7**, 93-104.

Dias, A., Pinto, A., Weiss, B. & Costa, M. J. Inquérito LQAS Pós Campanha "Viva a Vida com Saúde". Relatório Final. . Luanda.

Dietz, K. (1993). The estimation of the basic reproduction number for infectious diseases. *Stat Methods Med Res,* **2**, 23-41.

Dodge, H. & Romig, H. (1929). A method of sampling inspection. *Bell Syst Tech J,* **8**, 398.

Dondorp, A., Nosten, F., Stepniewska, K., Day, N. & White, N. (2005). Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet,* **366**, 717-25.

Dondorp, A. M., Fanello, C. I., Hendriksen, I. C., Gomes, E., Seni, A., Chhaganlal, K. D., Bojang, K., Olaosebikan, R., Anunobi, N., Maitland, K., Kivaya, E., Agbenyega, T., Nguah, S. B., Evans, J., Gesase, S., Kahabuka, C., Mtove, G., Nadjm, B., Deen, J., Mwanga-Amumpaire, J., Nansumba, M., Karema, C., Umulisa, N., Uwimana, A., Mokuolu, O. A., Adedoyin, O. T., Johnson, W. B., Tshefu, A. K., Onyamboko, M. A., Sakulthaew, T., Ngum, W. P., Silamut, K., Stepniewska, K., Woodrow, C. J., Bethell, D., Wills, B., Oneko, M., Peto, T. E., von Seidlein, L., Day, N. P. & White, N. J. (2010). Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet,* **376**, 1647-57.

Drakeley, C. J., Corran, P. H., Coleman, P. G., Tongren, J. E., McDonald, S. L., Carneiro, I., Malima, R., Lusingu, J., Manjurano, A., Nkya, W. M., Lemnge, M. M., Cox, J., Reyburn, H. & Riley, E. M. (2005). Estimating medium- and long-term trends in malaria transmission by using serological markers of malaria exposure. *Proc Natl Acad Sci U S A,* **102**, 5108-13.

Druilhe, P., Pradier, O., Marc, J. P., Miltgen, F., Mazier, D. & Parent, G. (1986). Levels of antibodies to Plasmodium falciparum sporozoite surface antigens reflect malaria transmission rates and are persistent in the absence of reinfection. *Infect Immun,* **53**, 393-7.

Duffy, P. E. & Fried, M. (2003). Antibodies that inhibit Plasmodium falciparum adhesion to chondroitin sulfate A are associated with increased birth weight and the gestational age of newborns. *Infect Immun,* **71**, 6620-3.

Duffy, P. E. & Fried, M. (2005). Malaria in the pregnant woman. *Curr Top Microbiol Immunol,* **295**, 169-200.

Dunyo, S. K., Afari, E. A., Koram, K. A., Ahorlu, C. K., Abubakar, I. & Nkrumah, F. K. (2000). Health centre versus home presumptive diagnosis of malaria in

southern Ghana: implications for home-based care policy. *Trans R Soc Trop Med Hyg,* **94**, 285-8.

Ebrahimzadeh, A., Fouladi, B. & Fazaeli, A. (2007). High rate of detection of mixed infections of Plasmodium vivax and Plasmodium falciparum in South-East of Iran, using nested PCR. *Parasitol Int,* **56**, 61-4.

Ediau, M., Babirye, J. N., Tumwesigye, N. M., Matovu, J. K., Machingaidze, S., Okui, O., Wanyenze, R. K. & Waiswa, P. (2013). Community knowledge and perceptions about indoor residual spraying for malaria prevention in Soroti district, Uganda: a cross-sectional study. *Malar J,* **12**, 170.

Einterz, E. M. & Bates, M. E. (1997). Fever in Africa: do patients know when they are hot? *Lancet,* **350**, 781.

Eisele, T. P., Keating, J., Littrell, M., Larsen, D. & Macintyre, K. (2009). Assessment of insecticide-treated bednet use among children and pregnant women across 15 countries using standardized national surveys. *Am J Trop Med Hyg,* **80**, 209-14.

Eisele, T. P., Larsen, D. A., Anglewicz, P. A., Keating, J., Yukich, J., Bennett, A., Hutchinson, P. & Steketee, R. W. (2012). Malaria prevention in pregnancy, birthweight, and neonatal mortality: a meta-analysis of 32 national cross-sectional datasets in Africa. *Lancet Infect Dis,* **12**, 942-9.

Erhart, A., Thang, N. D., Xa, N. X., Thieu, N. Q., Hung, L. X., Hung, N. Q., Nam, N. V., Toi, L. V., Tung, N. M., Bien, T. H., Tuy, T. Q., Cong, L. D., Thuan, L. K., Coosemans, M. & D'Alessandro, U. (2007). Accuracy of the health information system on malaria surveillance in Vietnam. *Trans R Soc Trop Med Hyg,* **101**, 216-25.

Esposito, F., Lombardi, S., Modiano, D., Zavala, F., Reeme, J., Lamizana, L., Coluzzi, M. & Nussenzweig, R. S. (1988). Prevalence and levels of antibodies to the circumsporozoite protein of Plasmodium falciparum in an endemic area and their relationship to resistance against malaria infection. *Trans R Soc Trop Med Hyg,* **82**, 827-32.

Estevez, P. T., Satoguina, J., Nwakanma, D. C., West, S., Conway, D. J. & Drakeley, C. J. (2011). Human saliva as a source of anti-malarial antibodies to examine population exposure to Plasmodium falciparum. *Malar J,* **10**, 104.

Ewing, V. L., Lalloo, D. G., Phiri, K. S., Roca-Feltrer, A., Mangham, L. J. & SanJoaquin, M. A. (2011). Seasonal and geographic differences in treatment-seeking and household cost of febrile illness among children in Malawi. *Malaria Journal,* **10**, 32.

Fancony, C., Sebastiao, Y. V., Pires, J. E., Gamboa, D. & Nery, S. V. (2013). Performance of microscopy and RDTs in the context of a malaria prevalence survey in Angola: a comparison using PCR as the gold standard. *Malar J,* **12**, 284.

FAO. (2007). *FAO Country Information: Malawi*. URL: http://coin.fao.org/cms/world/malawi/en/CountryInformation.html [18th February, 2014].

Fatiu, A., Abubakr, S., Muzamil, H., Aderoju, G., Funmilayo, O., Bola, O. & Adewale, A. (2011). Undiagnosed hypertension and proteinuria in a market population in Ile-Ife, Nigeria. *Arab J Nephrol Transplant,* **4**, 141-6.

Faye, O., Diallo, S., Gaye, O., Ndir, O. & Faye, O. (1992). [Comparative efficacy of the use of CDC light traps and humans to sampling anopheles populations. Results obtained in the area of Bignona (Senegal)]. *Bull Soc Pathol Exot,* **85**, 185-9.

Feachem, R. G. A. & The Malaria Elimination Group (2009). *Shrinking the Malaria Map: A Prospectus on Malaria Elimination.* San Francisco: The Global Health Group, Global Health Sciences, University of California.

Fillinger, U., Ndenga, B., Githeko, A. & Lindsay, S. W. (2009). Integrated malaria vector control with microbial larvicides and insecticide-treated nets in western Kenya: a controlled trial. *Bull World Health Organ,* **87**, 655-65.

Filmer, D. & Pritchett, L. (1999). The Effect of Household Wealth on Educational Attainment: Evidence from 35 Countries. *Population and Development Review,* **25**, 85-120.

Fleming, A. F. (1989). The aetiology of severe anaemia in pregnancy in Ndola, Zambia. *Ann Trop Med Parasitol,* **83**, 37-49.

Fried, M., Domingo, G. J., Gowda, C. D., Mutabingwa, T. K. & Duffy, P. E. (2006). Plasmodium falciparum: chondroitin sulfate A is the major receptor for adhesion of parasitized erythrocytes in the placenta. *Exp Parasitol,* **113**, 36-42.

Fried, M. & Duffy, P. E. (1996). Adherence of Plasmodium falciparum to chondroitin sulfate A in the human placenta. *Science,* **272**, 1502-4.

Gahutu, J. B., Steininger, C., Shyirambere, C., Zeile, I., Cwinya-Ay, N., Danquah, I., Larsen, C. H., Eggelte, T. A., Uwimana, A., Karema, C., Musemakweri, A., Harms, G. & Mockenhaupt, F. P. (2011). Prevalence and risk factors of malaria among children in southern highland Rwanda. *Malar J,* **10**, 134.

Garcia-Basteiro, A. L., Schwabe, C., Aragon, C., Baltazar, G., Rehman, A. M., Matias, A., Nseng, G. & Kleinschmidt, I. (2011). Determinants of bed net use in children under five and household bed net ownership on Bioko Island, Equatorial Guinea. *Malar J,* **10**, 179.

Garret-Jones, C. (1970). Problems of epidemiological entomology as applied to malariology. *Miscellaneous Publications of the Entomological Society of America,* **7**, 168–177.

Garrett-Jones, C. (1964). Prognosis for interruption of malaria transmission through assessment of the mosquito's vectorial capacity. *Nature,* **204**, 1173-1175.

Geman, S. & Geman, D. (1984). Stochastic relation, Gibbs distributions, and the Bayesian restoration of images. *IEEE Trans Pattern Anal Machine Intell,* **6**, 721-741.

Genton, B., al-Yaman, F., Beck, H. P., Hii, J., Mellor, S., Narara, A., Gibson, N., Smith, T. & Alpers, M. P. (1995). The epidemiology of malaria in the Wosera area, East Sepik Province, Papua New Guinea, in preparation for vaccine trials. I. Malariometric indices and immunity. *Ann Trop Med Parasitol,* **89**, 359-76.

Gething, P. W., Elyazar, I. R., Moyes, C. L., Smith, D. L., Battle, K. E., Guerra, C. A., Patil, A. P., Tatem, A. J., Howes, R. E., Myers, M. F., George, D. B., Horby, P., Wertheim, H. F., Price, R. N., Mueller, I., Baird, J. K. & Hay, S. I. (2012). A long neglected world malaria map: Plasmodium vivax endemicity in 2010. *PLoS Negl Trop Dis,* **6**, e1814.

Gething, P. W., Patil, A. P., Smith, D. L., Guerra, C. A., Elyazar, I. R., Johnston, G. L., Tatem, A. J. & Hay, S. I. (2011). A new world malaria map: Plasmodium falciparum endemicity in 2010. *Malar J,* **10**, 378.

Geyer, C. J. (1994). On the Convergence of Monte Carlo Maximum Likelihood Calculations. *Journal of the Royal Statistical Society. Series B (Methodological),* **56**, 261-274.

Geyer, C. J. & Thompson, E. A. (1992). Constrained Monte Carlo Maximum Likelihood for Dependent Data. *Journal of the Royal Statistical Society. Series B (Methodological),* **54**, 657-699.

Gilles, H., M. (2002). The epidemiology of malaria. *In:* D, A., Warrell.; H, M, Gilles. (ed.) *Essential Malariology: 4th edition.* India: Hodder Arnold.

Gilles, H. M., Lawson, J. B., Sibelas, M., Voller, A. & Allan, N. (1969). Malaria, anaemia and pregnancy. *Ann Trop Med Parasitol,* **63**, 245-63.

Giorgi, E., Sesay, S. S. S., Terlouw, D. J. & Diggle, P. J. (In press). Combining data from multiple spatially referenced prevalence surveys using generalized linear geostatistical models. *J R Stat Soc Series A*.

Giorgi E, S. S., Terlouw DJ, Diggle PJ. (2015). Combining data from multiple spatially referenced prevalence surveys using generalized linear geostatistical models. . *in press*. URL: http://arxiv.org/abs/1308.2790 [18th March 2014].

Githeko, A. K., Mbogo, C. N. M., Curtis, C. F., Lines, J. & Lengeler, C. (1996). Entomological monitoring of large-scale vector-control interventions. *Parasitology Today,* **12**, 127-128.

Gitonga, C. W., Karanja, P. N., Kihara, J., Mwanje, M., Juma, E., Snow, R. W., Noor, A. M. & Brooker, S. (2010). Implementing school malaria surveys in Kenya: towards a national surveillance system. *Malar J,* **9**, 306.

Goff, G. l., Carnevale, P., Fondjo, E. & Robert, V. (1997). Comparison of three sampling methods of man-biting anophelines in order to estimate the malaria transmission in a village of south Cameroon. *Parasite,* **4**, 75-80.

Golassa, L., Enweji, N., Erko, B., Aseffa, A. & Swedberg, G. (2013). Detection of a substantial number of sub-microscopic Plasmodium falciparum infections by polymerase chain reaction: a potential threat to malaria control and diagnosis in Ethiopia. *Malar J,* **12**, 352.

Gosling, R. D., Gesase, S., Mosha, J. F., Carneiro, I., Hashim, R., Lemnge, M., Mosha, F. W., Greenwood, B. & Chandramohan, D. (2009). Protective efficacy and safety of three antimalarial regimens for intermittent preventive treatment for malaria in infants: a randomised, double-blind, placebo-controlled trial. *Lancet,* **374**, 1521-32.

Greenhouse, B., Ho, B., Hubbard, A., Njama-Meya, D., Narum, D. L., Lanar, D. E., Dutta, S., Rosenthal, P. J., Dorsey, G. & John, C. C. (2011). Antibodies to Plasmodium falciparum Antigens Predict a Higher Risk of Malaria But Protection From Symptoms Once Parasitemic. *Journal of Infectious Diseases,* **204**, 19-26.

Griffith, D. A. & Amrhein, C. G. (1997). Information content in georeferenced data. *Multivariate Statistical Analysis for Geographers.* University of Michigan: Prentice Hall.

Guagliardo, M. F. (2004). Spatial accessibility of primary care: concepts, methods and challenges. *Int J Health Geogr,* **3**, 3.

Guerra, C. A., Hay, S. I., Lucioparedes, L. S., Gikandi, P. W., Tatem, A. J., Noor, A. M. & Snow, R. W. (2007). Assembling a global database of malaria parasite prevalence for the Malaria Atlas Project. *Malar J,* **6**, 17.

Gupta, S., Snow, R. W., Donnelly, C. & Newbold, C. (1999a). Acquired immunity and postnatal clinical protection in childhood cerebral malaria. *Proc Biol Sci,* **266**, 33-8.

Gupta, S., Snow, R. W., Donnelly, C. A., Marsh, K. & Newbold, C. (1999b). Immunity to non-cerebral severe malaria is acquired after one or two infections. *Nat Med,* **5**, 340-3.

Haider, B. A., Olofin, I., Wang, M., Spiegelman, D., Ezzati, M. & Fawzi, W. W. (2013). Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis. *Bmj,* **346**, f3443.

Hall, D. M. B. (1996). Health for all children. Report of the third joint working party on child health surveillance. 3rd ed (reprinted with corrections). 3rd ed. Oxford University Press.

Hamer, D. H., Ndhlovu, M., Zurovac, D., Fox, M., Yeboah-Antwi, K., Chanda, P., Sipilinyambe, N., Simon, J. L. & Snow, R. W. (2007). Improved diagnostic testing and malaria treatment practices in Zambia. *JAMA,* **297**, 2227-31.

Hammer, G. P., Some, F., Muller, O., Kynast-Wolf, G., Kouyate, B. & Becher, H. (2006). Pattern of cause-specific childhood mortality in a malaria endemic area of Burkina Faso. *Malar J,* **5**, 47.

Hancioglu, A. & Arnold, F. (2013). Measuring coverage in MNCH: tracking progress in health for women and children using DHS and MICS household surveys. *PLoS Med,* **10**, e1001391.

Hanson, K., Marchant, T., Nathan, R., Mponda, H., Jones, C., Bruce, J., Mshinda, H. & Schellenberg, J. A. (2009). Household ownership and use of insecticide treated nets among target groups after implementation of a national voucher programme in the United Republic of Tanzania: plausibility study using three annual cross sectional household surveys. *BMJ,* **339**, b2434.

Hardelid, P., Williams, D., Dezateux, C., Tookey, P. A., Peckham, C. S., Cubitt, W. D. & Cortina-Borja, M. (2008). Analysis of rubella antibody distribution from newborn dried blood spots using finite mixture models. *Epidemiol Infect,* **136**, 1698-706.

Harris, I., Sharrock, W. W., Bain, L. M., Gray, K. A., Bobogare, A., Boaz, L., Lilley, K., Krause, D., Vallely, A., Johnson, M. L., Gatton, M. L., Shanks, G. D. & Cheng, Q. (2010). A large proportion of asymptomatic Plasmodium infections with low and sub-microscopic parasite densities in the low transmission setting of Temotu Province, Solomon Islands: challenges for malaria diagnostics in an elimination setting. *Malar J,* **9**, 254.

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N. & Conde, J. G. (2009). Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform,* **42**, 377-81.

Hastings, W. K. (1970). Monte Carlo sampling methods using Markov chains and their applications. *Biometrika,* **57**, 97-109.

Hay, S., Guerra, C., Gething, P., Patil, A., Tatem, A., Noor, A., Kabaria, C., Manh, B., Elyazar, I., Brooker, S., Smith, D., Moyeed, R. & Snow, R. (2009). A world malaria map: Plasmodium falciparum endemicity in 2007. *PLoS Med,* **6**, e1000048.

Hay, S., Rogers, D., Toomer, J. & Snow, R. (2000). Annual Plasmodium falciparumentomological inoculation rates (EIR) across Africa: literature survey, internet access and review. *Trans R Soc Trop Med Hyg,* **94**, 113 - 127.

Hay, S. I., Guerra, C. A., Tatem, A. J., Atkinson, P. M. & Snow, R. W. (2005). Urbanization, malaria transmission and disease burden in Africa. *Nat Rev Microbiol,* **3**, 81-90.

Hay, S. I., Smith, D. L. & Snow, R. W. (2008). Measuring malaria endemicity from intense to interrupted transmission. *Lancet Infect Dis,* **8**, 369 - 378.

Hay, S. I. & Snow, R. W. (2006). The malaria Atlas Project: developing global maps of malaria risk. *PLoS Med,* **3**, e473.

Hay, S. I., Snow, R. W. & Rogers, D. J. (1998). From predicting mosquito habitat to malaria seasons using remotely sensed data: practice, problems and perspectives. *Parasitol Today,* **14**, 306-13.

Hay, S. I., Tatem, A. J., Graham, A. J., Goetz, S. J. & Rogers, D. J. (2006). Global environmental data for mapping infectious disease distribution. *Adv Parasitol,* **62**, 37-77.

Hedt, B. L. & Pagano, M. (2011). Health indicators: eliminating bias from convenience sampling estimators. *Stat Med,* **30**, 560-8.

Hunt, R., Edwardes, M. & Coetzee, M. (2010). Pyrethroid resistance in southern African Anopheles funestus extends to Likoma Island in Lake Malawi. *Parasit Vectors,* **3**, 122.

Ibidapo, C. A., Akinsanya, B., Adeoye, G. O., Otubanjo, A. O., Okeke, P., Okwuzu, J., Adejai, E. O. & Braide, E. (2008). Market survey of loiasis: prevalence and adverse reactions to ivermectin using a rapid procedure for loiasis. *West Indian Med J,* **57**, 152-6.

ICF International (2012a). Survey Organization Manual for Demographic and Health Surveys. December 2012 ed. Calverton, Maryland USA: MEASURE DHS.

ICF International (2012b). *Demographic and Health Survey Sampling and Household Listing Manual.* Calverton, Maryland, USA: ICF International.

INDEPTH (2002). *Demographic Surveillance Systems for Assessing Populations and Their Health in Developing Countries, Volume 1: Population, Health and Survival in INDEPTH Sites.* Ottawa: IDRC/CRDI.

INDEPTH Network (2002). DSS Concepts and Methods: Core Concepts of DSS. *In:* Sankoh, O. A. (ed.) *Population and Health in Developing Countries. Population, Health and Survival at INDEPTH Sites.* Canada: IDRC.

International Epidemiological Association (2008). *A Dictionary of Epidemiology: Fifth Edition.* New York: Oxford University Press.

Jensen, T. P., Bukirwa, H., Njama-Meya, D., Francis, D., Kamya, M. R., Rosenthal, P. J. & Dorsey, G. (2009). Use of the slide positivity rate to estimate changes in malaria incidence in a cohort of Ugandan children. *Malar J,* **8**, 213.

Kaatano, G. M., Mashauri, F. M., Kinung'hi, S. M., Mwanga, J. R., Malima, R. C., Kishamawe, C., Nnko, S. E., Magesa, S. M. & Mboera, L. E. (2009). Patterns

of malaria related mortality based on verbal autopsy in Muleba District, north-western Tanzania. *Tanzan J Health Res,* **11**, 210-8.

Kalowekamo, F. (2000). *Wildlife management in the Lower Shire.* Blantyre, Malawi: Community Partnerships for Sustainable Resource Management in Malawi (COMPASS).

Kamugisha, M. L., Gesase, S., Mlwilo, T. D., Mmbando, B. P., Segeja, M. D., Minja, D. T., Massaga, J. J., Msangeni, H. A., Ishengoma, D. R. & Lemnge, M. M. (2007). Malaria specific mortality in lowlands and highlands of Muheza district, north-eastern Tanzania. *Tanzan Health Res Bull,* **9**, 32-7.

Kantele, A. & Jokiranta, T. S. (2011). Review of cases with the emerging fifth human malaria parasite, Plasmodium knowlesi. *Clin Infect Dis,* **52**, 1356-62.

Kayentao, K., Garner, P., van Eijk, A. M., Naidoo, I., Roper, C., Mulokozi, A., MacArthur, J. R., Luntamo, M., Ashorn, P., Doumbo, O. K. & ter Kuile, F. O. (2013). Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa: systematic review and meta-analysis. *Jama,* **309**, 594-604.

Kazembe, L. N., Kleinschmidt, I. & Sharp, B. L. (2006). Patterns of malaria-related hospital admissions and mortality among Malawian children: an example of spatial modelling of hospital register data. *Malar J,* **5**, 93.

Kendjo, E., Agbenyega, T., Bojang, K., Newton, C. R., Bouyou-Akotet, M., Pedross, F., Kombila, M., Helbok, R. & Kremsner, P. G. (2013). Mortality patterns and site heterogeneity of severe malaria in African children. *PLoS One,* **8**, e58686.

Kiggundu, V. L., O'Meara, W. P., Musoke, R., Nalugoda, F. K., Kigozi, G., Baghendaghe, E., Lutalo, T., Achienge, M. K., Reynolds, S. J., Makumbi, F., Serwadda, D., Gray, R. H. & Wools-Kaloustian, K. K. (2013). High prevalence of malaria parasitemia and anemia among hospitalized children in Rakai, Uganda. *PLoS One,* **8**, e82455.

Kilian, A., Koenker, H. & Paintain, L. (2013). Estimating population access to insecticide-treated nets from administrative data: correction factor is needed. *Malar J,* **12**, 259.

Kirby, M. J., Ameh, D., Bottomley, C., Green, C., Jawara, M., Milligan, P. J., Snell, P. C., Conway, D. J. & Lindsay, S. W. (2009). Effect of two different house screening interventions on exposure to malaria vectors and on anaemia in children in The Gambia: a randomised controlled trial. *Lancet,* **374**, 998-1009.

Kirby, M. J., Bah, P., Jones, C. O. H., Kelly, A. H., Jasseh, M. & Lindsay, S. W. (2010). Social Acceptability and Durability of Two Different House Screening Interventions against Exposure to Malaria Vectors, Plasmodium falciparum Infection, and Anemia in Children in The Gambia, West Africa. *American Journal of Tropical Medicine and Hygiene,* **83**, 965-972.

Kitvatanachai, S., Janyapoon, K., Rhongbutsri, P. & Thap, L. C. (2003). A survey on malaria in mobile Cambodians in Aranyaprathet, Sa Kaeo Province, Thailand. *Southeast Asian J Trop Med Public Health,* **34**, 48-53.

Kochar, D. K., Das, A., Kochar, S. K., Saxena, V., Sirohi, P., Garg, S., Kochar, A., Khatri, M. P. & Gupta, V. (2009). Severe Plasmodium vivax malaria: a report on serial cases from Bikaner in northwestern India. *Am J Trop Med Hyg,* **80**, 194-8.

Korenromp, E. L., Armstrong-Schellenberg, J. R., Williams, B. G., Nahlen, B. L. & Snow, R. W. (2004). Impact of malaria control on childhood anaemia in Africa -- a quantitative review. *Trop Med Int Health,* **9**, 1050-65.

Kouanda, S., Bado, A., Yameogo, M., Nitiema, J., Yameogo, G., Bocoum, F., Millogo, T., Ridde, V., Haddad, S. & Sondo, B. (2013). The Kaya HDSS, Burkina Faso: a platform for epidemiological studies and health programme evaluation. *Int J Epidemiol,* **42**, 741-9.

Kramer, M. S. (1987). Determinants of low birth weight: methodological assessment and meta-analysis. *Bull World Health Organ,* **65**, 663-737.

Laishram, D. D., Sutton, P. L., Nanda, N., Sharma, V. L., Sobti, R. C., Carlton, J. M. & Joshi, H. (2012). The complexities of malaria disease manifestations with a focus on asymptomatic malaria. *Malar J,* **11**, 29.

Laly, R., Valadez, J. J., Gbangbade, S. & Vargas, W. (2009). Evaluation (par la méthode LQAS) de la campagne intégrée d'octobre 2007 de distribution des MIILD, de l'Albendazole et de la vitamine A aux enfants de moins de cinq ans et du niveau de quelques indicateurs de suivi de la lutte contre le paludisme. *Direction Nationale De La Protection Sanitaire Programme National De Lutte Contre Le Paludisme.*

Lanata, C. F. & Black, R. E. (1991). Lot quality assurance sampling techniques in health surveys in developing countries: advantages and current constraints. *World Health Stat Q,* **44**, 133-9.

Larson, P. S., Mathanga, D. P., Campbell, C. H., Jr. & Wilson, M. L. (2012). Distance to health services influences insecticide-treated net possession and use among six to 59 month-old children in Malawi. *Malar J,* **11**, 18.

Law, G. R. & Pascoe, S., W. (2013). Foundations of Epidemiology. *In:* Law, G. R. & Pascoe, S., W. (eds.) *Statistical Epidemiology.* Boston: CAB International.

Le Prince, J. A. & Orenstein, J. A. (1916a). Chapter I: The status of knowledge of anti-malaria work in 1904 and the campaign at Havana. *In:* Le Prince, J. A. & Orenstein, J. A. (eds.) *Mosquito control in Panama : the eradication of malaria and yellow fever in Cuba and Panama.* New York & London: G.P. Putnam's Sons.

Le Prince, J. A. & Orenstein, J. A. (1916b). Chapter II: The situation of the Isthmus in 1904, before American occupation. *In:* Le Prince, J. A. & Orenstein, J. A. (eds.) *Mosquito control in Panama : the eradication of malaria and yellow fever in Cuba and Panama.* New York & London: G.P. Putnam's Sons.

Le Prince, J. A. & Orenstein, J. A. (1916c). Chapter XVI: The results accomplished by the anti-malaria campaign. *In:* Le Prince, J. A. & Orenstein, J. A. (eds.) *Mosquito control in Panama : the eradication of malaria and yellow fever in Cuba and Panama.* New York & London: G.P. Putnam's Sons.

Lee, A. I. & Okam, M. M. (2011). Anemia in pregnancy. *Hematol Oncol Clin North Am,* **25**, 241-59, vii.

Lee, P. W., Liu, C. T., Rampao, H. S., do Rosario, V. E. & Shaio, M. F. (2010). Pre-elimination of malaria on the island of Principe. *Malar J,* **9**, 26.

Leenstra, T., Phillips-Howard, P. A., Kariuki, S. K., Hawley, W. A., Alaii, J. A., Rosen, D. H., Oloo, A. J., Nahlen, B. L., Kager, P. A. & ter Kuile, F. O. (2003). Permethrin-treated bed nets in the prevention of malaria and anemia in

adolescent schoolgirls in western Kenya. *American Journal of Tropical Medicine and Hygiene,* **68**, 86-93.

Lines, J. D., Curtis, C. F., Wilkes, T. J. & Njunwa, K. J. (1991). Monitoring human-biting mosquitos (Diptera: Culicidae) in Tanzania with light-traps hung beside mosquito nets. *Bull Entomol Res,* **81**, 77–84.

Liu, L., Johnson, H. L., Cousens, S., Perin, J., Scott, S., Lawn, J. E., Rudan, I., Campbell, H., Cibulskis, R., Li, M., Mathers, C. & Black, R. E. (2012). Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet,* **379**, 2151-61.

Lobel, H. O., Mathews, H. M. & Kagan, I. G. (1973). Interpretation of IHA titres for the study of malaria epidemiology. *Bull World Health Organ,* **49**, 485-92.

Lobel, H. O., Najera, A. J., Ch'en, W. I., Munroe, P. & Mathews, H. M. (1976). Seroepidemiologic investigations of malaria in Guyana. *J Trop Med Hyg,* **79**, 275-84.

Lubanga, R. G., Norman, S., Ewbank, D. & Karamagi, C. (1997). Maternal diagnosis and treatment of children's fever in an endemic malaria zone of Uganda: implications for the malaria control programme. *Acta Trop,* **68**, 53-64.

Lubell, Y., Reyburn, H., Mbakilwa, H., Mwangi, R., Chonya, S., Whitty, C. J. & Mills, A. (2008). The impact of response to the results of diagnostic tests for malaria: cost-benefit analysis. *Bmj,* **336**, 202-5.

Luby, J. P., Collins, W. E. & Kaiser, R. L. (1967). Persistence of malarial antibody. Findings in patients infected during the outbreak of malaria in Lake Vera, California, 1952-1953. *Am J Trop Med Hyg,* **16**, 255-7.

Macauley, C. (2005). Aggressive active case detection: a malaria control strategy based on the Brazilian model. *Social Science & Medicine,* **60**, 563-573.

Macdonald, G. (1952). The analysis of equilibrium in malaria. *Trop Dis Bull,* **49**, 813-29.

Macdonald, G. (1956a). Theory of the eradication of malaria. *Bull World Health Organ,* **15**, 369-87.

Macdonald, G. (1956b). Epidemiological basis of malaria control. *Bull World Health Organ,* **15**, 613-26.

MacDonald, G. (1957a). *The epidemiology and control of malaria.* London: Oxford University Press.

Macdonald, G. (1957b). Local features of malaria. *The epidemiology and control of malaria.* Oxford University Press.

Machado Filho, A. C., da Costa, E. P., da Costa, E. P., Reis, I. S., Fernandes, E. A., Paim, B. V. & Martinez-Espinosa, F. E. (2014). Effects of Vivax Malaria Acquired Before 20 Weeks of Pregnancy on Subsequent Changes in Fetal Growth. *Am J Trop Med Hyg*.

MacPherson, P., Choko, A. T., Webb, E. L., Thindwa, D., Squire, S. B., Sambakunsi, R., van Oosterhout, J. J., Chunda, T., Chavula, K., Makombe, S. D., Lalloo, D. G. & Corbett, E. L. (2013). Development and Validation of a Global Positioning System–based "Map Book" System for Categorizing Cluster Residency Status of Community Members Living in High-Density Urban Slums in Blantyre, Malawi. *American Journal of Epidemiology,* **177**, 1143-1147.

Malawi Metereological Services. (2006). *Climate of Malawi*. URL: http://www.metmalawi.com/climate/climate.php [18th February, 2014].

Malawi National Statistical Office & ICF Macro. (2011). 2010 Malawi Demographic and Health Survey. URL: http://www.nsomalawi.mw/images/stories/data_on_line/demography/MDHS2010/MDHS2010%20report.pdf.

Malenga, G., Wirima, J., Kazembe, P., Nyasulu, Y., Mbvundula, M., Nyirenda, C., Sungani, F., Campbell, C., Molyneux, M., Bronzan, R., Dodoli, W., Ali, D. & Kabuluzi, S. (2009). Developing national treatment policy for falciparum malaria in Africa: Malawi experience. *Trans R Soc Trop Med Hyg,* **103 Suppl 1**, S15-8.

malERA (2011a). malERA – a research agenda for malaria eradication. *PLoS Med,* **2013**, e1000398 - e1000405.

malERA (2011b). A research agenda for malaria eradication: monitoring, evaluation, and surveillance. *PLoS Med,* **8**, e1000400.

Mann, H. B. & Whitney, D. R. (1947). On a test whether one of two random variables is stochastically larger than the other. *Annals Math Stat,* **18**, 50-60.

Marchant, T., Hanson, K., Nathan, R., Mponda, H., Bruce, J., Jones, C., Sedekia, Y., Mshinda, H. & Schellenberg, J. (2011). Timing of delivery of malaria preventive interventions in pregnancy: results from the Tanzania national voucher programme. *J Epidemiol Community Health,* **65**, 78-82.

Marques, P. X., Saute, F., Pinto, V. V., Cardoso, S., Pinto, J., Alonso, P. L., Rosario, V. E. & Arez, A. P. (2005). Plasmodium species mixed infections in two areas of Manhica district, Mozambique. *Int J Biol Sci,* **1**, 96-102.

Masangwi, S. J., Ferguson, N. S., Grimason, A. M., Morse, T. D., Zawdie, G. & Kazembe, L. N. (2010). Household and community variations and nested risk factors for diarrhoea prevalence in southern Malawi: a binary logistic multi-level analysis. *Int J Environ Health Res,* **20**, 141-58.

Mathanga, D. P., Campbell, C. H., Jr., Vanden Eng, J., Wolkon, A., Bronzan, R. N., Malenga, G. J., Ali, D. & Desai, M. (2010). Comparison of anaemia and parasitaemia as indicators of malaria control in household and EPI-health facility surveys in Malawi. *Malar J,* **9**, 107.

Mathanga, D. P., Luman, E. T., Campbell, C. H., Silwimba, C. & Malenga, G. (2009). Integration of insecticide-treated net distribution into routine immunization services in Malawi: a pilot study. *Trop Med Int Health,* **14**, 792-801.

Mayo, E. (1945). *The Social Problems of an Industrial Civilization.* Boston: Division of Research, Graduate School of Business Administration, Harvad University.

Mazigo, H. D., Obasy, E., Mauka, W., Manyiri, P., Zinga, M., Kweka, E. J., Mnyone, L. L. & Heukelbach, J. (2010). Knowledge, Attitudes, and Practices about Malaria and Its Control in Rural Northwest Tanzania. *Malar Res Treat,* **2010**, 794261.

Mbogo, C. N., Glass, G. E., Forster, D., Kabiru, E. W., Githure, J. I., Ouma, J. H. & Beier, J. C. (1993). Evaluation of light traps for sampling anopheline mosquitoes in Kilifi, Kenya. *J Am Mosq Control Assoc,* **9**, 260-3.

McDowall, D., McCleary, R., Meidinger, E. E. & Hay, R. A. (1980). *Interrupted time series analysis.* Beverly Hills, California: Sage Publications.

McGregor, I. A. (1984). Epidemiology, malaria and pregnancy. *Am J Trop Med Hyg,* **33**, 517-25.

McGregor, I. A., Wilson, M. E. & Billewicz, W. Z. (1983). Malaria infection of the placenta in The Gambia, West Africa; its incidence and relationship to stillbirth, birthweight and placental weight. *Trans R Soc Trop Med Hyg,* **77**, 232-44.

McIntosh, N., Bates, P., Brykczynska, G., Dunstan, G., Goldman, A., Harvey, D., Larcher, V., McCrae, D., McKinnon, A., Patton, M., Saunders, J. & Shelley, P. (2000). Guidelines for the ethical conduct of medical research involving children. Royal College of Paediatrics, Child Health: Ethics Advisory Committee. *Arch Dis Child,* **82**, 177-82.

McKenzie, F. E. & Samba, E. M. (2004). The role of mathematical modeling in evidence-based malaria control. *Am J Trop Med Hyg,* **71**, 94-6.

MEASURE DHS (2012). Incorporating Geographic Information into Malaria Indicator Surveys: A Field Guide to GPS Data Collection. Calverton, Maryland: MEASURE DHS.

MEASURE DHS. (2013a). Malaria Indicator Survey: Guidelines for Sampling for the Malaria Indicator Survey. URL: http://www.malariasurveys.org/toolkitfiles/09%20Sampling%20Guidelines.pdf.

MEASURE DHS (2013b). Malaria Indicator Survey: Guidelines for Sampling for the Malaria Indicator Survey. Calverton, Maryland: MEASURE DHS.

MEASURE Evaluation, MEASURE DHS, PMI, RBM, UNICEF & World Health Organization Malaria Action Programme (2013a). Household Survey Indicators for Malaria Control. WHO.

MEASURE Evaluation, MEASURE DHS, President's Malaria Initiative, Roll Back Malaria Partnership, UNICEF & Programme., W. H. O. M. A. (2013b). Household Survey Indicators for Malaria Control. WHO.

Metropolis, N., Rosenbluth, A. W., Rosenbluth, M. N., Teller, A. H. & Teller, E. (1953). Equation of state calculations by fast computing machines. *J Chem Phys,* **21**, 1087-1092.

Metselaar, D. (1956). Spleens and Holoendemic Malaria in West New Guinea. *Bull World Health Organ,* **15**, 635-649.

Metzger, W. G., Giron, A. M., Vivas-Martinez, S., Gonzalez, J., Charrasco, A. J., Mordmuller, B. G. & Magris, M. (2009). A rapid malaria appraisal in the Venezuelan Amazon. *Malar J,* **8**, 291.

Ministry of Health (MoH) Malawi (2010). Malawi National Malaria Indicator Survey 2010. Lilongwe: Malawi Ministry of Health.

Ministry of Health (MoH) Malawi (2011). Malaria Strategic Plan: 2011—2015: Towards Universal Access. *In:* Programme, N. M. C. (ed.). Lilongwe, Malawi: Ministry of Health, Government of Malawi.

Ministry of Health (MoH) Malawi (2012). Malawi Health Management Information System (HMIS). Lilongwe, Malawi.

Ministry of Health of Eritrea (2008). *LQAS Survey Report Hamset I Program.* Asmara: Ministry of Health.

Mitja, O., Paru, R., Selve, B., Betuela, I., Siba, P., De Lazzari, E. & Bassat, Q. (2013). Malaria epidemiology in Lihir Island, Papua New Guinea. *Malaria Journal,* **12**, 98-98.

Molineaux, L., Storey, J., Cohen, J. E. & Thomas, A. (1980). A longitudinal study of human malaria in the West African Savanna in the absence of control measures: relationships between different Plasmodium species, in particular P. falciparum and P. malariae. *Am J Trop Med Hyg*, **29**, 725-37.

Monasch, R., Reinisch, A., Steketee, R. W., Korenromp, E. L., Alnwick, D. & Bergevin, Y. (2004). Child coverage with mosquito nets and malaria treatment from population-based surveys in African countries: A baseline for monitoring progress in roll back malaria. *American Journal of Tropical Medicine and Hygiene*, **71**, 232-238.

Mosha, J. F., Sturrock, H. J., Greenhouse, B., Greenwood, B., Sutherland, C. J., Gadalla, N., Atwal, S., Drakeley, C., Kibiki, G., Bousema, T., Chandramohan, D. & Gosling, R. (2013). Epidemiology of subpatent Plasmodium falciparum infection: implications for detection of hotspots with imperfect diagnostics. *Malar J*, **12**, 221.

Mtonya, B. & Chizimbi, S. (2006). Systemwide Effects of the Global fund in Malawi: Final Report. Abt Associates Inc., Bethseda, Maryland.

Muirhead-Thomson, R. C. (1951). The distribution of anopheline mosquito bites among different age groups; a new factor in malaria epidemiology. *Br Med J*, **1**, 1114-7.

Muirhead-Thomson, R. C. (1954). Factors determining the true reservoir of infection of Plasmodium falciparum and Wuchereria bancrofti in a West African village. *Trans R Soc Trop Med Hyg*, **48**, 208-25.

Mvondo, J. L., James, M. A., Sulzer, A. J. & Campbell, C. C. (1992). Malaria and pregnancy in Cameroonian women. Naturally acquired antibody responses to asexual blood-stage antigens and the circumsporozoite protein of Plasmodium falciparum. *Trans R Soc Trop Med Hyg*, **86**, 486-90.

Mwanziva, C., Shekalaghe, S., Ndaro, A., Mengerink, B., Megiroo, S., Mosha, F., Sauerwein, R., Drakeley, C., Gosling, R. & Bousema, T. (2008). Overuse of artemisinin-combination therapy in Mto wa Mbu (river of mosquitoes), an area misinterpreted as high endemic for malaria. *Malar J*, **7**, 232.

Mzilahowa, T., Hastings, I. M., Molyneux, M. E. & McCall, P. J. (2012). Entomological indices of malaria transmission in Chikhwawa district, Southern Malawi. *Malar J*, **11**, 380.

Naidoo, I. & Roper, C. (2011). Drug resistance maps to guide intermittent preventive treatment of malaria in African infants. *Parasitology*, **138**, 1469-79.

Najera, A. J. & Global Partnership to Roll Back Malaria. (1999). Malaria control : achievements, problems and strategies. **WHO/MAL/99.1087**. URL: http://www.who.int/iris/handle/10665/66640#sthash.c4WVbgmg.dpuf [4th January 2014].

Najera, J. A. (2000). Epidemiology in the strategies for malaria control. *Parassitologia*, **42**, 9-24.

National Statistical Office (2007). Malawi Multiple Indicator Cluster Survey 2006. National Statistical Office & United Nations Children's Fund.

National Statistical Office. (2013). *Population and Housing Census 2008*. URL: http://www.nsomalawi.mw/index.php/2008-population-and-housing-census/107-2008-population-and-housing-census-results.html [18th February, 2014].

Ndyomugyenyi, R. & Kroeger, A. (2007). Using schoolchildren's reports of bed net use monitored by schoolteachers as a proxy of community coverage in malaria endemic areas of Uganda. *Trop Med Int Health,* **12**, 230-7.

Newman, R. D., Hailemariam, A., Jimma, D., Degifie, A., Kebede, D., Rietveld, A. E., Nahlen, B. L., Barnwell, J. W., Steketee, R. W. & Parise, M. E. (2003). Burden of malaria during pregnancy in areas of stable and unstable transmission in Ethiopia during a nonepidemic year. *J Infect Dis,* **187**, 1765-72.

NMCP (Malawi) (2010). Malawi Malaria Program Performance Review. Lilongwe, Malawi.

NMCP (Malawi) (2012). Report on the Implementation of Indoor Residual Spraying Campaign in Malawi. Lilongwe, Malawi.

NMCP (Malawi) & ICF International (2012). Malawi Malaria Indicator Survey (MIS) 2012. Lilongwe, Malawi, and Calverton, Maryland, USA.

Nosten, F., McGready, R., Simpson, J. A., Thwai, K. L., Balkan, S., Cho, T., Hkirijaroen, L., Looareesuwan, S. & White, N. J. (1999). Effects of Plasmodium vivax malaria in pregnancy. *Lancet,* **354**, 546-9.

Nwakanma, D. C., Gomez-Escobar, N., Walther, M., Crozier, S., Dubovsky, F., Malkin, E., Locke, E. & Conway, D. J. (2009). Quantitative detection of Plasmodium falciparum DNA in saliva, blood, and urine. *J Infect Dis,* **199**, 1567-74.

Nyamongo, I. K. (2002). Health care switching behaviour of malaria patients in a Kenyan rural community. *Soc Sci Med,* **54**, 377-86.

Nyarango, P. M., Gebremeskel, T., Mebrahtu, G., Mufunda, J., Abdulmumini, U., Ogbamariam, A., Kosia, A., Gebremichael, A., Gunawardena, D., Ghebrat, Y. & Okbaldet, Y. (2006). A steep decline of malaria morbidity and mortality trends in Eritrea between 2000 and 2004: the effect of combination of control methods. *Malar J,* **5**, 33.

O'Meara, W. P., Bejon, P., Mwangi, T. W., Okiro, E. A., Peshu, N., Snow, R. W., Newton, C. R. & Marsh, K. (2008a). Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. *Lancet,* **372**, 1555-62.

O'Meara, W. P., Mwangi, T. W., Williams, T. N., McKenzie, F. E., Snow, R. W. & Marsh, K. (2008b). Relationship between exposure, clinical malaria, and age in an area of changing transmission intensity. *American Journal of Tropical Medicine and Hygiene,* **79**, 185-191.

Odhiambo, F. O., Hamel, M. J., Williamson, J., Lindblade, K., ter Kuile, F. O., Peterson, E., Otieno, P., Kariuki, S., Vulule, J., Slutsker, L. & Newman, R. D. (2010). Intermittent preventive treatment in infants for the prevention of malaria in rural Western kenya: a randomized, double-blind placebo-controlled trial. *PLoS One,* **5**, e10016.

Oduro, A. R., Bojang, K. A., Conway, D. J., Corrah, T., Greenwood, B. M. & Schellenberg, D. (2011a). Health centre surveys as a potential tool for monitoring malaria epidemiology by area and over time. *PLoS One,* **6**, e26305.

Oduro, A. R., Bojang, K. A., Conway, D. J., Corrah, T., Greenwood, B. M. & Schellenberg, D. (2011b). Health Centre Surveys as a Potential Tool for Monitoring Malaria Epidemiology by Area and over Time. *PLoS ONE,* **6**.

Okeke, T. A. & Okeibunor, J. C. (2010). Rural-urban differences in health-seeking for the treatment of childhood malaria in south-east Nigeria. *Health Policy,* **95**, 62-8.

Okiro, E. A., Kazembe, L. N., Kabaria, C. W., Ligomeka, J., Noor, A. M., Ali, D. & Snow, R. W. (2013). Childhood Malaria Admission Rates to Four Hospitals in Malawi between 2000 and 2010. *PLoS ONE,* **8**, e62214.

Okiro, E. A., Noor, A. M., Malinga, J., Mitto, B., Mundia, C. W., Mathanga, D., Mzilahowa, T. & Snow, R. W. (2014). An epidemiological profile of malaria and its control in Malawi. A report prepared for the Ministry of Health, the Roll Back Malaria Partnership and the Department for International Development, UK.

Okoh, F., Siddiqi, M., Olives, C. & Valadez, J. J. (2006). *Nigeria LQAS Baseline Household Survey.* Buja: National Malaria Control Program.

Oladokun, R. E., Lawoyin, T. O. & Adedokun, B. O. (2009). Immunization status and its determinants among children of female traders in Ibadan, South-Western Nigeria. *Afr J Med Med Sci,* **38**, 9-15.

Olotu, A., Fegan, G., Wambua, J., Nyangweso, G., Ogada, E., Drakeley, C., Marsh, K. & Bejon, P. (2012). Estimating individual exposure to malaria using local prevalence of malaria infection in the field. *PLoS One,* **7**, e32929.

Omokhodion, F. O., Oyemade, A., Sridhar, M. K., Olaseha, I. O. & Olawuyi, J. F. (1998). Diarrhoea in children of Nigerian market women: prevalence, knowledge of causes, and management. *J Diarrhoeal Dis Res,* **16**, 194-200.

Onori, E. (1967). Distribution of Plasmodium ovale in the Eastern, Western and Northern Regions of Uganda. *Bulletin of the World Health Organization,* **37**, 665-8.

Oomen, A. P. (1969). Studies on elephantiasis of the legs in Ethiopia. *Trop Geogr Med,* **21**, 236-53.

Oomman, N., Mehl, G., Berg, M. & Silverman, R. (2013). Modernising vital registration systems: why now? *Lancet,* **381**, 1336-7.

Oracle Corporation. (2014). *MySQL*. URL: http://www.mysql.com/ [25th February, 2014].

Oriero, E. C., Jacobs, J., Van Geertruyden, J. P., Nwakanma, D. & D'Alessandro, U. (2014). Molecular-based isothermal tests for field diagnosis of malaria and their potential contribution to malaria elimination. *J Antimicrob Chemother*.

Ouma, P., van Eijk, A. M., Hamel, M. J., Parise, M., Ayisi, J. G., Otieno, K., Kager, P. A. & Slutsker, L. (2007). Malaria and anaemia among pregnant women at first antenatal clinic visit in Kisumu, western Kenya. *Trop Med Int Health,* **12**, 1515-23.

Owusu-Agyei, S., Awini, E., Anto, F., Mensah-Afful, T., Adjuik, M., Hodgson, A., Afari, E. & Binka, F. (2007). Assessing malaria control in the Kassena-Nankana district of northern Ghana through repeated surveys using the RBM tools. *Malar J,* **6**, 103.

Pacific Malaria Initiative Survey Group (2010). Malaria on isolated Melanesian islands prior to the initiation of malaria elimination activities. *Malar J,* **9**, 218.

Pampana, E. (1969). *A textbook of malaria eradication, 2nd edn.* London: Oxford University Press.

Parekh, F. K., Hernandez, J. N., Krogstad, D. J., Casapia, W. M. & Branch, O. H. (2007). Prevalence and risk of Plasmodium falciparum and P. vivax malaria among pregnant women living in the hypoendemic communities of the Peruvian Amazon. *Am J Trop Med Hyg,* **77**, 451-7.

Parise, M. E., Lewis, L. S., Ayisi, J. G., Nahlen, B. L., Slutsker, L., Muga, R., Sharif, S. K., Hill, J. & Steketee, R. W. (2003). A rapid assessment approach for public health decision-making related to the prevention of malaria during pregnancy. *Bull World Health Organ,* **81**, 316-23.

Park, C., Chwae, Y., Kim, J., Lee, J., Hur, G., Jeon, B., Koh, J., Han, J., Lee, S., Park, J., Kaslow, D. C., Strickman, D. & Roh, C. (2000). Serologic responses of Korean soldiers serving in malaria-endemic areas during a recent outbreak of Plasmodium vivax. *American Journal of Tropical Medicine and Hygiene,* **62**, 720-725.

Petersen, M. R. & Deddens, J. A. (2008). A comparison of two methods for estimating prevalence ratios. *BMC Med Res Methodol,* **8**, 9.

Pinto, J., Sousa, C. A., Gil, V., Ferreira, C., Goncalves, L., Lopes, D., Petrarca, V., Charlwood, J. D. & do Rosario, V. E. (2000). Malaria in Sao Tome and Principe: parasite prevalences and vector densities. *Acta Trop,* **76**, 185-93.

PLoS Medicine. (2011). *malERA – a research agenda for malaria eradication*. URL: http://www.ploscollections.org/article/browseIssue.action?issue=info%3Adoi%2F10.1371%2Fissue.pcol.v07.i13#cover [3rd December 2013 2013].

Port, G. R., Boreham, P. F. L. & Bryan, J. H. (1980). The relationship of host size to feeding by mosquitoes of the Anopheles gambiae Giles complex (Diptera: Culicidae). *Bull Entomol Res,* **70**, 133–144.

Premier Medical Corperation Limited. (2012). *First Response Malaria Ag. pLDH/HRP2 Combo Card Test Rapid One Step Malaria Ag. pLDH/HRP2 Combo Test Package Insert*. URL: http://premiermedcorp.com/wp-content/uploads/2013/08/product_documents/Infectious_Diseases/I16FRC30-1.pdf [24th February, 2014].

President's Malaria Initiative. (2010). President's Malaria Initiative Malaria Operational Plan Malawi FY 2010. URL: http://www.fightingmalaria.gov/countries/mops/fy10/malawi_mop-fy10.pdf [7th May, 2014].

Price, E. W. (1976). Endemic elephantiasis of the lower legs in Rwanda and Burundi. *Trop Geogr Med,* **28**, 283-90.

Price, R. N., Douglas, N. M. & Anstey, N. M. (2009). New developments in Plasmodium vivax malaria: severe disease and the rise of chloroquine resistance. *Curr Opin Infect Dis,* **22**, 430-5.

Pringle, G. (1966). A quantitative study of naturally-acquired malaria infections in Anopheles gambiae and Anopheles funestus in a highly malarious area of East Africa. *Trans R Soc Trop Med Hyg,* **60**, 626-32.

Proietti, C., Pettinato, D. D., Kanoi, B. N., Ntege, E., Crisanti, A., Riley, E. M., Egwang, T. G., Drakeley, C. & Bousema, T. (2011). Continuing intense malaria transmission in northern Uganda. *Am J Trop Med Hyg,* **84**, 830-7.

Ramasamy, R., Nagendran, K. & Ramasamy, M. S. (1994). Antibodies to epitopes on merozoite and sporozoite surface antigens as serologic markers of malaria

transmission: studies at a site in the dry zone of Sri Lanka. *Am J Trop Med Hyg,* **50**, 537-47.
Ray, A. P. & Beljaev, A. E. (1984). Epidemiological surveillance: a tool for assessment of malaria and its control. *J Commun Dis,* **16**, 197-207.
RBM (2003). Monitoring and Evaluation Reference Group Anemia Task Force Meeting Minutes. Geneva.
RBM. (2007). Ethical Issues and Treatment Policies. URL: www.rbm.who.int/toolbox/docs/rbmtoolbox/MIS.../26-EthicalIssues.ppt [21st February 2014].
RBM (2008a). THE GLOBAL MALARIA ACTION PLAN: For a malaria free world. *In:* WHO/RBM (ed.).
RBM (2008b). 2. Control: Overcoming Malaria. *In:* Roll Back Malaria Partnership (ed.) *The Global Malaria Action Plan for a Malaria Free World.* Geneva.
RBM. (2010). Framework for monitoring progress and evaluating outcomes and impact. URL: http://www.rollbackmalaria.org/cmc_upload/0/000/012/168/m_e_en.pdf [4th January 2014].
RBM. (2013). *Malaria Indicator Survey: Basic Documentation for Survey Design and Implementation*. URL: http://malariasurveys.org/toolkit.cfm [26th December 2013].
RBM, MEASURE Evaluation, MEASURE DHS, USAID, UNICEF, Organization, W. H., CDC & MACEPA (2009). Guidelines for Core Population-Based Indicators. Calverton, MD.: MEASURE Evaluation.
RBM MERG (2005). Malaria Indicator Survey: Basic Documentation for Survey Design and Implementation. RBM.
Reyburn, H., Mbakilwa, H., Mwangi, R., Mwerinde, O., Olomi, R., Drakeley, C. & Whitty, C. J. (2007). Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial. *Bmj,* **334**, 403.
Reyburn, H., Mbatia, R., Drakeley, C., Bruce, J., Carneiro, I., Olomi, R., Cox, J., Nkya, W. M., Lemnge, M., Greenwood, B. M. & Riley, E. M. (2005). Association of transmission intensity and age with clinical manifestations and case fatality of severe Plasmodium falciparum malaria. *Jama,* **293**, 1461-70.
Ripley, B. D. (2004). Spatial sampling. *Spatial Statistics.* New Jersey: John Wiley and Sons, Inc.
Robert, V., Awono-Ambene, H. P., Le Hesran, J. Y. & Trape, J. F. (2000). Gametocytemia and infectivity to mosquitoes of patients with uncomplicated Plasmodium falciparum malaria attacks treated with chloroquine or sulfadoxine plus pyrimethamine. *Am J Trop Med Hyg,* **62**, 210-6.
Roberts, L. & Enserink, M. (2007). Malaria. Did they really say ... eradication? *Science,* **318**, 1544-5.
Robertson, S. E., Anker, M., Roisin, A. J., Macklai, N. & Engstrom, K. (1997). The lot quality technique: a global review of applications in the assessment of health services and diseases surveillance. *World Health Stat Quarterly* **50**, 199-209.

Robertson, S. E. & Valadez, J. J. (2006). Global review of health care surveys using lot quality assurance sampling (LQAS), 1984-2004. *Social Science & Medicine,* **63**, 1648-1660.

Roca-Feltrer, A., Kwizombe, C. J., Sanjoaquin, M. A., Sesay, S. S., Faragher, B., Harrison, J., Geukers, K., Kabuluzi, S., Mathanga, D. P., Molyneux, E., Chagomera, M., Taylor, T., Molyneux, M. & Heyderman, R. S. (2012a). Lack of decline in childhood malaria, Malawi, 2001-2010. *Emerg Infect Dis,* **18**, 272-8.

Roca-Feltrer, A., Lalloo, D. G., Phiri, K. & Terlouw, D. J. (2012b). Rolling Malaria Indicator Surveys (rMIS): a potential district-level malaria monitoring and evaluation (M&E) tool for program managers. *Am J Trop Med Hyg,* **86**, 96-8.

Rodrigues, A., Schellenberg, J. A., Kofoed, P. E., Aaby, P. & Greenwood, B. (2008). Changing pattern of malaria in Bissau, Guinea Bissau. *Trop Med Int Health,* **13**, 410-7.

Rogerson, S. J., van den Broek, N. R., Chaluluka, E., Qongwane, C., Mhango, C. G. & Molyneux, M. E. (2000). Malaria and anemia in antenatal women in Blantyre, Malawi: a twelve-month survey. *Am J Trop Med Hyg,* **62**, 335-40.

Ross, R. (1916). An Application of the Theory of Probabilities to the Study of a priori Pathometry. Part I. *Proceedings of the Royal Society of London. Series A, Containing Papers of a Mathematical and Physical Character,* **92**, 204-230.

Ross, R. & Hudson, H. P. (1917a). An Application of the Theory of Probabilities to the Study of a Priori Pathometry.--Part III. *Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character,* **89**, 507.

Ross, R. & Hudson, H. P. (1917b). An Application of the Theory of Probabilities to the Study of a Priori Pathometry.--Part II. *Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character,* **89**, 507.

Rota, M. C., Massari, M., Gabutti, G., Guido, M., De Donno, A. & Ciofi degli Atti, M. L. (2008). Measles serological survey in the Italian population: interpretation of results using mixture model. *Vaccine,* **26**, 4403-9.

Roucher, C., Rogier, C., Dieye-Ba, F., Sokhna, C., Tall, A. & Trape, J. F. (2012). Changing malaria epidemiology and diagnostic criteria for Plasmodium falciparum clinical malaria. *PLoS One,* **7**, e46188.

Rowe, A. K. (2005). Should verbal autopsy results for malaria be adjusted to improve validity? *Int J Epidemiol,* **34**, 712-3.

Rowe, A. K. (2009a). Potential of Integrated Continuous Surveys and Quality Management to Support Monitoring, Evaluation, and the Scale-Up of Health Interventions in Developing Countries. *Am J Trop Med Hyg,* **80**, 971-979.

Rowe, A. K. (2009b). Potential of integrated continuous surveys and quality management to support monitoring, evaluation, and the scale-up of health interventions in developing countries. *Am J Trop Med Hyg,* **80**, 971-9.

Rowe, A. K., Kachur, S. P., Yoon, S. S., Lynch, M., Slutsker, L. & Steketee, R. W. (2009). Caution is required when using health facility-based data to evaluate the health impact of malaria control efforts in Africa. *Malar J,* **8**, 209.

Rulisa, S., Kateera, F., Bizimana, J. P., Agaba, S., Dukuzumuremyi, J., Baas, L., de Dieu Harelimana, J., Mens, P. F., Boer, K. R. & de Vries, P. J. (2013). Malaria prevalence, spatial clustering and risk factors in a low endemic area of Eastern Rwanda: a cross sectional study. *PLoS ONE,* **8**, e69443.

Ryder, N. B. (1965). The cohort as a concept in the study of social change. *Am Sociol Rev,* **30**, 843-61.

Sacarlal, J., Nhacolo, A. Q., Sigauque, B., Nhalungo, D. A., Abacassamo, F., Sacoor, C. N., Aide, P., Machevo, S., Nhampossa, T., Macete, E. V., Bassat, Q., David, C., Bardaji, A., Letang, E., Saute, F., Aponte, J. J., Thompson, R. & Alonso, P. L. (2009). A 10 year study of the cause of death in children under 15 years in Manhica, Mozambique. *BMC Public Health,* **9**, 67.

Sahu, S. S., Gunasekaran, K., Vanamail, P. & Jambulingam, P. (2013). Persistent foci of falciparum malaria among tribes over two decades in Koraput district of Odisha State, India. *Malar J,* **12**, 72.

Saksena, P., Xu, K., Elovainio, R. & Perrot, J. (2010). Health services utilization and out-of-pocket expenditure at public and private facilities in low-income countries. *In:* WHO (ed.) *World Health Report (2010) Background Paper, 20.* Geneva.

Sankoh, O. & Binka, F. (2005). INDEPTH Network: generating empirical population and health data in resource-constrained countries in the developing world. *In:* Becher, H. & Kouyate, B. (eds.) *Health research in developing countries: a collaboration between Burkina Faso and Germany.* Berlin: Spinger.

Santos, C. A., Fiaccone, R. L., Oliveira, N. F., Cunha, S., Barreto, M. L., do Carmo, M. B., Moncayo, A. L., Rodrigues, L. C., Cooper, P. J. & Amorim, L. D. (2008a). Estimating adjusted prevalence ratio in clustered cross-sectional epidemiological data. *BMC Med Res Methodol,* **8**, 80.

Santos, L. M., Paes-Sousa, R., Silva Junior, J. B. & Victora, C. G. (2008b). National Immunization Day: a strategy to monitor health and nutrition indicators. *Bull World Health Organ,* **86**, 474-9.

Saphonn, V., Hor, L. B., Ly, S. P., Chhuon, S., Saidel, T. & Detels, R. (2002). How well do antenatal clinic (ANC) attendees represent the general population? A comparison of HIV prevalence from ANC sentinel surveillance sites with a population-based survey of women aged 15-49 in Cambodia. *Int J Epidemiol,* **31**, 449-55.

Sari, M., de Pee, S., Martini, E., Herman, S., Sugiatmi, Bloem, M. W. & Yip, R. (2001). Estimating the prevalence of anaemia: a comparison of three methods. *Bull World Health Organ,* **79**, 506-11.

Sarndal, C., Swensson, B. & Wretman, J. (2003). Survey Sampling in Theory and Practice. *In:* Sarndal, C., Swensson, B. & Wretman, J. (eds.) *Model Assisted Survey Sampling.* New York: Springer-Verlag.

Satoguina, J., Walther, B., Drakeley, C., Nwakanma, D., Oriero, E. C., Correa, S., Corran, P., Conway, D. J. & Walther, M. (2009). Comparison of surveillance methods applied to a situation of low malaria prevalence at rural sites in The Gambia and Guinea Bissau. *Malar J,* **8**, 274.

Savage, E. J., Msyamboza, K., Gies, S., D'Alessandro, U. & Brabin, B. J. (2007). Maternal anaemia as an indicator for monitoring malaria control in pregnancy in sub-Saharan Africa. *BJOG: An International Journal of Obstetrics & Gynaecology,* **114**, 1222-1231.

Schachterle, S. E., Mtove, G., Levens, J. P., Clemens, E. G., Shi, L., Raj, A., Munoz, B., Reller, M. E., West, S., Dumler, J. S. & Sullivan, D. (2011). Prevalence and

density-related concordance of three diagnostic tests for malaria in a region of Tanzania with hypoendemic malaria. *J Clin Microbiol,* **49**, 3885-91.

Schellenberg, D., Menendez, C., Aponte, J., Guinovart, C., Mshinda, H., Tanner, M. & Alonso, P. (2004). The changing epidemiology of malaria in Ifakara Town, southern Tanzania. *Trop Med Int Health,* **9**, 68-76.

Schellenberg, D., Menendez, C., Kahigwa, E., Aponte, J., Vidal, J., Tanner, M., Mshinda, H. & Alonso, P. (2001). Intermittent treatment for malaria and anaemia control at time of routine vaccinations in Tanzanian infants: a randomised, placebo-controlled trial. *Lancet,* **357**, 1471-7.

Schellenberg, J. A., Newell, J. N., Snow, R. W., Mung'ala, V., Marsh, K., Smith, P. G. & Hayes, R. J. (1998). An analysis of the geographical distribution of severe malaria in children in Kilifi District, Kenya. *Int J Epidemiol,* **27**, 323-9.

Schellenberg, J. R., Maokola, W., Shirima, K., Manzi, F., Mrisho, M., Mushi, A., Alonso, P., Mshinda, H., Tanner, M. & Schellenberg, D. M. (2011). Cluster-randomized study of intermittent preventive treatment for malaria in infants (IPTi) in southern Tanzania: evaluation of impact on survival. *Malar J,* **10**, 387.

Service, M. W. (1993). *Mosquito Ecology: Field Sampling Methods.* London: Elsevier's Applied Science.

Setel, P. W., Whiting, D. R., Hemed, Y., Chandramohan, D., Wolfson, L. J., Alberti, K. G. & Lopez, A. D. (2006). Validity of verbal autopsy procedures for determining cause of death in Tanzania. *Trop Med Int Health,* **11**, 681-96.

Shannon, G. W., Skinner, J. L. & Bashshur, R. L. (1973). Time and distance: the journey for medical care. *Int J Health Serv,* **3**, 237-44.

Sharp, B. L., Kleinschmidt, I., Streat, E., Maharaj, R., Barnes, K. I., Durrheim, D. N., Ridl, F. C., Morris, N., Seocharan, I., Kunene, S., JJ, L. A. G., Mthembu, J. D., Maartens, F., Martin, C. L. & Barreto, A. (2007). Seven years of regional malaria control collaboration--Mozambique, South Africa, and Swaziland. *Am J Trop Med Hyg,* **76**, 42-7.

Shekalaghe, S., Alifrangis, M., Mwanziva, C., Enevold, A., Mwakalinga, S., Mkali, H., Kavishe, R., Manjurano, A., Sauerwein, R., Drakeley, C. & Bousema, T. (2009). Low density parasitaemia, red blood cell polymorphisms and Plasmodium falciparum specific immune responses in a low endemic area in northern Tanzania. *BMC Infect Dis,* **9**, 69.

Shewhart, W. A. (1931). *Economic Control of Quality of Manufactured Product.* New York: D. Van Nostrand Company.

Shillcutt, S., Morel, C., Goodman, C., Coleman, P., Bell, D., Whitty, C. J. & Mills, A. (2008). Cost-effectiveness of malaria diagnostic methods in sub-Saharan Africa in an era of combination therapy. *Bull World Health Organ,* **86**, 101-10.

Shulman, C. E. & Dorman, E. K. (2003). Importance and prevention of malaria in pregnancy. *Trans R Soc Trop Med Hyg,* **97**, 30-5.

Shute, P. G., Maryon, M. E. & Pringle, G. (1965). A method for estimating the number of sporozoites in the salivary glands of a mosquito. *Trans R Soc Trop Med Hyg,* **59**, 285-8.

Singh, N., Shukla, M. M. & Sharma, V. P. (1999). Epidemiology of malaria in pregnancy in central India. *Bull World Health Organ,* **77**, 567-72.

Singh, S., Darroch, J. E. & Ashford, L. S. (2013). Adding It Up: The Need for and Cost of Maternal and Newborn Care - Estimates for 2012. New York.
Skarbinski, J., Mwandama, D., Luka, M., Jafali, J., Wolkon, A., Townes, D., Campbell, C., Zoya, J., Ali, D. & Mathanga, D. P. (2011). Impact of health facility-based insecticide treated bednet distribution in Malawi: progress and challenges towards achieving universal coverage. *PLoS ONE,* **6**, e21995.
Skarbinski, J., Mwandama, D., Wolkon, A., Luka, M., Jafali, J., Smith, A., Mzilahowa, T., Gimnig, J., Campbell, C., Chiphwanya, J., Ali, D. & Mathanga, D. P. (2012). Impact of indoor residual spraying with lambda-cyhalothrin on malaria parasitemia and anemia prevalence among children less than five years of age in an area of intense, year-round transmission in Malawi. *Am J Trop Med Hyg,* **86**, 997-1004.
Skarbinski, J., Patel, M., Winston, C. A., Patrick Kachur, S., Massaga, J. J., Bloland, P. B. & Rowe, A. K. (2006). Monitoring insecticide-treated bednet possession and use: Comparison of data collected via health facility and household surveys - Lindi Region and Rufiji District, Tanzania, 2005. *American Journal of Tropical Medicine and Hygiene,* **75**, 3-3.
Skarbinski, J., Winston, C. A., Massaga, J. J., Kachur, S. P. & Rowe, A. K. (2008). Assessing the validity of health facility-based data on insecticide-treated bednet possession and use: comparison of data collected via health facility and household surveys--Lindi region and Rufiji district, Tanzania, 2005. *Trop Med Int Health,* **13**, 396-405.
Slutsker, L., Khoromana, C. O., Hightower, A. W., Macheso, A., Wirima, J. J., Breman, J. G., Heymann, D. L. & Steketee, R. W. (1996). Malaria infection in infancy in rural Malawi. *Am J Trop Med Hyg,* **55**, 71-6.
Smith, D. L., Dushoff, J., Snow, R. W. & Hay, S. I. (2005). The entomological inoculation rate and Plasmodium falciparum infection in African children. *Nature,* **438**, 492-495.
Smith, D. L., Guerra, C. A., Snow, R. W. & Hay, S. I. (2007a). Standardizing estimates of the Plasmodium falciparum parasite rate. *Malar J,* **6**, 131.
Smith, D. L. & McKenzie, F. E. (2004). Statics and dynamics of malaria infection in Anopheles mosquitoes. *Malar J,* **3**, 13.
Smith, D. L., McKenzie, F. E., Snow, R. W. & Hay, S. I. (2007b). Revisiting the basic reproductive number for malaria and its implications for malaria control. *PLoS Biol,* **5**, e42.
Smith, T. (1995). Proportionality between light trap catches and biting densities of malaria vectors. *J Am Mosq Control Assoc,* **11**, 377-8.
Smits, H. L. (2009). Prospects for the control of neglected tropical diseases by mass drug administration. *Expert Rev Anti Infect Ther,* **7**, 37-56.
Snow, R. W., Amratia, P., Kabaria, C. W., Noor, A. M. & Marsh, K. (2012). The changing limits and incidence of malaria in Africa: 1939-2009. *Adv Parasitol,* **78**, 169-262.
Snow, R. W., Craig, M. H., Newton, C. R. J. C. & Steketee, R. W. (2003). The public health burden of Plasmodium faciparum malaria in Africa: Deriving the number. *Working Paper No. 11, Disease Control Priorities Project*. URL: http://www.cdc.gov/malaria/pdf/snow_wp11.pdf [11th December 2014].

Snow, R. W. & Gilles, H., M. (2002). The epidemiology of malaria. *In:* Warrell, D. A. & Gilles, H., M. (eds.) *Essential Malariology: 4th Edition.* London: Hodder Arnold.

Snow, R. W. & Marsh, K. (2002). The consequences of reducing transmission of Plasmodium falciparum in Africa. *Adv Parasitol,* **52**, 235-64.

Snow, R. W., Omumbo, J. A., Lowe, B., Molyneux, C. S., Obiero, J. O., Palmer, A., Weber, M. W., Pinder, M., Nahlen, B., Obonyo, C., Newbold, C., Gupta, S. & Marsh, K. (1997). Relation between severe malaria morbidity in children and level of Plasmodium falciparum transmission in Africa. *Lancet,* **349**, 1650-1654.

Some, E. S., Koech, D. K., Ochogo, J. O., Ocholla, F. & Mumbi, F. (1997). An evaluation of surveillance of malaria at primary health care level in Kenya. *East Afr Med J,* **74**, 573-5.

Stata-Press. (2013a). CORRGRAM — Tabulate and graph autocorrelations. URL: www.stata-press.com/manuals/ts_corrgram.pdf.

Stata-Press. (2013b). MARGINSPLOT — Graph results from margins. URL: http://www.stata.com/manuals13/rmarginsplot.pdf.

StataCorp. (2013a). LOWESS — Lowess smoothing. *Stata 13 Manual*. URL: www.stata.com/manuals13/rlowess.pdf.

StataCorp (2013b). Stata Survey Data Reference Manual: Release 13. College Station, TX: StataCorp LP: Stata-Press.

Steketee, R. W. & Campbell, C. C. (2010). Impact of national malaria control scale-up programmes in Africa: magnitude and attribution of effects. *Malar J,* **9**, 299.

Steketee, R. W., Wirima, J. J., Bloland, P. B., Chilima, B., Mermin, J. H., Chitsulo, L. & Breman, J. G. (1996). Impairment of a pregnant woman's acquired ability to limit Plasmodium falciparum by infection with human immunodeficiency virus type-1. *Am J Trop Med Hyg,* **55**, 42-9.

Stevenson, J. C., Stresman, G. H., Gitonga, C. W., Gillig, J., Owaga, C., Marube, E., Odongo, W., Okoth, A., China, P., Oriango, R., Brooker, S. J., Bousema, T., Drakeley, C. & Cox, J. (2013). Reliability of school surveys in estimating geographic variation in malaria transmission in the Western kenyan highlands. *PloS one,* **8**, e77641.

Stewart, L., Gosling, R., Griffin, J., Gesase, S., Campo, J., Hashim, R., Masika, P., Mosha, J., Bousema, T., Shekalaghe, S., Cook, J., Corran, P., Ghani, A., Riley, E. M. & Drakeley, C. (2009). Rapid assessment of malaria transmission using age-specific sero-conversion rates. *PLoS ONE,* **4**, e6083.

Stich, A., Oster, N., Abdel-Aziz, I. Z., Stieglbauer, G., Coulibaly, B., Wickert, H., McLean, J., Kouyate, B. A., Becher, H. & Lanzer, M. (2006). Malaria in a holoendemic area of Burkina Faso: a cross-sectional study. *Parasitol Res,* **98**, 596-9.

Stoltzfus, R. J. (1997). Rethinking anaemia surveillance. *Lancet,* **349**, 1764-6.

Struik, S. S. & Riley, E. M. (2004). Does malaria suffer from lack of memory? *Immunol Rev,* **201**, 268-90.

Subbarao, S. K., Vasantha, K., Raghavendra, K., Sharma, V. P. & Sharma, G. K. (1988). Anopheles culicifacies: siblings species composition and its relationship to malaria incidence. *J Am Mosq Control Assoc,* **4**, 29-33.

Takem, E. N., Affara, M., Amambua-Ngwa, A., Okebe, J., Ceesay, S. J., Jawara, M., Oriero, E., Nwakanma, D., Pinder, M., Clifford, C., Taal, M., Sowe, M., Suso, P., Mendy, A., Mbaye, A., Drakeley, C. & D'Alessandro, U. (2013). Detecting Foci of Malaria Transmission with School Surveys: A Pilot Study in the Gambia. *PLoS ONE,* **8**, e67108.

Tanner, M. & de Savigny, D. (2008). Malaria eradication back on the table. *Bull World Health Organ,* **86**, 82.

Taylor, S. M., van Eijk, A. M., Hand, C. C., Mwandagalirwa, K., Messina, J. P., Tshefu, A. K., Atua, B., Emch, M., Muwonga, J., Meshnick, S. R. & Ter Kuile, F. O. (2011). Quantification of the burden and consequences of pregnancy-associated malaria in the Democratic Republic of the Congo. *J Infect Dis,* **204**, 1762-71.

Tchuinkam, T., Mulder, B., Dechering, K., Stoffels, H., Verhave, J. P., Cot, M., Carnevale, P., Meuwissen, J. H. & Robert, V. (1993). Experimental infections of Anopheles gambiae with Plasmodium falciparum of naturally infected gametocyte carriers in Cameroon: factors influencing the infectivity to mosquitoes. *Trop Med Parasitol,* **44**, 271-6.

ter Kuile, F. O., Parise, M. E., Verhoeff, F. H., Udhayakumar, V., Newman, R. D., van Eijk, A. M., Rogerson, S. J. & Steketee, R. W. (2004). The burden of co-infection with human immunodeficiency virus type 1 and malaria in pregnant women in sub-saharan Africa. *Am J Trop Med Hyg,* **71**, 41-54.

Thacker, S. B., Parrish, R. G. & Trowbridge, F. L. (1988). A method for evaluating systems of epidemiological surveillance. *World Health Stat Q,* **41**, 11-8.

The malERA Consultative Group on Monitoring, E., and Surveillance (2011). A research agenda for malaria eradication: monitoring, evaluation, and surveillance. *PLoS Med,* **8**, e1000400.

Tikasingh, E., Edwards, C., Hamilton, P. J., Commissiong, L. M. & Draper, C. C. (1980). A malaria outbreak due to Plasmodium malariae on the Island of Grenada. *Am J Trop Med Hyg,* **29**, 715-9.

Tjitra, E., Anstey, N. M., Sugiarto, P., Warikar, N., Kenangalem, E., Karyana, M., Lampah, D. A. & Price, R. N. (2008). Multidrug-Resistant Plasmodium vivax Associated with Severe and Fatal Malaria: A Prospective Study in Papua, Indonesia. *PLoS Med,* **5**, e128.

Toure, Y. T., Doumbo, O., Toure, A., Bagayoko, M., Diallo, M., Dolo, A., Vernick, K. D., Keister, D. B., Muratova, O. & Kaslow, D. C. (1998). Gametocyte infectivity by direct mosquito feeds in an area of seasonal malaria transmission: implications for Bancoumana, Mali as a transmission-blocking vaccine site. *Am J Trop Med Hyg,* **59**, 481-6.

Tusting, L. S., Bousema, T., Smith, D. L. & Drakeley, C. (2014). Measuring changes in Plasmodium falciparum transmission: precision, accuracy and costs of metrics. *Adv Parasitol,* **84**, 151-208.

UNICEF (1990). Strategy for improved nutrition of children and women in developing countries. New York.

UNICEF. (2012a). *Expanded Immunization Coverage*. URL: http://www.unicef.org/immunization/index_coverage.html [19th April 2012].

UNICEF. (2012b). *Multiple Indicator Cluster Surveys - Round 5*. URL: http://www.childinfo.org/mics5.html [6th October 2014].
UNICEF. (2012c). *Antenatal Care*. URL: http://www.childinfo.org/antenatal_care.html [19th April 2012].
UNICEF. (2012d). *Multiple Indicator Cluster Survey (MICS)*. URL: http://www.unicef.org/statistics/index_24302.html [3rd December 2013].
UNICEF. (2013). *Antenatal Care.* URL: http://www.childinfo.org/antenatal_care.html [27th August 2012].
United Nations (2001). Principles and Recommendations for a Vital Statistics System: Revision 2. New York: Department of Economic and Social Affairs, Statistic Division, United Nations.
Valadez, J. J. (1991). *Assessing Child Survival Programs in Developing Countries: Testing Lot Quality Assurance Sampling*. Cambridge: Harvard University Press.
Valadez, J. J. & Devkota, B. R. (2002). Decentralized Supervision of Community Health Program Using LQAS in Two Districts of Southern Nepal. *In:* Rhode, J. & Wyon, J. (eds.) *Community-Based Health Care: Lessons from Bangladesh to Boston.* Boston: Management Sciences for Health.
van der Kaay, H. J. (1976). Malaria in Surinam, a sero-epidemiological study. *Acta Leiden,* **43**, 7-91.
van Eijk, A. M., Ayisi, J. G., ter Kuile, F. O., Misore, A. O., Otieno, J. A., Rosen, D. H., Kager, P. A., Steketee, R. W. & Nahlen, B. L. (2003). HIV increases the risk of malaria in women of all gravidities in Kisumu, Kenya. *AIDS,* **17**, 595-603.
Vanderbilt University. (2014). *REDCap: Research Electronic Database Capture*. URL: http://www.project-redcap.org/ [25th February, 2014].
Verhoeff, F. H., Brabin, B. J., Chimsuku, L., Kazembe, P., Russell, W. B. & Broadhead, R. L. (1998). An evaluation of the effects of intermittent sulfadoxine-pyrimethamine treatment in pregnancy on parasite clearance and risk of low birthweight in rural Malawi. *Ann Trop Med Parasitol,* **92**, 141-50.
Voller, A. & O'Neill, P. (1971). Immunofluorescence method suitable for large-scale application to malaria. *Bull World Health Organ,* **45**, 524-9.
Vundule, C. & Mharakurwa, S. (1996). Knowledge, practices, and perceptions about malaria in rural communities of Zimbabwe: relevance to malaria control. *Bull World Health Organ,* **74**, 55-60.
Walker-Abbey, A., Djokam, R. R., Eno, A., Leke, R. F., Titanji, V. P., Fogako, J., Sama, G., Thuita, L. H., Beardslee, E., Snounou, G., Zhou, A. & Taylor, D. W. (2005). Malaria in pregnant Cameroonian women: the effect of age and gravidity on submicroscopic and mixed-species infections and multiple parasite genotypes. *Am J Trop Med Hyg,* **72**, 229-35.
Wang, S. J., Lengeler, C., Smith, T. A., Vounatsou, P., Cisse, G., Diallo, D. A., Akogbeto, M., Mtasiwa, D., Teklehaimanot, A. & Tanner, M. (2005). Rapid urban malaria appraisal (RUMA) in sub-Saharan Africa. *Malar J,* **4**, 40.
Wanjala, C. L., Waitumbi, J., Zhou, G. & Githeko, A. K. (2011). Identification of malaria transmission and epidemic hotspots in the western Kenya highlands: its application to malaria epidemic prediction. *Parasit Vectors,* **4**, 81.

Wesolowski, A., Eagle, N., Tatem, A. J., Smith, D. L., Noor, A. M., Snow, R. W. & Buckee, C. O. (2012). Quantifying the impact of human mobility on malaria. *Science*, **338**, 267-70.
WHO (1951). Report on the Malaria Conference in Equitorial Africa. Geneva: WHO.
WHO. (1963). Terminology of Malaria and of Malaria Eradication: Report of a Drafting Committee. URL: http://whqlibdoc.who.int/publications/9241540141.pdf.
WHO (1968). Nutritional anaemias. Report of a WHO scientific group. Geneva.
WHO (1973). *Malaria. Handbook of resolutions and decisions of the World Health Assembly and the Executive Board.* Geneva: World Health Organization.
WHO (1975). *Manual on Practical Entomology. Part II. Methods and Techniques.* Geneva: WHO.
WHO (2006). Malaria vector control and personal protection: Report of a WHO study group. *WHO Technical Report Series, No. 936*. Geneva.
WHO (2007a). Malaria in pregnancy: Guidelines for measuring key monitoring and evaluation indicators. Geneva: World Health Organization.
WHO (2007b). Malaria elimination: a field manual for low and moderate endemic countries. Geneva: WHO.
WHO (2007c). Principles and Practice of Malaria Elimination. *Malaria elimination: A field manual for low an moderately endemic countries*. Geneva: WHO.
WHO. (2008). *Malaria Eradication Research Agenda (malERA) Initiative*. URL: http://www.who.int/malaria/elimination/maleraupdate.pdf [3rd December 2013].
WHO. (2009). WHO recommended insecticides for indoor residual spraying against malaria vectors (updated October 2009). URL: http://www.who.int/whopes/Insecticides_IRS_Malaria_09.pdf [31st January 2014].
WHO (2010). Guidelines for the treatment of malaria - second edition. Geneva: WHO.
WHO (2011a). Malaria rapid diagnostic test performance results of WHO product testing of malaria RDTs: Round 3 (2010-2011). Geneva.
WHO (2011b). Intermittent preventive treatment for infants using sulfadoxine-pyrimethamine (SP-IPTi) for malaria control in Africa: Implementation field guide. Geneva: WHO Global Malaria Programme (GMP)

Department of Immunization, Vaccines & Biologicals (IVB)

UNICEF.
WHO (2012a). Disease surveillance for malaria control: an operational manual. Geneva.
WHO (2012b). Disease surveillance for malaria elimination: an operational manual. Geneva: World Health Organization.
WHO. (2012c). Interim position statement: The role of larviciding for malaria control in sub-Saharan Africa. URL: www.who.int/entity/malaria/publications/atoz/larviciding_position_statement/en/ [31st January 2014].

WHO (2012d). Global plan for insecticide resistance management in malaria vectors. Geneva: WHO.
WHO (2012e). T3. Test. Treat. Track. Scaling up diagnostic testing, treatment and surveillance for malaria.
WHO (2013a). World Malaria Report 2013. *In:* WHO (ed.). Geneva.
WHO. (2013b). WHO recommended long-lasting insecticidal nets (updated May 2013). URL: http://www.who.int/whopes/Long_lasting_insecticidal_nets_May_2013.pdf [31st January 2014].
WHO. (2013c). WHO recommendations for achieving universal coverage with long lasting insecticidal nets in malaria control. URL: http://www.who.int/malaria/publications/atoz/who_recommendation_coverage_llin/en/index.html [31st January 2014].
WHO (2013d). Indoor residual spraying: An operational manual for IRS for malaria transmission, control and elimination. Geneva: WHO.
WHO (2013e). Larval source management – a supplementary measure for malaria vector control. An operational manual. Geneva: WHO.
WHO. (2013f). *WHO Document centre*. URL: http://www.who.int/malaria/publications/en/.
WHO & RBM. (2011). Refined/Updated GMAP Objectives, Targets, Milestones and Priorities Beyond 2011. URL: www.rollbackmalaria.org/gmap/gmap2011update.pdf [26th December 2013].
WHO, The World Bank, UNICEF, UNAIDS, USAID, Alliance, RBM, Stop TB Partnership & MEASURE Evaluation (2011). *Monitoring and Evaluation Toolkit: HIV, Tuberculosis, Malaria and Health and Community Systems Strengthening. 4th edition.* The Global Fund to Fight AIDS, Tuberculosis and Malaria.
WHO Global Malaria Programme. (2012). *WHO Policy Recommendation: Seasonal Malaria Chemoprevention (SMC) for Plasmodium falciparum malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa*. URL: http://www.who.int/malaria/publications/atoz/smc_policy_recommendation_en_032012.pdf?ua=1 [6th October 2014].
WHO/AFRO (2004). A strategic framework for malaria prevention and control during pregnancy in the African Region. Brazzaville.
WHO/MAL (2012). WHO/MAL series of OFFSET documents (1947 - 2000). Geneva: World Health Organization.
Wilcoxon, F. (1945). Individual comparisons by ranking methods. *Biometrics* **1**, 80-83.
Willey, B. A., Armstrong Schellenberg, J. R., Maokola, W., Shirima, K., Chemba, M., Mshinda, H., Alonso, P., Tanner, M. & Schellenberg, D. (2011). Evaluating the effectiveness of IPTi on malaria using routine health information from sentinel health centres in southern Tanzania. *Malar J,* **10**, 41.
William, T., Menon, J., Rajahram, G., Chan, L., Ma, G., Donaldson, S., Khoo, S., Frederick, C., Jelip, J., Anstey, N. M. & Yeo, T. W. (2011). Severe Plasmodium knowlesi malaria in a tertiary care hospital, Sabah, Malaysia. *Emerg Infect Dis,* **17**, 1248-55.

Wiseman, V., Scott, A., Conteh, L., McElroy, B. & Stevens, W. (2008). Determinants of provider choice for malaria treatment: experiences from The Gambia. *Soc Sci Med*, **67**, 487-96.

Worrall, E., Basu, S. & Hanson, K. (2005). Is malaria a disease of poverty? A review of the literature. *Trop Med Int Health*, **10**, 1047-59.

Wyss, K., Whiting, D., Kilima, P., McLarty, D. G., Mtasiwa, D., Tanner, M. & Lorenz, N. (1996). Utilisation of government and private health services in Dar es Salaam. *East Afr Med J*, **73**, 357-63.

Yates, F. (1981). The structure of various types of sample. *In:* Yates, F. (ed.) *Sampling Methods for Censuses and Surveys.* London and High Wycombe: Charles Griffin & Company Ltd.

Yekutiel, P. (1960). Problems of epidemiology in malaria eradication. *Bull World Health Organ*, **22**, 669-83.

Zyaambo, C., Siziya, S. & Fylkesnes, K. (2012). Health status and socio-economic factors associated with health facility utilization in rural and urban areas in Zambia. *BMC Health Serv Res*, **12**, 389.

Annex

Annexe 1: EPI EAG Consent Form

THE COLLEGE OF MEDICINE
Malawi-Liverpool-Wellcome Trust
Clinical Research Programme

www.mlw.medicol.mw

PATIENT INFORMATION DOCUMENT

STUDY TITLE: THE EVALUATION OF DIFFERENT EASY ACCESS GROUPS AS A TOOL FOR MONITORING TEMPORAL CHANGES IN MALARIA TRANSMISSION IN MALAWI: THE EVALMAL STUDY.

INTRODUCTION

The Malawi Liverpool Wellcome Trust Clinical Research Centre (MLW), the College of Medicine (CoM), and Liverpool School of Tropical Medicine (LSTM) are jointly testing a tool to see whether surveillance of trends in malaria can be successfully done by testing children and their siblings less than 15 years old once for malaria infection when they come for routine immunizations at district hospitals like the Chikwawa District Hospital (CDH). This would tell us how well the malaria prevention program of the government is working in Chikwawa and if there are any changes over time.

This study is jointly sponsored by the Wellcome Trust (through the Malaria Capacity Development Consortium) and the ACT consortium.

We invite your child to take part in this study. Before you decide it is important for you to understand why the surveillance is being done and what it will involve. Please take time to read/understand the following information carefully. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish your child to participate in the study.

WHAT IS THIS RESEARCH FOR?

We want to use the WHO's guide to see if the malaria situation in Malawi is changing and if the malaria interventions are working. We will ask you some questions about bednet use in your home and also about your child[ren]'s health. We will also see how common malaria is among your child[ren] by testing for parasites in the blood and also by testing for low levels of blood. We will first look at people that come to health facilities and later in people that find it too difficult to come to hospital either because they are too far away or because the road network doesn't allow them. This will help us learn how best to measure the effects of malaria control in the community.

WHY AM I BEING ASKED TO TAKE PART?

It is convenient for us to monitor a population that has already reported to the hospital for another reason (in EAGs). This way we can make use of your child[ren]'s hospital visit to gather additional information.

WHAT WILL HAPPEN TO MY CHILD?

If you agree to take part, we will ask you a few questions about you and your child[ren] to make sure that you and your child[ren]are eligible to enter into the study and a nurse/field worker will take 8 drops of blood from your finger and 8 drops of blood from your child[ren]'s finger.

We will ask you questions about bednet use in your home, and about other protective measures that are linked to malaria. We will also ask some questions about your child[ren]'s health. This should only take about 30 minutes.

If either you or your child[ren] have low levels of blood, malaria, or history of fever, we will refer you for treatment in the general OPD and under 5 clinic respectively. This will be the same treatment you or your child[ren] would get if you go there if you or your child[ren] is/are sick. This will cost you and your family nothing.

Even if you do not wish to take part and your child is ill today, your child will still be seen by the nurse and get the correct treatment.

When does my child[ren]'s participation in the study start/end? :

The study starts as soon as you give written informed consent to participate in the study. After we ask you a few questions and take the small blood sample from you and your child[ren] today you and your child[ren]'s participation in the study is finished. You and your child[ren]will not be required to participate in future hospital visits.

WHAT WILL HAPPEN TO MY SAMPLES?

One drop of blood will be wiped off. The second drop of blood will be used to test for malaria in the lab using a microscope. The third drop of blood will be used to test for malaria using a rapid test. The fourth drop of blood will be used to check for low levels of blood (anaemia). This will be done right here in the hospital. The remaining 4 drops of blood may be put on a special paper for additional laboratory analysis of malaria. You and your child[ren]'s sample collected in this special paper will be transported to the Malawi Liverpool Wellcome Trust laboratory in Blantyre for storage. These specimens will later be shipped to the London School of Hygiene and Tropical Medicine for analysis. The results for low levels of blood and for the rapid malaria diagnostic test will be given to you today.

WHAT IMPACT WILL THE STUDY HAVE ON ME/WHAT ARE THE BENEFITS AND RISKS?

RISKS

You and your child[ren] will feel a pinch that lasts a few seconds when we take the finger-prick blood tests. Collecting blood from you and your child[ren] will not harm you/him/her. Collecting a finger-prick may cause mild tenderness or bruising that quickly resolves without treatment.

BENEFITS

The knowledge gained from this study will help us improve our understanding of the burden of malaria affecting your children and your community. This will provide valuable supportive information on successful implementation of preventive measures by the Government. If you or your child[ren] are found to have malaria you and/or s/he will receive standard treatment from the government health staff.

WHO WILL HAVE ACCESS TO THE INFORMATION YOU COLLECT ABOUT ME?

If you consent to take part in the research all the information that we get from you and your child as part of this study will be kept private; however, by law, involved Research Ethics Committees (e.g. College of Medicine Research Ethics Committee) and Regulatory Bodies (e.g. the Ministry of Health) have access to this data if they so request. For example, the Research Ethics Committee may want to ensure that consent was properly administered during a later review by randomly contacting participants to interview. The records may be reviewed by staff from Malawi Liverpool Wellcome Trust Laboratories or the Liverpool School of Tropical Medicine as part of their duty to oversee the study and analyse the results. Any information about your child[ren] which leaves the study site in Malawi will have no name and address.

WILL I FIND OUT ABOUT THE STUDY RESULTS?

We will share the results of this study with many people and groups so that other people will benefit from our results. We will also inform the staff of the Ministry of Health and the National Malaria Control Programme. We will present the result at conferences. We will also publish the results in a magazine of science. The name of your child[ren] will not be used in any report resulting from this study

WHAT HAPPENS IF I DON'T WANT TO TAKE PART?

You and your child[ren]'s participation in the study is entirely voluntary. You are free to decide if you want you and your child[ren] to take part or not. If you refuse to take part, no one will know about it. If you do agree to help with the study, you can change your mind and withdraw at any time. This will not affect your child's healthcare now or in future.

WHO CAN I GO TO FOR MORE INFORMATION ABOUT THIS?

You may ask any member of our research team at any time. You may also contact Paul Chipeta, the study coordinator at Chikwawa District Hospital, Tel No. 01420366.

THE COLLEGE OF MEDICINE
Malawi-Liverpool-Wellcome Trust
Clinical Research Programme

www.mlw.medcol.mw

Centre	Study Number	Patient Identification Number

PARENT OR GUARDIANCONSENT FORM

STUDY TITLE: THE EVALUATION OF DIFFERENT EASY ACCESS GROUPS AS A TOOL FOR MONITORING TEMPORAL CHANGES IN MALARIA TRANSMISSION IN MALAWI: THE EVALMAL STUDY.

☐ Statement by parent/guardian:

Please circle Yes or No to confirm whether you agree or do not agree with each of the points below:

- I have read the information sheet or it has been read to me Yes / No
- I have had the chance to ask questions and I am satisfied with the answers that I have been given Yes / No
- I agree for my child[ren] to take part but I know that I can change my mind at a later date Yes / No
- I agree that the finger prick blood samples can be collected from me and my child[ren] for the purpose of this study Yes / No
- I agree that the finger prick blood samples collected from me and my child[ren] can be sent overseas for analysis for research purposes. Yes / No

Name of participant	Date	Signature
*Name of guardian	Date	Signature
**Name of witness	Date	Signature
Name of patient administering consent	Date	Signature

*If participant cannot give consent on their own e.g. children, mentally ill, unconscious patients

**If both participant and guardian cannot read or write.

Annexe 2: EPI EAG Child's Questionnaire

Confidential

Physical Assessment

Screening number _____

Physical Assessment of Index Child

Height/Length in metres _____
(Measure the height of children who can stand un-aided, otherwise measure length)

Weight in kilograms _____

Nutritional status
- ☐ greater than or equal to median
- ☐ less than median but greater than -1SD
- ☐ less than or equal to -1SD but greater than -2SD
- ☐ less than or equal to -2SD but greater than -3SD
- ☐ less than or equal to -3SD

Axillary temperature in degrees centigrade _____

Assessment Of Suitability Form

Screening number _____

Assessment of Suitability of Index Child

Inclusion criteria	☐ Malawian national ☐ Age greater than 4 months but less than 15 years ☐ Informed consent obtained from parent/guardian ☐ Resident in the study area (Chikhwawa) at enrollment (Select all the inclusion criteria the subject has satisfied.)
Exclusion criteria	☐ Participation in another study that is either an intervention study or may interfere with the EvalMal study ☐ Severe malnutrition (less than -3SD weight-for-height) ☐ Known HIV infection ☐ Previous enrollment in the EvalMal study (Select all the exclusion criteria the subject has failed.)
Did this participant satisfy all of the inclusion criteria and none of the exlusion criteria?	☐ No ☐ Yes

Screening And Enrolment Form

Screening number _____

Date of screening _____

Informed Consent

Consent given by parent/gaurdian?
- ☐ No
- ☐ Yes

Index child's demographic characteristics

Child's study identification number _____

Child's age in months _____
((For children less than 5 years old))

Child's age in years _____
((For children aged 5 years or more))

Child's sex
- ☐ Female
- ☐ Male

Child's village of residence _____

Index child's immunization history

Is this an imunization visit for the index child?
- ☐ No
- ☐ Yes

If this is an immunization visit; was it a scheduled visit?
- ☐ No
- ☐ Yes

(A scheduled visit is a planned immunization visit according to the National EPI schedule)

If this was a scheduled visit; which one is it?
- ☐ 14 weeks
- ☐ 9 months

Laboratory Results

Screening number _____

Laboratory results

Haemoglobin test result _____

Malaria rapid diagnostic test result
- ☐ Negative
- ☐ P. falciparum
- ☐ Other plasmodiae
- ☐ Invalid

Filter paper blood specimen (FPBS)

Filter paper blood specimen (FPBS) collected?
- ☐ No
- ☐ Yes

Sibling Physical Assessment

Index child's screening number _____

Physical Assessment of Sibling

Height/Length in metres _____
(Measure the height of children who can stand un-aided, otherwise measure length)

Weight in kilograms _____

Nutritional status
- ☐ greater than or equal to median
- ☐ less than median but greater than -1SD
- ☐ less than or equal to -1SD but greater than -2SD
- ☐ less than or equal to -2SD but greater than -3SD
- ☐ less than or equal to -3SD

Axillary temperature in degrees centigrade _____

Sibling Assessment Of Suitability Form

Index child's screening number _____

Assessment of Suitability of Sibling

Inclusion criteria	☐ Malawian national ☐ Age greater than 4 months but less than 15 years ☐ Informed consent obtained from parent/guardian ☐ Resident in the study area (Chikhwawa) at enrollment (Select all the inclusion criteria the subject has satisfied.)
Exclusion criteria	☐ Participation in another study that is either an intervention study or may interfere with the EvalMal study ☐ Severe malnutrition (less than -3SD weight-for-height) ☐ Known HIV infection ☐ Previous enrollment in the EvalMal study (Select all the exclusion criteria the subject has failed.)
Did this participant satisfy all of the inclusion criteria and none of the exlusion criteria?	☐ No ☐ Yes

Sibling Screening And Enrolment Form

Index child's screening number _____

Date of screening _____

Informed Consent

Consent given by parent/gaurdian?

☐ No
☐ Yes

Sibling's Demographic Characteristics

Sibling's study identification number _____

Sibling's age in months _____
((For children less than 5 years old))

Sibling's age in years _____
((For children aged 5 years or more))

Sibling's sex

☐ Female
☐ Male

Sibling Laboratory Results

Index child's screening number _____

Laboratory results

Haemoglobin test result _____

Malaria rapid diagnostic test result
- ☐ Negative
- ☐ P. falciparum
- ☐ Other plasmodiae
- ☐ Invalid

Filter paper blood specimen (FPBS)

Filter paper blood specimen (FPBS) collected?
- ☐ No
- ☐ Yes

Demographic Characteristics

Screening number of index child _____

Demographic Characteristics

Chikwawa Urban
- ☐ No
- ☐ Yes (Address of study child)

Birth order of index child _____
(Record the child's birth order with his/her siblings (if any) in terms of age. If only child, record 1.)

Ethnic group of index child
- ☐ Chewa
- ☐ Other

Other ethnicity (specify) _____

Respondent's relation to index child
- ☐ Parent/Guardian
- ☐ Other first degree relative
- ☐ Other relative
- ☐ Not related

Age of respondent (in years) _____

Sex of respondent
- ☐ female
- ☐ male

Marital status of respondent
- ☐ single
- ☐ married
- ☐ seperated
- ☐ widowed

Educational status of the respondent
- ☐ none
- ☐ non-formal
- ☐ primary
- ☐ secondary
- ☐ tertiary

Religion of respondent
- ☐ christianity
- ☐ islam
- ☐ traditional
- ☐ Other

Other religion (specify) _____

What is the primary occupation of the head of household?
- ☐ not working
- ☐ non-manual
- ☐ agricultural
- ☐ manual
- ☐ don't know
- ☐ other

Other occupation of head of household (specify) _____

What is the main source of drinking water for members of your household?

- ☐ pipe-borne water in residence
- ☐ protected well or borehole
- ☐ piped public faucet
- ☐ traditional public well
- ☐ piped water in yard or plot
- ☐ surface water (river, canal, etc.)
- ☐ Other

Other source of drinking water (specify) _____

What is the main type of toilet facility in your household?

- ☐ own flush toilet
- ☐ shared flush toilet
- ☐ traditional pit latrine
- ☐ VIP latrine
- ☐ bush or field as latrine
- ☐ Other

Other type of toilet facility (specify) _____

Does you household have any of the following?

- ☐ electricity
- ☐ a radio
- ☐ a television
- ☐ a landline telephone
- ☐ a cellular telephone
- ☐ a refrigerator
- ☐ a bed with a mattress
- ☐ a sofa set
- ☐ table and chairs
- ☐ a paraffin lamp
- ☐ a car
- ☐ a bicycle
- ☐ a motorcycle
- ☐ an ox cart
- ☐ a farm
- ☐ a domestic worker not related to the household head (Mutiple responses. Select all applicable.)

What type of fuel does your household mainly use for cooking?

- ☐ electricity
- ☐ natural gas
- ☐ kerosene
- ☐ charcoal
- ☐ firewood or straw
- ☐ other

Other household fuel (specify) _____

What is the principal material of the walls in your dwelling?

- ☐ mud or dung
- ☐ zinc sheets
- ☐ brick
- ☐ wood
- ☐ stone
- ☐ other

Other type of wall (specify) _____

How many people in your household are 15 years or above? _____

How many people in your household are less than 15 years old? _____

Total number of individuals in the household _____

How many rooms in your house are used for sleeping? _____

Fever In Children

Date of interview

_____

Has the index child OR any other child in your household been ill with fever in the past 2 weeks?

- ☐ no
- ☐ yes
- ☐ don't know

During the child's illness did you seek treatment?

- ☐ no
- ☐ yes

If treatment was sought from the public sector, where did you seek treatment?

- ☐ government hospital
- ☐ government health centre
- ☐ government health post
- ☐ health surveillance assistance
- ☐ other

(Mutiple responses. Select all applicable.)

Other public sector treatment (specify)

_____

If treatment was sought from the private sector, where did you seek treatment?

- ☐ private hospital
- ☐ private pharmacy
- ☐ private medical practitioner
- ☐ other

(Mutiple responses. Select all applicable.)

Other private sector treatment (specify)

_____

If treatment was sought from the informal sector, where did you seek treatment?

- ☐ shop
- ☐ drug peddler
- ☐ traditional practitioner
- ☐ other

(Mutiple responses. Select all applicable.)

Other informal sector treatment (specify)

_____

How many days after the onset of the fever did you seek treatment?

_____

(Record number of days. If treatment was sought in he same day record "0".)

At any time during the illness, was the child treated with any drugs?

- ☐ no
- ☐ yes
- ☐ don't know

(If the episode is documented in the child's health passport, record details below. If not documented in the child's health passport or the pasport is not available, use direct questioning.)

If the child was treated with antimalarials, which ones where used?

- ☐ arthemeter/lumefantrine (tabs/syr/sus)
- ☐ sulphadoxine/pyrimethamine (tabs/syr/sus)
- ☐ artesunate/amodiaquine (tabs/syr/sus)
- ☐ amodiaquine (tabs/syr/sus)
- ☐ chloroquine (tabs/syr/sus)
- ☐ traditional remedy (tabs/syr/sus)
- ☐ other

(Mutiple responses. Select all applicable.)

Other antimalarial treatment (specify)

_____

If the child was treated with antipyretics, which were used?

- ☐ paracetamol (tabs/syr/sus)
- ☐ aspirin (tabs/syr/sus)
- ☐ ibuprofen (tabs/syr/sus)
- ☐ other

(Mutiple responses. Select all applicable.)

Other antipyretic treatment (specify)

_____

If the child was treated with antibiotics, which were used?

- ☐ amoxil (tabs/syr/sus)
- ☐ bactrim or septrin or trimethoprim/sulphamethoxazole (tabs/syr/sus)
- ☐ other

(Mutiple responses. Select all applicable.)

Other antibiotic treatment (specify)

_____

If the child was treated with haematenics, which were used?

- ☐ iron (tabs/syr/sus)
- ☐ ferrous and folate (tabs/syr/sus)
- ☐ other

(Mutiple responses. Select all applicable.)

Other haematenic treatment (specify)

_____

If the child was treated with anithelminthics, which were used?

- ☐ mebendazole (tabs/sus/syr)
- ☐ albendazole (tabs/sus/syr)
- ☐ pyrantel palmitate (tabs/sus/syr)
- ☐ other

(Mutiple responses. Select all applicable.)

Any other drugs not previously listed?

_____

If the child was treated with an antimalarial, how long after the illness did the child receive an antimalarial?

_____

(Record number of days. If antimalarials were received in the same day record "0".)

Did you pay for any of these antimalarials?

- ☐ no
- ☐ yes
- ☐ don't know

How much did you pay for the antimalarials in Malawian Kwacha?

_____

(Record what the respondent says was paid. If the respondent cannot remember leave blank. If more than one antimalarials was purchased, give the total cost.)

General Malaria Knowledge

Date of interview _____

Have you ever had of a disease called malaria?
- ☐ no
- ☐ yes

Can you tell me the main signs and symptoms of malaria?
- ☐ fever
- ☐ feeling cold
- ☐ headache
- ☐ nausea and vomiting
- ☐ diarrhoea
- ☐ dizziness
- ☐ loss of appetite
- ☐ body ache or joint pains
- ☐ body weakness
- ☐ paleness
- ☐ jaundice
- ☐ altered consciousness or mental status
- ☐ seizures
- ☐ cough
- ☐ don't know
- ☐ other

(Mutiple responses. Select all applicable. Probe once. "Anything else?")

Other symptoms of malaria (specify) _____

In your opinion, what causes malaria?
- ☐ mosquito bites
- ☐ eating immature sugar cane
- ☐ eating dirty food
- ☐ drinking dirty water
- ☐ hunger
- ☐ getting soaked with rain
- ☐ cold or changing weather
- ☐ witchcraft
- ☐ don't know
- ☐ other

(Mutiple responses. Select all applicable. Probe once. "Anything else?")

Other cause of malaria (specify) _____

How can someone protect themselves against malaria?
- ☐ sleep under an ITN
- ☐ use mosquito coil
- ☐ fill in puddles of water (stagnant water)
- ☐ aerosol/repellent sprays
- ☐ cut grass around the hose
- ☐ burn leaves/herbs
- ☐ don't drink dirty water
- ☐ don't eat dirty food
- ☐ don't get soaked with rain
- ☐ eating well
- ☐ don't eat immature sugar cane
- ☐ don't know
- ☐ other

(Mutiple responses. Select all applicable. Probe once. "Anything else?")

Other form of malaria protection (specify) _____

What are the danger signs and symptoms of malaria in children?

- ☐ seizures or convulsions
- ☐ unconsciousness
- ☐ any fever
- ☐ very high fever
- ☐ severe weakness
- ☐ chills or shivering
- ☐ lack of appetite
- ☐ vomiting
- ☐ crying all the time or restless
- ☐ eating well
- ☐ diarrhoea
- ☐ don't know
- ☐ other

(Mutiple responses. Select all applicable. Probe once. "Anything else?")

Other danger signs (specify) _____

Malaria Control

Date of interview _____

Indoor Residual Spraying

At any time in the past 12 months, has anyone sprayed the interior walls of your dwelling against mosquitoes?
- ☐ no
- ☐ yes
- ☐ don't know

How many months ago was the house sprayed? _____
(If less than one month record "0". If the respondent does not know, leave blank.)

Who sprayed the house?
- ☐ government worker or programme
- ☐ private company
- ☐ don't know
- ☐ other

House sprayed by other (specify) _____

At any time in the past 12 months, have the walls in your household been plastered or painted?
- ☐ no
- ☐ yes
- ☐ don't know

How many months ago were the walls plastered or painted? _____

Use of bednets

Does your household have mosquito nets that can be used for sleeping?
- ☐ no
- ☐ yes
  (If the answer is yes use the ITN algorithm.)

How many mosquito nets are there in your household? _____
(Record the total number of bednets in the household.)

How many insecticide treated bednets are there in the household? _____
(This should be derived using the ITN algorithm.)

Where did you get the most recent ITN?
- ☐ government clinic/hospital
- ☐ health surveillance assistant
- ☐ retail shop
- ☐ private pharmacy
- ☐ public health campaign
- ☐ don't know
- ☐ other

Other source of ITNS (specify) _____

Did you pay for your most recent ITN?
- ☐ no
- ☐ yes
- ☐ don't know

How much did you pay for your most recent ITN? _____
(In Malawian Kwacha.)

How many times has the most recent ITN been washed since it has been in the household?

- ☐ none
- ☐ one
- ☐ two
- ☐ three or more

Did the study child sleep under an ITN last night?

- ☐ no
- ☐ yes
- ☐ don't know

What is the current general condition of the ITN?

- ☐ good (no hole)
- ☐ fair (no holes that fit a finger-sized torch battery)
- ☐ poor (1 - 4 holes that fit a finger-sized torch battery)
- ☐ unsafe (> 5 holes that fit a finger-sized torch battery)
- ☐ don't know

Annexe 3: ITN indicator algorithm