Health facility data to describe the epidemiology of malaria in sub-Saharan Africa

A thesis submitted for the degree of *Doctor of Philosophy*

Alice Kamau

Hertford College, University of Oxford

Michaelmas 2020

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Abstract

The current understanding of malaria burden in Africa relies on modelled estimates based on incomplete and outdated data. The WHO defines malaria disease surveillance as a central pillar of its Global Technical Strategy. The thesis examines the precision of existing models to predict malaria burden changes and interrogation of malaria metrics from health facility and community surveys on the Kenyan coast.

Geostatistical, epidemiological models provide approximations of malaria disease burden but are rarely tested against empirical data. A systematic review included 93 health facility sites across Africa with a minimum of 5 complete years of temporal data. There was a broad congruence in the matched changes at 70 sites, but significant discordance at 23 sites which showed stagnated or upward trends.

Data on the pathway from infection to death, necessary to parametrise models of morbidity and mortality risk are rare. Prospective 12-month surveillance at six health facilities, the county hospital and repeat surveys among 36 matched communities was used to describe the epidemiology of malaria in all age groups. Despite conditions of declining transmission intensity, immunity to disease and the fatal consequences of infection continue to be acquired in early childhood, faster than anti-parasitic immunity and without evidence of emerging burdens of severe malaria or mortality among young-older non-pregnant adults.

The value of routinely collected data from health facilities to define malaria risk was explored at 36 health facility-community pairs. There was a direct non-linear polynomial relationship between passively detected fever test-positivity and traditional community-based parasite prevalence. Information obtained through routine testing of febrile patients for malaria was able to identify spatial and temporal heterogeneities of malaria risk.

Routine data offers important insights into local malaria transmission patterns, disease burdens and changing patterns of disease. An increased effort is required to replace malaria burden models with empirical data.

Acknowledgements

There are many people who have, either directly or indirectly, contributed to the completion of this thesis and to then I am greatly indebted. My sincere gratitude goes to my supervisors Professors Bob Snow and Philip Bejon who assiduously guided me through the wide field of malaria epidemiology. It was a pleasure to be infected by their love of science and malaria. I am grateful to my third-party monitor Dr Eunice Nduati and my mentor Prof James Kahindi for constant encouragement. A special thank you to the training department at KEMRI-Wellcome Trust, Kilifi and Nuffield Department of Medicine Tropical Network Fund, Oxford for the funding and for providing the resources needed to undertake this DPhil training.

I extend special thanks to the sub-county health management teams, dispensary health committees, KEMRI community representatives' teams for their support during the implementation phase of the study. Special thanks to the Chiefs of Kilifi South, Kilifi North and Ganze who enabled us to conduct the research in their administrative areas. I am indebted to all the study participants who gave us their time and their cooperation. Clinical data collection for malaria at Kilifi county hospital would not have been possible without the dedication of KEMRI-Wellcome Trust fieldworkers, clinical and laboratory staff. Similarly, verbal autopsy data collection would not have possible without the dedicated efforts by George Mochamah and Gideon Nyutu. I am also grateful to Dr Ifedayo Adetifa, Prof Thomas Williams and Prof Anthony Scott for their continued support to the DSS and surveillance at Kilifi; and Dr Benjamin Tsofa for his support during the implementation phase of this study.

I would also like to acknowledge all the fieldworkers that were involved in the outpatient clinics and community-based study's data collection; Haprity Mwangata, Erick Shoboi, Mwanajuma Bakari, Dickson Mwarandu, Masudi Dzombo, Dennis Katana, Titus Mbaga, Emily Nazi, Victor Mwalewa, Timothy Mwaringa, Oscar Mwasambu, and Swabah Salim; and David Walumbe, Nehemiah Kombo, Gabriel Mwambingu and Agustus Kea who assisted in training the field workers. A special mention to Grace Mtanje who took a lot of responsibility in the daily running of the project. I would also like to thank all the staff at the outpatient clinic for their hard work and perseverance in the time of the study including the clinical officers at KEMRI Janet Musembi and Omar Ngoto. I would also like to acknowledge Edward Mundia and Michael Kinuthia for developing the data entry systems, assisting with handling bugs and resolving queries. David Amadi and Mark Otiende for their assistance with DSS data and all related data queries and Lilian Mwango for assisting with data curation. I want to extend my appreciation to Sebastian Nyawalo, David Kyalo, Paul Ouma and Peter Macharia who taught me how to use ArcGIS. Victor Alegana and Laurissa Suiyanka for assisting with DHIS2 data extraction and Peter Macharia for assisting with MAP parasite prevalence data extraction. I am appreciative to Paul Mwaniki, Kennedy Mwai, Dr Lucas Malla and Dr Polycarp Mogeni for their statistical advice and for Polycarp Mogeni's assistance on the systematic review. In addition, I am grateful to Dr Emelda Okiro for providing raw hospital data used during the systematic review in Chapter 2; and Dr Tabitha Mwangi for provision of raw community-based malaria survey data between 1999-2001 used in Chapters 1 and 3.

This work was supported through support to Prof Robert W Snow as part of his Wellcome Trust Principal Fellowship funding (103602 and 212176) and DELTAS Africa Initiative [DEL-15-003]. The DELTAS Africa Initiative is an independent funding scheme of the

African Academy of Sciences (AAS)'s Alliance for Accelerating Excellence in Science in Africa (AESA) and supported by the New Partnership for Africa's Development Planning and Coordinating Agency (NEPAD Agency) with funding from the Wellcome Trust [107769/Z/10/Z, 102975 and 090853] and the UK government.

Special thanks to my colleagues Ivy Kombe, Rodney Ogwang, Martha Mwangome, Juliet Otieno, James Tuju, Jackline Wafula, Pauline Mwatsuma, Martina Chome, and Juliet Odhiambo for your support, advice and friendship. I am profoundly grateful to my family and 'Ngamzz' for believing in me and for their support during this journey. Special thanks to my good friend 'Di' for ensuring I kept sane, for the constant reminder that I needed to take a break, and for believing in me.

Associated Publications

The chapters presented in this thesis (excluding the Introduction and Concluding remarks; Chapters 1 and 6) have been published, submitted or prepared for publication in academic journals.

Chapter 2: A systematic review of changing malaria disease burden in sub-Saharan Africa since 2000: comparing model predictions and empirical observations

Status: Published in BMC Medicine (April 2020)

Authors: Alice Kamau (AK), Polycarp Mogeni (PM), Emelda A Okiro (EAO), Robert W Snow (RWS), Philip Bejon

Authors' contributions: AK, RWS and PB conceived the idea of the study and together developed the protocol. AK and PM did the literature search, selected the studies and extracted the relevant information. AK and RWS synthesized the data. Data were analyzed by AK with input from PB and RWS. EAO provided additional data. AK, PB, and RWS wrote the first draft of the paper. AK, PB, RWS, PM, and EAO critically revised successive drafts of the paper and approved the final version.

Reference: Kamau, A., Mogeni, P., Okiro, E. A., Snow, R. W., Bejon, P. A systematic review of changing malaria disease burden in sub-Saharan Africa since 2000: comparing model predictions and empirical observations. BMC Medicine. 2020;18:1-11.

Chapter 3: Malaria infection, disease and mortality among children and adults on the coast of Kenya.

Status: Published in Malaria Journal (June 2020)

Authors: Alice Kamau (AK), Grace Mtanje (GM^1), Christine Mataza (CM), Gabriel Mwambingu (GM^2), Neema Mturi (NM), Shebe Mohammed (SM), Gerald Ong'ayo (GO) Gideon Nyutu (GN), Amek Nyaguara (AN), Philip Bejon (PB), Robert W Snow (RWS)

Authors' contributions: AK oversaw the implementation of field studies, analysed and interpreted the data and drafted the manuscript. GM^1 and CM coordinate the data collection process for the field studies. NM, SM, and GO were responsible for the paediatric and adult ward surveillance. GM^2, GN were responsible for the laboratory and VA data, respectively. AN was responsible for surveillance in the KHDSS. PB provided input on implementation and reviewed and revised the manuscript. AK and RWS conceived the study, reviewed and revised the manuscript. All authors approved the final manuscript, as submitted.

Reference: Kamau, A., Mtanje, G., Mataza, C., Mwambingu, G., Mturi, N., Mohammed, S., Ong'ayo, G., Nyutu, G., Nyaguara, A., Bejon, P., Snow, R. W. Malaria infection, disease and mortality among children and adults on the coast of Kenya. Malaria Journal. 2020;19:1-12.

Chapter 4: The relationship between facility-based malaria test positivity rate and community-based parasite prevalence.

Status: Published in PLoS One (October 2020)

Authors: Alice Kamau (AK), Grace Mtanje (GM), Christine Mataza (CM), Lucas Malla (LM), Philip Bejon (PB), Robert W Snow (RWS)

Authors' contributions: AK oversaw the implementation of field studies, analysed and interpreted the data and drafted the manuscript. GM and CM coordinated the data collection process for the field studies. LM assisted with data analysis. AK, PB and RWS conceived the study, reviewed and revised the manuscript. All authors approved the final manuscript, as submitted.

Reference: Kamau, A., Mtanje, G., Mataza, C., Malla, L., Bejon, P., & Snow, R. W. The relationship between facility-based malaria test positivity rate and community-based parasite prevalence. PLoS One. 2020;15:e0240058.

Chapter 5: Spatial-temporal clustering of malaria test positivity rate using routinely collected health facility data

Status: In preparation for publication

Authors: Alice Kamau (AK), Grace Mtanje (GM), Christine Mataza (CM), Philip Bejon (PB), Robert W Snow (RWS)

Authors' contributions: AK oversaw the implementation of field studies, analysed and interpreted the data and drafted the manuscript. GM and CM coordinated the data collection process for the field studies. AK, PB and RWS conceived the study, reviewed and revised the manuscript.

Reference: Kamau, A., Mtanje, G., Mataza, C., Bejon, P., & Snow, R. W. Spatial-temporal clustering of malaria test positivity rate using routinely collected health facility data.

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Abbreviations

ACT	Artemisinin Combination Therapy
ACD	Active Case Detection
AIC	Akaike Information Criteria
AL	Artemether-lumefantrine
An.	*Anopheles*
ANC	Ante-natal Care
API	Annual Parasite Index
CDA	Complete Diagnostic Autopsy
CFR	Case Fatality Rate
CHAMPS	Child Health and Mortality Prevention Surveillance
CHD	Chronic Heart Disease
CHERG	Child Health Epidemiology Group
CI	Confidence Interval
CMoH	County Ministry of Health
COD	Cause of Death
CS	Community Survey
DHIS2	District Health Information System version 2
DHS	Demographic and Health Surveys
DSS	Demographic Surveillance System
EIR	Entomological Inoculation Rate
EPI	Expanded Programme on Immunization
EZ	Enumeration Zones
G6PD	Glucose-6-Phosphate Dehydrogenase
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GMEP	Global Malaria Eradication Programme
GMP	Global Malaria Programme
GTS	Global Technical Strategy
HBHI	High Burden High Impact
HDU	High Dependency Unit
HF	Health Facility
HIS	Routine Health Information System
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information Systems
HRP2	Histidine-Rich Protein 2
ibppy	infectious bites per person per year
IDSR	Integrated Disease Surveillance and Response

Abbreviations continued…

INLA	Integrated Nested Laplace Approximations
InterVA-4	Interpreting Verbal Autopsy version 4
IPTi	Intermittent Preventive Treatment of Infants
IPTp	Intermittent Preventive Treatment for Malaria in Pregnancy
IQR	Interquartile Range
IRS	Indoor Residual Spraying
ITN	Insecticide-treated Nets
KCH	Kilifi County Hospital
KCSE	Kenya Certificate of Secondary Education
KEMRI	Kenya Medical Research Institute
KHDSS	Kilifi Health and Demographic Surveillance System
LAMP	Loop-Mediated Isothermal Amplification
LDH	Lactate Dehydrogenase
LiST	Live Saved Tool
LISA	Local Indicators of Spatial Autocorrelation
LLINs	Long-lasting Insecticidal Nets
LLR	Log Likelihood Ratio
LOESS	Locally Weighted Least Squares
P.	*Plasmodium*
*Pf*PR	*Plasmodium falciparum* Parasite Rate
PCD	Passive Case Detection
PR	Parasite Prevalence
PRISMA	Preferred Reporting Items for Systematic Reviews And Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PCR	Polymerase Chain Reaction
R_0	Basic Reproductive Number
RBM	Roll Back Malaria
RDT	Rapid Diagnostic Tests
rho	Correlation
RMSE	Root Mean Square Error
RR	Relative Risk
RTA	Road Traffic Accident
RTS,S	RTS,S/AS01
RxCQ	Radical Treatment with Chloroquine
SCD	Sickle Cell Disease
SD	Standard Deviation
SMAC	Severe Malaria in Africa Consortium
SMC	Seasonal Malaria Chemoprevention

Abbreviations continued…

SP	Sulphadoxine-Pyrimethamine
SPDE	Stochastic Partial Differential Equations
SPR	Slide Positivity Rate
SSA	sub-Saharan Africa
SaTScan	Martin Kulldorf's Spatial Scan statistic
T3	Test.Treat.Track Initiative
TPR	Test Positivity Rate
U5M	Under-five Mortality Rate
UNICEF	United Nations Children's Fund
VA	Verbal Autopsy
WHO	World Health Organization

Chapter 1 : Background & literature review

1.1 The context of malaria and its control in Africa

Since 1900, the global distribution of malaria has shrunk through concerted elimination efforts, urbanization and economic development [De Zulueta, 1987; Hay et al., 2004]. However, in Africa -south of the Sahara- the spatial extent of malaria transmission has changed little, with elimination being achieved only on several offshore islands (Mauritius and Reunion) and the geographic range of malaria reduced in South Africa [Sharp & Le Sueur, 1996; Colluzi, 1999; Snow et al., 2012; Snow et al., 2017]. The last 100 years have witnessed rapid population growth across Africa [Goldewijk & Batthes, 1997], accompanied by waves of escalating and declining parasite transmission [Snow et al. 2017]. During the late 1990s and early 2000s, malaria transmission and mortality had reached an unprecedented decadal peak [Snow et al., 2001; Trape, 2001; Nájera et al., 2011; Snow et al., 2012; Snow et al., 2017].

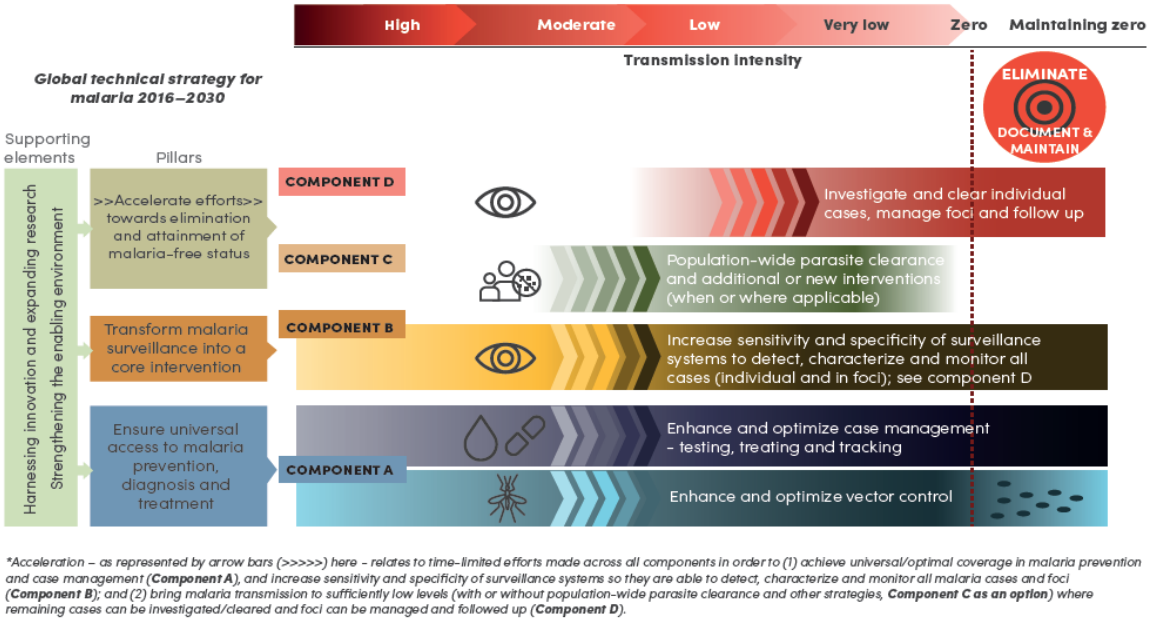
In the late 1960s, sub-Saharan Africa (SSA) had been excluded from the Global Malaria Eradication Programme (GMEP) [Nájera et al., 2011], however in 1998, the international community recognized Africa's importance in the emerging global epidemic and that malaria needed to be part of a global development agenda [Gallup & Sachs, 2001; Sachs & Malaney, 2002]. From 2000, Africa was placed at the centre of efforts to control the global burden of malaria led by the Roll Back Malaria (RBM) initiative [Nabarro & Tayler, 1998; WHO, 2000] and international funding, largely through the Global Fund to fight AIDs, TB and Malaria (GFATM) [Feachem & Sabot, 2006]. This, in turn, led to international and national partnerships to scale up the distribution of insecticide-treated nets (ITN) across Africa [Noor et al., 2009a; Flaxman et al., 2010; Bhatt et al., 2015a], revitalized efforts to provide indoor residual spraying (IRS) in 23 countries [Oxborough, 2016; Tangena et al., 2020], transitioning from failing cheap mono-therapies to efficacious artemisinin-based

combination therapies (ACT) [White, 1999; White et al., 1999] and the prevention of malaria in pregnancy [WHO, 2012a; van Eijk et al., 2011; Desai et al., 2018; Henry et al., 2018]. More recently the global malaria effort has involved the rolling out of the World Health Organisation's (WHO) Test, Treat and Track policy [Graz et al., 2011; WHO, 2012b; Boyce & O'Meara, 2017] to expand diagnostic capacities and avoid presumptive treatment of all fevers. Over the last five years, there have been advances in the scientific evidence and scale up of sub-regional partnerships to deliver seasonal malaria chemoprevention (SMC) in West Africa [Cairns et al., 2012; WHO, 2012c]; RTS,S vaccine under pilot introduction in Malawi, Ghana and Kenya [RTS,S Clinical Trials Partnership, 2015; Adepoju, 2019]; revised efforts to provide mass drug administration (MDA) to rapidly reduce transmission [von Seidlein & Greenwood, 2003; Alonso 2020; Eisele et al., 2020; Galatas et al., 2020]; and in some settings to new methods to identify local transmission foci and use of larval and environmental control [Keiser et al., 2005; Fillinger & Lindsay, 2011].

To accompany this expansion of funding and interest in the control of malaria, the WHO's Global Malaria Programme has developed a Global Technical Strategy (GTS) 2016-2030, to provide a technical framework based on best available scientific evidence [WHO, 2015]. The GTS has retained a global ambition for eradication, driven by a sense from philanthropists that this was possible within a lifetime [Roberts & Enserink, 2007]. Elimination should be the aim for all countries; however, countries will be at different stages on the pathway to elimination [Feachem et al., 2010; WHO, 2015]. Throughout the GTS there is a renewed emphasis on surveillance to ensure countries can track where they are on the malaria continuum to elimination. In setting where transmission remains relatively high, malaria surveillance will provide data on the overall trend, stratification and resource allocation while in low transmission setting, the objective of surveillance is to

identify, investigate and eliminate foci. In 2018, the High Burden High Impact (HBHI) initiative was launched, this was to ensure that the high burden areas of Africa remained the focus of global efforts [WHO, 2018a], initiated originally at the launch of RBM. The HBHI reflects the fact that 10 African countries account for close to 70% of the global malaria burden [WHO, 2019a]. The HBHI approach has at its core the use of data to guide a more effective allocation of limited resources based on malaria epidemiology, mortality and other features of health sub-nationally.

The GTS aims to reduce malaria incidence and mortality rates by at least 90% and eliminate malaria in at least 35 countries by 2030 [WHO, 2015]. The implementation of GTS was built on three pillars and two supporting elements to guide global efforts towards malaria elimination (Figure 1.1). The GTS recommends a continuous process as the rate of progress in countries, subnational areas and communities will differ depending on the level of investment, biological determinants, environmental factors, strength of the health systems as well as social, demographic, political and economic realities (Figure 1.1) [WHO, 2015].



Acceleration – as represented by arrow bars (>>>>>) here - relates to time-limited efforts made across all components in order to (1) achieve universal/optimal coverage in malaria prevention and case management (Component A**), and increase sensitivity and specificity of surveillance systems so they are able to detect, characterize and monitor all malaria cases and foci (**Component B**); and (2) bring malaria transmission to sufficiently low levels (with or without population-wide parasite clearance and other strategies, **Component C as an option**) where remaining cases can be investigated/cleared and foci can be managed and followed up (**Component D**).*

Figure 1.1*:* The WHO Global technical strategy. Reproduced from WHO, 2015, published CC BY-NC-SA 3.0 IGO

The three main pillars of GTS (Figure 1.1) are adapted to the level of malaria risk at country-levels. Pillar 1 aims to provide universal access to malaria prevention, diagnosis and treatment. In high-to-moderate transmission settings, the priority is to ensure that there are sustainable core interventions to prevent infection and reduces malaria case incidence and mortality, including vector control tools (ITN and IRS), drug-based infection prevention strategies including intermittent preventive treatment for malaria in pregnancy (IPTp), intermittent preventive treatment of infants (IPTi), SMC and context specific use of mass drug administration. A key component to reducing mortality is access to effective prompt diagnosis and treatment, both being expanded as a result of expanded rapid diagnostic testing (RDT), prompt use of ACTs, and a growing engagement of community-resource persons and the private retail sector in malaria diagnosis and treatment.

Pillar 2 considers how sustained disease prevention and control might be migrated into a more specific, tailored ambition of local parasite elimination. In SSA, this currently applies

to countries located in Southern Africa that have formed a consortium known as the E8 [E8, 2010] and offshore islands such as Cape Verde, Sao Tome & Principe and Mayotte.

Pillar 3 represents one of the most significant changes to the global malaria strategic plan. Pillar 3 recognizes the importance of malaria surveillance as an independent tool to accelerate the process of national disease burden reduction and tailoring sub-national control priorities based on data [malERA, 2011; Müller, 2011; WHO, 2015; WHO, 2019a]. This pillar is also a core intervention across all malaria risk strata from high burden to countries aiming for elimination or the prevention of re-introduction. As articulated in the GTS, the core principle of the design and establishment of malaria surveillance include: 1) accurate parasitological diagnosis using quality-assured malaria microscopy or rapid diagnostic test; 2) integration of major components of malaria surveillance systems into the broader health management information systems (HMIS); 3) staff training, standard operating procedures and adequate resourcing; 4) surveillance should address the heterogeneity of malaria within a country's boundaries; 6) surveillance data should be linked to other programmes and population to improve decision making (e.g. child deaths from all causes) and; 7) surveillance systems should be assessed routinely to ensure accuracy, reliability, completeness, precision, timeliness and integrity [WHO, 2018b].

Africa has clearly benefitted from a renewed interest in malaria financing and expanded disease prevention since 2000. International agencies have become engaged for the first time in over 50 years in the malaria problem in Africa. There is a consensus that across large parts of Africa malaria transmission and disease burden declined significantly from 2000, but there is a growing concern that this decline has stalled, and in some instance's infection prevalence and disease incidence is increasing [Snow et al., 2017; Alonso & Noor, 2017]. However, despite clear technical guidance on the importance of disease

surveillance, as presented in the GTS and HBHI initiatives, and the billions of overseas development assistance provided since 2000 [Snow et al., 2008; Pigott et al., 2012; Korenromp et al., 2013; Winskill et al., 2017], the precise burden attributed to malaria across the continent and at individual country-levels remains woefully uncertain.

This chapter considers the current understanding of the epidemiology of malaria infection, disease and mortality, how these elements are connected and how they are currently measured to inform malaria burden in Africa. The chapter concludes with the rationale and specific questions of the thesis regarding some of the uncertainties identified in the review of literature regarding the epidemiology of malaria as a disease, its measurement and prospects for future surveillance.

1.2 The malaria parasite and vector

Malaria is a vector-borne disease caused by the protozoan parasite of *Plasmodium (P.)* genus. Five *Plasmodium* parasites are known to infect humans: *P. falciparum, P. vivax P. malariae, P. ovale* (two sibling species *curtisi* and *wallikeri*) [Sutherland et al., 2010; Oguike et al., 2011], and *P. knowlesi.* Only *P. knowlesi* has not been described in sub-Saharan Africa (SSA). *P. falciparum* remains a leading cause of morbidity and mortality in SSA, accounting for >98% of all the estimated global malaria cases in 2018 [WHO, 2019a]. *P.* vivax infects <10% of all malaria cases in SSA partly due to the absence of the Duffy blood-group-antigen that is required by the parasite to invade the red blood cells [Miller et al., 1976]. However, there is growing evidence that shows *P. vivax* can lead to infection and cause disease among Duffy-negative individuals [Rosenberg, 2007; Culleton et al., 2008; Howes et al., 2011].

The sustained high burden of malaria in SSA has largely been attributed to the existence of the world's most effective vectors of the genus *Anopheles* (*An.*) [Coluzzi, 1984; McGregor & Wemsdorfer, 1988]. The most widespread mosquito species across SSA belong to the *An. gambiae* and *An. funestus* complexes [Gillies & De Meillon, 1968; Kyalo et al., 2017; Irish et al., 2020]. These species groups have long life expectancies, strong anthropophily (most marked for *An. gambiae sensu stricto*) and high abundance, which can lead to several hundred secondary malaria cases from a single infected individual. The ecological range within the *An. gambiae* complex includes the following dominant vectors *An. gambiae s.s*, *An. coluzzii*, *An*. *arabiensis*, and two salt breeding species *An. melas* and *An. merus*. The taxonomic complexities of *An. funestus* includes the dominant vector *An. funestus s.s*. and secondary vectors *An. parensis, An. rivulorum, An. vaneedeni,* and *An. leesoni*. Other dominant vectors are *An. moucheti s.l.* located principally in central Africa, and further west across Nigeria, Sierra Leone and Guinea, *An. mascarensis*, is constrained to Madagascar, Comoros and Mayotte, while *An. nili s.l.* has a more extended range [Kyalo et al., 2017]. Other secondary vectors include *An. pharoensis, An. squamosus, An. wellcomei, An. rufipes, An. hancocki, An. coustani, An. paludis An. marshallii* and *An. ziemanni*. These secondary vectors become increasingly important as contributors to residual malaria transmission which is maintained by vectors biting and resting outdoors [Afrane et al., 2016].

1.3 Life cycle

Malaria transmission is the process by which the malaria parasite completes its life cycle in the mosquito and human host (Figure 1.2). The cycle begins when an infected female *Anopheline* mosquito inoculates sporozoites into the human host during a blood meal. The sporozoites migrate to the liver where they invade the hepatocytes. Within the

hepatocytes, sporozoites multiply and mature into schizonts, which rupture and release merozoites into the bloodstream. In *P. vivax* and *P. ovale* a dormant stage (hypnozoite) can persist in the liver and is responsible for subsequent relapsing infections. Following the liver stage (pre-erythrocytic stage), the merozoites subsequently invade the erythrocytes (red blood cells) and begin the asexual cycle where the parasites undergoes multiplication (erythrocytic schizogony). The ring stage trophozoites mature into schizonts, which rupture releasing merozoites for the invasion of new erythrocytes and the cycle is repeated (Figure 1.2). The blood stage parasites are responsible for the clinical manifestations of the disease. A proportion of the parasites differentiate into sexual erythrocytic stages (male and female gametocytes), which are ingested by an *Anopheles* mosquito during a blood meal (Figure 1.2). In the mosquito's stomach, the male and female gametes fuse to form a zygote which undergoes a series of differentiation and growth that results in the production of sporozoites. These sporozoites make their way to the mosquito's salivary glands and the inoculation of the sporozoites into a new human host perpetuates the malaria life cycle (Figure 1.2).

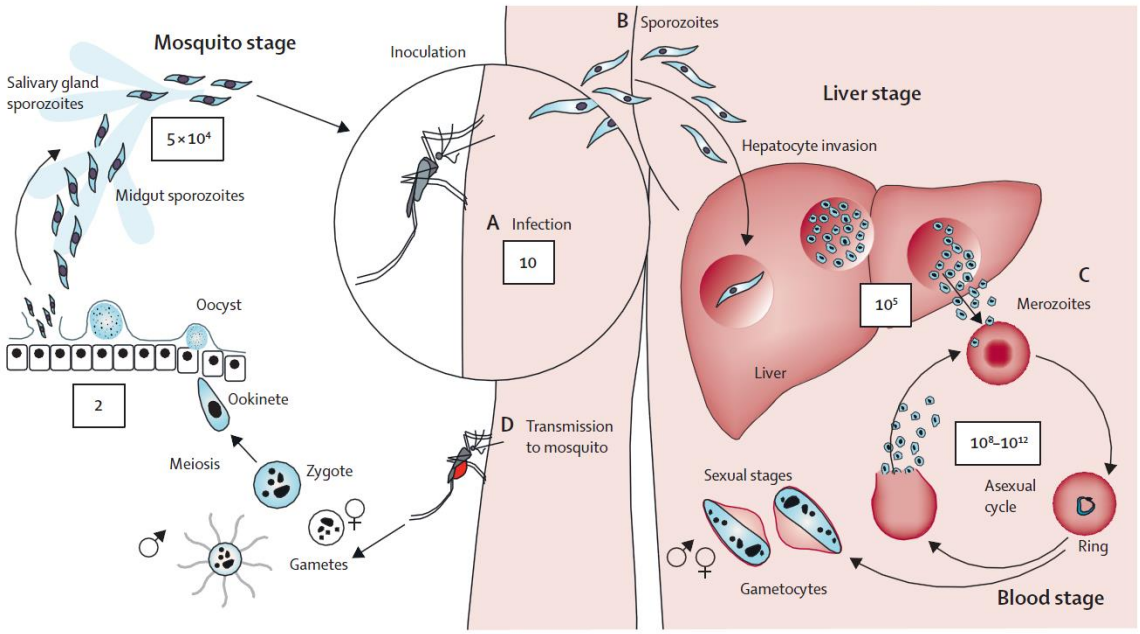


Figure 1.2: *Plasmodium falciparum* life cycle in the human host and mosquito. Reproduced from White et al., 2014, with permission (licence number 4952940667344)

1.4 Pathways from infection to death

The relationship between *P. falciparum* infection rate, morbidity and disease outcome are complex. In a human host, sporozoites could fail to advance to the blood stage by chance or as a consequence of acquired pre-erythrocytic immunity to malaria. Conversely, erythrocytic parasitaemia in the absence of fever or other acute symptoms are common as a result of immunity. Asymptomatic carriers serve as a reservoir of *P. falciparum* as they remain undetected in the community. In addition, when an individual has been inoculated with sporozoites an array of clinical manifestations may follow within the sequence: uncomplicated malaria–severe malaria–death. The progression of these clinical sequences depends on the speed at which peripheral blood parasitaemia replicates within the host. Using a hypothetical scenario, Greenwood et al. (1991) assumed that for every 200 infected children, 100 (50%) would develop a clinical episode attack, two (2%) would evolve to severe disease and with a 50% case-fatality, one would

die (0.5%). These figures differ between populations and the likelihood of progression from infection to death is determined by a variety of factors including the level of endemicity (Section 1.5), host genetic factors, for example haemoglobin AS, thalassemia or glucose-6-phosphate dehydrogenase (G6PD) deficiency, immunological factors, efficacy and timing of treatment and various interventions [Taylor et al., 2012; Greenwood et al., 1991; White et al., 2014].

Clinical malaria can be categorized as a continuum between uncomplicated (mild) and severe, life-threatening disease. If the level of peripheral blood parasitaemia is high enough, usually within the range of 1,000–10,000 parasites per µl, symptoms develop [Greenwood et al., 1991; White et al., 2014]. The first symptoms of acute *P. falciparum* (uncomplicated malaria) are non-specific but often characterized by fever, headache, dizziness, vomiting, sweating, anaemia, mild jaundice and occasionally a palpable spleen [WHO, 2014]. These initial signs and symptoms of malaria have limited value in differentiating malaria from other infectious diseases [Genton et al., 1994; Redd et al., 1996; Olaleye et al., 1998; Chandramohan et al., 2001; Chandramohan et al., 2002]. Therefore, clinical suspicion of malaria should be confirmed by performing a parasitological test. Most uncomplicated malaria infections resolve naturally or through prompt treatment with an effective antimalarial drug [White et al., 2014].

A relatively small proportion of uncomplicated *falciparum* malaria events will progress to severe malaria which is characterized by life-threatening organ damage or blood abnormalities [WHO, 2014]. These severe forms can arise as a result of adherence of infected erythrocyte to other infected erythrocytes (agglutination) or to uninfected erythrocytes (rosetting), microvascular obstruction due to parasite sequestration in blood vessels (especially in the brain), and the host reaction against infection [Miller et al., 2013;

White et al., 2014]. This leads to the presence of one or more clinical or laboratory features (Table 1.1) [WHO, 2014]. These syndromes differ between children and adults. Studies across several malaria endemic countries associated severe malaria anaemia, respiratory distress and cerebral malaria as the major complications that are on the causal pathway towards death (Table 1.1) [Marsh et al., 1995; Waller et al., 1995; Bejon et al., 2007; Dondorp et al., 2008; Dondorp et al., 2010; Jallow et al., 2012; WHO, 2014]. The presence of multiple overlapping syndromes is commonly observed in severe malaria and increases the risk of death [Marsh et al., 1995; Reyburn et al., 2005; Jallow et al., 2012; WHO, 2014]. Severe malaria anaemia is the most common manifestation among young children wheras cerebral malaria is far less common and found more often among older children [Snow et al., 1994c; Slutsker et al., 1994; Idro et al., 2006; Issifou et al., 2007; Snow et al., 1997; Marsh & Snow, 1997; Modiano et al, 1998; Snow & Marsh, 1998b; Reyburn et al., 2005; Okiro et al. 2009b; Carneiro et al., 2010; Roca-Felter et al., 2010; Akech et al., 2019; Mpimbaza et al., 2020a].

Table 1.1: Epidemiological definition of severity of *P. falciparum* infection

Uncomplicated malaria	
Defined as a patient presenting with symptoms of malaria and a positive parasitological test (microscopy or RDT) but with no features of severe malaria	
Severe malaria	**Definition**
Impaired consciousness	Glasgow Coma Score <11 in adults or Blantyre coma score <3 in children
Respiratory distress	The presence of either marked indrawing (recession) of the bony structure of the lower chest wall or deep (acidotic) breathing
Multiple convulsions	Two or more convulsions (one or more convulsions in adults) within 24 hours
Prostration	Generalized weakness: inability to sit upright or to drink without assistance
Compensated shock	Capillary refill ≥3 seconds or temperature gradient on leg, but no hypotension
Decompensated shock	Systolic blood pressure <70 mm Hg in children or <80 mm Hg in adults with evidence of impaired perfusion
Pulmonary oedema	Radiologically confirmed, or oxygen saturation <92% on room air with a respiratory rate >30/min
Abnormal bleeding	Recurrent or prolonged bleeding from nose, gums or venepuncture sites; haematemesis or melaena
Jaundice	Plasma or serum bilirubin >50 mmol/L (3 mg/dL) with a parasite count >100 000/µl
Severe anaemia	Haemoglobin concentration <5 g/dl or haematocrit of <15% in children <12 years of age (<7 g/dl and <20%, respectively, in adults) with a parasite count >10 000/µl
Hypoglycaemia	Blood or plasma glucose <2.2 mmol/L (<40 mg/dL)
Acidosis	Base deficit >8 mEq/L or plasma bicarbonate <15 mM or venous plasma lactate >5 mM.
Renal impairment	Plasma or serum creatinine >265 µmol/L (3 mg/dL) or blood urea >20 mmol/L
Hyperparasitaemia	*P. falciparum* parasitaemia >10%

Far less is known about the pathophysiology and phenotype of severe disease among non-pregnant adults in Africa. Among Asian adults' severe malaria generally presents with

acute respiratory distress, cerebral malaria, pulmonary oedema, acute renal impairment or severe jaundice [Dondorp et al., 2008; White et al., 2014]. There are few data in Africa on the pathology of severe malaria among adults [Giha et al., 2005; Eholie et al., 2004; Robinson et al., 2006; Wade et al., 2012; Abdallah et al., 2013]. In a study in Eastern Sudan, an area of unstable *P. falciparum* transmission, 139 adult patients presented with WHO defined severe malaria; predominantly as decompensated shock (27%), cerebral malaria (16%), and multiple convulsions (13%) [Abdallah et al., 2013].

Although the prognosis of *P. falciparum* malaria is very variable, mortality risks increase when the proportion of infected erythrocytes (parasitaemia) exceed 2% [White et al., 2014]. Even with optimal and timely treatment of *P. falciparum* malaria, case fatality is often in excess of 10-30% among those who develop severe disease and reaches 100% mortality if left untreated [Dondorp et al., 2010; Maitland et al., 2011; Manning et al., 2014; WHO, 2014]. Among paediatric severe malaria admissions to hospital, the majority of deaths occur within 24 hours of admission [Marsh et al., 1995; Berkley et al., 2003; Idro & Aloyo, 2004; Kazembe et al., 2006; Maitland et al., 2011; Kendjo et al., 2013].

The direct effects of infection upon malaria specific disease and death provides only part of the overall burden [Snow, 2000]. Processes associated with infection may increase the susceptibility to severe clinical outcomes related to other infectious diseases [Berkley et al., 2005; Scott et al., 2011] (Figure 1.3). In addition, infections can also lead to indirect detrimental health conditions such as chronic anaemia [Draper, 1960; Hotez & Molyneux, 2008] and under-nutrition [Scrimshaw et al., 1997; Caulfield et al., 2004] (Figure 1.3). Children who survive cerebral malaria might have residual neurological deficits, including epilepsy, cerebral palsy, cortical blindness, deafness, hemiplegia, cognitive and learning impairment (Figure 1.3) [John et al., 2008; White et al., 2014; Abuga et al., 2019; Conroy

et al., 2019]. These debilitating sequelae often carry their own risk of a fatal outcome. Among pregnant women, massive proliferation of *P. falciparum* in the placenta is associated with severe anaemia of the mother, low birth weight deliveries and subsequent increased premature infant mortality (Figure 1.3). In addition, malaria in pregnancy causes indirect mortality from abortion and intrauterine growth retardation, which consequently increases infant mortality [Guyatt & Snow, 2001a; Guyatt & Snow 2001b; Steketee, 2003; Guyatt & Snow, 2004; Desai et al., 2007; Beeson & Simpson, 2017; Rogerson et al., 2018]. The direct attribution of malaria as a cause of death is fraught with problems, as most deaths occur outside of health facilities [Korenromp et al., 2003]. Importantly the balance between the direct and indirect fatal consequences of malaria infection remains poorly defined [Snow, 2000].

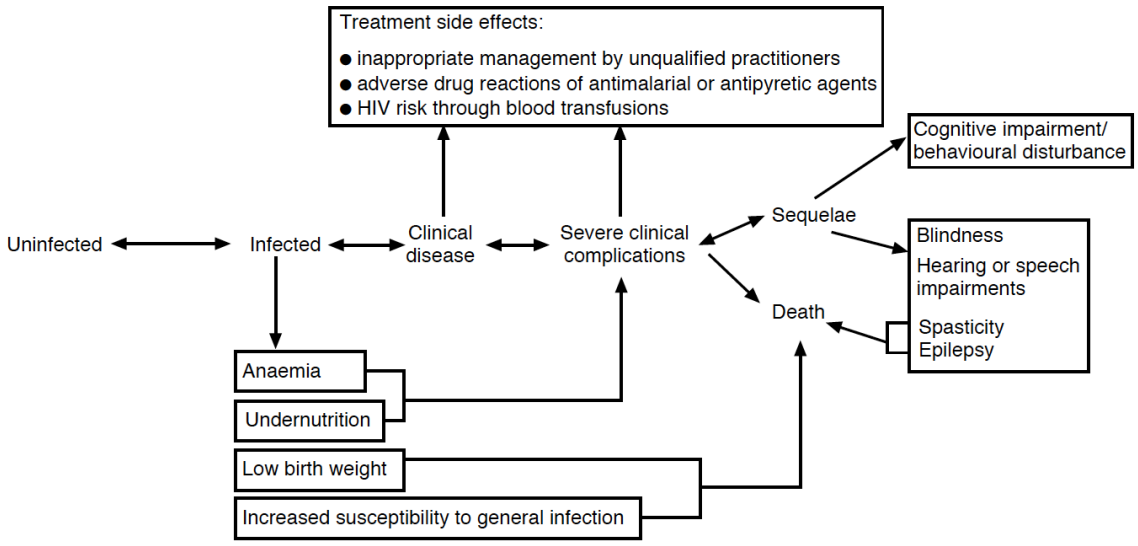


Figure 1.3: The direct and indirect consequences of *P. falciparum* infection. Reproduced from Snow, 2000, published CC-BY 4.0

1.5 Relationship between age, endemicity and malaria

Parasite exposure, age and immunity are intimately related [Anderson & May,1992]. The precise quantity and variation of malaria parasite exposure and its relationship to the

development of functional immunity remain unclear [Langhorne et al., 2008; Pinkevych et al., 2012]. One approach to understand acquired immunity is to study the humoral and cellular immune correlates of protection. However, this is frustrated by the absence of specific immune markers for clinical protection [Valletta & Recker, 2017]. Broadly, it is believed that repeated parasite exposure from birth first leads to the acquisition of functional immunity against severe disease and death, followed by immunity to mild, self-limiting disease, and finally to the ability to regulate infection *per se* (i.e. anti-parasitic immunity) [MacDonald, 1951; McGregor, 1987; Schofield & Mueller, 2006; Fowkes et al., 2016]. These different age patterns are stylised in Figure 1.4, and in the following sections empirical data in support of this figure are reviewed. The age at which these features of immunity occur depends on the quantity and timing of repeat infections and consequently varies in space and time. Analysis of a range of disease outcomes across different transmission settings in Africa has shown that the shape of the disease curves with age (0-15 years) consistently varies with the intensity of transmission. As the transmission intensity declines the mean age of disease increases and this in-turn varies between mild and severe disease [Trape & Rogier, 1996; Snow et al., 1997; Marsh & Snow, 1997; Marsh & Snow, 1999; Snow & Marsh, 2002; Okiro et al., 2009b; Carneiro et al., 2010; Griffin et al., 2015]. It is hard, however, to separate the independent effects of age and exposure as both are related. Studies in Indonesia among non-immune migrants suggest that age *per se* is an important regulator of severe disease, independent of previous exposure [Baird et al., 1998].

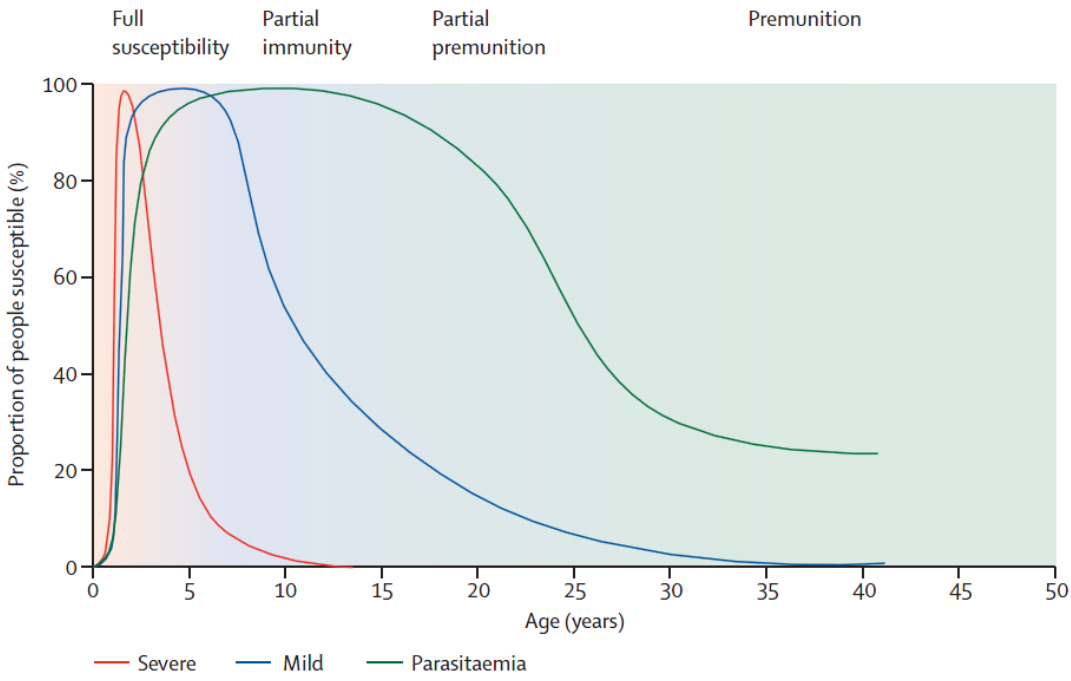


Figure 1.4: The relationship between age and malaria severity in an area with moderate transmission intensity. Reproduced from White et al., 2014, with permission (licence number 4952940667344)

1.5.1 Age and infection prevalence

Anti-parasite immunity acts to restrict the parasite densities that develop upon each subsequent infection, while anti-disease immunity increases the tolerance to high parasite densities without developing fever [Fowkes et al., 2015]. The prevalence of detectable asymptomatic parasitaemia from birth through old age were commonly described pre-1960 [Boyd, 1949] and during the Gharki Project in the 1970s [Molineaux & Gramiccia, 1980]. However, surprisingly little contemporary data exist on infection prevalence across age groups. The focus of malaria surveys today is on describing infection in children below the age of five years (Section 1.7.1). Three sites in East Africa where infection prevalence was documented continously across the entire communities during the 1990s-early 2000s are used here to demonstrate age-patterns of infection under different endemicities (Figure 1.5). Under conditions of very high transmission intensity, entomological inoculation rate (EIR) of >300 infectious bites per person per year (ibppy), parasite

prevalence saturates early in life and parasite regulation occurs in late adolescence (Figure 1.5). Conversely, in areas of lower EIR (10-35 ibppy), prevalence rises slowly through childhood before declining in adolescence and that the shape of the prevalence curve differs within this range of EIR (Figure 1.5). At no time is immunity sterilising and infection risks continue throughout life.

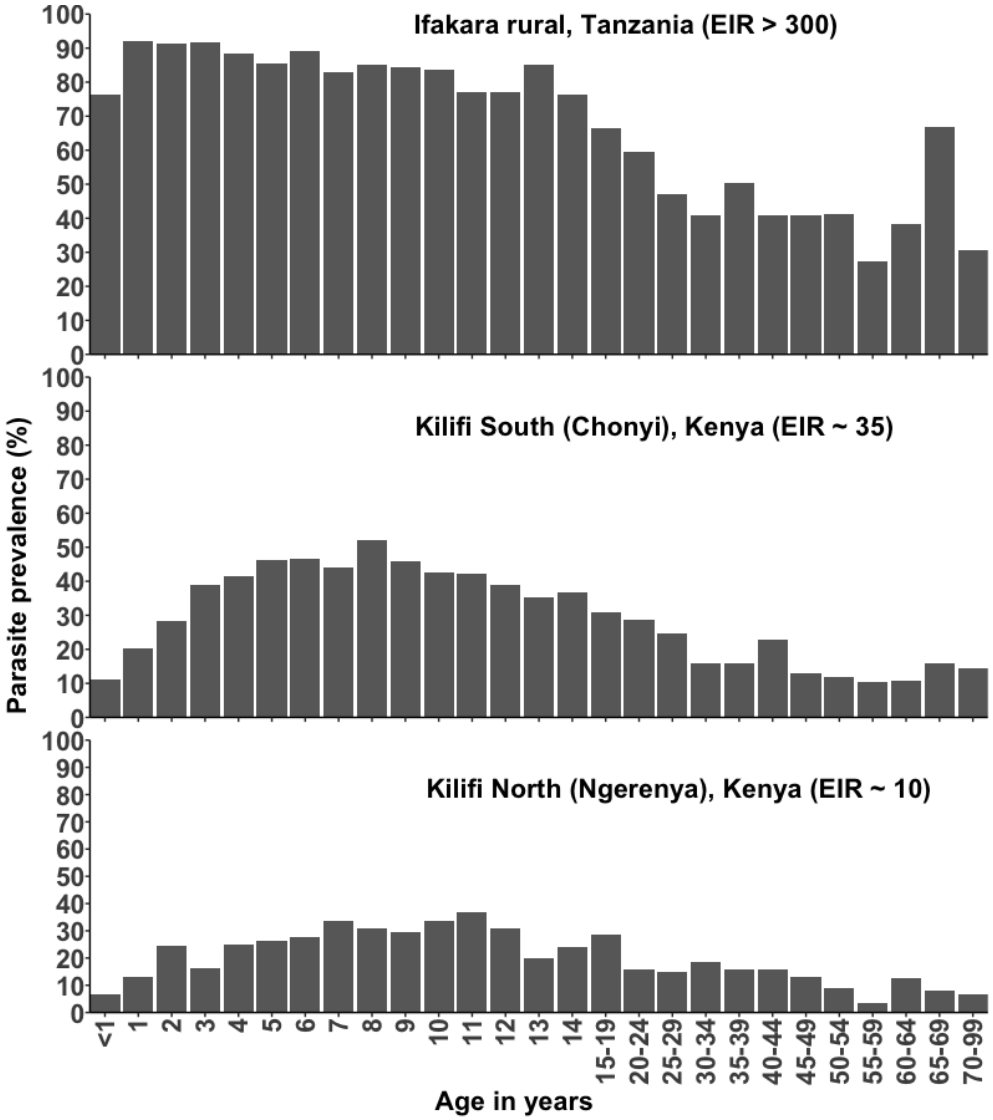


Figure 1.5: Infection prevalence measured using microscopy showing risks across all ages in studies conducted in rural Ifakara (Michenga & Nyamawala villages) Tanzania (fortnightly surveillance 1989-1991) [Smith et al., 1993; and raw data provided by Tom Smith]; Kilifi South (Chonyi) and Kilifi North (Ngerenya) Kenya (weekly surveillance 1999-2001) [Mwangi et al., 2005; and raw data provided by Tabitha Mwangi]

1.5.2 Age and clinical disease

The most intensive epidemiological surveillance of clinical malaria incidence in Africa comes from two villages in Senegal, with different transmission intensities [Trape & Rogier, 1996; Trape et al., 2014]. At Dielmo, a high transmission setting (EIR 200), the age-specific incidence of clinical malaria was seen to peak in the first five years of life and becomes much less common in adolescents and adults (Figure 1.6). Conversely, at Ndiop, an area with a log lower EIR (20), the clinical incidence rises throughout childhood and shows evidence of declining much later in adulthood (Figure 1.6). These observations highlight the differences in the speed of acquired immunity to mild clinical outcomes depending on the entomological rate of parasite exposure; a more rapid acquisition of immunity in settings where transmission intensity was higher.

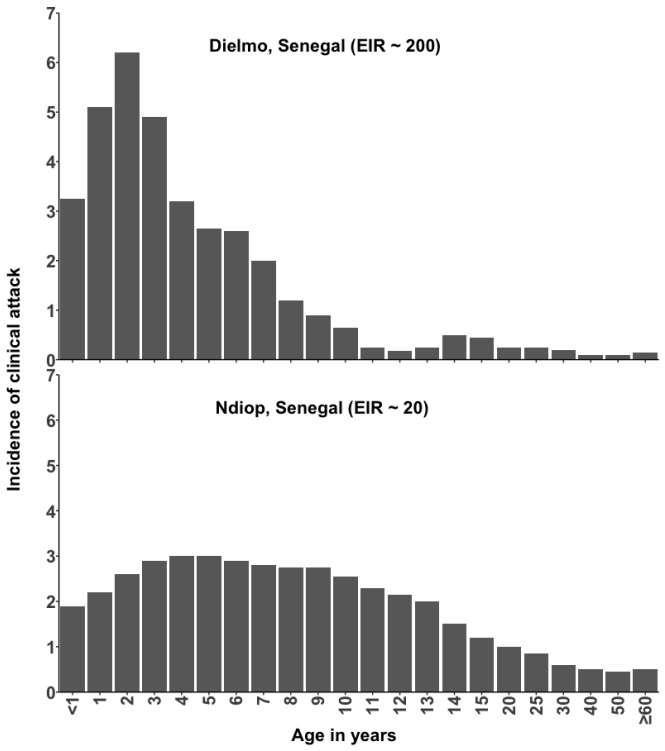


Figure 1.6: Incidence of clinical malaria across all ages in two Senegalese villages at different transmission intensities [Trape & Rogier, 1996]

There are few contemporary studies of clinical incidence in SSA that consider all age groups to replicate the findings in Figure 1.6. Furthermore, definitions of what constitutes a clinical episode, by age, against a high and changing proportion of asymptomatic infection remain problematic (Section 1.7.2)

1.5.3 Age and severe malaria

Between 1990 and 2005, studies of age, clinical phenotype and endemicity were undertaken across a range of transmission settings in SSA. These studies focussed on paediatric admissions to hospitals in Kenya, Tanzania, Uganda, Malawi, Gabon, The Gambia, Ethiopia, Burkina Faso, Ghana and Mozambique [Slutsker et al., 1994; Marsh et al., 1995; Snow et al., 1994c; Imbert et al. 1997; Issifou et al., 2007; Marsh & Snow, 1997; Snow et al. 1997; Modiano et al. 1998; Schellenberg et al., 1999; Reyburn et al., 2005; Idro et al., 2006; Okiro et al., 2009b; Roca-Feltrer et al., 2010; Achidi et al., 2012; Griffin et al., 2015]. The cumulative evidence was that as transmission intensity decreased the mean age of admission to hospital increased. As an example of the age-patterns of malaria hospitalisation at the three sites (Ifakara rural, Kilifi North and Kilifi South) were included in Figure 1.7. Malaria admissions were concentrated in infants under high transmission and then become more evenly spread across the first five years of life as transmission intensity declines (Figure 1.7). However, under all three transmission settings, during the 1990s, rates of admission to hospital with malaria were low after the 5th birthday (Figure 1.7).

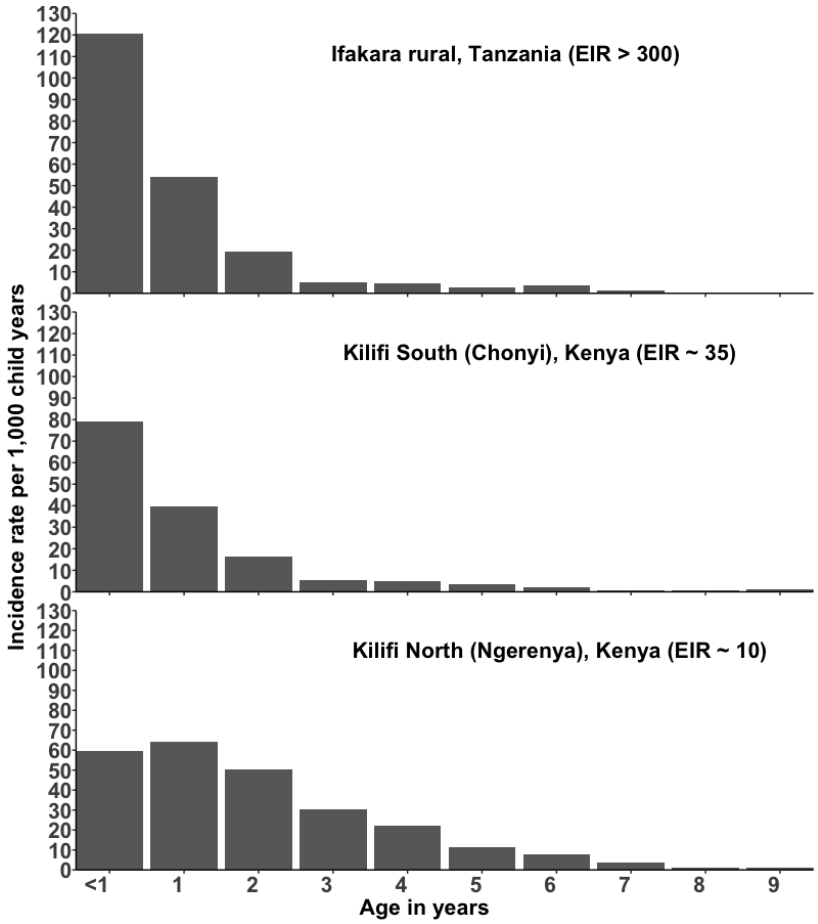


Figure 1.7: Incidence of severe hospitalized malaria showing risks among children aged between 1 month and 9 years in studies conducted in Tanzania [Snow et al., 1994c] and Kenya [Snow et al., 1997] at varying transmission intensities

The relationship between transmission intensity and the age-specific incidence of severe malaria may not be linear. Controversially, authors disagreed on whether annualised incidence of severe malaria plateaued or declined through moderate-to-high transmission settings [Trape & Rogier et al., 1996; Molineaux, 1997; Lengeler et al., 1997; Snow & Marsh, 2002].

An alternative to examining the effect of age and transmission intensity was undertaken by Okiro et al. (2009b) by expressing the proportion of malaria admissions among children aged under 10 years against the age corrected parasite prevalence in the hospital

catchment (Figure 1.8). This figure has been updated with additional data available from the Severe Malaria in Africa Consortium (SMAC) [Taylor et al., 2006] and data not previously included from Mozambique [Bassat et al., 2008], Malawi [Kazembe et al., 2006] and Kericho, Kenya [Shanks et al., 2000]. All data cover the period between 1991-2005, prior to the introduction of ACT (Figure 1.8). Malaria hospitalisation was concentrated among infants where the prevalence of infection in the surrounding community was > 60%; and the fraction of paediatric admissions that are infants declined with declining community-based parasite prevalence (Figure 1.8)

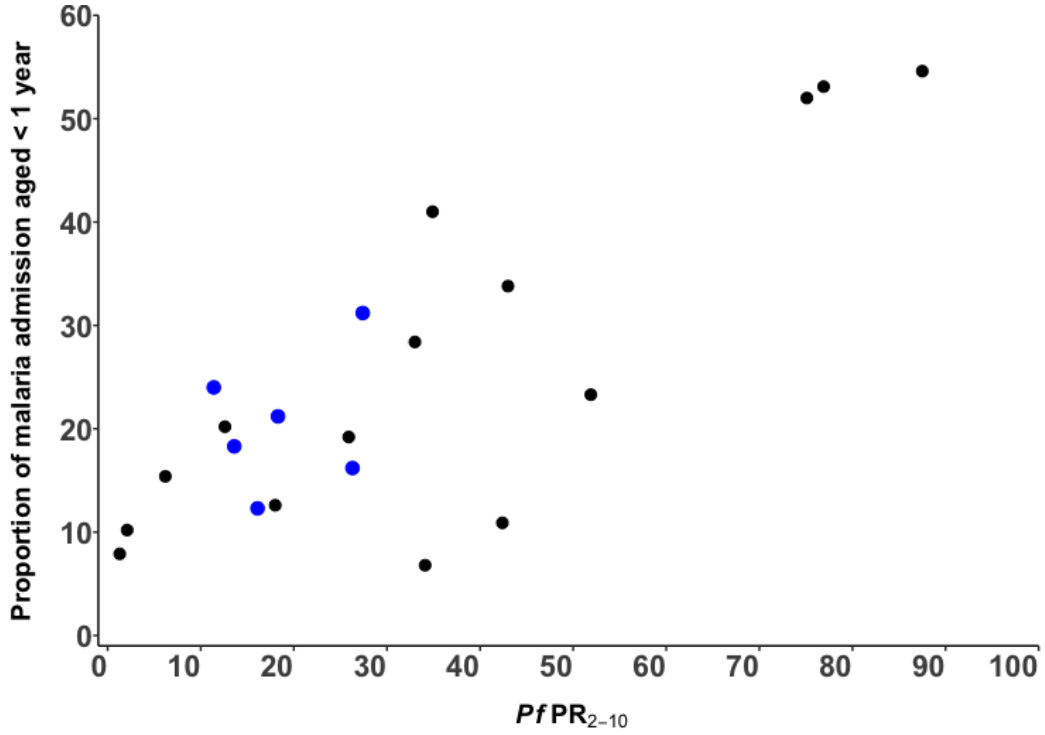


Figure 1.8: Proportion of hospitalized paediatric (<10 years) malaria cases aged <1 year between 1990 and 2005 under different transmission intensities (sites where matched to age-standardized *Pf*$PR_{2–10}$). Black dots – 15 sites reported by Okiro et al. (2009b); blue dots 6 updated points from additional data provided by Terrie Taylor and Bob Snow

In addition to different age-patterns of malaria hospitalisation by transmission intensity, studies also suggested that the clinical phenotype varied by malaria transmission. Higher

rates of severe malaria anaemia were reported in high transmission settings, among young children, while cerebral malaria was more often reported in lower transmission settings [Snow et al., 1997; Okiro et al., 2009b; Roca-Felter et al., 2010; Achidi et al., 2012].

Most studies on the clinical epidemiology of severe malaria have been undertaken over a decade ago. There is a renewed interest in defining the epidemiology of life-threatening malaria as the landscape of transmission and community treatment has changed. Recent studies in western Kenya [Akech et al., 2020] and Uganda [Mpimbaza et al., 2020a] confirm that despite a declining intensity of transmission in East Africa, malaria hospitalisation and severe malaria continue to be concentrated in young children aged <5 years. These studies have also highlighted the significance of severe malaria anaemia as a disease phenotype that might be more prevalent in older children than previously described and the increasing rarity of cerebral malaria across all transmission settings studied [Akech et al., 2020; Mpimbaza et al, 2020a].

1.5.4 Age and malaria mortality

The age-specific relationship between malaria mortality and transmission intensity is not well defined, largely because of imperfections in the tools used to define a death from malaria in the absence of clinical and parasitological diagnosis; discussed in detail in Section 1.7.4. However, early clinical studies on the causes of deaths are useful to provide a broad basis of age in relation to possible malaria mortality. Between 1944-48, 3,085 post-mortems among children aged 0-15 years undertaken in Lagos, Nigeria were re-analysed [Bruce-Chwatt, 1952]. Of the post-mortems undertaken, 9.3% were attributed to malaria, of malaria assigned deaths 23% were among infants, 61% among children under 5 years of age, 16% among children aged 5-15 years, suggesting a dramatic reduction in

malaria mortality after the 5th birthday [Bruce-Chwatt, 1952]. Between 1921-52, 3,406 post-mortems among residents of all ages in Accra, Ghana were reviewed, 89 (2.6%) deaths were indicative of malaria [Colbourne & Eddington, 1954]. Of malaria attributed deaths, 18% were among infants, 67% among children aged 1-5 years, 5.6% among children aged 6-15 years, only 7 (8%) were described in adolescents and adults aged 16-55 years and one death was described above >55 years of age [Colbourne & Eddington, 1954].

1.5.5 Summary of parasite exposure and age-specific malaria disease

This section provides some insights into the age-specific infection, disease and mortality profiles across a range of transmission settings in SSA. The observed ecological comparisons support the mathematical theory that a fixed quantity of parasite exposure will result in degrees of clinical immune protection and that these differ for mild and severe disease [Gupta et al., 1999; Ghani et al., 2009; Griffin et al., 2015; Pemberton-Ross et al., 2015].

Longitudinal evidence of the relationship between age and transmission intensity is emerging from studies at sites across SSA on the changing age-patterns of clinical incidence [Trape et al., 2014], fever test-positivity among out-patients or in-patients [Galatas et al., 2016; Kapesa et al., 2018; Kigozi et al., 2019; Mpimbaza et al., 2020b] and severe/hospitalised paediatric malaria [Ceesay et al., 2008; O'Meara et al., 2008a; O'Meara et al., 2008b; Ursing et al., 2014; Mogeni et al., 2016; Njuguna et al., 2019]. Across all studies, as transmission intensity declines through combinations of ITN/LLIN and community drug use, the mean age of disease outcomes increases.

Age remains our best epidemiological descriptor of acquired immune protection. However, contemporary examples of coincidental descriptions of the epidemiology of infection and disease in all age groups are rare [Smith et al., 1993; Trape et al., 1994; Rogier, 1996; Trape & Rogier, 1996; Giha et al., 2000; Boisier et al., 2002; Koram et al., 2003; Dolo et al., 2005; Mwangi et al., 2005; Rabarijaona et al., 2009; Trape et al., 2014; Khagayi et al., 2019]. The paucity of empirical data on the relationship between malaria infection, disease and mortality outcomes across all age groups hinders both the understanding of age-dependent stages of immunity and the reliable and complete description of malaria's contribution to the burden of disease in Africa.

1.6 Measures of malaria transmission and disease burden

Malaria transmission intensity underpins almost all aspects of malaria epidemiology and disease burden estimation. As malaria transmission declines in much of SSA, there is need to codify a set of measures that define endpoints for changes in transmission intensity and reduction in disease burden (Table 1.2 & Table 1.3) [Hay et al., 2008; Tusting et al., 2014]. Attempts had been made to define the criteria for the measurement of malaria on a continuum scale from intense to interrupted transmission during the era of the GMEP (1955-69) and were institutionalized into rules outlining defined action points for guiding malaria control, elimination and proposed eradication as illustrated in Figure 1.9 [Hay et al., 2008].

On different spatial and temporal scales, malaria transmission reflects changes in the dynamics of the vector and human host, as well as the interventions in place. Among entomological determinants, malaria transmission is strongly determined by the presence of effective mosquito vectors, their relative densities, and their associated biting, resting

and breeding behaviour and insecticide resistance. These factors are extrinsically affected by environmental and climatic factors including rainfall, vegetation, temperature, altitude, or the availability of appropriate breeding sites for the specific mosquito species [Pates & Curtis, 2005]. Vector-human interactions are determined by human behaviour, coverage and use of vector control tools and heterogeneous biting (some people are bitten more frequently than others) [Woolhouse et al., 1997; Smith et al., 2005]. These are, in turn, determined by socio-demographic factors including housing, education, socioeconomic status and urbanisation [Robert et al., 2003; Keiser et al., 2004; Tusting et al., 2017; Willis & Hamon, 2018].

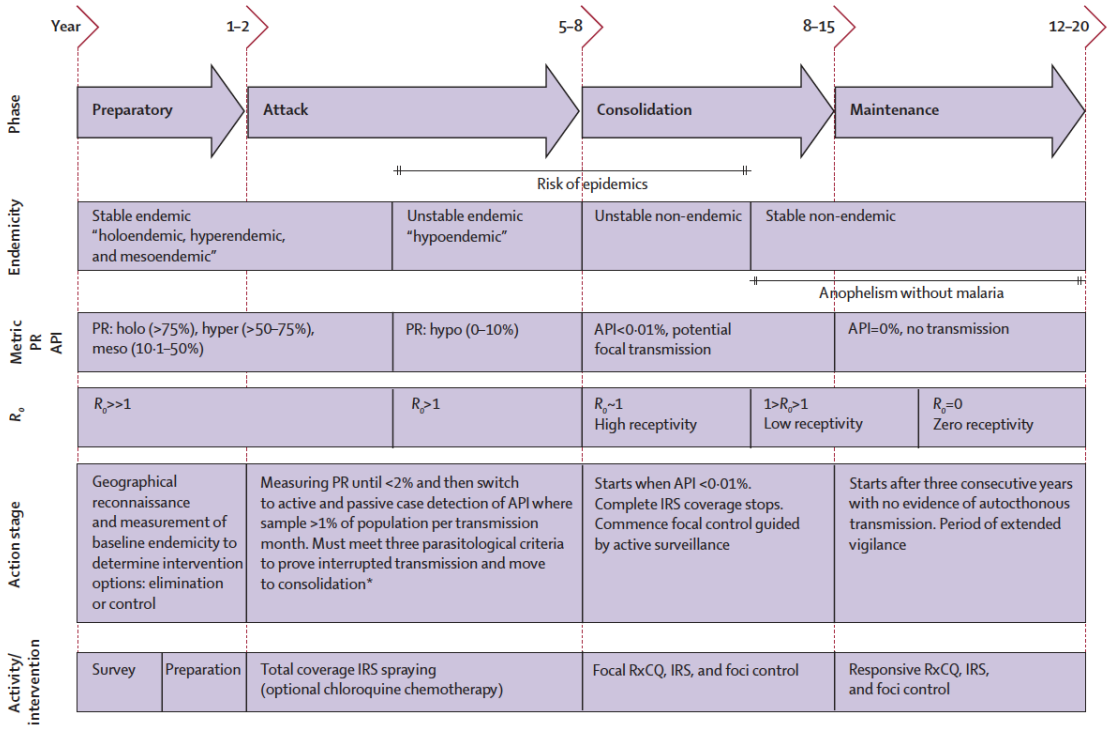


Figure 1.9: Malaria endemicity, classification and timelines for action phases of the Global Malaria Eradication Programme. Reproduced from Hay et al., 2008, published CC-BY 4.0

Legend: The scheme derives details of the phase, approximate timings, action stage, and activity/ intervention undertaken during the era of Global Malaria Eradication Programme and integrates these with malaria endemicity classifications defined by the host prevalence, vector stability indices and the basic reproductive number. The year row presents an estimate of the duration of each phase. API: annual parasite incidence; IRS: indoor residual spraying; PR: parasite rate; R_0: basic reproductive number; RxCQ: radical treatment with chloroquine.

Malaria programmes today, as much as during the GMEP era, require a combination of approaches to detect changes in malaria transmission and the effects of interventions, highlighted in both the GTS and HBHI initiative (Section 1.1). There are several points during the parasite's life cycle (Figure 1.2) at which transmission intensity can be measured using various metrics connected to mosquitoes, parasites, and humans [Hay et al., 2008; Tusting et al., 2014]. The value of different metrics depends on the intensity of transmission, coverage of intervention, immunity and demographics. Although many of the metrics are causally inter-related, their relationship is non-linear when considered across the spectrum of transmission intensity [Smith et al., 2010]. The suitability of metrics as endpoints for measuring malaria transmission and disease burden must be determined by their reliability, completeness, reproducibility, accuracy and the underlying variability across time and space. A range of endemicity measurements that should be measured but are difficult to obtain are described in Table 1.2, including basic reproductive number, net infectiousness of human to mosquito, entomological inoculation rate, force of infection, seroconversion rate and multiplicity of infection. The primary measurements of transmission intensity and disease burden are described in Table 1.3 and the subsequent Section 1.7.

Table 1.2: Summary of metrics used to measure transmission intensity

Metric	Definition	Source and measurement	Formula	Interpretation	Limitations
Basic Reproductive Number (R_0)	The average number of secondary cases that a single infectious person would generate in a completely susceptible population [Ross, 1911; MacDonald & Göeckel, 1964; Anderson & May,1992;].	Although central to epidemiological theory, R_0 is almost impossible to measure directly. However, this metric underpins mathematical models of transmission that are central to contemporary questions in malaria control [Gething et al., 2011].	R_0= (((ma)^2 bc)/gr) × e^(-gn) where 'm' is the ratio of mosquitoes to humans, 'a' is the number of mosquito bites per human per day, 'b' is the probability than a human becomes infected after being bitten by an infectious mosquitoes, 'c' is the probability a mosquito becomes infected after biting an infected human, 'g' is the mosquito instantaneous death rate, 'n' is the number of days from infection to infectiousness in the mosquito (sometimes referred to as the extrinsic incubation period) and 'r' is the duration of infectiousness of the human host.	R_0 is an index of both how well malaria spreads and the effort required to eliminate it. If R_0 exceeds one, infection prevalence increases to a steady state, and if less than one, prevalence declines. In the presence of a range of intervention, the maximum transmission potential is described by a lower effective reproductive number R_C, which is analogous to R_0 [Smith et al., 2012a].	In theory all the components can be collected, however, measuring all the entomological component is technically complex and difficult including ethical concerns of exposing human beings to malaria infection and measurement errors [Smith et al., 2005; Tusting et al., 2014].
Net infectiousness of human to mosquito (κ)	The proportion of mosquitoes that become infected after feeding on humans.	Direct skin feeding and standard membrane-feeding assays are used where laboratory-reared mosquitoes are fed either directly on infected humans or using blood from an infected human to determine the proportion that become infected [Killeen et al., 2006; Churcher et al., 2012].	A simple rule for approximating these rates is $y \approx S\kappa p^o$, and $z \approx S\kappa p^n$, where S is the expected number of human bites a mosquito will give over its lifetime, p is the probability of surviving one day, o is the day after infection on which oocysts appear, and n is the day on which sporozoites appear [Killeen et al., 2006].	The limited number of observations make an assessment of the interpretation of κ difficult.	Due to its relatively low precision and accuracy, κ is not considered a robust metric for detecting a change in malaria transmission intensity [Tusting et al., 2014].

Table 1.2 continued…

Metric	Definition	Source and measurement	Formula	Interpretation	Limitations
Entomological inoculation rate (EIR)	The expected number of infectious bites received per person per period of time	EIR can be obtained from direct field measurements of human biting rate (ma) and sporozoite rate [Hay et al., 2000; Tusting et al., 2014].	EIR= ma × SR where 'm' is the ratio of mosquitoes to humans, 'a' is the number of mosquito bites per human per day, 'SR' is the proportion of mosquitoes with sporozoites in their salivary glands	Typically, when EIR is less than 1, transmission is unstable or low to moderate and saturates above an EIR of around 10. EIR has been estimated to be as high as 1,500 [Gething et al., 2011].	EIR is not suited to routinely estimate transmission intensity because of its imprecise as a result of micro-heterogeneity in malaria transmission (especially in low transmission areas) and hard to compare between estimates when different sampling techniques are used to measure m and a [Hay et al., 2000].
Force of infection (FOI)	The incidence of new infections in the human population per unit time. Alternatively, the molecular FOI refers to the number of new parasite clones acquired per unit time.	Since the prevalence of malaria saturates quickly, the best way to determine the FOI is to measure infant's parasite conversion rate using a simple catalytic conversion model [MacDonald, 1950].	X(a)=1 - e^(-ha) where 'X(a)' denotes the proportion of individuals of age 'a' that have been exposed (infected at least once) to the parasite, and 'h' is the force of infection.	Due to the decline in transmission efficiency at high transmission levels, FOI plateaus above a certain transmission intensity, and is therefore not useful for measuring a change in transmission in highly endemic areas [Tusting et al., 2014].	Both FOI require multiple field visits to a study cohort or repeated cross-sectional surveys hence they are neither cost effective nor feasible as a routine approach. However, infant age-structured prevalence among those attending welfare clinics have been used historically. Infection in young infants is a means to track rapid changes in malaria transmission.

Table 1.2 continued…

Metric	Definition	Source and measurement	Formula	Interpretation	Limitations
Seroconversion rate (SCR)	A function of antimalaria antibodies which is a marker of cumulative exposure to infection in a population.	Blood samples for generating seroprevalence data can be collected in cross-sectional surveys, school surveys or in health facilities. The most commonly used methods for measuring seroprevalence is the enzyme-linked immunosorbent assay [Corran et al., 2007; Stewart et al., 2009; Tusting et al., 2014].	SCR is obtained by fitting a reversible catalytic model to age-specific seroprevalence data obtained for malaria parasite specific antigen [Pull & Grabs, 1974; Drakeley et al., 2005].	SCR has high sensitivity at low transmission intensities since the longevity of the antibody response generates higher seroprevalence rates. SCR is less sensitive at very high transmission intensities due to saturation of infection in the population [Tusting et al., 2014].	SCR has been proposed as a measure of transmission in the pre-elimination and elimination phase of malaria control [malERA, 2011] but have limited value in very low and high transmission levels [Tusting et al., 2014] where other measures of infection prevalence might be cheaper.
Multiplicity of infection (MOI)	The number of concurrent parasite clones in an infected host.	MOI can be measured by genotyping parasites using polymorphic markers such as merozoite surface protein-1 (MSP1) or MSP2 [Smith et al., 1999; Felger et al., 2003; Atroosh et al., 2011; Mueller et al., 2012].	Mathematical theory suggests that, in a cohort of uninfected people acquiring infections and clearing infections independently and naturally, that MOI would reach a Poisson distribution with the mean given by the FOI divided by the clearance rates. With heterogeneous biting, this would become a negative binomial distribution [Dietz, 1988].	In malaria-endemic regions, multiple infections are common, and MOI closely correlates with endemicity. Reduced MOI has also been observed to be a reasonable indicator of transmission intensity [Mueller et al., 2012].	MOI has been developed as a metric of malaria transmission only recently as tools for disentangling the molecular complexity of natural parasite infections emerge, as such methods for validation require development [Tusting et al., 2014].

Table 1.3: Primary metrics used to measure transmission intensity and disease burden

Metric	Definition	Source and measurement	Formula	Interpretation	Other remarks
Parasite Rate (PR) (see section 1.7.1)	The proportion of individuals found to carry asexual malaria parasites in their blood at a given point in time which varies by the diagnostic method used (section 1.7.1)	PR can be measured by examining the blood from cross-sectional surveys of a representative sample of the population e.g. the whole community, school-based survey, during blood transfusion or by fever screening.	PR = n/N × 100 where 'n' is the number of infected individuals, 'N' is the number of individuals tested.	Cut-offs used for routine purposes are: <1%: Very Low 1-10%: Low 10-29%: Moderate ≥30%: High	Mechanism have been developed that can be used to estimate R_0, and EIR using the more readily measured PR [Smith et al., 2005; Smith et al., 2007b; Gething et al., 2011].
Fever test positivity rate (TPR)/Slide positivity rate (SPR) (see section 1.7.3)	The proportion of those examined by microscopy or rapid diagnostic test with parasitaemia	TPR/SPR can be measured through routine health facility data, using RDTS or blood slides.	TPR = n/N × 100 where 'n' is the number of infected individuals, 'N' is the number of individuals tested.	TPR/SPR have been used to define temporal trends, to understand sub-national variation in malaria risk and to understand intervention impact [Tukei et al., 2017; Jemal & Ketema, 2019; Thawer et al., 2020], yet the accuracy of TPR/SPR as a measure of transmission is not well established.	TPR/SPR can be used as a surrogate measure of malaria incidence in the absence of accurate determination of the denominator [Jensen et al., 2009]. This metric is affected by care-seeking patterns among infected individuals with a fever or malaria-like symptoms, by the testing rates at a given health facility, and by the accuracy of the diagnostic test used.

Table 1.3 continued…

Metric	Definition	Source and measurement	Formula	Interpretation	Other remarks
Malaria incidence rate/ Annual parasite index (API) (see section 1.7.2)	The number of new cases of clinical malaria that occur in a population in a given period of time per 1,000 person-years at risk	The measurement of malaria incidence requires all suspected malaria cases to be diagnosed through a comprehensive surveillance system [Pull, 1972; Fox et al., 1987; Hay et al., 2008].	Clinical incidence rate = n/P × 1,000, where 'n' is the number of infected individuals with symptoms, 'P' is the population at risk. Another related metric: Annual parasite index (API) = (ABER × TPR)/10 where 'ABER' is the annual blood examination rate, defined as the proportion of the total population examined for parasitaemia	The incidence of clinical malaria increases with transmission intensity but at high transmission levels, incidence does not exceed that observed at intermediate transmission levels, partly due to acquired immunity and multiple infections [Trape & Rogier, 1996; Ghani et al., 2009]. As transmission falls, a threshold must be crossed before a significant reduction in cases and hospital admissions is observed [Trape et al., 1987; Smith et al., 2004b].	The bottleneck in case detection in SSA stems from poor healthcare access and treatment seeking behaviour, cases not confirmed by a diagnostic test and reports are mostly obtained from public health sector only; where testing and reporting rates are mostly incomplete. Therefore, adjustment for testing and reporting completeness and treatment seeking in other health sectors is required before using malaria incidence rate [WHO, 2019a].
Malaria mortality rate (see section 1.7.4)	The number of malaria deaths that occur in a population in a given period of time per 1,000 person-years at risk	In countries with good civil registration and vital statistics system, death recording systems offer the most reliable information to quantify mortality rate by age. In most of SSA this system is non-existent [Rao et al., 2004; Ye et al., 2012] therefore, complete birth histories and summary birth histories, often done every five years, are the main source of mortality data especially in children under-5 years of age [Rajaratnam et al., 2010]. Verbal Autopsy (VA) interviews are used to attribute a cause of death.	Direct and indirect methods are applied using the information from the birth histories. Causes of deaths are inferred from verbal autopsy interview using the InterVA-4 model, an expert opinion-based algorithm that uses Bayes theorem [Byass et al., 2012; Ndila et al., 2014; Nichols et al., 2018].	In the absence of clinical and parasitological data, malaria-specific mortality is difficult to ascertain. It is indirectly quantified through a cause of death fraction derived from verbal autopsy data.	Identifying the causes of death is a much more difficult issue in populations where most deaths do not occur in health facilities.

1.7 Primary measures of transmission and disease burden

1.7.1 Parasite rate

The prevalence of malaria infection (referred to in the literature as the “Parasite Rate (PR)”) has been used for over a century as a marker of the quantity of malaria (endemicity) in a location [Metselaar & Van Thiel, 1959; Lysenko & Semashko,1968; Hay et al., 2008; Snow & Noor, 2015b; Snow et al., 2017]. This measure of malaria transmission gradually replaced spleen rates as a quantity of malaria endemicity in communities after 1950 [Metselaar & Van Thiel, 1959]. Historically, PR had an important role during the first phase of the GMEP [Hay et al., 2008] and was used to classify malaria transmission as presented in Table 1.4 [Metselaar & Van Thiel, 1959]. PR was used to generate national epidemiological maps of malaria risk from as early as 1912 in North Africa, and the 1940s in SSA [Snow & Noor, 2015b; Snow et al., 2017].

Table 1.4: Classification of malaria transmission

Type	Parasite rate	Description
Holoendemic	Constantly over 75% among infants aged 0-11 months	Perennial, intense transmission resulting in a considerable degree of immunity outside early childhood
Hyperendemic	Constantly over 50% among children aged 2-9 years	Areas where transmission is intense but seasonal where immunity is insufficient in all age groups
Mesoendemic	Between 11 -50% in children aged 2-9 years but may be higher for part of the year	Typically found among rural communities in sub-tropical zones when wide geographical variations in transmission risk exist
Hypoendemic	Not exceeding 10% among children aged 2-9 years but may be higher for part of the year	Areas where there is little transmission and the effect during the average year upon the general population are unimportant

Maps of parasite prevalence continue to be used today as a means of identifying sub-national variations in the intensity of malaria transmission [Omumbo et al., 2013; Alegana

et al, 2020]. However, the criteria used to define classifications of malaria risk shown in Table 1.4 has changed over time, with increasing use of <1% [Cohen et al., 2010] or <5% *P. falciparum* Parasite Rate (*Pf*PR) to define very low transmission and ≥30% or ≥40% *Pf*PR for areas regarded as high transmission [Noor et al., 2009b, Noor et al., 2014; Macharia et al., 2018; Giorgi et al., 2018; Thawer et al., 2020; and Figure 1.10]

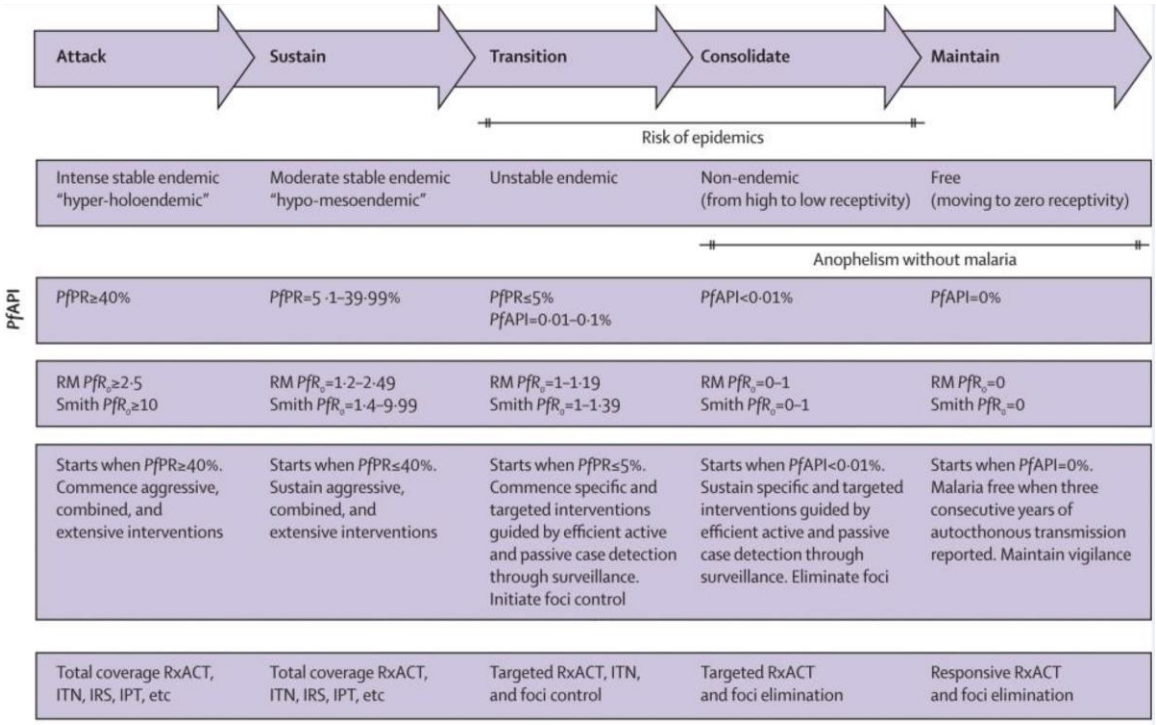


Figure 1.10: Malaria endemicity and classification and practical consideration. Reproduced from Hay et al., 2008, published CC-BY 4.0

Legend: *Pf*PR: *P. falciparum* parasite rate; *Pf*API: *P. falciparum* annual parasite incidence; *Pf*R0: *P. falciparum* basic reproductive number calculated using the RM (Ross-Macdonald) and Smith transmission models; IRS: indoor residual spraying; IPT: intermittent preventive therapy; ITN: insecticide-treated net; RxACT: radical treatment with artemisinin-combination therapy.

Contemporary maps are often based on PR data from malaria indicator surveys (MIS) or Demographic Health Surveys (DHS) with malaria testing organised in collaboration with national statistical offices and National Malaria Control Programmes (NMCPs). PR maps serve as the entry point for estimating disease burdens at national and regional levels (Section 1.9.1.2). However, there are limitations to the representativeness of national

household surveys to accurately define small area community transmission intensity. Contemporary national, household surveys are undertaken among small, randomly selected clusters aimed to be representative of large sub-national administrative units and surveys are powered to measure ITN use rather than infection prevalence [WHO, 2005; Alegana et al., 2017]. National household surveys occur infrequently, every 3-5 years and some SSA countries have not undertaken a national survey since 2000 (Niger, Mauritania, Peoples Republic of Congo and Central African Republic). Cross-sectional surveys are often undertaken at one single time point, and several national household surveys have been conducted during non-malaria (dry) seasons for logistical reasons [Massoda Tonye et al., 2018]. With a few exceptions (Sudan, Somalia, Djibouti and Kenya) contemporary household surveys have focussed on measuring malaria infection in young children aged 6 months to five years. Under-fives represent an important target for intervention coverage as they bear the brunt of the disease burden. However, infection prevalence as a marker of endemicity is better described in children aged 2-10 years [Metselaar & Van Thiel, 1959; Smith et al., 2007a]. A few countries have augmented household surveys with national parasitological surveys among school children [Brooker et al., 2009; Gitonga et al., 2010; Okebe et al., 2014; Ashton et al., 2015; Houngbedji et al., 2016; Chacky et al., 2018; Swana et al., 2018], an approach first promoted over 60 years ago in Africa [Brooker et al., 2009]. Household surveys are logistically demanding and expensive; for example, in Tanzania, the average cost of a recent school survey was US$ 10 per subject examined compared to US$ 410 per subject for the household survey [Chacky et al., 2018]. Various statistical approaches have been developed to model the spatial and temporal structures of sparse community-based PR survey data [Diggle et al., 1998], and these are described in more detail in Section 1.9.1.1.

Measuring malaria parasite infection by light microscopy has been the gold standard for malaria research for more than a century and remains relatively widespread as a point-of-care diagnostic in clinical and epidemiological settings [Wu et al., 2015]. Light microscopy relies on the examination of Giemsa-stained thick and thin blood smears under a microscope with a detection threshold in field conditions of 50-100 parasites/µL [Zimmerman & Howes, 2015]. Although light microscopy can define parasite density, parasite stage, and speciation, this method is labour-intensive and requires a well-trained expert. In addition, the sensitivity and specificity are highly affected by the staining techniques used, quality of stains and the microscope, as well as the skill level of the microscopist [Khairnar et al., 2009].

The introduction of rapid diagnostic tests (RDTs), a valuable adjunct to microscopy, made the diagnosis of malaria faster and easier to perform. RDTs detect malaria parasite antigens such as lactate dehydrogenase (LDH) or histidine-rich protein 2 (HRP2). RDTs may be species-specific or pan-specific. They have detection limits in the range of 100-200 parasites/µL and 80-95% sensitivity and 85% specificity using microscopy as a gold standard [Hopkins et al., 2008] (Table 1.5). The accuracy of an RDT varies depending on the antigen targeted. HRP2 for example can persist for approximately four weeks after parasite clearance, which causes false positives after the infection has cleared. There are reports of emerging selection of parasite clones with deleted HRP2/3 proteins to evade detection [Menegon et al., 2017; Amoah et al., 2020; Bosco et al., 2020; Kojom & Singh, 2020], suggesting the development of diagnostic resistance. Beyond clinical diagnostic applications, RDTs are increasingly becoming important for epidemiological characterization because of their low cost and field applicability.

Table 1.5: Diagnostic performance of established malaria diagnostics

Assay	Limit of detection	Sensitivity	Specificity	Reference
Light microscopy	50 parasites/μL	95.7% (PCR)	97.9% (PCR)	Zimmerman & Howes, 2015
RDTs	> 100 parasites/μL	80–95%(microscopy)	85% (microscopy)	Hopkins et al., 2008
LAMP	≤2.0 parasites/μL	97% (PCR)	96% (PCR)	Picot et al, 2020
PCR	0.022–5 parasites/μL	100% (used as the gold standard)	100% (used as the gold standard)	Perandin et al., 2004; Imwong et al., 2014

The development of nucleic acid amplification tests improved the detection limit for malaria infection to 0.5-5 parasites/μL [Perandin et al., 2004] by quantitative polymerase chain reaction (qPCR) [Andrews et al., 2005]. PCR may be used to differentiate new from recrudescent *P. falciparum* infections in drug efficacy trials, or as the reference method to assess the performance of other diagnostic tools (Table 1.5). However, PCR techniques remain impractical for wide-spread use in field studies due to their high cost, long processing time, and lack of appropriate laboratory facilities in many endemic countries [Cordray & Richards-Kortum, 2012; Wu et al., 2015]. The scope of performing molecular diagnosis in resource-limited settings has been expanded by the introduction of loop-mediated isothermal amplification (LAMP); an easier and cheaper assay than PCR [Lucchi et al, 2016]. LAMP is an isothermal molecular method using a DNA polymerase from *Bacillus stearothermophilus;* mostly targeting the mitochondrial genome of *Plasmodium* parasites [Picot et al., 2020]. LAMP has been shown to have a higher sensitivity than microscopy and RDT [Picot et al., 2020]. LAMP also gave similar results to a real-time PCR reference test with limits of detection of ≤2.0 parasites/μl depending on the sample preparation method used (Table 1.5) [Lucchi et al, 2016].

1.7.2 Clinical incidence

The malaria incidence rate is defined as the number of new cases of clinical malaria that occur in a specific population in a given period of time per 1,000 person-years at risk (Table 1.3). The measurement of malaria incidence requires that all suspected cases are diagnosed through a comprehensive surveillance system comprising passive case detection (PCD) and/or active case detection (ACD). The measurement of true incidence requires the prospective, longitudinal surveillance of populations to detect new febrile events associated with malaria infection. However, there are complexities in the diagnosis of malaria in endemic countries, since parasitaemia accompanied by fever does not necessarily mean that they are causative given the high levels of asymptomatic infection [Rougemont et al., 1991]. During clinical trials, which serve as the source of most data on the true incidence of mild clinical malaria, daily, weekly, fortnightly or monthly ACD surveillance of defined populations are used to detect fevers and the parasite density associated with these fevers [Pull, 1972; Snow et al., 1989; Patil et al., 2009; Cameron et al., 2015]. Various epidemiological definitions of parasite density have been proposed depending on the level of endemicity (likely asymptomatic infection rate), age, season and method of case detection [Trape et al., 1985; Schellenberg et al., 1994; Smith et al., 1994; Rogier et al., 1996; Bloland et al., 1999; Mwangi et al., 2005; Olotu et al. 2010]. In areas where malaria is unstable, or among children without significantly acquired immunity aged <1 year, clinical malaria has been defined as fever accompanied by peripheral parasitaemia of any density detected using microscopy [Mwangi et al., 2005]. In malaria-endemic areas and among individuals ≥1 year, clinical malaria is often defined as fever accompanied by parasite density ≥2,500 parasite/μL [Mwangi et al., 2005; Olotu et al. 2010] or ≥5,000 parasite/μL detected using microscopy [Trape et al., 1985; Smith et al., 1994]. The measurement of true clinical malaria incidence in most settings in SSA is

dependent on the frequency of surveillance, age-dependent thresholds of parasite density, the use of ACD with or without PCD, the use of measured or reported fever and whether investigators treat new events, and drop from the subsequent analysis for a fixed, post-treatment period. Despite the difficulties in standardising between ACD incidence survey data, they were first used to provide crude estimates of malaria case burdens in Africa [Snow et al., 1999] and globally [Snow et al., 2005] and continue to be used to define malaria case burdens in Africa [Hay et al., 2008; Bhatt et al., 2015; Weiss et al., et al., 2019], discussed in more detail in Section 1.9.1.2.

Outside of epidemiological study settings, malaria case surveillance is entirely PCD and in the absence of defined cohorts, there is often a difficulty in the accurate determination of the denominator. Traditionally, countries have relied on PCD to detect and report malaria cases (usually febrile cases with any detectable parasitaemia) among individuals seeking treatment at a health facility. In addition, the precision of the estimate of clinical incidence also depends on consistency in diagnostic practice, health-seeking behaviour and complete record keeping [Oduro et al., 2016; Plucinski et al., 2018a; Alegana et al., 2018; Alegana et al., 2020]. In countries that are aiming to eliminate malaria, all new incident cases of malaria must be detected. Furthermore, in non-eliminating countries, routine surveillance varies enormously, as such the WHO adjusts measures of malaria incidence differently by country (Section 1.9.2).

The transition from control to elimination is complex, requiring robust systems that detect symptomatic and asymptomatic cases including those who do not seek treatment. The framework for malaria surveillance intensity and frequency of activities along the information cycle increases on the pathway towards elimination [WHO, 2015; WHO, 2018c]. As transmission is progressively reduced, detailed case investigations are

particularly important. Relying on PCD alone is unlikely to have impact on the parasite population required to interrupt transmission [Moonen et al., 2010] and the WHO recommends using surveillance to target infectious pool in low transmission settings [WHO, 2012d]. In these settings, another form of ACD is reactive case detection (rACD) whereby ACD is restricted to individuals living near passively detected cases which might be indicative of location of asymptomatic malaria reservoirs [Moonen et al., 2010; Stresman et al., 2010; Sturrock et al., 2013a]. This method takes advantage of spatial and temporal clustering of malaria infections associated with transmission 'hotspots' [Gaudart et al., 2006; Bejon et al., 2010; Bousema et al., 2010] and is being implemented widely in several countries in the pre-elimination and elimination phase. The use of routine PCD and ACD data in hotspot identification is considered in more detail in Section 1.8.

1.7.3 Fever test positivity rate from routine data

A hybrid metric related to PCD case data and community-based parasite prevalence is fever test positivity (TPR) rates as recorded at health facilities. The advantage over community parasite prevalence is that it is a more continuous, and spatially ubiquitous, source of information. Traditionally, this was referred to as slide positivity rate (Table 1.3) and was recommended as a transmission surveillance metric when community-based prevalence fell below 2%; a point where community sampling became financially impractical and PR was no longer sensitive enough to measure further progress [Pull, 1972; Ray & Belajev, 1984; Hay et al., 2008]. TPR is, however, affected by health-seeking behaviour among infected individuals with fever, the testing rate at the facility and the accuracy of the diagnostic test used (Table 1.3).

While the detection of all malaria cases represents a core intervention for elimination [Moonen et al., 2010; GMP, 2017], the use of routine health facility TPR data for malaria

endemicity stratification and surveillance at national scale remains underutilised in the high burden areas of SSA [Alegana et al., 2020]. Several examples of the use of routine TPR data exist to understand the sub-national variations in malaria risk [Oduro et al., 2011; Doudou et al., 2012; Githinji et al., 2016; Plucinski et al., 2020; Thawer et al., 2020], or at smaller spatial scales to define temporal trends [Brasseur et al., 2011; Salvador et al., 2015; Yimer et al., 2015; Galatas et al., 2016; Gebretsadik et al., 2018; Githeko et al., 2018; Tesfa et al., 2018; Jemal & Ketema, 2019; Diallo et al., 2020] or intervention impact [Okech et al., 2008; Kigozi et al., 2012; Kesteman et al., 2016; Tukei et al., 2017]. TPR has also been shown to be significantly associated with malaria incidence and to be a strong predictor of malaria transmission [Fox et al., 1987; Jensen et al., 2009; Boyce et al., 2016; Kigozi et al., 2019].

An alternative routine source of infection prevalence data has recently been proposed, which captures malaria prevalence in pregnant women attending antenatal care (ANC) visits [van Eijk et al., 2015; Willilo et al., 2016; Brunner et al., 2019; Mayor et al., 2019; Thawer et al., 2020]. The high attendance rate of pregnant women at ANC makes them an easily accessible surveillance population to track malaria transmission intensity and provides a simple routine real-time measure of malaria prevalence at higher spatial and temporal resolutions. A recent systematic review showed a strong correlation between infection prevalence among pregnant women and children under five years from the same communities [van Eijk et al., 2015].

1.7.4 Malaria mortality

The most severe consequence of malaria infection is death. However, estimates of malaria-specific mortality in resource poor countries remain challenging [Cibulskis et al., 2007; Cibulskis et al., 2011; Rowe et al., 2007; Snow, 2014]. In most lower income

countries deaths occur outside the health care system and are not recorded through civil registration and death certification systems [Rao et al., 2004; Mahapatra et al., 2007; Setel et al., 2007; Mikkelsen et al., 2015]. The absence of comprehensive, reliable death detection and causal attribution data has meant that the estimation of malaria-specific mortality in SSA relies upon the extrapolation of epidemiological data from specific demographic surveillance systems [Sankoh & Byass, 2012; Ye et al., 2012] where deaths are investigated by Verbal Autopsy (VA).

VA is a method of deriving the cause(s) of death (COD) by interviewing the family of the deceased about the chronological sequence of events leading to death and signs and symptoms during the terminal illness using the standard 2012 WHO verbal autopsy tools [Fottrell et al., 2010; Byass et al., 2012; WHO, 2012e; Scanlon et al., 2013]. The VA tool uses a combination of an open structured narrative followed by a series of binary indicators representing the presence or absence of an event. From the responses, causes of deaths are inferred using the InterVA-4 model based on an expert opinion algorithm that uses Bayes theorem [Byass et al., 2012; Ndila et al., 2014; Nichols et al., 2018]. The algorithm assigns at most three probable causes of death with corresponding likelihood. The secondary and tertiary causes are only reported if the likelihood is more than half of the most likely cause. If none of the causes has a probability >0.4, then death is considered ‘indeterminate’. The InterVA-4 algorithm, however, has the disadvantage of being relatively inflexible, the open history question is lost no matter how relevant it might be in determining the COD.

Although the VA maybe the only means of establishing cause specific mortality in Africa, the definition of mortality events directly attributed to malaria are fraught with difficulties [Snow, 2014; Menéndez et al., 2020], leading to misclassification and inconsistent results

[Kalter et al., 1990; Snow et al., 1992; Anker, 1997; Anker et al., 1999; Quigley et al., 1999; Leitao et al., 2014]. Malaria is principally a febrile illness, associated with many co-presenting symptoms, including respiratory complications, vomiting, altered consciousness and seizures. These symptoms are often associated with other common causes of death within the same community and age groups. Furthermore, soliciting histories weeks or months following death can lead to recall biases [Alonso et al., 1987; Snow & Marsh, 1992; Snow et al., 1993b]. Published estimates on various global cause-specific mortality [Murray et al., 2012] stirred a profound debate about the validity and adequacy of VA to estimate cause of death [Chamber, 2012; Lynch et al., 2012; White et al., 2012; Byass et al., 2013].

Defining the validity of the VA depends upon a "gold standard", which as discussed below might be difficult in the absence of physical post-mortems and the fact that malaria may be an indirect cause of death. However, several studies have attempted to validate VA defined malaria deaths against hospital-based deaths with reliable diagnostic facilities in SSA (Table 1.6). It has been shown that the VA provides only a broad syndromic approach, but the performance for a malaria-specific diagnosis is poor, with widely varying levels of sensitivity and specificity by transmission intensity (Table 1.6). Although the median specificity of VA was somewhat similar among children (83%; IQR: 79%, 89%) and adults (90%; IQR: 87%, 95%), the median sensitivity was much lower for adults VA (36%; 19%, 48%) compared to children (56%; IQR: 46%, 67%) (Table 1.6). During a study of causes of death among adults in rural Burkina Faso the authors stated that "*As malaria and fever are not easily distinguishable causes through verbal autopsy, they are combined*" [Sankoh et al., 2003]. The imperfect sensitivity and specificity of VA may lead to an over/underestimation of the impact of the control efforts on malaria-specific mortality.

Complete diagnostic autopsy (CDA) is considered the gold standard method for causes of death ascertainment, but it requires a high degree of expertise and infrastructure that are rarely available or accepted in African countries. The introduction of minimally invasive autopsy techniques (MIA), which can be conducted relatively rapidly and less obtrusively than CDA, might offer opportunities to explore the true contribution of malaria to deaths in Africa [Castillo et al., 2016; Bassat et al., 2017; Menéndez et al., 2020]. This approach involves sampling of key organs using a needle biopsy and it provides the possibility of a thorough histopathological and microbiological investigation of the obtained tissues and fluids and, therefore, more robust and plausible explanations for the cause of death [Castillo et al., 2015]. Further studies, from carefully selected sites across Africa, may provide more biologically credible estimates of the fractions of deaths with organ failure associated with malaria as proposed by the Child Health and Mortality Prevention Surveillance (CHAMPS) Network [Taylor et al., 2020].

Table 1.6: Validation studies in SSA on the sensitivity and specificity of VA *versus* hospital diagnosed malaria

			Children			Adults		
Study	**Site, Country**	**Algorithm used**	**Total deaths (malaria-specific deaths)**	**Sensitivity**	**Specificity**	**Total deaths (malaria-specific deaths)**	**Sensitivity**	**Specificity**
Snow et al., 1992	Kilifi, Kenya	VA[PR]	217 (52)	46%	89%	-	-	-
Quigley et al., 1996	Kilifi, Kenya	VA[EA]	295 (87)	47%	79%	-	-	-
	Kilifi, Kenya	VA[DA]	150 (48)	71%	80%	-	-	-
Todd et al., 1994	Basse, The Gambia	VA[PR]	89 (32)	55%	80%	-	-	-
Mobley et al., 1996	Northwest, Namibia	VA[PR]	135 (33)	45%	87%	-	-	-
Mobley et al., 1996	Northwest, Namibia	VA[PR]	18[a]	72%	85%	-	-	-
Mpimbaza et al., 2011	Tororo, Uganda	VA[PR]	67 (32)	63%	89%	-	-	-
	Kampala, Uganda	VA[PR]	600 (51)	57%	90%	-	-	-
	Kisoro, Uganda	VA[PR]	52 (0)	0%	0%	-	-	-
Setel et al., 2006	Dar es Salaam, Hai and Morogoro district, Tanzania	VA[PR]	582 (213)	67%	67%	1912 (345)[b]	63%	90%
Chandramohan et al., 1998	Ifakara, Tanzania	VA[EA]	-	-	-	315 (36)	36%	95%
	Jimma, Ethiopia	VA[EA]	-	-	-	249 (39)	39%	97%
	Bawku, Ghana	VA[EA]	-	-	-	232 (10)	0%	87%
Quigley et al., 1999	Tanzania, Ethiopia and Ghana	VA[PR]	-	-	-	796 (85)	33%	93%
	Tanzania, Ethiopia and Ghana	VA[EA]	-	-	-	796 (85)	19%	90%
	Tanzania, Ethiopia and Ghana	VA[DA]	-	-	-	796 (85)	48%	80%

VA, verbal autopsy; [PR] Physician review – completed VA questionnaires are reviewed by one or more physicians who assigns a probable cause of death; [EA] Expert algorithm – pre-defined diagnostic criteria were applied to signs and symptoms from VA deemed by physician to be essential, confirmatory or supportive in diagnosing cause of death; [DA] Data-driven algorithm – standard statistical methods were applied to a set of signs and symptoms obtained from VA; [a] Symbol denotes the one study that included cerebral malaria cases only; [b] VA was done for ages of 5 years and over including adults.

In addition, as outlined in Section 1.4 (Figure 1.3), malaria infection can lead to several different indirect mortality outcomes and serves as a risk-factor for all-cause mortality rather than a direct, single attributable cause [Molineaux, 1997; Smith et al., 2001; Snow et al., 2004]. Evidence from historical, large-scale efforts to eliminate parasite exposure through IRS in Guyana [Giglioli, 1972], Sri Lanka [Meegama, 1967], Tanzania [Smith & Draper, 1959; Draper & Smith, 1960], Kenya [Payne et al., 1976] and more recently on Bioko Island, Equatorial Guinea [Kleinschmidt et al., 2009] all suggest that the impact on all-cause infant and childhood mortality is greater than would be expected if only malaria deaths were averted and malaria might be considered a risk factor for mortality rather than a direct-cause of death [Snow et al., 2004; Snow, 2014].

Despite the limitations of the VA for direct attribution of malaria mortality, assemblies of prospective surveillance studies using the VA have been used to define the possible malaria mortality burden in Africa, stratified by crude estimates of malaria risk [Sturchler, 1989; Greenwood, 1990; Snow et al., 1999; Snow et al., 2003; Rowe et al., 2006]. For SSA, much of the data is derived from the network of INDEPTH, Demographic Surveillance Sites (DSS) [INDEPTH, 2002; Adjuik et al., 2006; Abdullah et al., 2008; Streatfield et al., 2014a; Streatfield et al., 2014b]. Over time these approaches have been refined and adapted as part of the Global Burden of Diseases study [Murray et al., 2012; Murray et al., 2014], and the most recent examples of this are presented in Section 1.9.1.3.

1.8 Hotspots detection

The Pareto principle states that for many outcomes approximately 80% of consequences come from only 20% of the causes, the 80/20 rule. The concept was developed under economic theory but has been applied to models of infectious disease

epidemiology [Woolhouse et al., 1997; Galvani & May, 2005; Lloyd-Smith et al., 2005]. In malaria, events are often over-distributed in space and time driven by variations in local vector ecology, host susceptibility to infections or outcomes of infections. For example, variations in malaria risk between households are defined by proximity to vector breeding sites, altitude and housing structures. Variations between individuals and families within households can be defined by human protective genetic polymorphisms and differences in parasite genetic structures. By its very nature malaria is a heterogeneously distributed disease. The 80/20 rule of infection has recently been incorporated in the basic mathematical models of malaria transmission to understand the relationships between the entomological inoculation rate, host parasite prevalence and R_0 [Smith et al., 2005].

During the phases of malaria elimination, malaria transmission, and consequently cases, are found in small foci and the active detection of foci forms a fundamental part of efforts to eliminate the parasite (Figure 1.1; Section 1.7.2) [Coleman et al., 2009; Moonen et al., 2010; Stresman et al., 2010; Pinchoff et al., 2015; DePina et al., 2019; Hsiang et al., 2020]. However, the broader concept that malaria is over-distributed in space has led to attempts to define “hotspots” in more stable, endemic areas of Africa [Mogeni et al., 2017a]. Here the presumption is that defining hotspots might serve as a more effective strategy to target local disease control that would have a greater impact on transmission reduction compared to universal district wide control measures [Woolhouse et al., 1997; Carter et al., 2000; Gaudart et al., 2006; Bousema et al., 2010; Bousema et al., 2012; Sturrock et al., 2013b; Mosha et al., 2014; Bejon et al., 2014; Stresman et al., 2018; Shaffer et al., 2020]. This concept is linked to the notion of “super-spreaders” [Rodriguez-Barraquer et al., 2016; Cooper et al., 2019].

Table 1.7 provides examples of studies undertaken in SSA that have attempted to statistically define clustering of malaria vector transmission, infection prevalence, and

active or passively detected disease burdens. Very few studies have examined the spatial heterogeneity of much rarer events such as severe malaria [Snow et al., 1993] or malaria-specific mortality within DSS sites [Selemani et al., 2015; Dadzie et al., 2018].

Across all metrics and studies shown in Table 1.7, the most widely used test of the space-time local heterogeneity is the spatial scan statistic [Kulldorff, 1997]. While this approach allows identification of clusters using statistical hypothesis testing, it may ignore more subtle small-scale spatial heterogeneity and clusters that do not fit within circular or elliptical windows [Jackson et al., 2009; Cramb et al., 2016]. Other alternative methods that have been used to detect clustering include Moran's I, Ripley's K function, local indicators of spatial autocorrelation (LISA), Getis-Ord Gi* statistic, Kernel density estimation and Bayesian techniques [Mosha et al., 2014; Cramb et al., 2016]. There is no definitive approach for cluster detection, but the choice of a technique can be guided by its sensitivity, specificity and power to detect clusters [Jackson et al., 2009; Cramb et al., 2016].

Table 1.7: Studies evaluating the heterogeneity of malaria in sub-Saharan Africa

Study	Site, Country	Study design	Metric	Method/Statistic
Zhou et al., 2007	Iguhu, Kenya	Cross-sectional survey	Mosquito vector abundance	Cross-correlaton statistic and Getis-Ord Gi* statistic
Sissoko et al., 2015	Sotuba and Kollé, Mali	Cross-sectional survey	Mosquito density	SaTScan
Kangoye et al., 2016	Kilifi, Kenya	Cross-sectional survey	Mosquito vector	SaTScan
Kaindoa et al., 2016	Ulanga, Tanzania	Longitudinal study	Mosquito density	Getis-Ord Gi* statistic
Bousema et al., 2010	Korogwe, Tanzania	Cross-sectional survey	EIR	SaTScan
Esayas et al., 2020	Kolla-Shara, Ethiopia	Cross-sectional survey	EIR	SaTScan
Gaudart et al., 2006	Bancoumana, Mali	ACD	Infection prevalence	SaTScan
Stresman et al., 2018	The Gambia	ACD	infection prevalence	Bayesian geostatistical model
Shaffer et al., 2020	Dangassa and Dioro, Mali	ACD	Infection prevalence	SaTScan
Shaffer et al., 2020	Gambissara, The Gambia	ACD	Infection prevalence	SaTScan
Shaffer et al., 2020	Madina Fall, Senegal	ACD	Infection prevalence	SaTScan
Coulibaly et al., 2017	Bandiagara, Mali	ACD	Infection prevalence	SaTScan
Mogeni et al., 2017a	Kambila, Mali	ACD	Infection prevalence	SaTScan, Moran's I and Ripley's K function
Munyekenye et al., 2005	Iguhu, Kenya	Cross-sectional survey	Infection prevalence	Global weighted K function and local spatial statistic Gi*(d)
Mirghani et al., 2010	Gezira, Sudan	Cross sectional surveys	Infection prevalence	SaTScan
Cook et al., 2011	Bioko, Equatorial Guinea	Cross-sectional survey	Infection prevalence	SaTScan
Nourein et al., 2011	Khartoum, Sudan	Cross-sectional survey	Infection prevalence	SaTScan
Ashton et al., 2011	Oromia, Ethiopia	Cross-sectional survey	Infection prevalence	Bayesian geostatistical model and SaTScan
Magalhães et al., 2012	Bengo, Angola	Cross-sectional survey	Infection prevalence	Bayesian geostatistical model
Mosha et al., 2013	Misungwi, Tanzania	Cross-sectional survey	Infection prevalence	Distance weighted local prevalence analysis
Townes et al., 2013	Nsamala and Sitola, Malawi	Cross-sectional survey	Infection prevalence	Getis-Ord Gi* statistic
Ndiath et al., 2014	Keur Soce, Senegal	Cross-sectional survey	Infection prevalence	SaTScan
Sissoko et al., 2015	Sotuba and Kollé, Mali	Cross-sectional survey	Infection prevalence	SaTScan

Table 1.7 continued

Study	Site, Country	Study design	Metric	Method/Statistic
Bejon et al., 2010; Kangoye et al., 2016; Mogeni et al., 2017b	Kilifi, Kenya	Cross-sectional survey	Infection prevalence	SaTScan
Gómez-Barroso et al., 2017	Bata district, Equatorial Guinea	Cross-sectional survey	Infection prevalence	Getis-Ord Gi statistic and SaTScan
Mogeni et al., 2017a	Asembo, Kenya	Cross sectional surveys	Infection prevalence	SaTScan, Moran's I and Ripley's K function
Mogeni et al., 2017a	Saponé, Burkina Faso	Cross sectional surveys	Infection prevalence	SaTScan, Moran's I and Ripley's K function
Esayas et al., 2020	Kolla-Shara, Ethiopia	Cross-sectional survey	Infection prevalence	SaTScan
Mosha et al., 2014	Mwanza, Tanzania	2-year repeated population-based survey	Infection prevalence	SaTScan, Kernel analysis and weighted local prevalence analysis
Brooker et al., 2004	Nandi, Kenya	ACD	Clinical disease	SaTScan
Bejon et al., 2010	Kilifi, Kenya	ACD	Clinical disease	SaTScan
Bousema et al., 2010	Korogwe, Tanzania	ACD	Clinical disease	SaTScan
Pullan et al., 2010	Mulanda, Uganda	ACD	Clinical disease	Semi-variograms and Monte Carlo envelopes
Mogeni et al., 2017a	Kiang West, The Gambia	ACD	Clinical disease	SaTScan, Moran's I and Ripley's K function
Mogeni et al., 2017a	Asembo, Kenya	ACD	Clinical disease	SaTScan, Moran's I and Ripley's K function
Mogeni et al., 2017a	Kambila, Mali	ACD	Clinical disease	SaTScan, Moran's I and Ripley's K function
Mogeni et al., 2017a	Walukuba, Kihihi and Nagongera, Uganda	ACD	Clinical disease	SaTScan, Moran's I and Ripley's K function
Mogeni et al., 2017a	Korogwe and Same, Tanzania	ACD	Clinical disease	SaTScan, Moran's I and Ripley's K function
Clark et al., 2008	Mulago, Uganda	ACD and PCD[¶]	Clinical disease	SaTScan
Loha et al., 2012	Chano Mille Kebele, Ethiopia	ACD and PCD[¶]	Clinical disease	SaTScan
Coulibaly et al., 2013; Coulibaly et al., 2017	Bandiagara, Mali	ACD and PCD[¶]	Clinical disease	SaTScan
Mogeni et al., 2017a	Afigya-Sekyere, Ghana	ACD and PCD[¶]	Clinical disease	SaTScan, Moran's I and Ripley's K function
Solomon et al., 2019	Adami Tullu, Ethiopia	ACD and PCD[¶]	Clinical disease	SaTScan
Ernst et al., 2006	Nandi, Kenya	PCD	Clinical disease	SaTScan and Moran's I

Table 1.7 continued

Study	Site, Country	Study design	Metric	Method/Statistic
Yeshiwondim et al., 2009	East Shoa, Ethiopia	PCD	Clinical disease	Global Moran's I, Local Moran's I and Getis-Ord Gi* statistic
Rulisa et al., 2013	Ruhuha, Rwanda	PCD	Clinical disease	SaTScan
Alemu et al., 2013	Gondar, Ethiopia	PCD	Clinical disease	SaTScan
Alemu et al., 2014	Dabat, Ethiopia	PCD	Clinical disease	SaTScan
Bejon et al., 2014; Kangoye et al., 2016	Kilifi, Kenya	PCD	Clinical disease	SaTScan, Kernal smoothing, Moran's I and Semivariograms
Ndiath et al., 2015	Keur Soce, Senegal	PCD	Clinical disease	Empirical Bayesian kriging model, Moran's I, Ordinary least squares and geographically weighted regression spatial statistic
Bisanzio et al., 2015	Msambweni, Kenya	PCD	Clinical disease	Getis-Ord Gi* statistic and space–time Bayesian model
Sissoko et al., 2015	Sotuba and Kollé, Mali	PCD	Clinical disease	SaTScan
Mlacha et al., 2017	Dar es Salaam, Tanzania	PCD	Clinical disease	Moran's I and FleXScan
Mogeni et al., 2017a	Saponé, Burkina Faso	PCD	Clinical disease	SaTScan, Moran's I and Ripley's K function
Ouedraogo et al., 2018	Ouagadougou, Burkina Faso	PCD	Clinical disease	SaTScan
Rouamba et al., 2019	Nanoro DSS, Burkina Faso	PCD	Clinical disease	SaTScan
Gwitira et al., 2020	Zimbabwe	PCD	Clinical disease	SaTScan and Moran's I
Hamre et al., 2020	Nandi, Kenya	PCD	Clinical disease	Kernel density estimation

[¶] The ACD and PCD studies were prospective cohort studies

Mosquito vector densities and EIR have been shown to be statistically clustered between households across communities of low transmission intensity (Ethiopia, highland Kenya), moderate transmission areas (Kenyan Coast), seasonal transmission areas (Mali) and higher transmission settings (Tanzania) (Table 1.7). Equally, spatial clustering of infection prevalence at household levels as measured through single or repeat cross-sectional surveys has been demonstrated across a wide range of transmission intensities common to SSA (Table 1.7). Active case-detection of clinical cases of malaria have also shown spatial clustering under a wide variety of transmission conditions (Table 1.7). In Kilifi, a longitudinal survey of children aged less than 12 years identified statistically robust household hotspots of asymptomatic infection that remained stable over time but could only be predicted using remote sensed proxy data on environmental features with 81% sensitivity and 63% specificity [Bejon et al, 2010]. Actively detected hotspots of febrile cases of malaria could be statistically defined but these were not temporally stable [Bejon et al., 2010]. A detailed review of 19 site-specific studies of hotspot/clustering in SSA has been undertaken where active case-detection of infection and malaria cases were linked to household spatial coordinates [Mogeni et al., 2017a; included in Table 1.7]. While spatial clustering of malaria disease events appears across most malaria transmission conditions there was some evidence that their detectability is endemicity dependent, with increased clustering in lower transmission settings but hard to define under very low transmission settings because of reduced power resulting from small number of malaria cases [Mogeni et al., 2017a]. Temporal instability of actively defined hotspots of clinical malaria was also shown suggesting that the hotspots were not always located among the same households with time [Mogeni et al., 2017a]. Data included in the review by Mogeni and colleagues are shown in Table 1.7 where a single methodology was undertaken across sites. Other studies of ACD and/or PCD are included in Table 1.7 where data has been analysed separately.

The active detection of cases or infection linked to household coordinates of population censuses provides valuable insights on the extent and frequency of definable hotspots of potential disproportionately high burden/clustered households. However, under stable endemic settings that remain under the control phases (Figure 1.1) PCD data from routine health information systems is all that is typically available to define households or communities with the highest burdens.

Several studies have examined the use of routine PCD data to define household clustering of disease risks (Table 1.7). In Dar es Salaam, Tanzania routinely defined malaria test-positive cases were matched to local government authority area addresses and were able to demonstrate one statistically significant hotspot [Mlacha et al., 2017]. In Ouagadougou, Burkina Faso 110 spatial administrative areas were matched to address details of routine malaria testing data between 2011-2015 to examine the temporal and spatial clustering of malaria incidence rate ratios across the city, highlighting eight major high intensity hotspots [Ouedrago et al., 2018]. Routinely reported malaria case-data from four health facilities located in the Nanoro demographic surveillance site in Central Burkina Faso between 2010-2014 was linked to residential information from the DSS [Rouamba et al., 2019]. The authors describe two significant hotspots during the low, transmission period, two during the intermediate transmission period and five during the high transmission period, notably these hotspots did not overlap between seasons [Rouamba et al., 2019]. Passively detected microscopy confirmed cases over 6 months in 2013 across the Keur Soce DSS site in Senegal were linked to the geo-coded household database and demonstrated three hotspot areas using Bayesian kriging methods [Ndiath et al., 2015].

In the low, unstable transmission area of East Shoa, Ethiopia between 2002-2006, circa 81,000 routine slides confirmed malaria cases were linked to geo-coded database of 497 settlements, here the authors were unable to identify any statistically significant clustering of cases, however, 4 villages were marginally significant in their high incidence of *P. falciparum*/*P. vivax* case burdens [Yeshiwondim et al., 2009]. At other low, unstable transmission sites in Ethiopia routine data has been able to identify small numbers of significant clusters [Alemu et al., 2013; Alemu et al., 2014]. However, at a low transmission health facility site at Ruhuha, Rwanda there was no household level spatial clustering among 175 malaria confirmed febrile cases [Rulisa et al., 2013]. In a highland area in Kenya during a 10-year period of very low and unstable transmission, hotspots of malaria incidence were not consistent before and after a period of possible malaria interruption [Hamre et al., 2020]. These observations are consistent with the findings from reviews of ACD studies [Mogeni et al., 2017a], where significant spatial clustering at household levels might prove difficult in very low, unstable transmission settings.

The challenge remains to develop programmatically affordable and scalable approaches using routine data that allows for the identification of local spatial heterogeneity to consider targeted supplementary control efforts.

1.9 How is the burden of malaria measured in SSA?

There are numerous uncertainties in the estimation of malaria burden globally [Lynch et al., 2012; White et al., 2012; Snow, 2014; Rowe, 2017; WHO, 2019a]. The current understanding of the declining burden of malaria has relied on modelled estimates based on historical epidemiological data, predictions in time and space based on sparse parasite prevalence data, and presumed impact of interventions [Bhatt et al., 2015b; Cameron et

al., 2015; Gething et al., 2016; Weiss et al., 2019]. These input data are described in subsequent sections (1.9.1.1 - 1.9.1.3)

The last two decades have witnessed generous financing of advanced mathematical modelling, using multiple assumptions [Murray et al., 2012; Murray et al., 2014; Bhatt et al., 2015b; Gething et al., 2016; Winskill et al., 2017; Weiss et al., 2019], and production of persuasive maps of malaria risk [Bhatt et al., 2015b; Gething et al., 2016; Weiss et al., 2019]. Unfortunately, the impression given by these maps is that they are based on an abundance of data and have led to a sense of “truth” without any appreciation of their limitations.

1.9.1 Framework used by Malaria Atlas Project (MAP)

1.9.1.1 Defining spatio-temporal changes in parasite prevalence

MAP was established in Nairobi, Kenya in 2005 [Hay & Snow, 2006] as an extension to the Mapping malaria risk in Africa (MARA) pan-African collaboration, first established in 1996 [Snow et al., 1996]. The initial ambition was to assemble empirical, geo-coded PR survey data globally from a variety of published and unpublished sources [Hay & Snow, 2006; Guerra et al., 2007]. By 2015, a total, 27,573 spatially and temporally age-standardised (2-10 years) estimates of *Pf*PR_{2-10} from 43 SSA countries from 1995-2014 were assembled and were used to map the interpolated risks of malaria at 5 × 5 km grids [Bhatt et al., 2015b]. In 2019, this was repeated using 43,187 *Pf*PR_{2-10} 2000-2017 survey points [Weiss et al., 2019]

To help predictions at locations without empirical data, a literature review was undertaken to identify variables used in the past malaria mapping to provide a series of raster layers of 20 environmental covariates (Annex 1) [Bhatt et al., 2015b]. In addition, various

intervention covariates were included as these were presumed to directly impact the prediction of *Pf*PR. These included data on insecticide-treated net (ITN) ownership and use obtained from DHS, MIS, Multiple Cluster Indicator Surveys (MICS), while the WHO provided the annual number of people by country protected by IRS between 2000 and 2013. The estimated annual proportion of febrile children treated with ACT was obtained by modelling the annual proportion of febrile children treated with ACT in a country as a function of ACT per capita distributed [Bhatt et al., 2015b]. Finally, 24,868 ITN survey points; 96 ACT coverage national survey reports; 688 country-year reports on ITN, ACT and IRS national program distribution; and 20 environmental and socioeconomic covariates were used and fitted within a spatiotemporal Bayesian geostatistical model to 27,573 or 43,187 *Pf*PR_{2-10} survey points [Bhatt et al, 2015b; Weiss et al., 2019]. The model was adjusted for age, season, type of diagnostic used, flexible functional forms of each intervention as a function of coverage. The only differences in the Bhatt et al. (2015b) and Weiss et al. (2019) models were the volume of input *Pf*PR_{2-10} data and the increase in ACT treatment seeking data used in 2019. The model-based geostatistical methods interpolate data at known locations and time to provide prediction of quantities and estimates at locations and times where data does not exist [Diggle et al., 1998]. However, the underlying principle of mapped predictions become increasingly uncertain as the density of and proximity to nearby empirical *Pf*PR_{2-10} data points decreases [Diggle et al., 1998]. A hierarchical latent Gaussian model was fitted using an integrated Laplace approximation (INLA) of the posterior. The Bayesian framework was used to link the distinct sources of uncertainty through the predictive model and represented as predictive posterior distributions around all point estimates. The components contributing to uncertainty included: sample size, spatiotemporal density of the *Pf*PR surveys, uncertainty in the fitted relationship between *Pf*PR and the suite of environmental and intervention

covariates [Bhatt et al., 2015b]. The changing intensity of malaria transmission predicted by MAP 2000 and 2015 is shown in Figure 1.11.

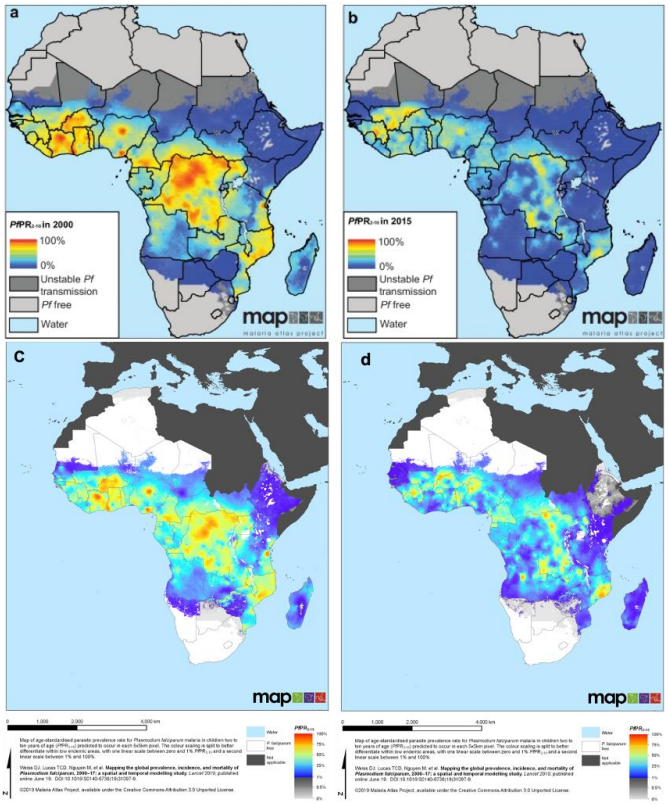


Figure 1.11: Changes in 5 × 5 km gridded *P. falciparum* infection prevalence in 2000 and 2015. Panel A shows *Pf*PR$_{2\text{-}10}$ for the year 2000 predicted by Bhatt et al. (2015); Panel B shows *Pf*PR$_{2\text{-}10}$ for the year 2015 predicted by Bhatt et al. (2015b); Panel C shows *Pf*PR$_{2\text{-}10}$ for the year 2000 predicted by Weiss et al. (2019); Panel D shows *Pf*PR$_{2\text{-}10}$ for the year 2015 by Weiss et al. (2019). Reproduced from Malaria Atlas Project, published CC-BY 3.0

1.9.1.2 Defining temporal and country-level clinical incidence

The MAP *Pf*PR$_{2\text{-}10}$ surfaces were used as the entry point to develop a functional form that transforms *Pf*PR$_{2\text{-}10}$ surfaces to malaria incidence rate maps. *Pf*PR$_{2\text{-}10}$-to-incidence modelled relationship was obtained by using the ensemble fit of three mechanistic malaria transmission models (OpenMalaria) [Smith et al., 2006a; Smith et al., 2012b], the EMOD DTK [Eckhoff, 2011; Wenger & Eckhoff, 2013], and the Imperial model [Griffin et al., 2014]. The ensembled model was calibrated using 32 estimates of epidemiologically measured incidence from 30 sites between 1981 and 2011 [Battle et al., 2015; Cameron et al., 2015]

(Annex 2). The uncertainty in the predictions of disease burden was measured through out-of-bag sampling and reported as Bayesian credible intervals [Bhatt et al., 2015b; Weiss et al., 2019]. The components contributing to uncertainty included: uncertainty in the input data on observed clinical incidence rates, and uncertainty in the mechanistic model parameters defining the *Pf*PR-incidence relationship [Bhatt et al., 2015b]. The relationship between clinical incidence (IR) and $PfPR_{2-10}$ was defined as $f(IR) = 2.616PfPR_{2-10} - 3.596PfPR_{2-10}^2 + 1.594PfPR_{2-10}^3$ [Weiss et al., 2019]. These predictions showed that the estimated country-level malaria clinical incidence decreased between 2000 and 2015 (Figure 1.12) [Bhatt et al., 2015b].

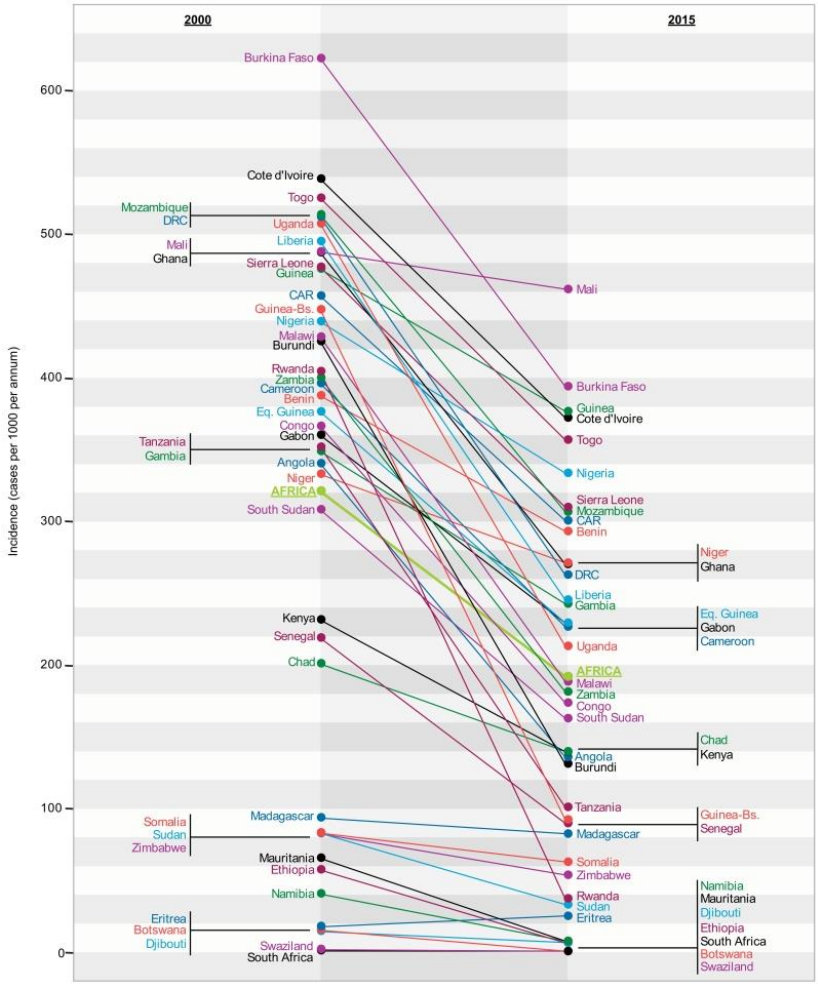


Figure 1.12: Predicted changing incidence rate of clinical malaria by country for 2000 and 2015 [Bhatt et al., 2015b]. Reproduced from Malaria Atlas Project, published CC-BY 3.0

1.9.1.3 Defining spatio-temporal malaria mortality

The Global burden of disease (GBD) study estimates malaria mortality in Africa by systematically collating data on malaria mortality from published and unpublished verbal autopsy studies, irrespective of cause [Murray et al., 2012]. Data were assembled for the period 1980 to 2010 yielding results from 149 'subnational' VA studies and 14 'national' studies globally [Murray et al., 2012]. There were several standardization processes that were carried out to estimate malaria-specific mortality: 1) mapping of cause codes (e.g. ICD10 codes) or study specific causes from VA to the GBD cause hierarchy; 2) age-sex splitting in view of the differential pattern of mortality: significant amount of data were aggregated by age and sex which did not match the neonatal and 5-year age groups used by the GBD. The age pattern of malaria deaths was derived from estimates of the underlying untreated incidence rate; 3) once data had been standardised to match the GBD demographic groups, 'death due to fever from unknown origin', were redistributed to malaria; and 4) using the CODCorrect algorithm, the sum of causes at the individual level was rescaled since the sum of cause-specific mortality estimates for age, sex, country and year must equal all-cause mortality estimate [Murray et al., 2012; Murray et al., 2014].

A range of predictive models, including cause of death ensembled modelling approach (CODEm), were developed to estimate malaria mortality with uncertainties by age, sex, country and year [Foreman et al., 2012; Murray et al., 2012; Murray et al., 2014]. The following covariates were included in the modelling: *Pf*PR from MAP, WHO population-at-risk, prevalence-weighted first-line drug resistance, health-system access, IRS and ITN coverage, rainfall, education, and lagged gross domestic product (GDP). CODEm generated uncertainty intervals for predicted death rates by sampling the posterior

distribution for each component in the ensemble model. The predictive accuracy of the model was assessed using test-train datasets [Murray et al., 2012; Murray et al., 2014].

MAP extended work on malaria mortality in Africa [Gething et al., 2016; Weiss et al., 2019] using the fraction of deaths attributable to malaria from the GBD Cause of Death (COD) Database [GBD 2013]. This included 94 site-year geo-reference data from 51 sites in 19 countries (Annex 3). In each site-year for which malaria cause fraction data were available, MAP estimated a site-year malaria specific mortality rate, as the product of malaria cause fraction and all-cause mortality rate. To generate site-year case fatality rate (CFR), the malaria mortality rate was divided by the site-year specific estimate of untreated malaria incidence rate. A mixed effects regression model was fitted on the logit transformed CFR as a function of log all-cause mortality rated to estimate pixel-year CFR for each 5 × 5 km grid cell. The regression model was weighted by sample size (i.e. the number of all-cause deaths observed in each study site-year) [Gething et al., 2016; Weiss et al., 2019]. Additional covariates used in the model were night-time lights, accessibility and fractional landcover classes, and study-specific age and sex, with the location of each study site included as a national level random effect [Gething et al., 2016; Weiss et al., 2019]. Uncertainty levels were determined using simulation analysis by randomly drawing 1,000 iterations of the coefficients from the variance-covariance matrix of the regression. The country level malaria death estimates were derived from these iterations which were transformed using an inverse logit function and multiplied by country-level untreated incidence [Gething et al., 2016].

Pixel-year (5 × 5 km) predictions of CFR were then multiplied by the corresponding untreated incidence rate cube to yield a pixel-year mortality rate estimate, which was then multiplied by pixel-year population to compute pixel-year malaria death estimates. These

estimates were then aggregated to yield the required GBD national or subnational death estimates. Death totals were then linearly distributed within each country-year over the incidence count surfaces [Gething et al., 2016; Weiss et al., 2019]. To ensure consistency in relation to other diseases estimated within the GBD, mortality estimates were adjusted using the CODCorrect algorithm applied to all-cause mortality envelope [Murray et al., 2012]. The consequence of applying this algorithm was that the modelled link between malaria case incidence and malaria mortality was dissociated to enable malaria mortality to be adjusted where required. This resulted in some areas with low-malaria burden to have implied CFRs that are outside expected ranges (i.e. implausible mortality given the modelled incidence) [Gething et al., 2016; Weiss et al., 2019]

1.9.2 Framework used by World Health Organization (WHO)

The World Health Organization (WHO) adopted three methods to estimate the burden of malaria in all SSA countries due to differences in coverage and quality of surveillance systems [WHO, 2017; WHO, 2018c; WHO, 2019a]. For countries considered to have reliable case reporting systems, data reported by National Malaria Control Programme (NMCP) were adjusted for factors that bias the estimates which included: incomplete reporting, private sector use, cases not confirmed by a diagnostic test and incidence among those who do not seek treatment. The number of cases is calculated using equation 1:

$$Number\ of\ cases = \left(\frac{a+(c\times e)}{d}\right) \times \left(\frac{1+\frac{f}{g}+\frac{(1-g-f)}{2}}{g}\right) \quad (1)$$

where a is malaria cases confirmed in public sector; b is suspected cases tested; c is presumed cases (not tested but treated as malaria); d is reporting completeness; e is test

positivity rate = a/b; f is fraction seeking treatment in private sector; g is fraction seeking treatment in public sector

In high transmission countries considered to have unreliable reporting systems, the WHO adopted the methods used by MAP described in Section 1.9.1.2. The third approach involved using data reported by NMCP without adjustments for countries with high quality surveillance systems and are near elimination [WHO, 2017; WHO, 2018c; WHO, 2019a]. In 2017, the WHO included adjusted and unadjusted empirical routine data for Botswana, Cape Verde, Comoros, Eswatini, Ethiopia, Namibia, Rwanda, Sao Tome and Principe and South Africa [WHO, 2017]. In 2018, the list of countries where routine data was used expanded to include Eritrea, The Gambia, Madagascar, Mauritania, Mayotte, Senegal and Zimbabwe [WHO, 2018c]. In 2019, the list was extended to include Djibouti [WHO, 2019a] (Table 1.8).

Table 1.8: Methods used by WHO to estimate malaria burden in SSA

2017	2018	2019
Adjusted routine data	**Adjusted routine data**	**Adjusted routine data**
Botswana	Botswana	Botswana
Ethiopia	Eritrea	Eritrea
Namibia	Ethiopia	Ethiopia
Rwanda	The Gambia	The Gambia
	Madagascar	Madagascar
	Mauritania	Mauritania
	Mayotte	Mayotte
	Namibia	Namibia
	Rwanda	Rwanda
	Senegal	Senegal
	Zimbabwe	Zimbabwe
Unadjusted routine data	**Unadjusted routine data**	**Unadjusted routine data**
Cape Verde	Cape Verde	Cape Verde
Comoros	Comoros	Comoros
Sao Tome and Principe	Sao Tome and Principe	Djibouti
South Africa	South Africa	Sao Tome and Principe
Eswatini	Eswatini	South Africa
		Eswatini

The WHO adopted three methods in the estimation of the number of malaria deaths. Where estimates of case incidence were derived from routine reporting systems (low-transmission countries), the number of deaths was estimated by multiplying the estimated number of *P. falciparum* malaria cases by a fixed CFR (0.256%) for each country as described in the World malaria reports [WHO, 2008; Black et al., 2010; WHO, 2019a]. Uncertainty in the CFR is assumed to be arbitrarily uniformly distribution between 0.225% and 0.675% [WHO, 2008; Black et al., 2010; WHO, 2019a]. Countries in this category included Botswana, Eritrea, Eswatini, Ethiopia, Madagascar, Namibia, Somalia, Sudan and Zimbabwe [WHO, 2019a].

Countries in the pre-elimination and elimination phases and with vital registration systems that reported more than 50% of all deaths (determined by comparing the number of reported deaths with those expected given a country's population size and crude deaths rate), the number of malaria deaths was derived from the number of reported deaths, adjusting for completeness of reporting. SSA countries in this category included Cape Verde, Djibouti and South Africa [WHO, 2019a].

In countries with a high proportion of deaths due to malaria, the causes of death for children aged 1-59 months were estimated using a verbal autopsy multi-cause model developed by the WHO Maternal and Child Health Epidemiology Estimation Group (MERG) [Liu et al., 2015] with post-hoc adjustments for estimated malaria parasite prevalence. For each country and year, the cause-specific estimates were adjusted to fit the estimated 1-59 months mortality envelopes. A bootstrap method was used to estimate uncertainty interval by re-sampling from the study-level data to estimate the distribution of the predicted percent of deaths due to each cause [WHO, 2019a].

Using the relationship between levels of malaria mortality in different age groups and the intensity of malaria transmission, deaths in those aged over-5 years were inferred from malaria mortality rate in children under-5 years [Ross et al., 2006]. Assuming a non-linear relationship between under-5 years mortality and over-5 years mortality, the relationship was defined as proportion of $\text{deaths}_{\text{over-5 years}} = -(0.293 \times \text{Mortality}_{\text{under-5 years}}^2) + (0.8918 \times \text{Mortality}_{\text{under-5 years}}) + 0.2896$ [WHO, 2019a]. Malaria death rates were derived by dividing annual malaria deaths by the mid-year population at risk of malaria within each country.

1.9.3 Alternatives to estimating impact on malaria mortality

Alternative all-cause and cause-specific mortality estimation methods have been developed by the Child Health Epidemiology Group (CHERG) [Black et al., 2003; Bryce et al., 2003; Jones et al., 2003; Lee, 2003; Venis, 2003; Victora et al., 2003]. These are developed independently of the Institute for Health Metrics GBD estimates. The CHERG estimates of mortality have been used within a framework called the Live Saved Tool (LiST model) developed through a partnership with UNICEF and RBM [RBM, 2010; Eisele et al., 2012]. The ambition of RBM from 2006 was to document reductions in all-cause under-five mortality as a result of scaled malaria interventions in SSA [Hazel et al., 2010; RBM, 2010; Eisele et al., 2012]. The LiST model estimates the number of lives saved using known trial or pre-post assessments of intervention efficacy (ITNs, IRS and IPTp). These estimates are integrated into the knowledge of intervention coverage from national household surveys, a county's population and growth rate, under-five mortality rate (U5M) and cause-of-death patterns [RBM, 2010; Eisele et al., 2012]. To estimate the number of lives saved for a given cause-of-death as a result of scale-up of interventions, the following data was used: the projected number of children's death each year, the protective effect of each intervention on cause-specific mortality and the coverage of each intervention

(ITNs, IRS and IPTp). Using the LiST model, it was estimated that malaria control intervention scale-up (IPTp, ITN, IRS), when compared with rates in the year 2000, averted 736,700 child deaths (95% CI: 483,600, 1,021,800) in 34 African countries between 2001 and 2010 [RBM, 2010].

Several applications of the LiST model have been used for other diseases and contexts [Friberg et al., 2010; Hazel et al., 2010; Walker et al., 2013; Stegmuller et al., 2017] and has recently been integrated into a broader UNICEF tool called Spectrum [Stover et al., 2010] and Spectrum-Malaria [Hamilton et al., 2017; Korenromp et al., 2017]. The attraction of the LiST approach is that it considers U5M and therefore the overall impact of a reduction in malaria exposure on all-cause mortality (Section 1.7.4). However, it only considers children under-fives years, ignoring the impact among older age groups, and intervention impact quotients derived from randomized controlled trials are assumed to be equivalent across a wide range of transmission conditions. The LiST model has not been widely used at country-levels for malaria, the RBM report in 2010 provided only estimates for SSA and not by country. The model, by definition, always shows a reduction in U5M where intervention coverage of one fixed effect has increased. Therefore, it is driven by changing coverage and unchanging intervention efficacy (important when considering mass-effects of vector control and insecticide resistance).

Other approaches to exploring the impact of scaled malaria control on mortality have been proposed which follow a “plausibility analysis” as first suggested by Bradford Hill in the 1960s [Lucas & McMichael, 2005]. Here the principles are based on complex systems evaluations which presume a progressive relationship between environment or intervention access, use, effect size, contextual factors and data are analysed temporally for plausible/credible associations with changes in disease and mortality outcomes

[Habicht et al., 1999; Rowe et al., 2007; RBM-MERG, 2007; Hershey et al., 2017; Ye et al., 2017]. While useful for plausible malaria impact evaluations and increasing the interrogation of available local data, these approaches do not provide any quantifiable outcomes on malaria events or deaths averted.

1.10 Comparison of burden estimates and their limitations

Table 1.9 shows a comparison of the MAP/GBD and WHO estimates of rates and numbers of malaria clinical events and deaths for 2000 and 2015/17. All estimates suggest a substantive decline in malaria burden since 2000 and that malaria continues to be a major public health threat. However, there are significant differences in the actual numbers of estimated events between MAP/GBD and WHO, for example in 2017 MAP/GBD estimated 35% more malaria deaths than WHO, conversely WHO estimated 16% more clinical attacks compared to MAP/GBD, despite WHO using MAP methodologies for 36 SSA countries (Table 1.9). In some ways this is to be expected as methods, input data volumes and denominators change, as noted: "*Some uncritical users may need to be reminded that the differences between the different estimates reflect mainly methodological developments, not real trends over time*" [Smith, 2006b].

Table 1.9: Comparison of estimated malaria clinical incidence and malaria-specific mortality by MAP/GBD and WHO

Description	Bhatt et al., 2015b & Gething et al., 2016	Weiss et al., 2019	WHO, 2015, 2017, 2019a
Clinical incidence (per 1,000) in 2000	321 (253, 427)	283 (235, 336)	427
Clinical incidence (per 1,000) in 2015	192 (135, 265)	-	246
Clinical incidence (per 1,000) in 2017	-	170 (135, 212)	219
Clinical events (millions) in 2000	-	189 (157, 227)	214
Clinical events (millions) in 2015	187 (132, 259)	-	199 (184, 219)
Clinical events (millions) in 2017	-	183 (145, 229)	212 (192, 240)
Mortality rate (per 100,000) in 2000	125 (83, 170)	111 (70, 162)	153
Mortality rate (per 100,000) in 2015	54 (34, 79)	51 (37, 77)	52
Mortality rate (per 100,000) in 2017	-	51 (37, 77)	44
Mortality events (thousands) in 2000	1,007 (666, 1,376)	739 (470, 1085)	764
Mortality events (thousands) in 2015	631 (394, 914)	-	432
Mortality events (thousands) in 2017	-	545 (333, 825)	403

While the MAP models show a broad decline in SSA the assumption is that each country's decline can be predicted with equivalent precision (Figure 1.11). However, during predictions made for 2015 [Bhatt et al., 2015b; Gething et al., 2016], less than 10 *Pf*PR_{2-10} data points since 2000 were used to make national predictions in Niger, Peoples Republic of Congo, Central African Republic, Mauritania, Comoros, Botswana and South Sudan. As such the risks of malaria infection in these seven countries were mapped almost entirely as a result of included covariates or data from neighbouring countries. In addition, despite the predictions being made to 2015, no data were included from infection prevalence surveys in that year, only seven countries had data between 2013 and 2014 [Bhatt et al., 2015]. The reliance on covariates in predicting prevalence, where data are sparse, has been the subject of recent debate and could result in over-fitting and bias. *Pf*PR_{2-10} data volumes were increased during the Weiss et al. (2019) predictions, which may explain the differences in the 2000 and 2015 estimates of morbidity and mortality provided by MAP (Table 1.9). While MAP states that the *Pf*PR_{2-10} data are "very substantial", this masks a fundamental presumption, the ambition is to map 900,000 5 × 5

km grids over 15 years from 2000 across malaria endemic SSA (13.5 million grids); as such input data is at the best representative of only 0.2% [27,573; Bhatt et al., 2015] or 0.32% [43,187; Weiss et al., 2019] of the time-space predicted surface.

The *Pf*PR_{2-10} malaria risk surfaces (Figure 1.11) serve as the entry point to computing clinical events and malaria deaths used by MAP and in poor routine data quality countries by WHO. The data that underpin the relationships between infection prevalence and clinical outcomes and mortality are based on incomplete historical data. For clinical incidence versus *Pf*PR_{2-10} the ensembled model was calibrated using 32 estimates of epidemiologically measured incidence from 30 sites between 1981 and 2011 (Annex 2) [Cameron et al., 2015]. 19 (59%) studies were undertaken during the 1980s-1990s, during a time of escalating drug resistance and only three (9%) of the included studies were undertaken between 2007 and 2011 when ACTs were used, and Africa had begun to scale up vector control (Annex 2). There were also differences between surveillance frequency among the studies included in the calibration and it is not clear how these were adjusted for during incidence measurements (Annex 2) [Cameron et al., 2015]. No consensus yet exists on the appropriate functional form of the relationship between *Pf*PR and clinical incidence for use in disease burden estimation. This relationship is likely to be non-linear and dependent on endemicity-age-specific relationships [Griffin et al., 2014]. In 2000, the clinical incidence rate (321 per 1,000 individuals) estimated by Bhatt et al. (2015b) differed from the rate (283 per 1,000 individuals) estimated by Weiss et al. (2019) and was much higher in the WHO report (427 per 1,000 individuals) (Table 1.9). These differences may arise because of variations in case-definitions used between MAP (fever and a parasite density ≥5,000) and WHO (fever and any level of infection). The absence of a consensus on the epidemiological relationships between prevalence and incidence or the lack of contemporary data are major limitations to reliably calibrate the clinical incidence model.

Equivalent problems exist for the estimation of malaria mortality in relation to prevalence. Notwithstanding the inherent problems of poor sensitivity and specificity of the VA in the accurate determination of malaria-specific mortality (Section 1.7.4 & Table 1.9). These continue to be used in the estimation of the malaria mortality burden in Africa [Murray et al., 2012; Murray et al., 2014; Gething et al, 2016; Weiss et al., 2019]. The current input data used to parameterise mortality risks was derived from 94 site-year survey data from 51 sites in 19 SSA countries (Annex 3). However, only 21 site-years geo-reference data from 13 sites in 8 countries were obtained after 2006, with no data included in the models post-2009 (Annex 3). The CFR was estimated by dividing the malaria mortality rate by untreated malaria incidence rate using a mixed effects regression model using a suite of covariates (Section 1.9.1.3). This approach resulted in an estimated untreated/unprotected mortality rate of between 11.1 and 12.5 per 1,000 population in 2000 (Table 1.9). The MAP models use intervention coverage (IRS and LLIN distributions) in their predictions of *Pf*PR_{2-10} (Section 1.9.1.1). However, the mortality and incidence estimations are derived from the *Pf*PR_{2-10} surface and used to define the number of clinical and fatal events averted as a result of IRS and LLIN [Bhatt et al., 2015b]. This inherent circularity is often ignored. The WHO adopts a hybrid approach that accepts data from countries with reliable vital registration data and modelled estimates using the VA and estimates of CFR from clinical incidence (Section 1.9.2) and makes no direct assumptions on the individual contributions of intervention to mortality reductions [WHO, 2019a]. An alternative approach used by RBM has been the LiST model (Section 1.9.3), which presumes an LLIN or IRS impact from trial results on all-cause under-five mortality, and computes intervention coverage and changing U5M as a result of scale-up of these interventions. This has the advantages of presuming a wider impact on child survival

beyond malaria-specific mortality (Section 1.9.3) but will inherently always show an attributable reduction at all levels of percentage intervention increase.

Overall, there are problems with all methods of disease and mortality incidence that stem from the paucity of contemporary infection prevalence, clinical incidence and quality assured (and possibly better diagnosed, Section 1.7.4) data of malaria mortality. The relationship between incidence and mortality (CFR) is especially poorly defined, using data pre-2000, and yet drives most of the mortality incidence data in all models [MPAC, 2018]. The models performance across the range of malaria endemicities typical of areas of SSA where they are expected to perform is rarely tested and the assumption is that available data are representative of the entire range of current malaria conditions. Equally the absence of any meaningful data on the impact of infection on disease and death in adult populations remains unknown (Section 1.4) and VA diagnosis of malaria in adults is particularly poor (Table 1.6). Importantly the age-structures from birth of infection, disease and death remain poorly defined to parameterise modelled estimation of burden (Section 1.5). At best the models might provide us with a crude sense of the order of magnitude of the malaria burden and whether this might have changed across SSA for global advocacy but lack enough data with adequate precision necessary to estimate the national changes in burden for every country in SSA [Lynch et al., 2012; White et al., 2012; Snow, 2014].

1.11 Rationale for the DPhil

The current understanding of the declining disease burden posed by malaria in SSA has, to date, largely relied on modelled estimates. These modelled predictions currently provide the only source of information on the public health impact of sustained malaria control investment in Africa [Bhatt et al, 2015; Gething et al., 2016; Weiss et al., 2019]. The

predictions associated with control are rarely tested against empirical data. The over-dependence on modelled estimates of disease burden has increasingly come under criticism [Victora & Boerma, 2018]. Modelling imperfect data offers no solution to the future of malaria control in Africa. For malaria, there is a growing move to replace models with actual data from routine surveillance, with the GMP/WHO making surveillance the 3rd pillar within its Global Technical Strategy [WHO, 2015].

Increasing numbers of SSA countries report actual rather than modelled data on malaria morbidity and mortality to the WHO as part of their annual reporting in the World Malaria Report (Table 1.8 & Section 1.9.2). However, 36 high burden countries in SSA (86% of SSAs malaria risk population) still depend on modelled estimates of annual malaria morbidity and mortality. These models have several limitations (Section 1.10) and the precise relationship between infection rates, clinical disease and mortality consequences across all age-groups remains poorly defined (Section 1.5). The need for better, contemporary data on the pathways from infection to death are required to parametrise model estimates of morbidity and mortality risk notably among age groups beyond the first five years of life (Section 1.5). Existing models of disease burden should not be taken at face-value or regarded as “truth”, there is a need to triangulate these predictions with independent data to test their accuracy.

Routinely collected data will provide invaluable epidemiological data on seasonal, temporal and spatial heterogeneity of malaria and serve as a replacement to the more expensive community-based prevalence surveys. As we move towards improving the use of routine data, alternatives to expensive community-based infection prevalence studies need to be explored (Section 1.7.3). These new metrics of the quantity of malaria must be compared to traditional measures of malaria endemicity to provide a means to integrate,

triangulate and exploit their added value. Countries are being encouraged to stratify responses to malaria control according to their sub-national epidemiological context [WHO, 2018a; WHO, 2019a]. This will require a migration from using occasional parasite prevalence surveys, imperfectly powered to provide qualities of risk for sub-national planning, to an increasing use of routine data.

Malaria surveillance is a pivotal component of any programme aiming to interrupt transmission and now forms a central pillar of the GTS for malaria [WHO, 2015]. Routine data will serve as the entry point to detecting local foci of disease transmission (Section 1.8). How routine data perform in identifying hotspots has not been fully explored. The programmatic focus of malaria control involves rapid detection, diagnosis and effective treatment of clinical malaria through passive surveillance and prevention of disease through scaling-up and maintaining high coverage of vector control measures.

1.12 Research Objectives

The overall aim of this research project was to examine the potential utility of routine data in describing the epidemiology and the endemicity of malaria. Specifically,

(i) Review the current literature on changing malaria disease burden in Africa and compare modelled estimates of temporal estimates of changing clinical incidence with empirical data (Chapter 2).

(ii) Describe the infection, disease and mortality patterns of malaria on the Kenyan coast across all age groups (Chapter 3).

(iii) Examine the utility of routine surveillance at health facilities in defining local parasite transmission intensity on the Kenyan Coast (Chapter 4).

(iv) Examine the extent to which spatial heterogeneity of malaria risk can be described using health facility data (Chapter 5).

Chapter 2 : A systematic review of changing malaria disease burden in sub-Saharan Africa since 2000: comparing model predictions and empirical observation

2.1 Introduction

Estimates of the burden of malaria in Africa depend entirely on complex, modelled predictions from imperfect data (Section 1.9.1) [Bhatt et al., 2015b; Gething et al., 2016; Weiss et al., 2019; WHO, 2019a]. The limitations of these models are described in Section 1.10. There are concerns that these models are unable to provide accurate predictions on the magnitude of declining malaria at the spatial scale they have been developed versus the input data they use (Section 1.10) [Lynch et al., 2012; White et al., 2012; Snow, 2014; Rowe, 2017; WHO, 2018d]. The models come with levels of statistical uncertainty and prediction accuracy (Section 1.9.1) however, they have never been tested against collateral temporal data on changing disease incidence not included in the models. For the first time, this chapter aims to compare temporal data on changing malaria cases with modelled predictions of changing clinical incidence at the same localities.

The analysis presented in this chapter used malaria incidence surfaces made publicly available by MAP in 2015 [Bhatt et al., 2015]. In June 2019, MAP produced an updated set of Global modelled predictions, including SSA, for *Pf*PR_{2-10}, malaria incidence and malaria-specific mortality at 5 × 5 km spatial resolutions from 2000 to 2017 [Weiss et al., 2019]. The output data surfaces developed from the more recent modelled predictions were not available during the analysis of this chapter. The direction of the trends in malaria morbidity by country was consistent with those reported by Bhatt et al. (2015b), largely because the same modelling suite was employed, and the only differences were the volumes of input survey data (Section 1.9.1). As such it seems unlikely that the general conclusions drawn here would have changed significantly. Moreover, the general principle of triangulating all new modelled predictions with empirical observations is one that should be promoted.

2.2 Previous reviews on the malaria burden transition in SSA

Three reviews on the transition of malaria disease burden in SSA have previously been undertaken [O'Meara et al., 2010; Gething et al., 2014; Nkumama et al., 2017]. The first review, by O'Meara and colleagues, performed a literature search in PubMed database using the following Medical Subject Headings terms: “Africa South of the Sahara”, “Malaria/epidemiology”, “Malaria/mortality”, “Malaria/prevention and control”, and “Malaria/transmission”, they omitted articles that contained the keywords “Malaria/immunology”. The last search was performed on March 29, 2010 and they limited their search to articles published between 1999-2009 [O'Meara et al., 2010]. The subsequent review by Gething et al. (2014) used a similar search strategy but limited their search to studies published after January 1, 2000. The literature search was conducted in PubMed and performed on March 1, 2013 [Gething et al., 2014]. In the most recent review by Nkumama et al. (2017), a literature search was performed in PubMed, however, the search terms used and date the search was conducted were not indicated [Nkumama et al., 2017].

2.2.1 Inclusion criteria

The first review to be published was by O’Meara et al. (2010) included articles that reported data for at least two years on malaria-specific indicators, i.e. clinical or slide diagnosed case numbers, slide positivity rate, incidence, prevalence, or malaria-specific mortality. They excluded: single timepoint cross-sectional studies, studies on pregnant women only, one year or less follow-up time for intervention studies, and studies reporting entomological data without clinical or parasitological components [O'Meara et al., 2010]. The subsequent review by Gething et al. (2014) slightly modified the inclusion and exclusion criteria used by O'Meara and colleagues and included articles reporting

entomological data, data on pregnant women, and seroconversion rate. They excluded studies reporting single entomological data and studies published before 2000 [Gething et al., 2014]. The third review by Nkumama et al. (2017) included studies on malaria burden in Africa with data for more than two consecutive years and excluded studies published before 2006 and those that were designed to test an intervention.

2.2.2 Data abstracted during previous reviews

The search by O'Meara and colleagues identified 1,528 publications. Following a full text review, 46 published reports (one abstract) met the inclusion criteria. Data from 144 unique study sites were identified across 22 countries with data spanning between 1933-2008 [O'Meara et al., 2010]. The search by Gething and colleagues yielded 2,266 publications. Following full text review, data was extracted from 89 publications reporting data from 268 unique sites in 29 countries between 1933-2012 [Gething et al., 2014]. The review by Nkumama and colleagues identified and included 79 unique study sites across 22 countries covering the period between 1974-2014 from 50 publications [Nkumama et al., 2017].

The three reviews included data from 315 unique study sites identified in 119 published articles across 34 countries. These reviews limited their searches to one search database and did not include unpublished data. Additionally, the reviews by O'Meara and Nkumama did not present an account of the numbers of studies included and excluded at each stage of the study selection process.

While geostatistical and epidemiological models provide us with broad approximations of malaria disease burden, they are rarely tested or triangulated with empirical data. In particular, the three reviews [O'Meara et al., 2010; Gething et al., 2014; Nkumama et al.,

2017] did not compare the empirical observations from published literature with the modelled outputs used by international agencies to define malaria burden in Africa [Bhatt et al., 2015b; Gething et al., 2016; WHO, 2019a]. Here the objective was to conduct a systematic review of published observations of temporal changes in malaria disease burden in SSA since 2000, updated from previous reviews [O'Meara et al., 2010; Gething et al., 2014; Nkumama et al., 2017], and compare this with the modelled predictions of changing clinical incidence of malaria over the same time period.

In the present review, the last literature search was conducted in August 2018 and compared to the only publicly available MAP modelled incidences surfaces at the time [Bhatt et al., 2015b] (Section 1.9.1). While there are factors that might impact malaria cases recorded by health facilities, an attempt to assess whether trends in malaria cases agree with MAP incidence surfaces was made.

2.3 Material and Methods

2.3.1 Search strategy and selection criteria

A systematic review and meta-analysis were conducted using PRISMA guidelines [Moher et al., 2009] and the protocol registered in PROSPERO International Prospective Register of systematic reviews (ID= CRD42019116834).

A literature search was performed in PubMed, MEDLINE, EMBASE, Web of Science, and reference lists of publications between January 2000 and August 2018 on the test positivity rate/incidence of clinical malaria in SSA. A search strategy combining relevant terms and the names of the African countries were applied (Table 2.1). Studies considered included: published papers in peer-reviewed journals, reports, book chapters, and theses.

All relevant studies with data collected between 2000 and 2015 were considered. Additional studies were identified by manually screening the citations of relevant articles. In addition, authors of published hospital data were contacted to provide help with actual annual data not possible to extract directly from the published source.

Table 2.1: Search terms. Reproduced from Kamau et al., 2020, published CC-BY 4.0

(malaria OR plasmodium) AND (trend OR time series OR recession OR resurgence OR temporal OR decline OR increase OR change OR changing) AND (incidence OR prevalence) AND (Africa* OR Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Central African Republic OR Chad OR Congo* OR Cote d'Ivoire OR Equatorial Guinea OR Eritrea OR Ethiopia OR Gabon OR Gambia* OR Ghana OR Guinea* OR Kenya OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Senegal OR Sierra Leone OR Somalia OR Sudan OR Tanzania OR Togo OR Uganda OR Zambia OR Zimbabwe) AND “humans” [MeSH Terms] AND year="2000 -2018"

For studies to be included in the review, they had to fulfil the following criteria: (i) articles reporting data from SSA; (ii) articles that included data on the following outcomes of interest: clinical malaria test positivity rate, malaria case period prevalence, incidence from facility-based surveillance, or community-based disease surveillance; (iii) articles reporting continuous data for five or more years since 2000. Studies were excluded if: (i) they reported data from countries wherein 2017 the WHO used empirical routine data for morbidity estimation, and where most countries are near malaria elimination: Cape Verde, Comoros, Sao Tome and Principe, South Africa, and Swaziland (Eswatini) (Table 1.8); (ii) they reported only repeat cross-sectional survey data on parasite prevalence or vector sporozoite rates in the community; (iii) they reported modelled disease projections without empirical data; (iv) they reported only on verbal autopsy defined malaria mortality. For studies published in more than one report, the most comprehensive (years covered or availability of data for extraction) report was included.

The study selection process began by screening titles and abstracts retrieved from different electronic databases. The full text of eligible articles was then reviewed and compared to articles included in previous reviews [O'Meara et al., 2010; Gething et al., 2014; Nkumama et al., 2017] to ensure that there were no studies missed. Of the 119 articles identified in the previous reviews, 35 were eligible for the present study; 84 were ineligible as they either reported data on parasite prevalence (24 reports), entomology (5 reports), mortality (2 reports), regions of Africa specifically excluded (11 reports), pregnant women (1 report), same site (8 reports) or did not meet the five-year restriction (33 reports).

2.3.2 Data abstracted

Two people (AK and a colleague, Dr Polycarp Mogeni) independently screened the article titles and abstracts for inclusion, extracted data on general information, i.e. first author name, year of publication, study location, country, setting, source of data (hospital surveillance, cohort studies or clinic registers), sample size, age range, number of cases, test positive rate or incidence rate of malaria from tables, figures, text or summary data in the articles. All data were extracted using a standardized extraction form. Disagreements between reviewers were resolved through consensus. Gwet's AC1 statistic was used to assess the inter-rater agreement for study inclusion [Gwet, 2008; Wongpakaran et al., 2013]. Gwet's AC1 (a chance-corrected agreement statistic) was used to quantify the extent of agreement between the two authors as a surrogate for accuracy.

2.3.3 Critical appraisal

The quality of all the studies that met the inclusion criteria was assessed using the Joanna Briggs Institute Prevalence Critical Appraisal Tool [Munn et al., 2014]. Each study was assessed on 10 items, a score of 10% (yes) or 0% (no/unclear) was assigned and was

summed across all items to generate an overall quality score that ranged from 0% to 100% (Annex 4). Based on the overall score, two tertiles were used to split the studies into three groups. Studies were then classified as having a high (<34%), moderate (34%-67%) or low (>67%) risk of bias.

2.3.4 Geographic information

Georeferencing was undertaken through matching to previous health facility geo-coded master facility lists [Ouma et al., 2018; Maina et al., 2019] and where not available using Google Earth or coordinates provided in the original publication. For purposes of matching to modelled predictions, a representative study area of a radial distance of 30 km was assumed for each hospital [Okiro et al., 2009a], 10 km for large health centres and 5 km for dispensaries/clinics/health posts [Noor et al., 2009c].

2.3.5 Data analysis

Empirical data extracted from published reports were annualized, classified as hospital in-patient admissions, out-patient case burdens, or community cohort incidence. An African region was assigned to each study based on the country of enrolment. The average endemicity at the start of the study's surveillance period was defined using the MAP predicted *Pf*PR in children aged 2-10 years per site [Bhatt et al., 2015b]. Although this method has limitations, it is currently the widely accepted predictive models of malaria burden in SSA (Section 1.10). Study-level characteristics included: quality of study (low, moderate and high risk of bias), geographic regions (East Africa, Central Africa, Horn of Africa, Southern Africa, and West Africa), source of data (in-patient and/or out-patient), reported measure of malaria – (incidence, test positivity rate or number of cases), average starting endemicity (classified as, low: <10%; moderate: 10-50%; or high: >50%), sum of residuals, slope and sample size.

For each study, empirically recorded clinical incidence/test positivity rate of *P. falciparum* was time-spaced matched to the modelled predictions of clinical malaria incidence developed by MAP (https://www.map.ox.ac.uk/) [Bhatt et al., 2015b]. The mean clinical malaria incidence was extracted for all pixels in the specified raster that fell within the circular buffer for each georeferenced point and each year of the empirical data. To assess the robustness of the extracted mean clinical malaria incidence, a sensitivity analysis was conducted by doubling and halving the radial distance of the circular buffer.

The correlation (*rho*) between changes in empirical clinical incidence/test positivity rate and modelled predictions of clinical malaria incidence was assessed using the Spearman's Rank correlation. Correlations were then classified as strong positive association ($rho \geq 0.6$); moderate positive association ($0.2 < rho < 0.6$); or weak association ($rho \leq 0.2$). To account for between-study heterogeneity, a random effects meta-analysis was used to summarize the *rho* and the confidence intervals obtained. The meta-analysis methods weight each study as a function of the between-study variance and within-study variance. The level of heterogeneity was assessed using Cochran's *Q* statistic and quantified using the I^2 (a ratio of between-study variance to the sum of between-study variance and within-study variance) due to methodological differences. The forest plot was used to summarize the *rho* and the confidence intervals obtained. Outliers were identified using the leave-one-out method, whereby the meta-analysis was rerun reiteratively removing studies. The funnel plot and the Egger's test were used to assess for publication bias [Egger et al., 1997].

The meta-regression and subgroup analysis were performed to explore possible sources of heterogeneity. In the sub-group analysis, studies were split into sub-groups according to the categorical covariate, the random-effect model was used to combine study effects within each sub-group. A pooled correlation in each sub-group and within-group heterogeneity was obtained. A meta-regression analysis was used to examine the relationship between the study-level characteristics and the correlation of the two metrics using study as the unit of analysis. Meta-regressions (i) allow larger studies to have more weight on the relationship than smaller studies because studies are weighted by the precision of their effect estimate; and (ii) incorporates extra variability in the same way as in a random-effect meta-analysis i.e. allows for the residual heterogeneity among effects estimates not modelled by the study-level characteristics [Thompson et al., 1999]. Meta-regression also allows the effect of continuous and categorical study characteristics to be investigated. A correlation coefficient and residual heterogeneity were obtained. Data analysis was performed using Stata, version 13 (Stata Corporation, College Station, TX) and R version 3.5.1 (R Core Team (2018), Vienna, Austria).

2.4 Results

2.4.1 Search results and characteristics of the included studies

The initial search terms yielded 4,203 articles (Figure 2.1). After examining previous reviews [O'Meara et al., 2010; Gething et al., 2014; Nkumama et al., 2017], an additional four articles relevant to the present review were found which had been missed using the search terms [Larru et al., 2009; Hamel et al., 2011; Ollivier et al., 2011; Wragge et al., 2015]. 2,098 articles were removed as they were duplicates between different electronic databases. After screening titles and abstracts of the remaining 2,109 articles, 1,994 articles were excluded because they did not fulfil the inclusion criteria; these were articles

that reported immunological or entomological data, parasite prevalence, data less than five years, modelled data or regions of Africa specifically excluded. Following a full text review of 115 articles, a further 48 articles were excluded because they either reported data from the same site, reported smoothed data, reported parasite prevalence, or did not meet the complete five-year restriction (Figure 2.1). Finally, the study included data from 67 articles, where in some cases one publication reported data from more than one site. Three articles reported data from the same site but in different time periods, and/or from in-patient or out-patient records [Raouf et al., 2017; Tukei et al., 2017; Ogwang et al., 2018]. Primary data, not possible to extract directly from the published source, was obtained for six publications related to hospital admissions at 24 sites across three countries (Malawi, Uganda, and Kenya) [Okiro et al., 2009a; Okiro et al., 2010; Okiro et al., 2011; Stern et al., 2011; Chaves et al., 2012; Okiro et al., 2013] (Table 2.2). The level of agreement for study selection between the two reviewers was 96.4% (Gwet's AC1 = 0.961), disagreements were resolved after discussion.

The median risk of bias score of the 67 articles was 60% (IQR 30%, 70%); 19 (28%), 27 (41%) and 21 (31%) articles were classified as having high, moderate and low risk of bias, respectively. The 67 articles resulted in a total of 124 geo-referenced locations where data were available for five or more years, covering 24 African countries since 2000 (Table 2.2 & Figure 2.2). This included 16 sites in three countries where, in 2017 the WHO had already begun using routine data (Ethiopia, Namibia, and Rwanda). Of the 124 geo-referenced locations, 13 (11%) study sites from seven countries reported data at either national or sub-national wide areas (Djibouti, Eritrea, Ghana, Sudan, Zambia, Zanzibar and Zimbabwe). Additionally, 76/124 (61%) were individual health facilities or community-cohorts that were spatially unique to a single setting while, 19/124 (15%) covered a single district, or small island extent (Zanzibar) (Table 2.2). Overall, 36% of the studies were from

East Africa, 23% from Southern Africa, 21% from West Africa, 16% from Horn of Africa and only 3% from Central Africa. The majority of the data (41%) was obtained from the out-patient records, 30% from in-patient records, 27% from both out-patient and in-patient records and only 2% (2/124) from cohort studies (Table 2.3).

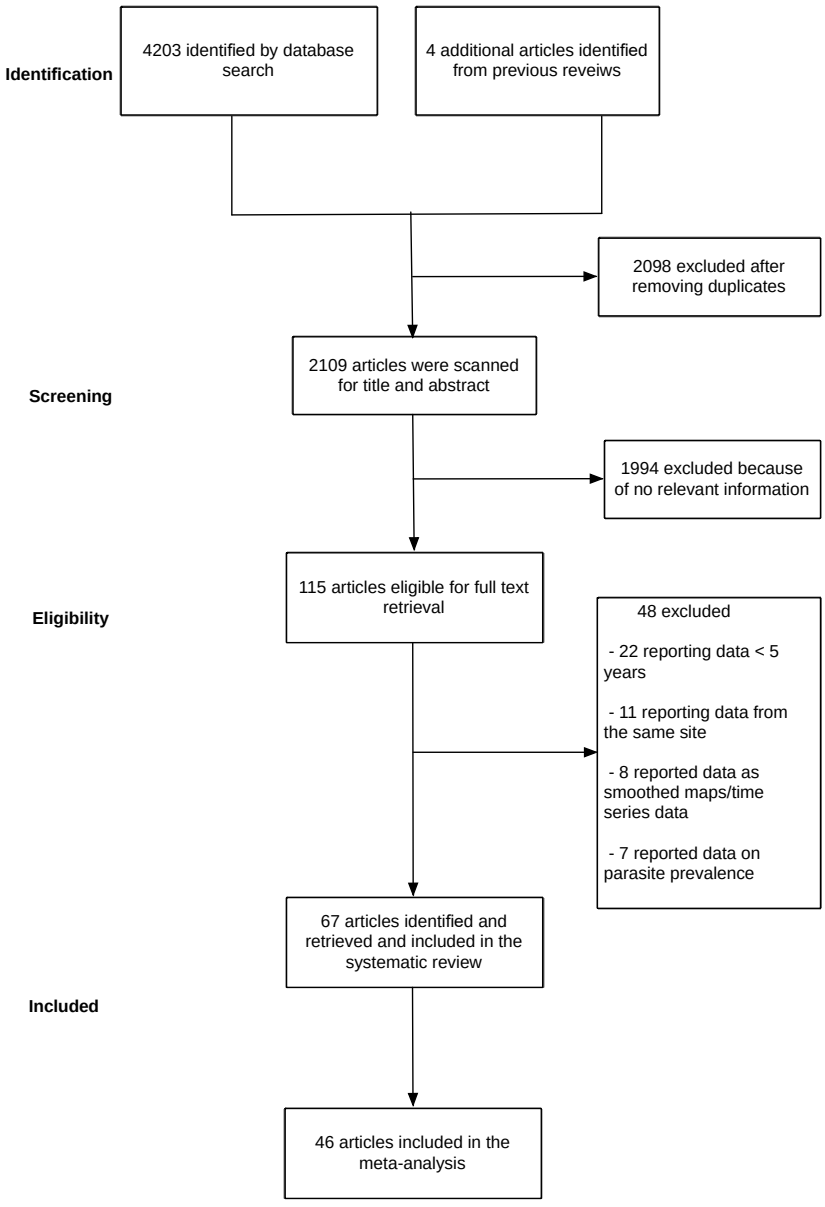


Figure 2.1: A summary flow of study selection process. Reproduced from Kamau et al., 2020, published CC-BY 4.0

Table 2.2: Summary characteristics of included studies

Ref code	1st Author, year	Country	Site name	Data spatial level	Hospital in-patients/out-patients/morbidity incidence-cohort studies	Years	Sample size	Malaria cases
1	Aregawi et al., 2014	Ethiopia	41 Hospitals	Country	In-patient & Out-patient	2001 - 2011	3,696,410	
2	Otten et al., 2009	Ethiopia	5 in-patient health facilities from Amhara, Tigray, and Afar states	Country	In-patient	2001 - 2007	13,106	4,920
3	Otten et al., 2009	Ethiopia	8 facilities with out-patient data from Amhara, Tigray, Oromiya and SNNPR states	Country	Out-patient	2001 - 2007	252,840	29,600
4	Alemu et al., 2011	Ethiopia	Jimma town	Point	In-patient & Out-patient	2000 - 2009		19,798
5	Alemu et al., 2012	Ethiopia	Kola Diba Health Centre	Point	Out-patient	2002 - 2011	59,208	17,597
6	Ergete et al., 2018	Ethiopia	Hana and Keyafer Health Centres	Point	Out-patient	2008 - 2014	54,160	13,727
7	Gebretsadik et al., 2018	Ethiopia	Kombolcha Health Centre	Point	Out-patient	2009 - 2015	24,529	1,155
8	Sena et al., 2014	Ethiopia	Villages around a man-made lake, GGHD, within a distance of 10 km	Point	Out-patient	2004 - 2010	53,624	16,929
9	Tesfa et al., 2018	Ethiopia	Adi Arkay Health Centre	Point	Out-patient	2000 - 2013	18,782	4,467
10	Yimer et al., 2015	Ethiopia	Walga Health Centre	Point	Out-patient	2008 - 2012	34,060	5,889
11	Yimer et al., 2017	Ethiopia	Felegehiwot Referral Hospital	Point	In-patient	2010 - 2014	14,750	397
12	Smith et al., 2014	Namibia	Kunene Regions	Region	In-patient & Out-patient	2000 - 2011	NR	NR
13	Smith et al., 2014	Namibia	Ohangwena Regions	Region	In-patient & Out-patient	2000 - 2011	NR	NR
14	Smith et al., 2014	Namibia	Omusati Regions	Region	In-patient & Out-patient	2000 - 2011	NR	NR
15	Otten et al., 2009	Rwanda	10/439 health centers out-patient cases	Country	In-patient	2001 - 2007	366,711	71,683
16	Otten et al., 2009	Rwanda	9/39 hospitals in-patient cases	Country	Out-patient	2001 - 2007	93,829	49,616
17	Ollivier et al., 2011	Djibouti	Djibouti National Healthcare Insurance Program	Country	In-patient & Out-patient	2001 - 2009	19,411	1,898
18	Nyarango et al., 2006	Eritrea	Eritrea	Country	In-patient & Out-patient	2000 - 2004	NR	NR
19	Aregawi et al., 2017	Ghana	Ghana	Country	In-patient & Out-patient	2005 - 2014		733,271
20	Kamuliwo et al.,2013	Zambia	Zambia	Country	In-patient & Out-patient	2006 - 2014		53,052,500
21	Sande et al., 2017	Zimbabwe	Zimbabwe	Country	In-patient & Out-patient	2003 - 2015	NR	NR

Table 2.2 continued….

Ref code	1st Author, year	Country	Site name	Data spatial level	Hospital in-patients/out-patients/morbidity incidence-cohort studies	Years	Sample size	Malaria cases
22	Mba et al., 2006	Ghana	Volta Region	Region	In-patient & Out-patient	2000 - 2004		827,959
23	Hussien et al., 2017	Sudan	Gadaref State	Region	In-patient & Out-patient	2009 - 2013		26,567
24	Hussien et al., 2017	Sudan	Gezira State	Region	In-patient & Out-patient	2009 - 2013		108,006
25	Hussien et al., 2017	Sudan	Khartoum State	Region	In-patient & Out-patient	2009 - 2013		39,383
26	Hussien et al., 2017	Sudan	North Kordofan State	Region	In-patient & Out-patient	2009 - 2013		53,233
27	Hussien et al., 2017	Sudan	Northern State	Region	In-patient & Out-patient	2009 - 2013		25,491
28	Aregawi et al., 2011	Zanzibar (Tanzania)	6 hospitals in Zanzibar	Region	Out-patient	2000 - 2008	373,060	
29	Mutsigiri et al., 2017	Zimbabwe	Manicaland Province	Region	In-patient & Out-patient	2005 - 2014		947,462
30	Trape et al., 2014	Senegal	Dielmo village	Point	Cohort	2000 - 2012	5,445	
31	Coulibaly et al., 2014	Mali	Bandiagara town	Point	Cohort	2009 - 2013	400	
32	Salvador et al., 2015	Angola	Hospital Nossa Senhora da Paz, Cubal	Point	In-patient & Out-patient	2009 - 2013	23,106	3,279
33	Ndong et al., 2014	Cameroon	Mbakong Health Area, Mezam	Point	Out-patient	2006 - 2012	4,158	1,239
34	M'Bra et al., 2018	Côte d'Ivoire	4 Health Centres, Korhogo	Point	Out-patient	2004 - 2013		78,980
35	Ollivier et al., 2011	Djibouti	Bouffard French Military Hospital	Point	In-patient & Out-patient	2002 - 2009	18,963	513
36	Ollivier et al., 2011	Djibouti	Peltier General Hospital	Point	In-patient & Out-patient	2000 - 2009	24,722	1,436
37	Assele et al., 2015	Gabon	Urban Health Center and Regional Hospital of Makokou	Point	Out-patient	2006 - 2012	21,337	11,600
38	Bouyou-Akotet et al., 2009	Gabon	Centre Hospitalier de Libreville	Point	In-patient & Out-patient	2001 - 2008	26,603	6,927
39	Ceesay et al., 2008	Gambia	Brikama Health Centre	Point	Out-patient	2001 - 2009	85,600	
40	Ceesay et al., 2008	Gambia	Fajara MRC outpatient Clinic	Point	Out-patient	2000 - 2009	161,631	
41	Ceesay et al., 2008	Gambia	Keneba MRC Clinic	Point	Out-patient	2001 - 2009	7,686	
42	Ceesay et al., 2008	Gambia	Sibanor Health Centre	Point	Out-patient	2001 - 2007	18,389	
43	Ceesay et al., 2010	Gambia	Bansang Hospital	Point	In-patient	2003 - 2009	65,441	
44	Ceesay et al., 2010	Gambia	Basse Hospital	Point	In-patient	2003 - 2009	14,070	
45	Ceesay et al., 2010	Gambia	Sulayman Junkung Memorial Hospital, Bwiam	Point	In-patient	2004 - 2009	19,098	

Table 2.2 continued….

Ref code	1st Author, year	Country	Site name	Data spatial level	Hospital in-patients/out-patients/morbidity incidence-cohort studies	Years	Sample size	Malaria cases
46	Ceesay et al., 2010	Gambia	Fajikunda Health Centre	Point	Out-patient	2003 - 2009	51,003	
47	Ceesay et al., 2010	Gambia	Farafenni AFPRC Hospital	Point	In-patient	2003 - 2009	27,621	
48	Ceesay et al., 2010	Gambia	Serekunda Health Centre	Point	Out-patient	2003 - 2009	61,786	
49	Ceesay et al., 2010	Gambia	Soma Health Centre	Point	Out-patient	2003 - 2009	15,384	
50	Ursing et al., 2014	Guinea-Bissau	Bandim Health Centre	Point	Out-patient	2000 - 2012		2,629
51	Chaves et al., 2012	Kenya	Maseno Mission Hospital	Point	In-patient	2000 - 2009		3,957
52	Kapesa et al., 2017	Kenya	Iguhu, Kakamega County	Point	Out-patient	2011 - 2015		24,550
53	Kapesa et al., 2017	Kenya	Kombewa, Kisumu County	Point	Out-patient	2011 - 2015		28,550
54	Kapesa et al., 2017	Kenya	Marani, Kisii County	Point	Out-patient	2011 - 2015		39,250
55	Mogeni et al., 2016	Kenya	Kilifi County Hospital	Point	In-patient	2000 - 2014		15,145
56	Okech et al., 2008	Kenya	Kimbimbi sub-District Hospital, Mwea division	Point	Out-patient	2000 - 2007	46,842	9,392
57	Okiro et al., 2009a	Kenya	Bondo District General Hospital	Point	In-patient	2000 - 2008		7,263
58	Okiro et al., 2009a	Kenya	Bungoma District General Hospital	Point	In-patient	2000 - 2008		16,273
59	Okiro et al., 2009a	Kenya	Busia District General Hospital	Point	In-patient	2000 - 2010		22,408
60	Okiro et al., 2009a	Kenya	Homa Bay District General Hospital	Point	In-patient	2000 - 2010		16,174
61	Okiro et al., 2009a	Kenya	Kitale District General Hospital	Point	In-patient	2000 - 2010		34,471
62	Okiro et al., 2009a	Kenya	Makueni District General Hospital	Point	In-patient	2000 - 2008		2,814
63	Okiro et al., 2009a	Kenya	Narok District General Hospital	Point	In-patient	2000 - 2008		4,884
64	Okiro et al., 2009a	Kenya	Voi District General Hospital	Point	In-patient	2000 - 2010		6,984
65	Okiro et al., 2009a	Kenya	Wajir District General Hospital	Point	In-patient	2000 - 2008	8,320	3,137
66	Okiro et al., 2010	Kenya	Kericho District General Hospital	Point	In-patient	2004 - 2008	NR	NR
67	Okiro et al., 2010	Kenya	Kisii District General Hospital	Point	In-patient	2000 - 2010		35,981
68	Okiro et al., 2010	Kenya	Kisumu District General Hospital	Point	In-patient	2004 - 2008	NR	NR
69	Okiro et al., 2010	Kenya	Malindi District General Hospital	Point	In-patient	2000 - 2010		7,437
70	Okiro et al., 2010	Kenya	Msambweni District General Hospital	Point	In-patient	2000 - 2010		6,332

Table 2.2 continued….

Ref code	1st Author, year	Country	Site name	Data spatial level	Hospital in-patients/out-patients/morbidity incidence-cohort studies	Years	Sample size	Malaria cases
71	Okiro et al., 2010	Kenya	Siaya District General Hospital	Point	In-patient	2000 - 2010		21,274
72	Stern et al., 2011	Kenya	Kericho Unilever Tea Kenya Ltd Hospital	Point	In-patient	2000 - 2010		3,439
73	Okiro et al., 2013	Malawi	Mwanza District General Hospital	Point	In-patient	2000 - 2010	34,461	18,293
74	Okiro et al., 2013	Malawi	Rumphi District General Hospital	Point	In-patient	2000 - 2010	25,914	12,636
75	Okiro et al., 2013	Malawi	Salima District General Hospital	Point	In-patient	2001 - 2010	40,771	18,746
76	Okiro et al., 2013	Malawi	Zomba District General Hospital	Point	In-patient	2000 - 2010	158,489	49,097
77	Roca-Feltrer et al., 2012	Malawi	Queen Elizabeth Central Hospital, Blantyre	Point	Out-patient	2001 - 2010	242,953	61,320
78	Wragge et al., 2015	Mali	Mine health department in the SEMOS mine clinics, Sadiola District	Point	Out-patient	2004 - 2014		9,233
79	Galatas et al., 2016	Mozambique	Ilha Josina Machel Health Post	Point	Out-patient	2004 - 2013	70,698	28,316
80	Orimadegun et al., 2007	Nigeria	University College Hospital, Ibadan	Point	In-patient	2000 - 2005	16,031	1,806
81	Brasseur et al., 2015	Senegal	St Joseph dispensary of Mlomp	Point	Out-patient	2000 - 2012	19,089	6,946
82	Brasseur et al., 2011	Senegal	Mlomp village	Point	Out-patient	2000 - 2010	30,685	10,786
83	Munier et al., 2009	Senegal	3 dispensaries in Niakhar Demographic Surveillance site	Point	Out-patient	2000 - 2004	NR	NR
84	Kigozi et al., 2012	Uganda	Aduku Health Centre	Point	Out-patient	2007 - 2015	164,596	
85	Ogwang et al., 2018	Uganda	Kitgum Government Hospital2	Point	In-patient	2011 - 2015	58,496	21,766
86	Okiro et al., 2011	Uganda	Apac Hospital	Point	In-patient	2000 - 2009		29,871
87	Okiro et al., 2011	Uganda	Jinja Hospital	Point	In-patient	2000 - 2009		35,189
88	Okiro et al., 2011	Uganda	Kambuga Hospital	Point	In-patient	2000 - 2010		20,300
89	Okiro et al., 2011	Uganda	Mubende Hospital	Point	In-patient	2001 - 2009		12,476
90	Okiro et al., 2011	Uganda	Tororo Hospital	Point	In-patient	2000 - 2009		43,887
91	Raouf et al., 2017	Uganda	Apac Hospital	Point	In-patient	2011 - 2015	14,595	
92	Tukei et al., 2017	Uganda	Awach Health Centre IV	Point	Out-patient	2007 - 2011	7,462	2,264
93	Tukei et al., 2017	Uganda	Gulu Independent hospital	Point	Out-patient	2007 - 2011	16,802	2,640

Table 2.2 continued….

Ref code	1st Author, year	Country	Site name	Data spatial level	Hospital in-patients/out-patients/morbidity incidence-cohort studies	Years	Sample size	Malaria cases
94	Tukei et al., 2017	Uganda	Gulu Regional Referral Hospital	Point	Out-patient	2007 - 2011	24,698	8,539
95	Tukei et al., 2017	Uganda	Kitgum Government Hospital	Point	Out-patient	2007 - 2015	91,442	38,229
96	Tukei et al., 2017	Uganda	Lacor Hospital	Point	Out-patient	2007 - 2011	289,288	95,207
97	Tukei et al., 2017	Uganda	Lalogi Health Centre IV	Point	Out-patient	2007 - 2011	26,092	15,299
98	Tukei et al., 2017	Uganda	Military hospital	Point	Out-patient	2007 - 2011	11,347	2,981
99	Tukei et al., 2017	Uganda	Namokora Health Centre IV	Point	Out-patient	2007 - 2011	5,857	2,798
100	Tukei et al., 2017	Uganda	St Joseph's hospital	Point	Out-patient	2007 - 2011	75,915	30,097
101	Chanda et al., 2009	Zambia	Chongwe Rural Health Centre	Point	Out-patient	2003 - 2008	NR	NR
102	Comfort et al., 2014	Zambia	Macha Mission Hospital	Point	Out-patient	2000 - 2008		26,235
103	Gunda et al., 2017	Zimbabwe	Buvuma ward	Point	Out-patient	2010 - 2014		74
104	Gunda et al., 2017	Zimbabwe	Ntalale ward	Point	Out-patient	2010 - 2014		47
105	Gunda et al., 2017	Zimbabwe	Selonga ward	Point	Out-patient	2010 - 2014		125
106	Donovan et al., 2012	Ghana	20 health facilities in Accra	District	Out-patient	2001 - 2006	4,308,469	1,670,357
107	Khagayi et al., 2017	Kenya	Siaya County	District	Out-patient	2007 - 2012	NR	NR
108	Rose-Wood et al., 2010	Mali	7 Urban community health centres located in Mopti and Sévaré	District	Out-patient	2000 - 2006	NR	NR
109	Ferrao et al., 2016	Mozambique	6 public health centres and 1 Provincial hospital, Chimoio municipality	District	In-patient & Out-patient	2006 - 2014		490,554
110	Efe et al., 2013	Nigeria	5 health facilities from Warri metropolis	District	In-patient & Out-patient	2000 - 2009		56,746
111	Landoh et al., 2012	Togo	Est Mono district	District	Out-patient	2005 - 2010	222,338	114,654
112	Simple et al., 2018	Uganda	Gulu District	District	Out-patient	2006 - 2015		2,304,537
113	Masaninga et al., 2012	Zambia	Livingstone District	District	Out-patient	2004 - 2009		153,200
114	Mukonka et al., 2014	Zambia	Nchelenge District	District	In-patient & Out-patient	2006 - 2012	1,019,453	411,934
115	Bhattarai et al., 2007	Zanzibar (Tanzania)	13 public health facilities North A district	District	In-patient & Out-patient	2000 - 2005	9,425	5,283
116	Mharakurwa et al., 2013	Zimbabwe	Mutasa District	District	In-patient & Out-patient	2003 - 2011	1,971,621	587,120

Table 2.2 continued….

Ref code	1st Author, year	Country	Site name	Data spatial level	Hospital in-patients/out-patients/morbidity incidence-cohort studies	Years	Sample size	Malaria cases
117	Muchena et al., 2018	Zimbabwe	Beitbridge District	District	In-patient & Out-patient	2011 - 2015	NR	NR
118	Muchena et al., 2018	Zimbabwe	Bulilima District	District	In-patient & Out-patient	2011 - 2015	NR	NR
119	Muchena et al., 2018	Zimbabwe	Gwanda District	District	In-patient & Out-patient	2011 - 2015	NR	NR
120	Muchena et al., 2018	Zimbabwe	Insiza District	District	In-patient & Out-patient	2011 - 2015	NR	NR
121	Muchena et al., 2018	Zimbabwe	Mangwe District	District	In-patient & Out-patient	2011 - 2015	NR	NR
122	Muchena et al., 2018	Zimbabwe	Matobo District	District	In-patient & Out-patient	2011 - 2015	NR	NR
123	Muchena et al., 2018	Zimbabwe	Umzingwane District	District	In-patient & Out-patient	2011 - 2015	NR	NR
124	Sande et al., 2016	Zimbabwe	Mutare District	District	In-patient & Out-patient	2003 - 2013	NR	NR

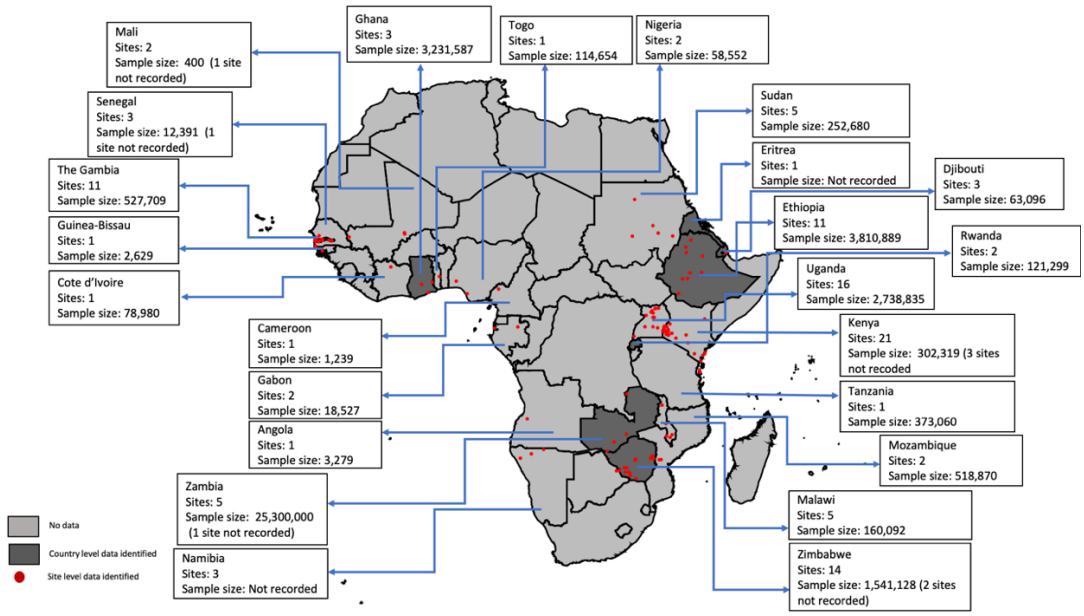


Figure 2.2: Assembled data by country, the number of sites and the sample size. Reproduced from Kamau et al., 2020, published CC-BY 4.0

Legend: Dark grey indicates countries that reported national routine malaria case data and the red dots indicate unique single setting sites where data was identified.

Table 2.3: Characteristics of the 124 geo-referenced locations from 67 published articles. Reproduced from Kamau et al., 2020, published CC-BY 4.0

Characteristics	Summary statistics
Geographical Region, n (%)	
East Africa	45 (36.3%)
Southern Africa	29 (23.4%)
West Africa	26 (21.0%)
Horn of Africa	20 (16.1%)
Central Africa	4 (3.2%)
Quality of the study, n (%)	
High risk of bias	41 (32.5%)
Moderate risk of bias	52 (41.3%)
Low risk of bias	33 (26.2%)
Data source, n (%)	
In-patient	37 (29.8%)
In-patient and out-patient	34 (27.4%)
Out-patient	51 (41.1%)
Cohort studies	2 (1.6%)
Duration of reported data, n (%)	
5 years	38 (30.6%)
6-9 years	42 (33.9%)
10-15 years	44 (35.5%)
Reported data spanning period, n (%)	
2000-2005	5 (4.0%)
Post 2005	43 (34.7%)
Pre and post 2005	76 (61.3%)
Average starting endemicity, n (%)	
< 10%	40 (32.3%)
10-50%	64 (51.6%)
> 50%	20 (16.1%)
Measure of malaria, n (%)	
Number of cases	40 (32.3%)
Test positive rate	62 (50.0%)
Incidence rate	22 (17.7%)
Data spatial level, n (%)	
Country	10 (8.1%)
District	19 (15.3%)
Point	84 (67.7%)
Region	11 (8.9%)
Sample size, median (IQR)	18,389 (5,889, 49,616)

In the subsequent comparative analyses of modelled predictions of changing disease burden, 31/124 study sites from 21 publications were not included; these are the first 31 study sites in Table 2.2. The reasons for exclusion were: (i) 16 study sites in Ethiopia, Namibia, and Rwanda classified as having reliable routine data to estimate malaria burden by WHO (Table 1.8) since the comparison would not be relevant in countries where surveillance data already feeds into the WHO report; (ii) 13 study sites in Djibouti, Eritrea, Ghana, Sudan, Zambia, Zanzibar, and Zimbabwe that reported malaria case at the national or regional level, the wide spatial extents of these data with likely inherent large variations in disease risk, precluding comparisons with modelled estimates; and (iii) two study sites (Dielmo, Senegal and Bandiagara, Mali) that reported intensive, repeat community-cohort ACD data which are considered to be methodologically different from PCD (Section 1.7.2) (Table 2.2).

The remaining 93 sites from 46 publications, included 28 (30%) sites that reported 5 years temporal data, 33 (36%) sites reported temporal data between 6-9 years and 32 (34%) sites reported data between 10-15 years. Three sites (3%) reported data between 2000-2005, 32 (34%) sites reported data post-2005 and 58 (63%) sites reported data spanning the period pre-and post-2005. The average starting endemicity level was <10% in 19 sites, 10-50% in 53 sites and >50% in 19 sites (Table 2.3).

2.4.2 Comparing changes in empirical versus modelled disease burden

Among the 93 sites included in the comparative analysis, 33% (31/93) showed evidence of a rise during the surveillance interval, 67% (62/93) showed evidence of a decline. This compares with 23 sites where the modelled estimates predicted a rise and 70 sites where the modelled estimates predicted a decline. 47% of the studies showed a strong positive association ($rho \geq 0.6$), 15% (14/93) showed a moderate positive association ($0.2 < rho < 0.6$)

and 38% (35/93) of the studies showed a weak association (*rho*≤0.2) (Figure 2.3). Eight sites, four in Kenya [Kapesa et al., 2017; Okiro et al., 2009a], one in Mozambique [Ferrao et al., 2016], two in Uganda [Okiro et al., 2011; Raouf et al., 2017] and one in Zimbabwe [Muchena et al., 2018] showed strong negative correlations (*rho* ≥-0.6) (Figure 2.3) indicating that the trends in the observed data versus the predicted estimates were markedly different. Four of the eight sites were in low malaria transmission areas and were classified as having a moderate risk of bias score. When the outliers were assessed using the leave-one-out method, there was no single study that was a substantial cause of heterogeneity (Figure 2.4). Further, there was no evidence of publication bias (Egger's test for small study effect: p=0.727) as shown by the distribution of the Fisher's Z transformed correlation coefficient (arctanh(*rho*)) vs. the standard errors of arctanh (*rho*) (Figure 2.5). The summary meta-analysis of these studies showed a moderate positive association between empirically recorded changes in clinical incidence/test positivity rate and MAP modelled predictions of clinical malaria incidence (*rho*=0.51; 95% CI: 0.37; 0.63; p<0.001; unadjusted I^2=69.63%), indicating substantial heterogeneity.

When alternative radial distances of the circular buffer were used to extract MAP mean clinical malaria incidence, the correlation in some sites varied somewhat but were not significantly different from the correlations obtained in Figure 2.3. For example, when the radial distance was doubled, 48% of the studies showed a strong positive association (*rho*≥0.6), 16% (15/93) showed a moderate positive association (0.2<*rho*<0.6) and 36% (33/93) of the studies showed a weak association (*rho* ≤0.2). The summary meta-analysis was (*rho*=0.51; 95% CI: 0.37; 0.63; p<0.001; unadjusted I^2 = 70.3%).

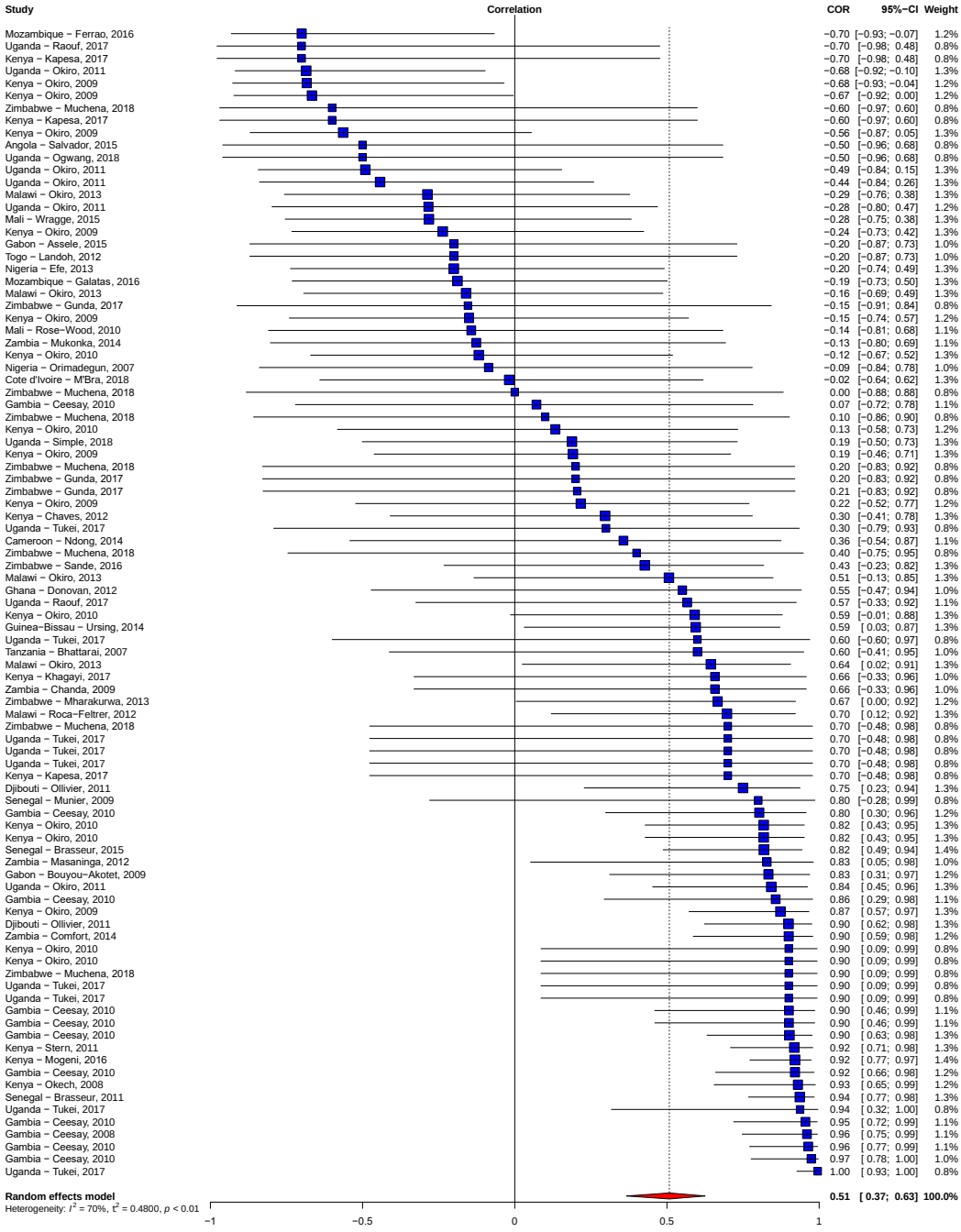


Figure 2.3: Forest plot of ordered correlations between empirically recorded clinical incidence/test positivity rate of *P. falciparum* and MAP modelled predictions of clinical malaria disease incidence

Legend: Blue squares represents the correlation of each study; the error bars through the blue boxes are the uncertainty intervals; the red diamond shows the overall pooled correlation; the horizontal tips of the red diamond are the uncertainty level; weights are computed as the inverse of within and between variances; references are listed alphabetically in the reference material.

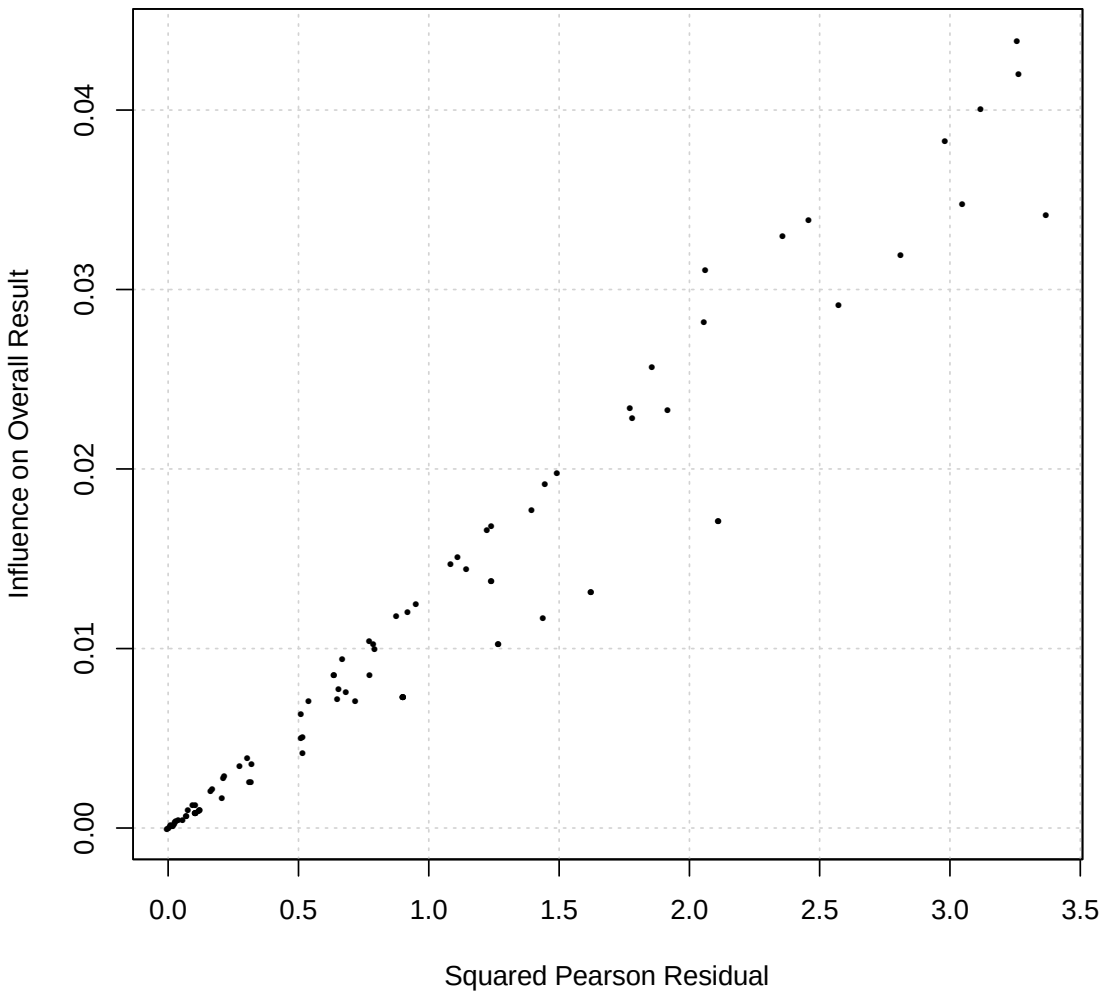


Figure 2.4: Plots used to visualize the leave-one-out estimates, to identify outliers, or influential studies. A built-in function *(*Baujat Plot) using the package metafor in R statistical software was used to identify outlying effect sizes

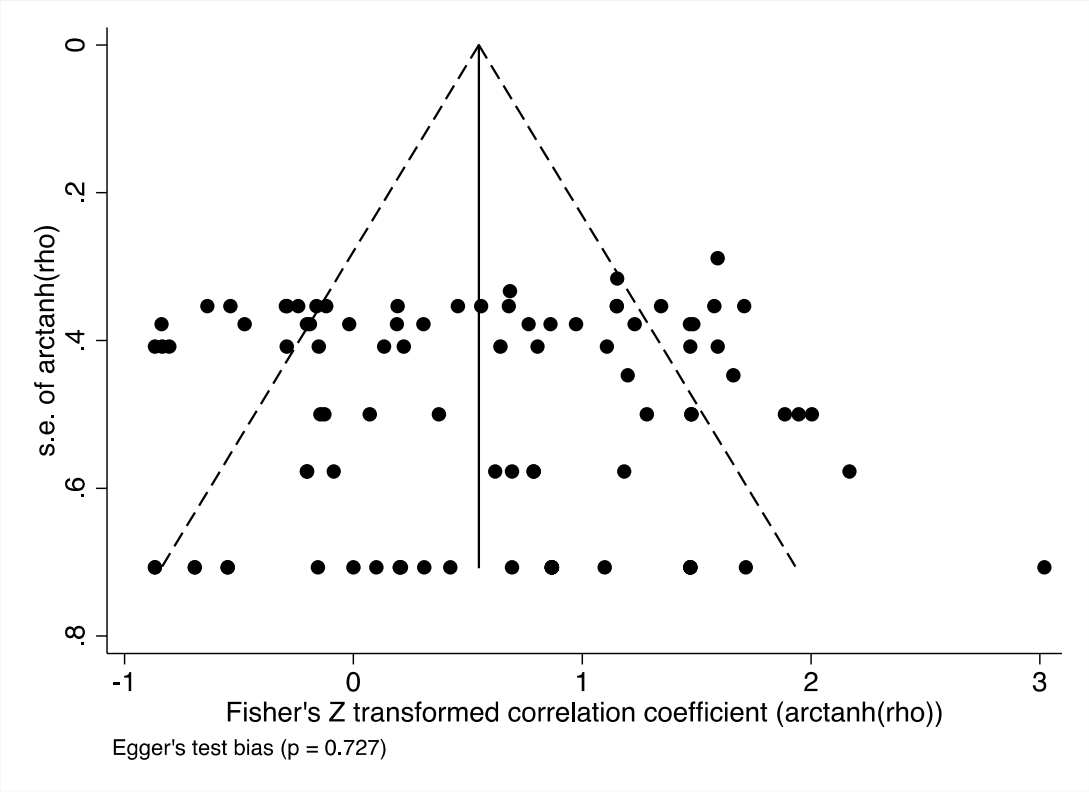


Figure 2.5*:* Funnel plot with pseudo 95% confidence limits showing the Fisher's Z transformed correlation coefficient (arctanh(r)) against the standard errors of arctanh(r)

Legend: The funnel plot was used to examine whether the distribution of effect size estimates were less variable (i.e. whether higher number of studies were roughly symmetrical around the mean) and to detect whether the small-study effect was present. The Egger's regression was used to assess for publication bias by using precision to predict the standardized effect, a significant result suggests the possibility of publication bias. The Egger's regression test is a weighted linear regression test in which the standardized effect estimates (i.e. the quotient of effect size and its standard error) are regressed against precision (i.e., the inverse of the standard error).

When possible sources of the observed heterogeneity were explored using a meta-regression, the slope of empirically recorded clinical incidence/test positivity rate was found to be the single most important covariate, accounting for a 16% change in I^2 (*rho*= -0.989; 95% CI: -0.998, -0.939; p<0.001; residual I^2=58.8%) (Table 2.4). The quality of data extracted, geographical region, reported measure of malaria, source of data, average starting endemicity, and slope of modelled clinical malaria incidence were additional possible sources of heterogeneity. However, the percentage change in I^2 from these factors was minimal (which were responsible for percentage changes from 2% up to 9%)

(Table 2.4). Sample size and sum of residuals did not seem to explain the heterogeneity observed (Table 2.4).

Table 2.4: Sources of heterogeneity assessment based on meta-regression analyses (93 geo-referenced locations). Reproduced from Kamau et al., 2020, published CC-BY 4.0

Factors	Summary statistics	Pooled Correlation (*rho*)	[95% CI]	P value	Residual I^2	Percent change in I^2
Geographical Region, n (%)						
Eastern Africa	42 (45.2%)	0.43	0.18, 0.62			
Southern Africa	23 (24.7%)	0.33	0.07, 0.54	**0.01**	67.7%	2.8%
Western Africa	22 (23.7%)	0.73	0.53, 0.86			
Central Africa	4 (4.3%)	0.30	-0.42, 0.79			
Horn of Africa	2 (2.1%)	0.84	0.60, 0.94			
Quality of the study, n (%)						
High risk of bias	28 (30.1%)	0.54	0.30, 0.71			
Moderate risk of bias	41 (44.1%)	0.25	0.02, 0.46	**<0.001**	63.2%	9.3%
Low risk of bias	24 (25.8%)	0.78	0.63, 0.87			
Data source, n (%)						
In-patient	34 (36.6%)	0.36	0.07, 0.59			
In-patient and out-patient	17 (18.3%)	0.38	0.03, 0.65	**0.01**	68.1%	2.3%
Out-patient	42 (45.1%)	0.67	0.52, 0.78			
Measure of malaria, n (%)						
Number of cases reported	30 (32.3%)	0.26	-0.01, 0.49			
Test positive rate	47 (50.5%)	0.69	0.54, 0.79	**0.001**	66.2%	4.9%
Incidence rate	16 (17.2%)	0.30	-0.06, 0.59			
Average starting endemicity, n (%)						
< 10%	19 (20.4%)	0.33	-0.08, 0.64			
10-50%	55 (59.2%)	0.64	0.50, 0.75	**0.002**	66.2%	4.9%
> 50%	19 (20.4%)	0.11	-0.20, 0.41			
Sample size, median (IQR)	15,779 (3,957, 35,981)	0.01	-0.09, 0.11	0.83	71.8%	-3.1%
Sum of residuals of empirical clinical incidence/test positivity rate, median (IQR)	0.94 (0.06, 2.05)	0.07	-0.03, 0.17	0.07	69.3%	0.5%
Sum of residuals of MAP modelled clinical incidence, median (IQR)	0.12 (0.06, 0.30)	-0.02	-0.65, 0.62	0.24	69.8%	-0.3%
Slope of empirical clinical incidence/test positivity rate, median (IQR)	-0.003 (-0.16, 0.001)	-0.989	-0.998, -0.939	**<0.001**	58.8%	15.5%
Slope of modelled MAP clinical incidence, median (IQR)	-0.02 (-0.03, 0.0001)	-0.99995	-1.00, -0.997	**0.003**	67.5%	3.1%

Summary unadjusted I^2 = 69.63%; Percentage change in I^2 computed as: (Summary unadjusted I^2 - Residual I^2)/ Summary unadjusted $I^2 \times 100$

The slope of clinical incidence/test positivity rate remained robust as a predictor of correlation even after excluding studies with a high risk of bias (*rho*=-0.989; 95% CI: -0.998, -0.923; p<0.001) and after adjusting for the other study-level characteristics (*rho*= -0.967; 95% CI: -0.997, -0.689; p=0.005) (Table 2.5). As a sensitivity analysis, the slope

of empirically observed data was stratified, showing a decrease (<0) or increase (≥0), and a significant association in the mean difference of the correlation between the observed data and the modelled prediction was also found (*rho*=-0.75; 95% CI: -0.86, -0.60; p<0.001) (Figure 2.6).

Table 2.5: Sources of heterogeneity assessment based on multivariable meta-regression analyses

Factors	Meta-regression coefficient (Fisher's Z transformed correlation coefficient)	[95% CI]	P value	Holm-Bonferroni corrected P value
Geographical Region, n (%)				
Southern Africa	0.19	-0.37, 0.75	0.05	0.33
Western Africa	0.22	-0.31, 0.75		
Central Africa	-0.43	-1.35, 0.50		
Horn of Africa	0.93	-0.28, 2.14		
Quality of the study				
Moderate risk of bias	-0.48	-0.95, -0.02	0.04	0.33
Low risk of bias	-0.39	-1.00, 0.22		
Data source				
In-patient and out-patient	-0.21	-0.98, 0.56	0.09	0.46
Out-patient	0.21	-0.22, 0.65		
Measure of malaria				
Test positive rate	0.22	-0.27, 0.70	0.19	0.58
Incidence rate	-0.09	-1.13, 0.94		
Average starting endemicity				
10-50%	0.14	-0.41, 0.68	0.04	0.33
> 50%	-0.30	-0.94, 0.34		
Sample size	-0.04	-0.15, 0.08	0.55	0.58
Sum of residuals of empirical clinical incidence/test positivity rate	-0.03	-0.15, 0.09	0.27	0.58
Sum of residuals of MAP modelled clinical incidence	0.49	-0.26, 1.24	0.11	0.46
Slope of empirical clinical incidence/test positivity rate	-2.04	-3.23, -0.85	**<0.001**	**0.005**
Slope of MAP modelled clinical incidence	-9.37	-18.11, -0.64	0.02	0.18

Geographical Region (Eastern Africa vs Southern Africa/Western Africa/Central Africa/Horn of Africa)**; Quality of the study** (High risk of bias vs Moderate risk of bias/Low risk of bias); **Data source** (In-patient vs In-patient and out-patient/Out-patient); **Measure of malaria (**number of cases reported/test positive rate/incidence rate); **Average starting endemicity (**low: <10% vs moderate: 10 - 50%/high: >50%)

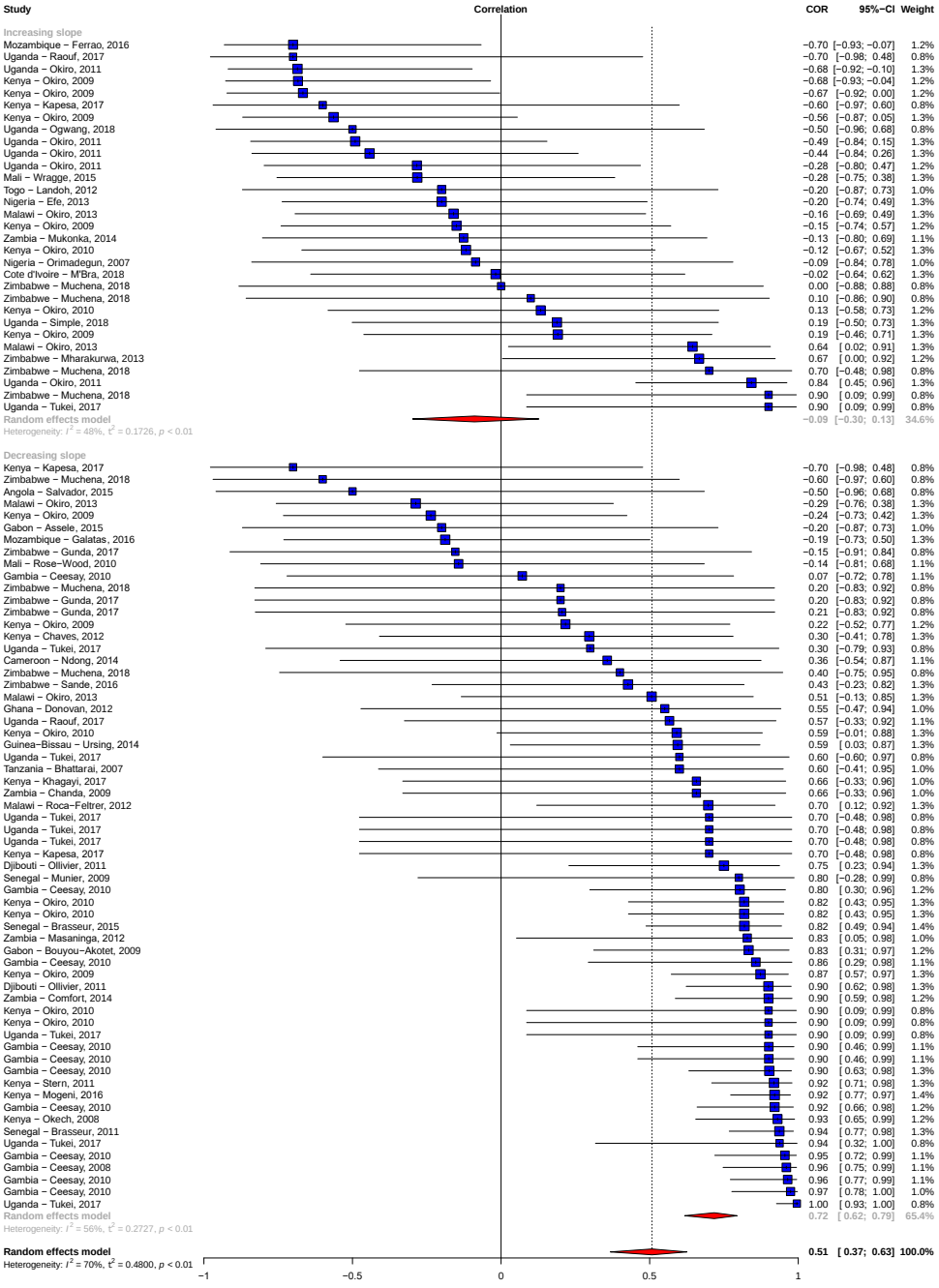


Figure 2.6: Forest plot of ordered correlation between empirically recorded clinical incidence/test positivity rate of *P. falciparum* and MAP modelled predictions of clinical malaria disease incidence stratified by the increasing or decreasing slope of empirically recorded changes in clinical malaria. See the legend in Figure 2.3 for symbol representations**.** Reproduced from Kamau et al., 2020, published CC-BY 4.0

2.5 Discussion

The demand for annual and timely progress assessments of key malaria indicators has fuelled an increased use of advanced mathematical modelling tools to estimate and predict malaria trends and burden (Section 1.9) [Murray et al., 2012; Murray et al., 2014; Bhatt et al., 2015b; Gething et al., 2016; Weiss et al., 2019]. The application of these models, which use multiple assumptions, has enabled the production of predictive maps of malaria risk [Bhatt et al., 2015b; Gething et al., 2016; Weiss et al., 2019]. However, these predictions become increasingly uncertain as the density and proximity of nearby data points decreases and the input data are outdated or heavily dependent on covariates (Section 1.10). This chapter assesses whether trends in malaria cases from empiric surveillance agree with the predictive model of malaria burden in SSA developed by MAP. Empirically reported malaria data obtained from 93 health facility-based study sites from 46 published articles were used.

The empirical data obtained in this review included sites across the spectrum of malaria transmission intensity in SSA. The majority (60%) of sites were in moderate malaria transmission areas, 20% in low transmission and 20% in high transmission areas (Table 2.4). Despite previous reviews on the trends of malaria burden in Africa [O'Meara et al., 2010; Gething et al., 2014; Nkumama et al., 2017], this updated review is the first to make a comparison between empirical observations and the increasingly used modelled predictions.

There was a significant variation in the association between empirical data on malaria burden and the modelled predictions across study sites (Figure 2.3). Specifically, 47% of the study sites showed a strong positive association, while 38% of the studies showed a

weak association. The single most important factor explaining this variation was the slope of the empirically observed data (i.e. steep declines were associated with stronger correlations with the predicted estimates). If empirically recorded changes in malaria burden in a specific geographical area were on a downward trend, then the MAP modelled prediction was a good reflection of this change (Figure 2.6). Conversely, MAP modelled predictions performed poorly in sites that showed a stalling in progress or resurgence in empirically reported malaria burden. For instance, in West Africa, sites in Senegal, Guinea-Bissau and Ghana showed a declining burden of malaria and consequently correlated well with modelled predictions. However, data on clinical malaria cases from Côte d'Ivoire, Mali, Nigeria and Togo exhibited an increase in malaria burden and poorly correlated with the modelled predictions of clinical malaria incidence. Not surprising, the greatest uncertainties coincided in these areas. This is particularly important considering the stalling malaria control gains as reported by WHO [WHO, 2018c; WHO, 2019a; WHO, 2020]. Although quality of study seemed to explain some of the variations, it was not a major cause of the heterogeneity observed when tested using meta-regression. One might expect studies classified as having a high risk of bias to correlate poorly with the modelled predictions, but this was not the case in this analysis (Figure 2.7).

The burden of malaria in large parts of SSA is unknown especially in countries with high and seasonally intense transmission. Literature indicates that several countries in Central and West Africa have not yet had a significant reduction in malaria burden [O'Meara et al., 2010]. Generally, the MAP model predicted a decline in malaria burden (i.e. in 70 out of 93 sites) and an increase in 23 out of 93 sites. The modelled predictions from 12 of these 23 sites (52%) correlated poorly with the observed data. For example, empirical data from four sites in Central Africa indicated that the burden of malaria has been declining, however, in two sites MAP predicted an increase in clinical malaria incidence (Figure 2.8).

There was only a handful of studies including hospital surveillance data obtained from Central and West Africa. In general, data on empirical clinical series tended to be more plentiful in areas where parasite survey data were plentiful. This suggests that if more empirical data was obtained from areas where parasite survey data are sparse then even less concordance would be seen between modelled predictions and empiric data.

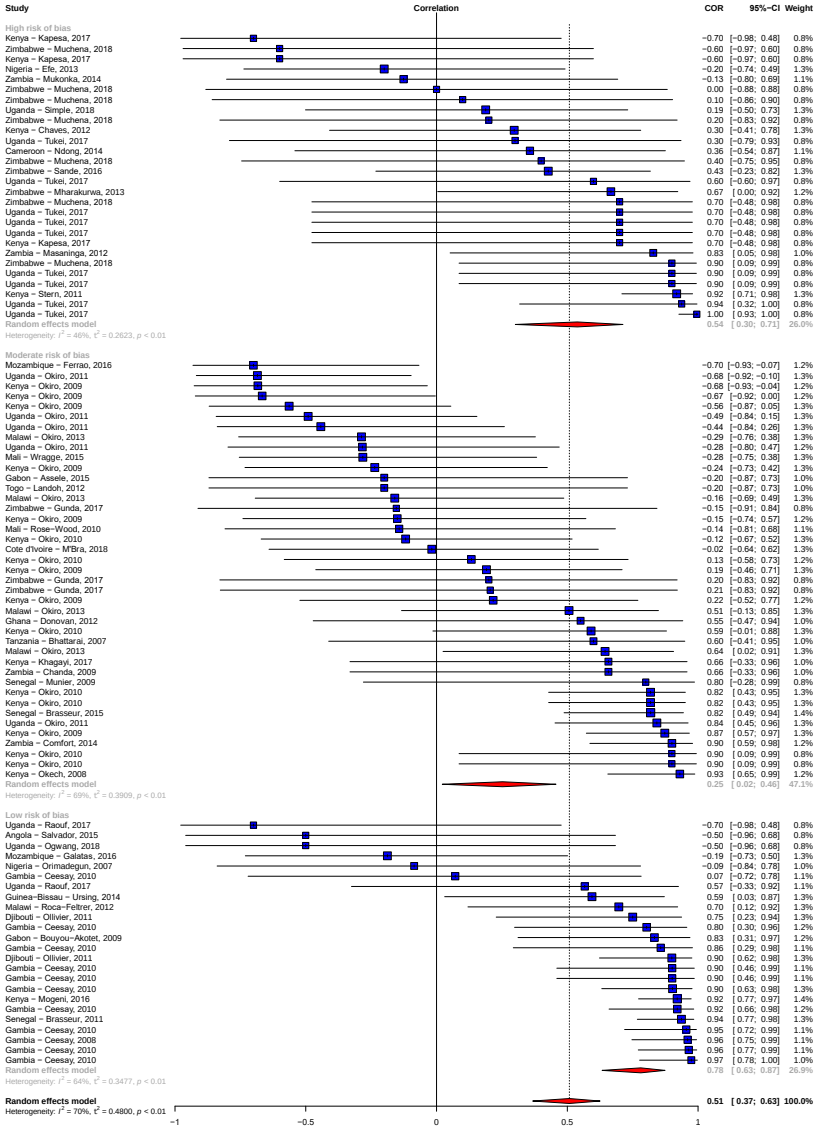


Figure 2.7: Forest plot of ordered correlation between empirically recorded clinical incidence/test positivity rate of *P. falciparum* and MAP modelled predictions of clinical malaria disease incidence stratified by quality of the study. See the legend in Figure 2.3 for symbol representations

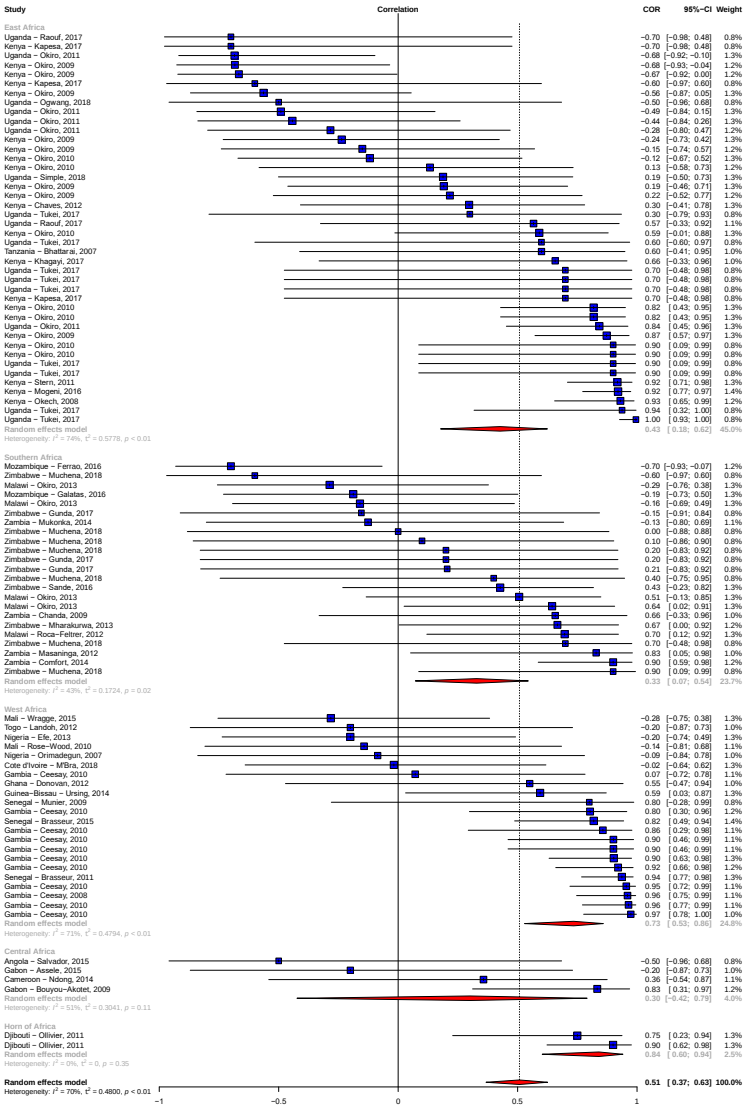


Figure 2.8: Forest plot of ordered correlation between empirically recorded clinical incidence/test positivity rate of *P. falciparum* and MAP modelled predictions of clinical malaria disease incidence stratified by African region. See the legend in Figure 2.3 for symbol representations

Although surveillance data on malaria cases recorded by health facilities were used, such data are not yet considered sufficiently reliable to track change in endemic countries in Africa [WHO, 2019a]. This stems from varying clinical definitions of malaria between sites, changing case definitions, changes in healthcare access and treatment seeking behaviour, changes in diagnostic practice, and reporting procedures or completeness

within health systems which could have potentially affected the trends of malaria burden observed [WHO, 2019a] (Section 1.7.2). As a sensitivity analysis, the effect of the method of diagnosis on the overall correlation was examined. The overall correlation among studies with parasitological confirmation was higher compared to studies with unclear methods of malaria diagnosis (Figure 2.9). Nevertheless, even among those with documented parasitological confirmation, 41% (29/70) of the sites had *rho* <0.5. While not all parasitologically diagnosed fevers are attributable to malaria [Dalrymple et al., 2017], both coincidental infection and attributable fever may act as a valuable guide of malaria transmission. For example, in Chimoi municipality, Mozambique, the weak correlation was maintained (*rho* = -0.6) when the analysis was restricted to the years when diagnostic test was conducted indicating that the negative correlation was not an artefact of changes in diagnostic practice. The role of other factors on the impact of observed trends could not be evaluated as most of the articles did not report on all the required information. However, this review was limited to data published in peer review journals with the assumption that data quality was examined during the peer review process.

A leading premise for the development and implementation of malaria risk models was to provide international agencies with a high-level view of changing malaria trends enabling priority setting. International agencies and the public health community remain fixated on single point estimates generated from these mathematical models. Agencies do not consider the range of predictions reported with these estimates. This is a major concern to malaria control efforts as there are reports that show significant inconsistencies in modelled malaria indicators compared to empirical observations [Lynch et al., 2012; White et al., 2012; WHO, 2018d]. This is further highlighted by the heterogeneity observed in this review. These modelled predictions were less accurate in sites where stalling in progress or resurgence of malaria burden was empirically observed. Possible explanations for the

inadequacies in the modelled estimates include interpolating and extrapolating relatively sparse data; use of multiple assumptions around key determinants being used in the models; using different case definitions; relying on covariates to impute data where direct observations are lacking; and failing to adequately capture the parasite prevalence-to-incidence relationship may lead to an exaggerated sense of certainty in the predicted data (Section 1.9). Additionally, the MAP model is less reliable in capturing recent trends as there is a lag for inputting contemporary data into the model

At broad regional scales, these models may offer some guide to the overall temporal trends but may have limited usefulness at local scales, necessary for national malaria control programmes to define sub-national strategies and progress. In addition, the threat of malaria resurgence continues to be a concern [Pascual et al., 2006; Hamel et al., 2011; Hashizume et al., 2012; Ursing et al., 2014; Raouf et al., 2017; Ogwang et al., 2018; Alonso & Noor, 2017], yet these predictive models are unable to detect subtle changes in malaria transmission dynamics. Models provide a broad picture of changing global disease burden but cannot replace empirical data, particularly where fine-grained precision is required.

Empirical reporting of malaria indicators should be a vital component of national control programs, and now forms a central pillar of the GTS for malaria [WHO, 2015] (Section 1.1). Improvements in routine data capture platforms [Braa & Sahay, 2017; Alegana et al., 2020], fever parasitological testing rates [WHO, 2012b], and geo-spatial techniques to interpreting routine data [Alegana et al., 2013; Bennett et al., 2014] has improved data availability in Africa [WHO, 2019a]. Approaches that facilitate individual national malaria control programs to analyse and report malaria incidence estimates relevant to their control that are accepted as their own, rather than the global estimated, needs to be

adopted. Given the emphasis on disaggregated statistics, investment in tools that measure local malaria transmission, and infrastructure that support routine reporting systems are urgently needed. In this review, assembled data from published literature was patchy and was disproportionately from sites with research investment. Despite two decades of substantive investment in malaria control in Africa, only 67 published studies on the changing burden of malaria over this period were identified. In many countries, routine data remain imperfect, is often unpublished, and hence modelling will still be required unless further investments are made in surveillance capacity. Models are valuable in making predictions and generating hypotheses, it is essential that commensurate investments are made in surveillance data to support and test these predictions. Another option is to develop sentinel hospitals to validate and use alongside current models of disease burden. While there are factors that might impact the definition of a malaria case, temporal trends in hospitalized malaria cases may serve as a valuable barometer of community trends in disease burden and may have value more broadly than just in malaria [English et al., 2018].

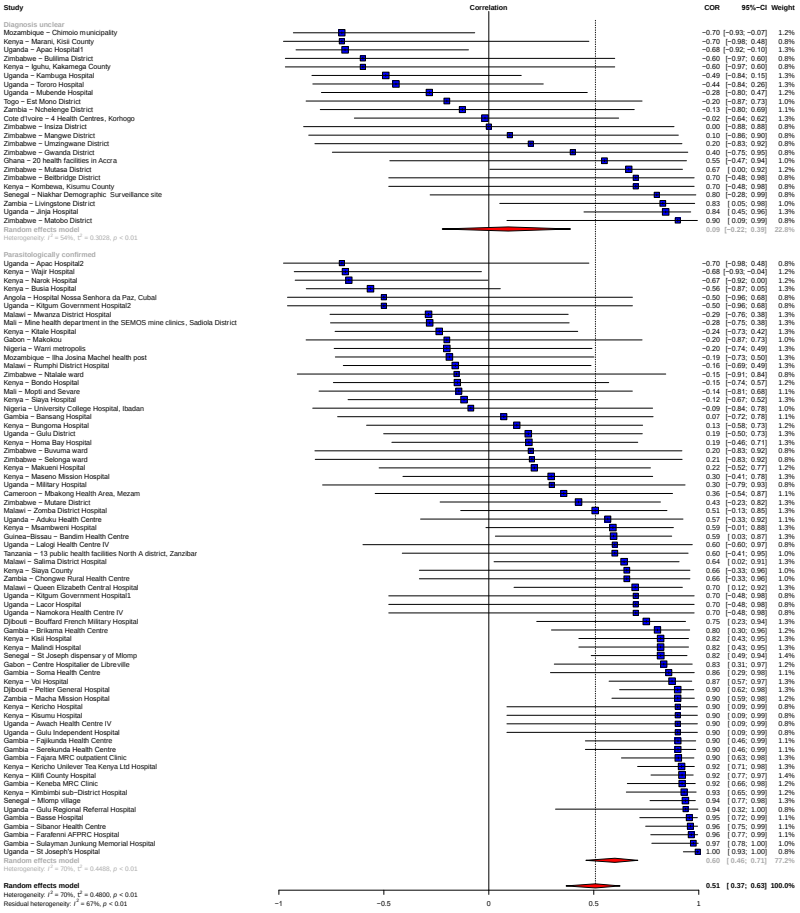


Figure 2.9: Forest plot of ordered correlation between empirically recorded clinical incidence/test positivity rate of *P. falciparum* and MAP modelled predictions of clinical malaria disease incidence stratified by method of diagnosis. See the legend in Figure 2.3 for symbol representations

2.5.1 Caveats

This review had some limitations. Some articles did not report on all the required information. For example, 33% of the articles included in this review had a high risk of bias due to the inherent methodological insufficiencies in the published articles. The critical appraisal tool used in this review was based on a scale in which various components of the quality were scored and it is possible that it included fewer items that were critical in maintaining internal validity. In addition, some studies had five years' worth of data which might have led to large uncertainty in the correlation. There is limited published literature

on trends of malaria risk in certain regions, particularly in Central Africa. The studies reported in this review represent just 24 of the 45 countries reported to be endemic for malaria in WHO African region. Although there was no evidence of publication bias, there are limitations of using published literature to validate the modelled prediction. For instance, bias might be introduced if publication of data that suggest malaria burden is worsening to encourage further investment in malaria control or data that reflects a decline to justify investment are favoured. More importantly, the use of incidence or number of cases could have led to over-or under-estimation of malaria burden since passive surveillance can rarely be conducted with certainty regarding the population accessing care at any specific facility. Hence, variations in the population access to a local facility, behavioural changes or policy changes may lead to artefactual trends in malaria in the absence of actual variation in transmission.

2.6 Conclusion

In many locations, both local surveillance data and modelled estimates showed declines in malaria burden and hence similar trends. However, there was spatial heterogeneity, and some areas of Africa may have stable case numbers or upward trends. In these areas, there was a weak association between individual surveillance datasets and the modelled predictions. At broad regional scales, models may offer some guide on the overall trends in disease burden but have reduced predictive accuracy at local scales. The paucity of high quality, temporal clinical data in Africa must be redressed, to avoid a continued dependence on models or to help train future models. A public health priority should be high quality, temporally and spatially dense clinical data in Africa to empower national malaria control programmes and to strengthen both empiric reporting and modelled predictions.

Chapter 3 : The age-specific relationship between malaria infection, facility-based fever test positivity rate, malaria admission, severe disease, and mortality on the Kenyan Coast

3.1 Introduction

The components of malaria surveillance, as articulated in one of the first textbooks on malaria, emphasized the importance of defining infection and morbidity among all age groups, enabling a complete understanding of risks within a community [Boyd, 1949]. Models of disease burden are based on old data (Section 1.9.1.2-1.9.1.3) that rarely consider older age groups leading to lack of contemporary understanding of the pathways from infection to death to improve parameters used in disease burden modelling (Sections 1.5 and 1.10). The present chapter presents a detailed epidemiological understanding of parasite prevalence, the incidence of fevers associated with infection, severe hospitalized disease and mortality among a population aged older than 6 months on the Kenyan coast to better define patterns of malaria infection to death, notably among adult populations where information in SSA remains sparse (Section 1.4). The Chapter begins with a broader national context (Section 3.2), Kilifi County (Section 3.3) and the specific study area (Section 3.4.1).

3.2 Kenyan context

3.2.1 Geography, population, and administration

Kenya is situated in East Africa and lies on the equator. It encompasses Great Rift Valley and extends from Lake Turkana to Lake Victoria and further south-east to the Indian Ocean (Figure 3.1a). A new constitution was adopted in August 2010 that decentralized policy setting, financing, and health to 47 county governments (Figure 3.1a).

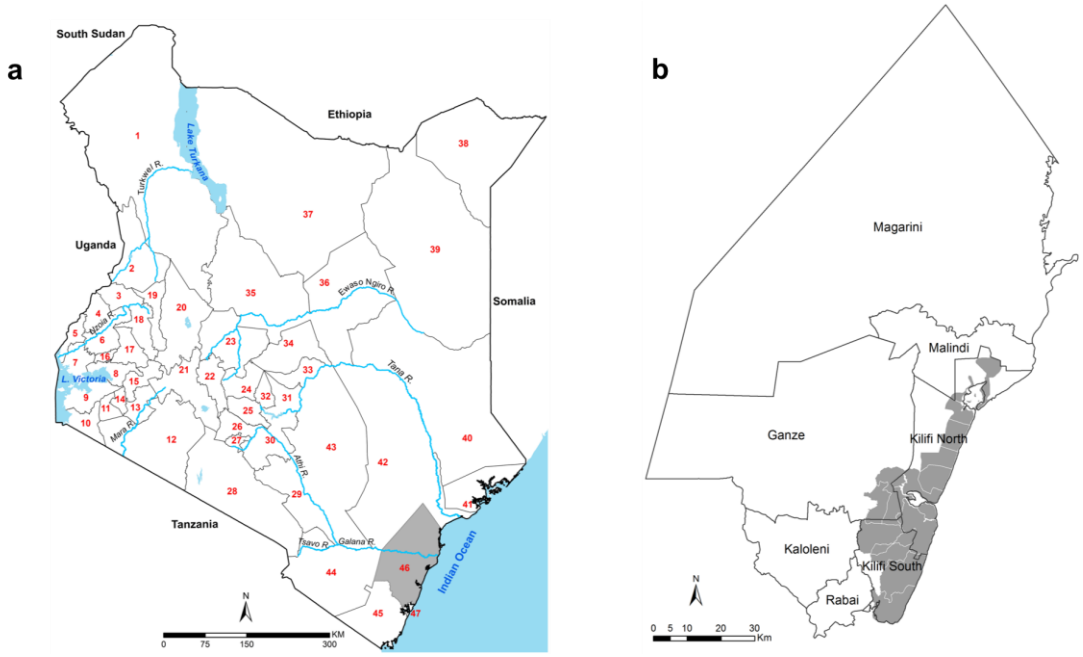


Figure 3.1: Map of Kenya, Kilifi county and Kilifi health and demographic surveillance area

Legend: (a) Kenya's 47 counties shown as dark lines with the extents of major rivers and lakes (light blue). Turkana (1), West Pokot (2), Trans Nzoia (3), Bungoma (4), Busia (5), Kakamega (6), Siaya (7), Kisumu (8), Homa Bay (9), Migori (10), Kisii (11), Narok (12), Bomet (13), Nyamira (14), Kericho (15), Vihiga (16), Nandi (17), Uasin Gishu (18), Elgeyo Marakwet (19), Baringo (20), Nakuru (21), Nyandarua (22), Laikipia (23), Nyeri (24), Murang'a (25), Kiambu (26), Nairobi (27), Kajiado (28), Makueni (29), Machakos (30), Embu (31), Kirinyaga (32), Tharaka Nithi (33), Meru (34), Samburu (35), Isiolo (36), Marsabit (37), Mandera (38), Wajir (39), Garissa (40), Lamu (41), Tana River (42), Kitui (43), Taita Taveta (44), Kwale (45), Kilifi (46) (highlighted in gray), Mombasa (47).

(b) Kilifi's county seven sub-counties shown as dark lines and the situation of Kilifi health and demographic surveillance area (highlighted in gray).

Health service delivery was formally transferred to the counties in August 2013. Health services in Kenya are integrated and delivered through a four-tier system, starting at the community level (tier 1), and through a hierarchy, to the national referral hospitals managed by the government (tier 4). Tier 2 comprises primary referrals i.e. dispensaries and health centres while tier 3 consists of primary and secondary care hospitals managed by the county governments [MoH, 2017].

3.2.2 Epidemiology of malaria

Plasmodium falciparum is responsible for the vast majority (96%) of malaria infections in Kenya [MoH, 2016]. *P. malariae and P. ovale* are relatively rare causing 4% of the infections [MoH, 2016]. *P. vivax* infections have been described in Kenya among Duffy negative populations [Ryan et al., 2006]. The most important mosquito vectors in Kenya responsible for malaria transmission are *An. gambiae s.s, An. arabiensis and An. funestus. s.s* [Bayoh et al., 2010; Okara et al., 2010; Kyalo et al., 2017]. Secondary vectors including *An. merus*, *An. rivulorum*, *An. leesoni*, *An. parensis*, *An. vaneedeni*, *An. nili s.l*, *An. moucheti s.l*, *An. pharoensis*, *An. marshalli*, *An. squamous*, *An. rufipes*, *An. coustani s.l and An. ziemanni* contribute to transmission in localized areas of the country [Okara et al., 2010; Kyalo et al., 2017]. The relative contributions of primary and secondary vectors vary considerably across the country [Okara et al., 2010].

There has been a decline in *An. gambiae s.s* attributed to the wide-scale use of insecticide-treated nets [Bayoh et al., 2010; Mwangangi et al., 2013]. Consequently, *An. arabiensis* which has a broader range of feeding times and biting behaviour has replaced *An. gambiae s.s* as the dominant vector within the *An. gambiae* complex [Bayoh et al., 2010; Mwangangi et al., 2013]. While some vectors have recently been found biting early in the evening and outdoors, >90% of bites still occur indoors hence, IRS and LLINs are still appropriate tools for malaria vector control [Bayoh et al., 2014; Kamau et al, 2017a]. In Western Kenya, the re-emergence of *An. funestus* has been described following long-term use of LLINs [McCann et al., 2014].

Malaria risk across Kenya has always been described as very heterogeneous, based on its varied climate and ecology [Butler et al., 1959; Omumbo et al., 1998; Snow et al.,

1998c; Noor et al., 2009b; Macharia et al., 2018]. The distribution of malaria risk across Kenya has most recently been modelled from empirical survey data on community-based *P. falciparum* parasite prevalence (*Pf*PR) from 1990-2015 [Macharia et al., 2018]. These data were modelled within a Bayesian hierarchical space-time model implemented through an adapted Stochastic Partial Differential Equations (SPDE) approach using Integrated Nested Laplace Approximations (INLA) to provide 1×1 km gridded surfaces of malaria prevalence for every year since 1990 [Macharia et al., 2018]. The model did not adjust for environmental or intervention covariates because of the abundance of empirical input data and the authors regarded the *Pf*PR estimates as products of these covariates in time and space [Macharia et al., 2018]. As such this model differed from those used by MAP [Bhatt et al., 2015b; Weiss et al., 2019] (Section 1.9.1.1).

In Kenya, the national estimated mean *P. falciparum* malaria infection in children aged 2-10 years reduced from 17% in 2000 to 3% in 2015 (Figure 3.2) [Macharia et al., 2018]. The most significant reduction occurred between 2003 and 2007 but, the decline was not uniform across the country. In the period between 2013 and 2015, 23/47 counties had an average parasite prevalence of <1%, however, in four counties prevalence remained ≥30% (Busia, Homabay, Migori, Siaya; in Figure 3.1a) [Macharia et al., 2018]. By 2015, there were no areas with parasite prevalence >50%. The largest reductions were observed in the lake and coastal endemic regions where malaria transmission is highest.

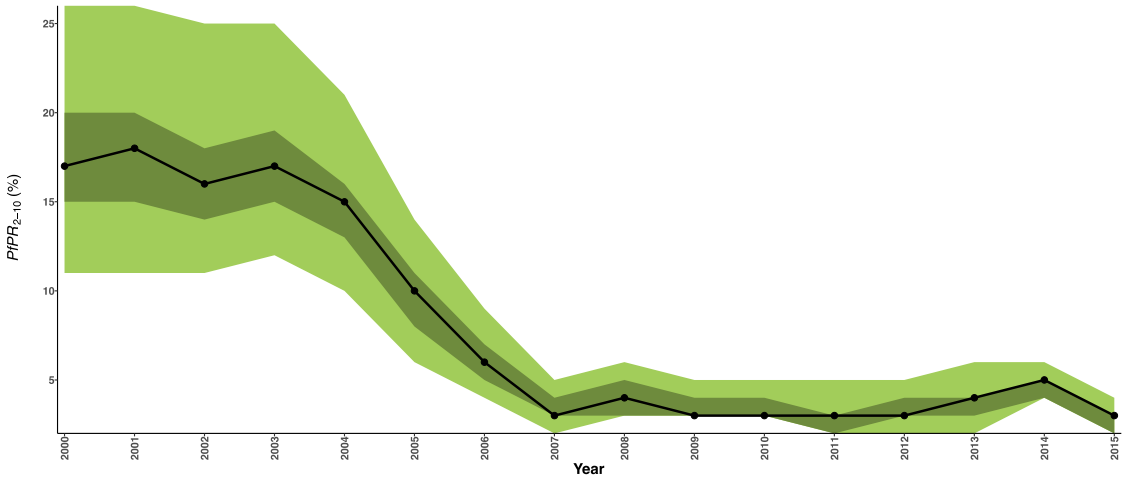


Figure 3.2: The national annual mean (black line), 2.5–97.5% (light green boundaries) interquartile credibility range (ICR) and 25–75% ICR (dark green boundaries) of the posterior *P. falciparum* parasite rate in children aged 2 – 10 years (*Pf*$PR_{2–10}$) predictions in Kenya between 2000 and 2015 [Macharia et al., 2018]

In Kenya, data on the changing landscape of the malaria burden comes from a variety of sources. The most ubiquitous data on changing risk and disease impact comes from temporally and spatially imputed community-based parasite prevalence models [Snow et al., 2015a; Macharia et al., 2018]. In addition, three further sources are available i) selected time-series analysis of hospital data [Okiro et al., 2007; Okiro et al., 2009a; Okiro et al., 2010; O'Meara et al., 2008a; O'Meara et al., 2008b; Stern et al., 2011; Chaves et al., 2012; Mogeni et al., 2016; Kapesa et al., 2017; Njuguna et al., 2019: Githeko et al., 2018]; ii) mortality among health and demographic survey sites in western Kenya [Desai et al., 2014; Khagayi et al., 2017; Khagayi et al., 2019] and the coast [Deribew et al., 2016]; and iii) modelling impact on all-cause under-five mortality using the LiST model (Section 1.9.3) [Kenya impact evaluation team, 2016] or linear probability regression models [Demombynes & Trommlerova, 2016]. The combined evidence suggests that the rising and declining trends in prevalence, hospitalisation and under-five mortality can be attributed to failing monotherapies, El Niño anomalies in rainfall during the 1990s, increasing use of ITN/LLINs, and the use of IRS. Despite evidence that shows that the risk

and epidemiology of malaria in Kenya has changed over the last 15 years, the country is still in the control phase of the malaria elimination continuum (Section 1.1) [WHO, 2015].

3.2.3 Current national malaria strategy

The current ambition of Kenya's malaria strategic framework (2019-2023) is to reduce malaria incidence and malaria deaths by at least 75% of the 2016 levels by 2023 [NMCP, 2019a]. To achieve this goal, six objectives were outlined which include: (i) to protect 100% of people living in malaria risk areas by appropriate malaria preventive interventions; (ii) to manage 100% of suspected malaria cases according to the Kenya malaria treatment guidelines; (iii) to establish systems for malaria elimination by introducing a case-based investigation in selected counties especially those in low-risk areas; (iv) to increase utilization of appropriate malaria interventions in Kenya to at least 80% by addressing barriers; (v) to strengthen malaria surveillance and use of information by reinforcing routine health information system, monitoring and evaluating programme performance, and using evidence to inform the NMCP; and (vi) to provide a conducive environment and the resources necessary to optimally implement Kenya's malaria strategic plan by strengthening leadership, management, and coordination of efforts at all levels [NMCP, 2019a].

Strengthening surveillance (objective v) is in line with the WHO's GTS to transform surveillance into a central pillar of future control in SSA (Section 1.1) [WHO, 2015]. In line with this, the NMCP revised its Monitoring and Evaluation (M&E) Plan in 2019 [NMCP, 2019b]. The M&E framework follows the input-process-outputs-outcome-impact logic model. The M&E framework is heavily weighted toward input indicators and resources available developed from national household surveys (for example DHS and MIS), routine health information system (HIS) data or reports implemented by various government

institutions in collaboration with international partners. Impact measures include the reduction of hospital-based malaria deaths and overall case incidence as defined by routine data. Despite a broad ambition of reducing malaria mortality by 75% of the 2016 levels by 2023 [NMCP, 2019a], it seems unlikely that relying on hospital-based deaths will meet the needs of the programme. In addition, the M&E plan mentions the measurement of annual reductions in the EIR, but this is a complex measure, requiring standardised methods (Table 1.2) to implement at a national scale. The current M&E strategic plan lacks indicators related to the changing malaria transmission intensity as measured in communities (PR) or facilities (TPR). This oversight means that there is no plan to continuously monitor the changing parasite transmission epidemiology, as developed over the last decade [Noor et al., 2009b; Macharia et al., 2018], that has been used previously to guide the re-orientation of sub-national ambitions and interventions for sustained control and/or elimination.

3.2.4 Malaria control measures

The main tools for malaria control in Kenya represent those supported by the WHO's GTS (Section 1.1) [WHO, 2015]. Prevention is based on reducing vector-human contact, stratified sub-nationally, with LLINs and in specific areas IRS or county-specific targeting of IPTp. Presently, LLINs are distributed routinely, and free, through maternal and child health (MCH) or expanded programme on immunization (EPI) clinics to all pregnant women and young children, and by mass catch-up campaigns in 16 counties around Lake Victoria and along the endemic counties of the Kenyan coast [Noor et al., 2007; Fegan et al., 2007; NMCP, 2019b]. The last mass campaigns distributed 15 million LLINs between 2017 and 2018. There has been no national Malaria Indicator Survey (MIS) in Kenya since 2015. The MIS in 2015 reported 73% of children in western Kenya used an LLIN the night before the survey and 72% in coastal Kenya [NMCP, 2015]. In 2005, coverage of IRS

began in 3 endemic counties (Migori, Homa Bay, and part of Kisumu) and 12 epidemic-prone counties of western highland. However, IRS activities did not occur between 2012 and 2016 following high resistance to pyrethroids [Kawada et al., 2011; Ondeto et al., 2017]. Since 2017, IRS has only been undertaken in Homa Bay and Migori Counties, using annual rounds of Actellic 300 CS and SumiShield 50 WG [Gimnig et al., 2016; Abong'o et al., 2020]. In September 2019, half of the sub-counties in western Kenya were randomly allocated to receive the RTS,S/AS01 (RTS,S) vaccine and form part of an ongoing evaluation of safety and effectiveness [WHO, 2016; WHO, 2019b]. Larviciding was undertaken experimentally in Mbita and Homa Bay county for 52-months between July 2001 and September 2005 [Fillinger et al., 2006].

3.2.5 Drug use and efficacy

After increasing therapeutic failure of Sulphadoxine-Pyrimethamine (SP) by 2003, the treatment policy changed recommending the use of Artemether-Lumefantrine (AL) as first-line malaria therapy in 2004 [Amin et al., 2007]. However, SP was still in use until the beginning of 2007 since drug supply, revised guidelines and training were not implemented until the end of 2006 [Amin et al., 2007]. The treatment policy further endorsed AL in the second and third trimester of pregnancy. IPTp, recommends SP as a preventive measure of malaria in pregnant women living in areas of moderate to high malaria transmission (western and coastal areas of Kenya). For pre-referral and severe malaria treatment, parenteral artesunate is recommended while quinine is the recommended treatment in the first trimester of pregnancy [MoPHS, 2010].

3.2.6 Malaria testing and treatment landscape

In Kenya, the shift from presumptive treatment of fever to a universal parasitological diagnosis of all suspected cases, i.e. "test" and "treat" policy, became the malaria case-

management standard in 2010 [MoPHS, 2010]. It is recommended that only patients who test positive should be treated for malaria [MoPHS, 2010]. The increasing availability of quality-assured and cheap rapid diagnostic tests aided the implementation of the T3 policy especially in remote areas lacking microscopic services [Zurovac et al., 2014; Amboko et al., 2020]. As systems continue to improve, for example owing to greater use of RDTs in health facilities, the quality of malaria case-management is increasing [Zurovac et al., 2014; Githinji et al., 2017; Amboko et al., 2020]. Among screened public health facilities in malaria-endemic regions in Kenya, the capacity of malaria blood testing was estimated at 80% [Musuva et al., 2017]. However, during the last MIS in 2015, only 39% of children who had a fever in the two weeks preceding a large household malaria survey reported having been tested for malaria [NMCP, 2015].

3.2.7 Coverage of routine reporting of malaria

Reliable data are essential for the NMCP to make an informed decision on resource allocations, as reflected in the objectives of the latest national strategic plan (Section 3.2.3). The M&E plan puts significant emphasis on the use of routine data from the District Health Information System (DHIS2), replacing any reference to community-based measures of malaria risk or burden. Kenya adopted the DHIS2 in 2011 [Manya et al., 2012; Karuri et al., 2014]. In 2016, previous fragments of reporting, i.e. malaria commodities, laboratory reporting, and the Integrated Disease Surveillance and Response (IDSR) system, were integrated into the DHIS2 to serve as a single-harmonized platform. DHIS2 offers a platform where all health and service delivery data, including malaria testing and positivity, are captured. There are 31 malaria indicators reported in DHIS2 which include the number of clinical and confirmed malaria cases, AL treatments, IPTp with SP doses, long-lasting insecticidal bed nets distributed, and malaria tests performed. The data are aggregated over health facilities, age groups (<5 years and >5 years) and

time, no information is currently available on precise age or pregnancy status [Githinji et al., 2016].

Every month, data recorded on paper-based registers are collated, summarized into monthly reporting forms in each health facility and submitted to the sub-county health records offices for entry into DHIS2. These data can be aggregated and reported at all levels of the health system (i.e. facility, sub-county, county, and national levels), by reporting forms, or by selected indicators (e.g. the number of pregnant women who received IPTp). Although DHIS2 data are increasingly being used to provide bulletins for sub-national malaria risk in Kenya [Malaria surveillance bulletin, 2014], the national completeness and coverage of these data across the public health system remain variable [Dehnavieh et al., 2019; Githinji et al., 2017; Maina et al., 2017].

3.3 Kilifi County

3.3.1 Physical location and features

The focus of the thesis is a study area within Kilifi county, one of the six counties located in the coastal region of Kenya. The county lies between latitude 2° and 4° South and longitude 39° and 40° East. It borders the Indian Ocean to the east, Mombasa, and Kwale to the south, Taita-Taveta to the west and Tana River county to the north (Figure 3.1a). The county covers an area of 12,245 km^2 and is sub-divided into seven sub-counties (Figure 3.1b), 54 locations, and 165 sub-locations.

The county has four topographic zones with diverse potential land use. This includes the narrow belt which forms the coastal plains, which extends 20 km inwards and is 30 m above the sea level. The zone is composed of sediments that support marine and agriculture. The coastal plain is made of savannah type vegetation, dry thorn bushes,

dense forests, seasonal swamps and several plantations interspersed with uncultivated land. There is the foot plateau that falls between 60 m and 150 m above the sea level. The zone is made up of clay and sandstone and is covered by stunted shrubs and grassland. The third zone is the coastal range that has fertile soil. The fourth zone occupies the arid and semi-arid areas suitable for ranching known as the Nyika plateau [CIDP, 2018].

3.3.2 Demography

The county's population was estimated to be 1,453,787 in 2019 with 47% of the population aged <15 years [KNBS, 2019]. Most of the county's population live in rural areas (63.2%) [CIDP, 2018]. The people of Kilifi county are predominately Mijikenda consisting of nine sub-tribes namely: the Giriama, Chonyi, Rabai, Kambe, Kauma, Ribe, Digo, Duruma, and Jibana, there are a small number of other ethnic groups. The Mijikenda are said to have originated from the southern tip of Somalia and settled in and around a network of 'kayas' (forested lands) and subsequently migrated from the hinterland to the current coastal settlements [Parkin, 1991].

3.3.3 Climate

The county has a bimodal rainfall pattern with average annual precipitation ranging from 300 mm to 1,300 mm. The major influence of Kenya's coast weather is the inter-tropical convergence zone of the north-east and south-east trade winds. The hot northeast monsoon (*kaskazi*) from the Persian Gulf occurs from November to March/April and includes the short rains, variably between October and December. The moist monsoon blowing in from the southeast (*kusi*) occurs from April/May to October leading to the heaviest rain, referred to as the long rains (April, May, and June) [Foeken, 1994]. The annual temperature ranges between 21°C and 34°C. However, rainfall is the most

important weather variable that drives the intra-inter-annual periodicity in malaria transmission along the coast, which followings the bimodal seasonal pattern associated with the rainy seasons [Kurui & Snow, 2016].

3.3.4 The changing epidemiology of malaria in Kilifi since 1990

Kilifi has undergone marked changes in malaria vector dynamics [Mwangangi et al., 2013], transmission intensity [Snow et al., 2015a; Macharia et al., 2018; Muthui et al., 2019] malaria hospital burden, disease phenotype [O'Meara et al., 2008a; O'Meara et al., 2008b; Okiro et al., 2009b; Mogeni et al., 2016; Njuguna et al., 2019], and child survival [Deribew et al., 2016; Macharia et al., 2019] over the last 20 years.

There has been a reduction in the abundance of mosquito vectors [Mwangangi et al., 2013]. A sibling species switch, from *An. gambiae. s.s* to *An. arabiensis,* occurred during the period of LLINs scale-up [Mwangangi et al., 2013; Kamau et al., 2017a]. Additionally, the *An. funestus* group has been shown to be abundant in the dry season compared to the wet season [Mwangangi et al., 2013]. Studies have reported a low rate of pyrethroid resistance among *An. arabiensis* and *An. gambiae.s.s* but, a high rate of resistance among *An. funestus.s.s* [Ondeto et al., 2017]. Over the last 20 years, the *P. falciparum* sporozoite rate has significantly declined, with the lowest rates being observed in 2007 (0.19%) and 2008 (0.34%) [Mwangangi et al., 2013], however, in 2016 a higher sporozoite rate (3.3%) was reported [Kamau et al., 2017a].

Concurrent parasite rates and gametocyte carriage studies suggest a marked reduction in transmission intensity [Snow et al., 2015a; Macharia et al., 2018; Muthui et al., 2019]. In the early 1990s, the intensity of malaria transmission rose, and peaked in 1998, before declining to low levels in 2007 (Figure 3.3) [Snow et al., 2015a; Macharia et al., 2018].

During this period of increase, massive therapeutic failure of chloroquine was reported in 1987 [Brandling-Bennett et al., 1988; Shretta et al., 2000] and SP in 2003 [Mberu et al., 2000; EANMAT, 2003]. The variation of parasite prevalence was however minimal after 2007 when highly effective artemisinin combination therapy (ACT) was introduced; parasite prevalence in this period ranged between 5% and 2% except in 2014 when parasite prevalence was 11% (Figure 3.3). Also, the level of gametocytaemia fell in the community as the parasite prevalence fell and was associated with the treatment of acute febrile malaria cases with ACTs [Muthui et al., 2019].

Previous studies in Kilifi evaluated the role of transmission intensity, age and asymptomatic parasitaemia in determining the risk of developing febrile malaria [O'Meara et al., 2008b; Wamae et al., 2019]. In low-moderate transmission areas, asymptomatic parasitaemia was associated with an increased risk of febrile malaria in children of all ages up to 15 years [Wamae et al., 2019].

The burden of malaria, requiring hospital admission, among children has been shown to be spatially and temporarily heterogeneous [Snow et al., 1993a; Mogeni et al., 2016; Njuguna et al., 2019]. The proportion of hospital admissions with malaria infection peaked in 1999 (61%) before declining to as low as 7% in 2009 and a resurgence was reported thereafter [Mogeni et al., 2016]; a similar trend was observed among severe malaria cases (Figure 3.3) [Njuguna et al., 2019]. A recent immunological study also reported a reduction in malaria-specific antibody titres as transmission declines [Mugyenyi et al., 2017].

In the 1990s, severe malaria largely affected children <5 years (88%) but in 2015, 44% of the children with severe malaria were above 5 years of age. Before 2004, the ratio of children with severe malaria anaemia to cerebral malaria changed from 2:1 to 2:3 after

2009 [O'Meara et al., 2008a; Njuguna et al., 2019]. Interestingly, these reductions occurred during a period of poor LLINs coverage and when SP treatment was failing. Although the landscape of LLINs use increased concurrently following the October 2006 mass campaign, the prevalence of malaria infection had begun declining before LLINs use reached 43% in 2010 [Snow et al., 2015a]. The temporal associations between declining transmission, with climatic variations, failing efficacy of treatments, or increasing effective intervention are complex and hard to disentangle [Snow et al., 2015a].

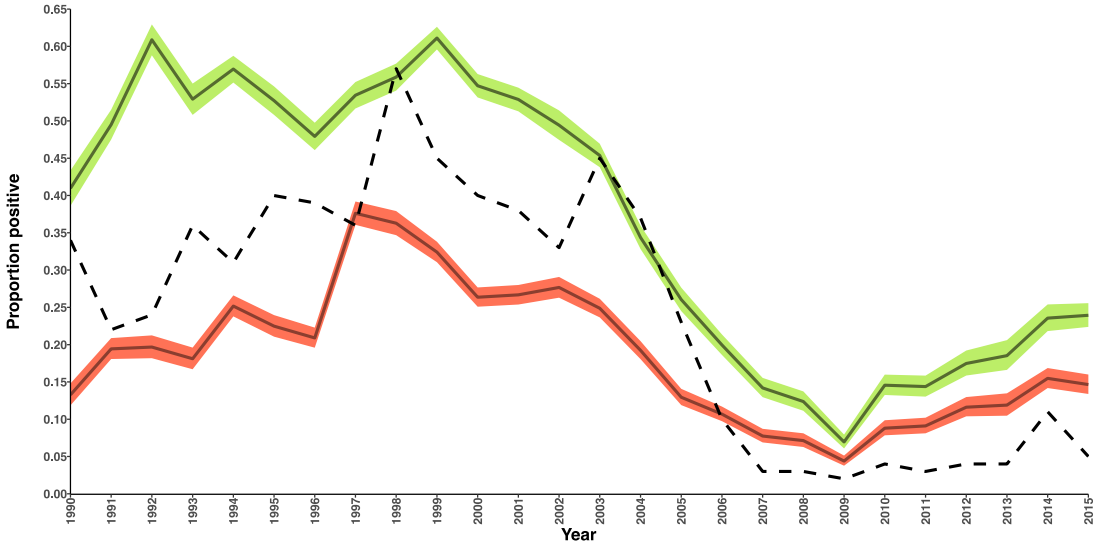


Figure 3.3: Temporal trend of malaria positive fraction, severe malaria and *P. falciparum* parasite rate in children aged 2 – 10 years (*Pf*$PR_{2–10}$) between 1990 and 2015. Malaria positive fraction (green line) with 95% confidence intervals (CI) (light green boundaries) [Mogeni et al., 2016]; severe malaria positive fraction (red line), 95% CI (light red boundaries) [Njuguna et al., 2019]; and annual mean of the posterior *Pf*$PR_{2–10}$ predictions (dashed line) [Macharia et al., 2018; Snow et al., 2015b]

Legend: Malaria positive fraction was defined as all acute admissions with malaria positive slides. Severe malaria was defined using the clinical criteria specified by the WHO [21] (i.e. any one of the following: (a) cerebral malaria (defined as Blantyre coma score of < 3), (b) severe malaria anaemia (defined as haemoglobin concentration < 5 g/dL), (c) respiratory distress (defined as deep breathing as assessed by a clinician), (d) prostration (defined as inability to stand in children who can usually stand, inability to sit in children who cannot usually stand but can sit, or inability to breastfeed in children who cannot usually sit or stand), (e) multiple convulsions (defined as two or more convulsions in the 24-h period prior to admission), (f) jaundice (defined clinically), (g) compensated shock (defined by age-specific increases in heart rate (in beats per minute (bpm) > 180 for children < 12 months of age; > 160 bpm for 12 months to 5 years of age; and > 140 bpm for children > 5 years of age) plus a capillary refill time of > 2 s), (h) decompensated shock (defined as systolic blood pressure < 50 mmHg), (i) kidney injury (defined according to age-specific pRIFLE criteria to calculate estimated glomerular filtration rates, using actual height and weight), (j) hypoglycaemia (defined as glucose < 2.2 mmol/l in accordance with WHO guidelines, although a threshold of 3 mmol/l was used for clinical management), (k) hyperparasitaemia (defined as parasite density > 250,000 parasites per µl).

3.3.5 County adaptation of national malaria strategy

Kilifi county has 291 health facilities (10 hospitals, 18 health centres, 143 dispensaries, and 120 clinics); 49% are government-sponsored, 46% are private, for-profit, and 5% are faith-based organizations [CIDP, 2018]. RDTs are used in lower-level facilities where malaria microscopy is not available. In the coast endemic region during the 2015 MIS, only 44% of children with fever in the 2 weeks preceding a large household malaria survey had a malaria diagnostic test done and only 18% received antimalarial treatment [NMCP, 2015]. In Kilifi county, IRS and larval control have not been undertaken since the 1960s, the mainstay of vector control has been ITN/LLIN since the first ITN trials in Kenya during the early 1990s [Nevill et al., 1996]. Between 2008 and 2015 LLINs use in 15 locations (Figure 3.1b- highlighted grey area) was reported at 62% and was associated with a 33% reduction in the incidence of malaria hospitalization among children aged <5 years [Kamau et al., 2017b]. The last free-mass LLIN distribution campaign was conducted in September 2017.

A study on the coverage of data recorded in DHIS2 shows very low reporting rates in the coast region; only 1% of the facilities reported data consistently between November 2015 and October 2016 [Maina et al., 2017]. Lack of reliable health data essential for planning forms the basis of this study. This study aims to assess what might be gained by improving testing rates, collecting more granular information on patient-level data and improving the coverage of routine data.

3.4 Material and methods

3.4.1 Surveillance area

In 1989, a partnership between the Kenya Medical Research Institute (KEMRI) and the

University of Oxford developed a linked paediatric clinical surveillance in Kilifi county hospital (KCH). A community-based census in an area north of Kilifi creek was also developed [Snow et al., 1994a; Snow et al., 1994b; Snow et al., 1998a] and this was subsequently used as a platform for a community-randomized controlled trial of ITN [Nevill et al., 1996]. In 2000, the principles of the demographic surveillance system were expanded to cover a wider geographic area, including south of Kilifi creek, that became the Kilifi health and demographic surveillance system (KHDSS). The system provides a platform for multiple, integrated hospital-community-based disease surveillance investigations [Scott et al., 2012].

The KHDSS research site (Figure 3.1b) covers an area of 891 km^2. It consists of 15 administrative locations subdivided into 186 enumeration zones (EZs) each with approximately 226 homesteads per EZ [Scott et al., 2012]. The EZ was the smallest population unit used in the 2019 Kenya national census [KNBS, 2019]. There are 61 geo-coded private and public health facilities offering outpatient general services in the area. The area is predominantly rural, with less than 20% of the population living in the urban area of Kilifi town. The KHDSS area has been mapped using Magellan (Magellan Navigation Inc., Santa Clara, CA) and e-Trex (Garmin Ltd., Olathe, KS) Geographic Positioning Systems technology, providing detailed information on topography, footpaths and roads, and human occupation of the area, including the geospatial coordinates (longitude and latitude) of all homesteads. In the northern area, Giriama is the largest group and in the southern area, the majority are from Chonyi ethnic group [CIPD, 2018].

Fieldworkers visit every participating homestead approximately three times a year to monitor births, deaths, and migration events. The area contains ~300,000 residents (unpublished data). The sex and age structure of the population varies within the KHDSS

area, with fewer men aged 20-50 years in the rural regions than in the semi-urban regions because of selective outmigration of this group to nearby towns in search of employment. Within the KHDSS area, the fertility rate (4.73), crude birth rate (34.7 per 1000 person-years of observation), population growth rate (2.79% per year), and proportion of the population younger than 15 years (49%) are similar to the rates across other areas of rural Kenya [Scott et al., 2012; KNBS, 2019]. However, in 2013 the under 5-mortality rate (13 per 1000 live births) [Deribew et al., 2016] was lower than the Kenyan national averages (54 per 1000 live births) (Figure 3.4) [Macharia et al., 2019].

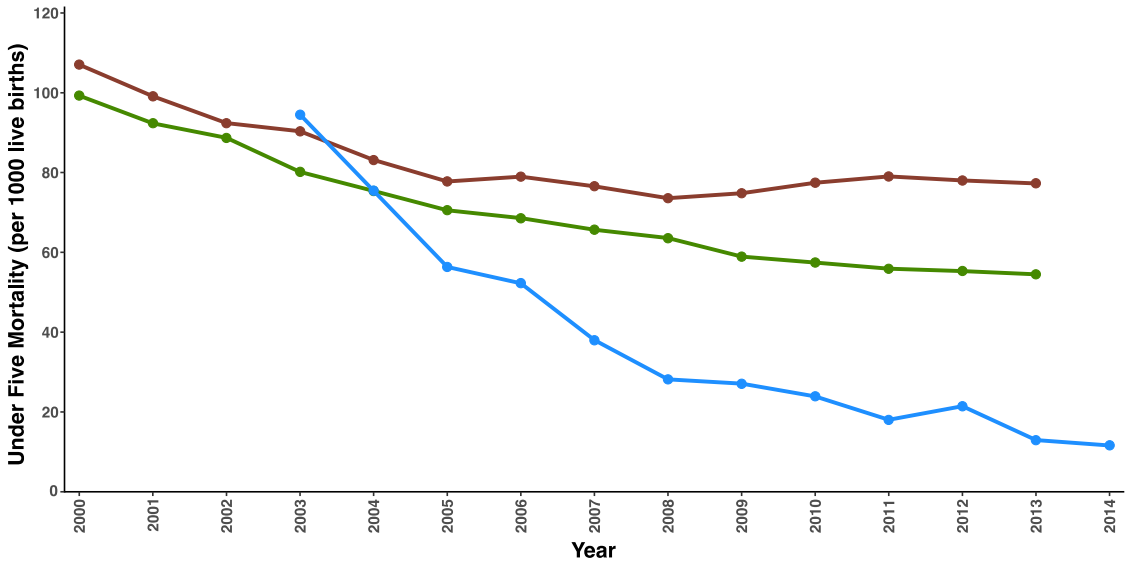


Figure 3.4: The mortality rate among children under-five years in Kenya. The national annual mean (green line), Kilifi county annual mean (red line), and KHDSS annual mean (blue line)

Legend: The national annual mean (green line) and Kilifi county annual mean (red line) of all cause under-five mortality per 1000 live births between 2000 and 2013 were computed using direct demographic methods [Macharia et al., 2019]. KHDSS annual mean (blue line) of all cause under-five mortality per 1000 live births between 2003 and 2014 was computed using collate longitudinal data in the KHDSS geographically defined population (Figure 3.1b- highlighted grey area) [Deribew et al., 2016]. A compilation of household surveys and population censuses with data on birth histories undertaken between 1989 and 2014 were used to understand spatio-temporal variation and progress towards a reduction in U5M between 2000 and 2013 using the demographic methods and a Bayesian spatio-temporal Gaussian model [Macharia et al., 2019]. Under-five mortality rates in the KHDSS sites were determined using number of under-five deaths (numerator) and live births (denominator) at any given year.

3.4.2 Selection of the current study area

Malaria in the KHDSS area is spatially heterogeneous [Mogeni et al., 2016]. There is ongoing active malaria surveillance in Ngerenya dispensary, north of KHDSS, with approximately 1 episode per 100 children per year being reported (unpublished data). Given that malaria transmission intensity north of KHDSS was very low, the study was conducted in the southern parts of the KHDSS, south of Kilifi creek (Figure 3.5).

The southern KHDSS consists of eight administrative locations, 17 sub-locations and 86 enumeration zones covering an area of 558 km^2 with a population of ~ 150,000 residents (Figure 3.5). Homesteads were clustered in small villages with farms located some distance from the homestead. Sisal plantations in the area are extensive along the national trunk road (Figure 3.5). The soil is predominantly red soil that is more fertile, and the land is hillier than in the north of KHDSS. Major farming activities among the rural communities include growing cassava, maize, millet, and beans for subsistence while cashew nut, mangoes, citrus, and coconuts are cash crops. There are two main types of housing, these are the Mijikenda and Swahili housing. The traditional Mijikenda housing mainly consists of framed poles and branches from top to bottom covered with grass. Mud is often used to support the upper structure while palm leaves often replace grass as the roofing material. The Swahili houses, on the other hand, are made of mud walls with coral stones occasionally mixed with mud and the roofs made of woven dry palm leaves.

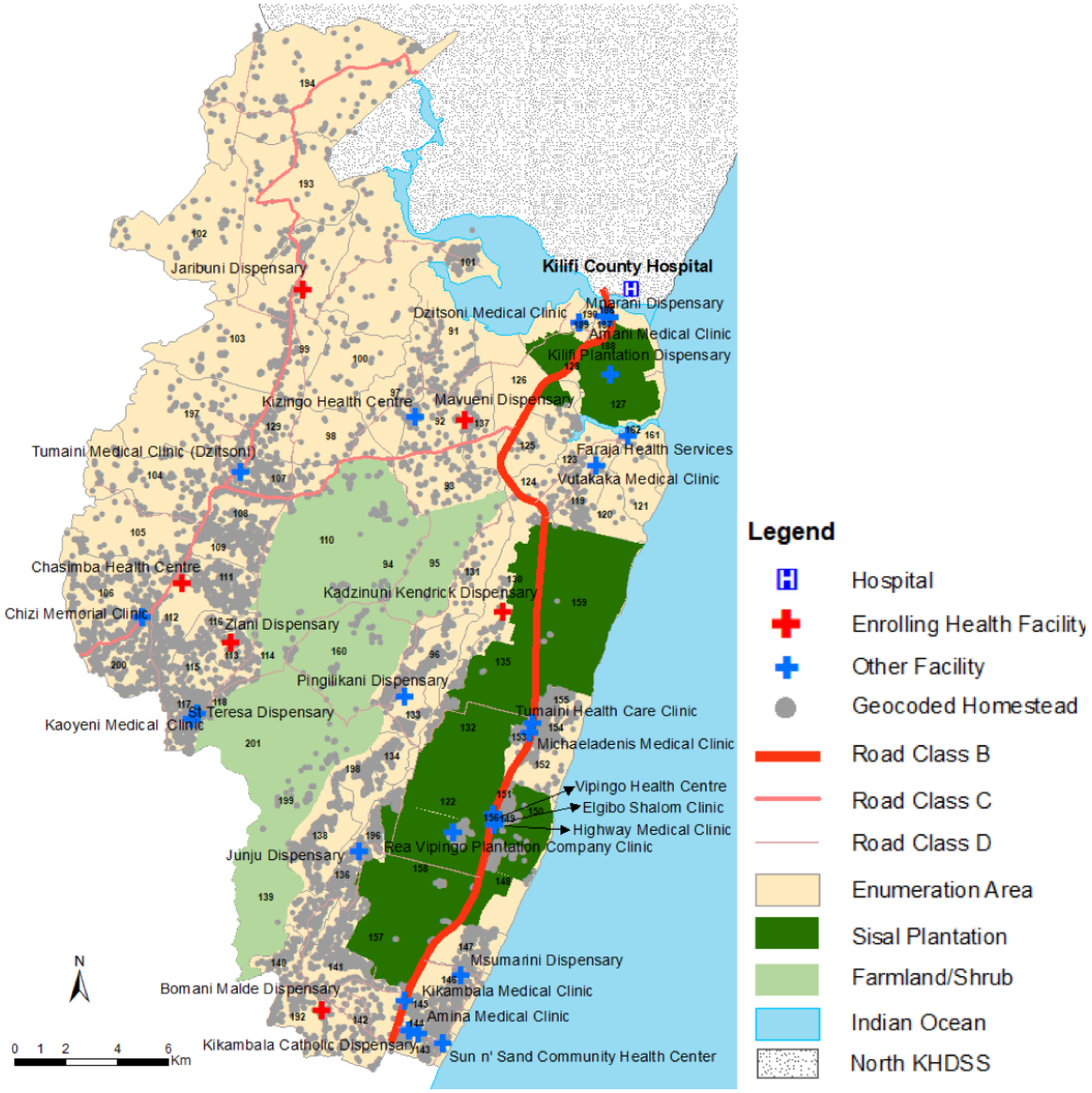


Figure 3.5: Location of 29 geo-coded health facilities south of KHDSS overlaid on the geocoded homesteads, location of the sisal plantation, farmlands or shrubs and the roads

Legend: Health facility where patients were enrolled are shown by the red crosses, blue cross are other health facilities in the area; Enumeration zones are the cream polygons; Road class means: B, National Trunk Road; C, Primary Roads; D, Secondary Roads.

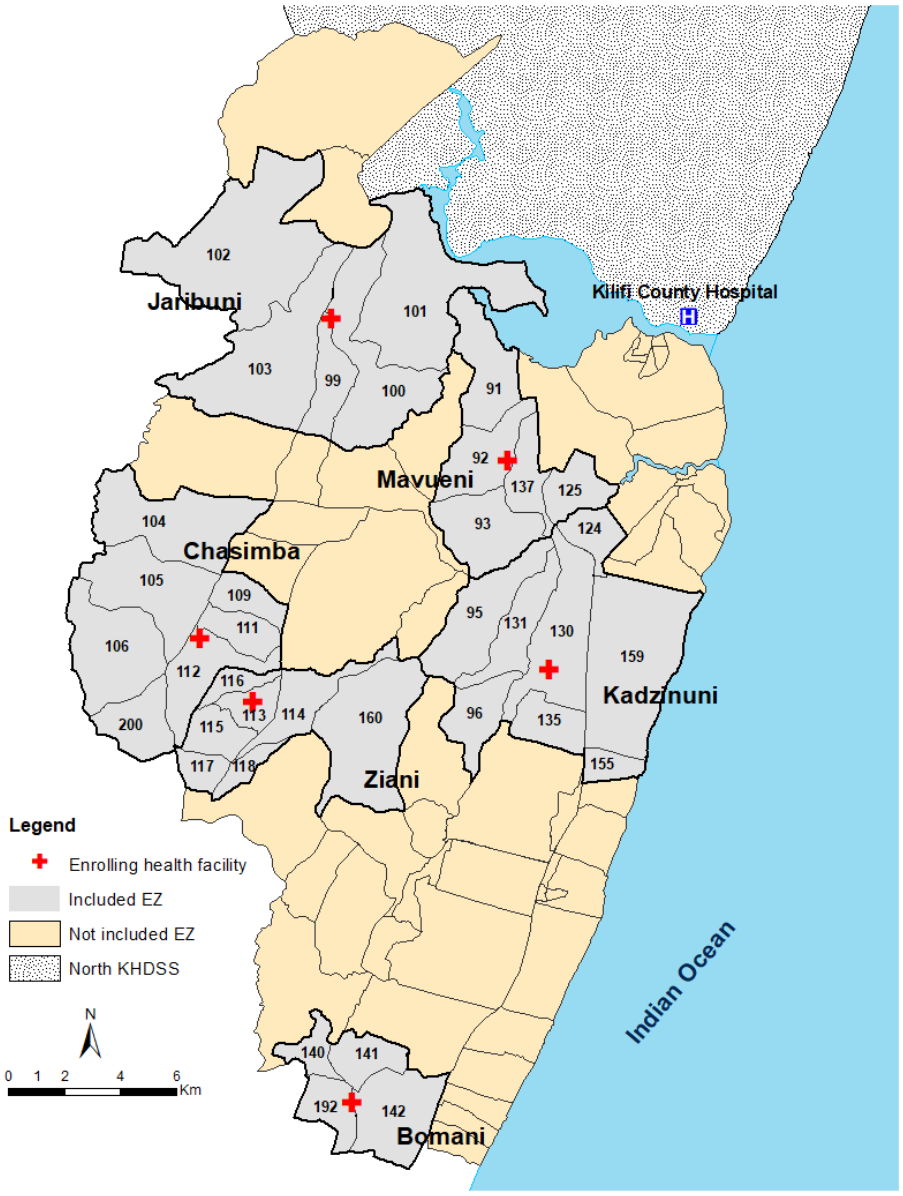


Figure 3.6: Enrolling health facilities and enumeration zones included in the study. Reproduced from Kamau et al., 2020, published CC-BY 4.0

Legend: The catchment area for the community surveys was defined as the EZs immediately surrounding health facilities that fell within a 2 km radius. The catchment areas were estimated as the boundary within which probability of attending the health facility was relatively high using the travel impedance by distance [Guagliardo, 2004].

This study first identified all health facilities (n=29) in the southern KHDSS. For facilities to be included in the present study, they had to fulfil the following criteria: (i) public health facilities as they were more likely to comply with government policies on diagnosis,

treatments and participate in routine reporting of data; (ii) facilities with a high burden of patients, i.e. health facilities that treated a minimum of 10 patients per day; and (iii) facilities that agreed to participate in the study. Facilities were excluded if they: (i) had ongoing active surveillance (Pingilikani and Junju dispensaries [Bejon et al., 2010; Bejon et al., 2014]); (ii) were close to the active surveillance health facilities due to competition (Kaoyeni medical clinic); (iii) were located in urban areas (Mnarani dispensary, Msumarini dispensary and Vipingo health centre); (iv) had a low burden of patients (Kikambala medical clinic); or (v) were private health facilities (n=16). The remaining six health facilities were Mavueni dispensary, Jaribuni dispensary, Kadzinuni Kendrick dispensary, Bomani Malde dispensary, Ziani dispensary, and Chasimba health centre (Figure 3.6).

3.4.3 Health facility-based passive surveillance of fever infections

At the six eligible health facilities, the study involved records of all patients ≥6 months of age that sought treatment between March 2018 and February 2019. The catchment area for the health facilities was defined as the enumeration zones immediately surrounding health facilities. The catchment areas were estimated as the boundary within which the probability of attending the health facility was relatively high using the travel impedance by distance [Guagliardo, 2004] (i.e. the grey shaded area in Figure 3.6). Only patients that came from these selected EZs formed the universe of the population of interest, records of patients from outside the catchment areas were excluded from the analysis. The study was established as a partnership with the County Ministry of Health (CMoH) and developed to reflect routine practices as far as was possible. The national standard treatment guidelines for malaria in Kenya specify that all patients presenting with fever should be investigated parasitologically [MoPHS, 2010] and the current information system mandates recording of malaria rapid diagnostic test results. The study aimed to ensure that all patients of all ages presenting with fever were tested and that all information

was documented [MoPHS, 2010]. This is a likely departure from standard practice, where not all fevers are tested and not all information is documented [Zurovac et al., 2014; Maina et al., 2017]. The study, however, did not interfere with the drug management systems, nor DHIS2 reporting. One fieldworker was stationed at each facility to offer staffing support for 12 months, to monitor, and ensured that data were collected and recorded appropriately.

Workflow patterns were established for patients in each health facility and supported the pattern of work by ensuring there were no stock-outs of rapid diagnostic kits, another possible departure from reality, where stock-outs of diagnostics have been reported in Kenya [Nyandigisi et al., 2011]. Together with the CMoH staff, patterns of work were developed, with the following alternatives: (i) the fieldworkers sat with the healthcare worker and recorded temperatures, conduct RDTs and other basic observations as part of the consultation under the supervision of the healthcare worker in charge. This pattern of work was implemented in three facilities i.e. Bomani, Ziani, and Jaribuni dispensaries; or (ii) the healthcare worker saw the patient first and confirmed that a rapid malaria test was required, before asking the patient to see the fieldworker for the rapid malaria test and to record other basic observations. The healthcare worker reviewed the patient again once the test result and other information were available. This pattern of work was implemented in three facilities i.e. Chasimba health centre, Kadzinuni, and Mavueni dispensaries.

For each patient, information was recorded on basic demographics, usual residence (linked to the KHDSS), assessment of adherence with LLIN by self-reporting (did the patient sleep under a bednet last night), and recent travel history (Annex 5). In malaria low-risk areas, it is recommended that travel history should increasingly form part of

standard questions [Shanks et al., 2005]. Pregnancy status was recorded for women aged between 15 and 49 years. Fever was documented for every presentation, assessed either by (i) axillary temperature i.e. ≥37.5°C (not always done under routine conditions); or (ii) history of reported fever in the last 24-hours. If the patient had fever, malaria rapid diagnostic test was done using CareStart™ RDT to detect HRP2 specific to *P. falciparum*. If the RDT results were positive, the patient received appropriate treatment as per the Government of Kenya guidelines for malaria-case management [MoPHS, 2010] (Section 3.2.3). The fieldworkers were trained to perform and interpret the results of RDTs using KEMRI standard operating procedures and training schedules.

3.4.4 Community-based parasite prevalence surveillance

A community-based prevalence survey was conducted among randomly selected homestead members who lived within the catchment area of the six health facilities. A stratified two-stage sampling technique was used where the first stage was the health facility catchment area, and the second stage were the homesteads within each cluster. To capture seasonal variation, sampling was conducted four times in one year, i.e. in May–June 2018, August 2018, October 2018 and December 2018–January 2019. During each survey round, random homesteads were selected and in the subsequent sampling frames, previously selected homesteads were excluded. A sample size of at least 4,341 participants was obtained based on the local prevalence estimated to be ≤30% [Macharia et al., 2018], a precision of 1.5% and an expected refusal rate of 5%. The surveillance of infection prevalence in the community therefore required a minimum of four participants in 60 randomly selected homesteads in the catchment area of the six health facilities during each survey round. For a participant to be included in the study they had to be ≥6 months of age, residents of the catchment area of the facility and had agreed to participate

in the study. The participants enrolled in the survey were frequency-matched to cases in the health facility by season and age group.

For each consenting participant, the fieldworkers obtained information on the participant's demographics, travel history, and assessment of adherence with LLIN by self-reporting (did the participant sleep under a bednet last night, where it was assumed all nets were LLIN) (Annex 6). Fever was assessed either by (i) axillary temperature i.e. temperature ≥37.5°C; or (ii) history of reported fever in the last 24-hours. An RDT (CareStart™) was done for all participants, irrespective of their fever status. Malaria rapid diagnostic test were chosen over microscopy for the community surveys to ensure comparability in parasite detection between the health facility and community-based surveys. Pregnancy status was recorded for women aged between 15 and 49 years. Where participants identified themselves or family members to be severely ill during the community survey, the fieldworker sought advice from a study-team clinician, and the study team facilitated referral to an appropriate treatment centre. Otherwise, participants with fever and/or a positive rapid test were advised to seek treatment at the nearest health facility. A note was issued to those advised to seek treatment to avoid recruiting them in the health facility survey.

3.4.5 Community engagement, sensitization, and feedback

Before the start of the study, a community engagement plan was developed. The plan included communication and engagement strategies that provided forums to discuss the study plans with the sub-county health management teams, dispensary health committees, KEMRI community representatives' teams, the community and participants with the support of the well-established community liaison group at KEMRI. This included informal meetings and public meetings. Between December 2017 and February 2018,

three formal meetings with the community liaison group at KEMRI and sub-county health management teams (the six sites were situated in three sub-counties, (Figure 3.1b) and two separate meetings in each site with the dispensary health committees, and KEMRI community representatives' teams were held. In the six sites, public meetings were also held to sensitise the community and study participants about the study objectives, what the study involved, and the study's benefits and risks. Since the study used a rapid (on the spot) test for malaria, each participant was given their results at the time of enrolment. Study results and feedback were shared with the six health facilities and the three sub-county health management teams at the end of the study.

3.4.6 Fieldworker qualification and enrolment

There were 12 fieldwork positions formally advertised with the following qualifications: KCSE mean grade C; basic computer literacy; 20 years of age and above; prior experience working in health facilities and dealing with the local communities; resident within one of the six-study areas; spoke fluent Mijikenda; a certificate of good conduct and a letter from the chief and village elder; and ability to understand and speak Kiswahili and English languages. After interviewing 36 people, 12 fieldworkers were employed. One field supervisor was selected who oversaw the smooth running of the study. The author was responsible for the overall supervision and training of all the field staff.

3.4.7 Supervision and quality assessment in the field

At the study sites, the field supervisor held weekly meetings with the fieldworkers and was responsible for relating all the problems encountered in the field to me. Meetings were held at the KEMRI offices once every 3 months to discuss all the issues that had arisen in that period. Refresher training on finger pricking and RDT testing was also conducted at these meetings and common issues that had arisen in the six study sites were also

discussed. In the community, random spot checks were performed once every 3 months by visiting households that had been approached to participate in this study. Random spot checks were also performed in health facilities by monitoring how the participants were enrolled in the study and by physically confirming their residency.

3.4.8 Clinical surveillance at Kilifi county hospital

Kilifi county hospital (KCH) is located centrally within the KHDSS and the main route of access is through the road class B, (Mombasa-Malindi road, Figure 3.5). The Kenya Ministry of Health classifies KCH as a level IV hospital [MoH, 2017]. The hospital provides primary care and serves as the first-level referral centre to both adults and children for the KHDSS area. The minimum distance covered by patients within the study area (Figure 3.6) to KCH was 5.0 km and the maximum distance was 32.2 km. The hospital provides a 24/7 medical admission service run by a medical team of more than 40 staff that include four consultants, 10 medical and clinical officers, nurses and support staff. The in-patient services are provided for adults in the adult male, female, and maternity wards, and paediatric patients in the general paediatrics ward and the high dependency unit (HDU). The HDU is run by the KEMRI-Wellcome Trust Research Programme.

Medical care is provided according to national and WHO guidelines. Laboratory facilities include parasitological, haematological and biochemical test capacity and advanced microbiological culture facilities. At a minimum, all admitted patients undergo a full blood count and HIV antibody test in keeping with the Kenya Ministry of Health opt-out policy on HIV testing.

3.4.9 Paediatric in-patient surveillance

The general paediatric ward has a 70-bed capacity and the HDU has 6 beds, 6 cots, and 4 incubators. Both wards are staffed by research clinicians and nurses. Approximately, 20% of the paediatric patients are admitted at the HDU. For each paediatric in-patient admission to KCH, clinical history, vital signs and symptoms, demographic details, residency, laboratory analysis, and outcomes are recorded in a central database. Every child admitted to the hospital is investigated with a thick or thin blood smear for microscopy to ascertain *Plasmodium* infection, regardless of presentation. At discharge, a clinician reviews the hospital notes which included clinical, radiological and laboratory data, and assigns a primary and/or secondary diagnostic term(s). All discharge diagnoses were amalgamated to form broad categories and were assigned codes. The discharge diagnosis was grouped as lower respiratory tract infection, trauma-injury-accident-poisoning-snake bite, gastroenteritis, meningitis, sickle cell disease (SCD), malaria, and malnutrition. Other diseases included epilepsy, upper respiratory tract infection, septicaemia/sepsis, tuberculosis, urinary tract infection, cerebral palsy, bronchiolitis and neonatal sepsis. A diagnosis was deemed undetermined if there was insufficient laboratory or clinical evidence to assign a unique diagnosis.

Malaria was defined as a primary clinical diagnosis with a confirmed positive malaria slide and not including another major secondary clinical diagnosis. A confirmed positive malaria slide was retrospectively defined as a positive slide taken at any point during admission. Severe malaria was defined as per the WHO definition [WHO, 2014], and categorized as a malaria admission with a positive malaria slide and: cerebral malaria (Blantyre Coma Score of <3); severe malaria anaemia (haemoglobin concentration <5 g/dL); respiratory

distress (deep acidotic breathing); and multiple convulsions (two or more convulsions in the 24-hour period prior to admission).

3.4.10 Adult in-patient surveillance

Adult in-patient surveillance was initiated in 2007 [Etyang et al., 2014]. The surveillance was started by the KEMRI-Wellcome Trust Research Programme, with funding from GAVI. The key elements of the surveillance were the standardization of clinical investigations to follow Kenya Ministry of Health guidelines, real-time electronic medical records and the linking of hospital admissions to the population register of the KHDSS. For each patient admitted, clinical history, vital signs and symptoms, demographic details, residency, laboratory analysis, and outcomes were recorded in a central database. Thick or thin blood smears for microscopy to ascertain *Plasmodium* infection were only taken among patients suspected to have an infectious disease or were febrile. At discharge, a medical staff assigned a primary and/or secondary diagnosis based on all clinical, radiological and laboratory data available. The discharge diagnosis was grouped as stroke/chronic heart disease (CHD), hypertension, cancers, obstetric complications, trauma-injury-accident-snake bite, sickle cell disease, organ infections – appendicitis, pyelonephritis, cholecystitis, pancreatitis, tuberculosis, malaria, meningitis, and skin infections/cellulitis. Other diseases included acute renal failure, hepatic failure, elective surgery, and intestinal obstruction. A diagnosis was deemed undetermined if there was insufficient laboratory or clinical evidence to assign a unique diagnosis. Admissions of pregnant women for labour and delivery were excluded; however, admissions with pregnancy-related disorders, such as abortion and post-partum sepsis, were included if admitted to the adult female ward.

Malaria was defined as a primary clinical diagnosis with a confirmed positive malaria slide and not including another major secondary clinical diagnosis. Severe malaria was defined

as per the WHO definition [WHO, 2014], and categorized as a positive malaria slide with: cerebral malaria (Glasgow coma score of <11); severe malaria anaemia (haemoglobin concentration <7 g/dL); and respiratory distress (deep breathing). Multiple convulsions were not recorded in adults.

In both the paediatric and adult admissions, the definition of severe malaria did not include hyperparasitaemia, haemoglobinuria (blackwater), jaundice, shock, pulmonary oedema, renal impairment and prostration as it was difficult to standardize across age groups. In the final dataset for the in-patient surveillance, the primary underlying cause of admission was re-evaluated. For example, patients with a primary discharge diagnosis of sickle cell disease were regarded as SCD even if present with malaria. However, febrile convulsion or anaemia was re-classified as malaria if they occurred with an acute illness with a peripheral parasitaemia. Slide negative malaria or febrile convulsion was re-classified as an unspecified disease (UN) in the absence of a secondary diagnosis.

3.4.11 Cause of deaths in the selected study area

Deaths among residents of the catchment areas were detected immediately if they occurred at KCH or during 4 monthly homestead re-enumerations. Causes of death among individuals aged ≥6 months were attributed through a multi-stage process. Causes were first attributed to the primary diagnosis assigned through clinical and laboratory investigations if the death occurred in hospital. If the death occurred within 30 days post-discharge from hospital, details of the discharge diagnoses were used to provide information related to the subsequent cause of death. If death occurred following contact with the hospital during the preceding 24 months and was diagnosed with a chronic condition (e.g. HIV, SCD, cancer, diabetes, epilepsy) this was used to attribute the primary cause of death.

For all remaining deaths, without hospital contact, a verbal autopsy (VA) was used. In this study area, the prevalence of malaria and HIV were considered to be high in the model in order to determine the likelihood of death being related to malaria or HIV. Details provided in the free-text fields related to the primary and underlying cause of death were re-evaluated. For example, coded responses in the Inter-VA might attribute fever to malaria, however, on the questionnaire there was information that the individual was known to have SCD. SCD, assault, diabetes, HIV, road traffic accident (RTA)/trauma, known epilepsy, and suicide were regarded as unambiguous if the likelihood was 100% or from processing open text responses.

For individuals who had no contact with the hospital and for whom a VA was not done, after three attempts to interview the bereaved relatives or refusal to be interviewed, multiple imputation was used to assign a plausible cause based on the distribution of known causes of death [Rowe, 2006]. The multivariate imputation by chained equations (MICE) algorithm was used to create 100 datasets that used the same distribution of known COD but differed on the imputed values. The magnitude of these differences reflects uncertainty about the imputed values [Marshall et al., 2009]. The variables age and sex of the individuals were included in the imputation model. MICE was conducted in R version 3.6.1 (R Core Team (2019), Vienna, Austria). Details of the imputation process can be found elsewhere [Rubin, 2004].

3.4.12 Ethical approval

The health facility surveillance did not impose any changes in the national treatment guidelines and data used in the analysis were gathered as part of routine care; therefore, individual patient consent was not sought. All the records were pseudo-anonymized at the

point of data capture in the healthcare facilities but linked to the demographic surveillance by an ID number. During the community surveys, written informed consent was sought from participants ≥18 years of age or the parents/guardians for children aged 10 years and below. With parental guidance, children aged over 10 and less than 18 years were asked to sign an assent form. These documents were available in Kigiriama, Kiswahili, and English. The community and health facility surveys were approved by the Kenya Medical Research Institute Scientific Ethics Review Unit (KEMRI/SERU/CGMR-C/106/3592) and the Oxford tropical research ethics committee (OxTREC Reference: 511-18). Hospital surveillance and KHDSS surveillance were approved by the Kenya Medical Research Institute Scientific Ethics Review Unit (KEMRI/SERU/SSC/1433) and (KEMRI/SERU/SSC/3057), respectively.

3.4.13 Data entry, checks and storage

Data collection and entry were electronically done using tablets (for the community survey) and laptops (for the health facility survey) by the study team on a PHP web-based interface and data saved onto MySQL database resident on the devices. The laptops, tablets, and the database employed password-protected access to prevent unauthorized access. To ensure more accurate and clean data, the study database had automatic data entry checks and alerts for missing values for required fields. The database allowed changes to be made to the data by users to make simple/self-evident corrections. However, to minimize errors, edits of data collected from the previous day was not possible. The data collected was synchronized and archived every week onto the server. The database was appropriately secured based on security policies and procedures.

3.4.14 Data analysis

Data for this analysis cover the period between March 2018 and February 2019. Descriptive statistics included proportions with 95% confidence intervals (CI), means with standard deviations, or medians with interquartile ranges. Straight-line distance to the health facility from the household was estimated using the ArcGIS point distance tool (ESRI, Inc.) between the centroid point of the household and the coordinate point of the health facility. Chi-square test was used to compare difference in proportions and the logistic regression model was used to analyse the risk of malaria. Adjusted odds ratios (aOR) quoted have been adjusted for factors specified in the text. For continuous measures, the ttest, ANOVA tests, or Kruskal Wallis were used to compare means/medians of two or more groups. Crude and age-specific incidence measures were computed using exact Poisson distribution.

Measures of infection, disease and mortality were defined as follows: the community parasite prevalence (PR) was defined as the proportion of participants tested found with a positive RDT. The health facility TPR was defined as the number of positive diagnostic tests as a proportion of the total tests performed among febrile patients. Malaria passive period prevalence was defined as all cases testing RDT positive including re-attendance expressed per 1,000 person-years of observation. Malaria passive incidence rate was defined using records of first cases only of RDT positive patients expressed per 1,000 person-years of observation. Malaria admission incidence rate was defined as the number of episodes of confirmed malaria admissions expressed per 1,000 person-years of observation. Severe malaria incidence rate was defined as the number of severe forms of confirmed malaria admissions expressed per 1,000 person-years of observation. Malaria mortality rate was defined as the number of death attributable to malaria (derived either

from hospital records, by the InterVA-4 model, or by MICE algorithm) expressed per 1,000 person-years of observation.

The curves for parasite prevalence, test positivity rate, period prevalence and incidence rates were fitted using locally weighted least squares (loess) regression with standard errors estimated with 1,000 bootstrapping replicates, with resampling at the subject level. Data analysis was performed in Stata, version 13 (Stata Corporation, College Station, TX) and R version 3.6.1 (R Core Team (2019), Vienna, Austria). ArcMap version 10.5 (ESRI Inc., Redlands, CA, USA) was used to develop the maps presented in all chapters. The shapefiles were downloaded from an open-source website (http://www.diva-gis.org/gdata).

3.5 Results

This section provides descriptive data of the population in the study area as well as those enrolled in the community-based survey and six out-patient health facilities across all ages. These descriptive data form the basis of further detailed analysis on spatial and temporal relationships between test positivity rate and parasite prevalence (Chapter 4) and spatial heterogeneity in fever and malaria infection presenting to health facilities (Chapter 5).

3.5.1 Characteristics of the study population

In September 2018, there were 12,065 homesteads with 72,560 residents living within the study area (Section 3.4.2); 48% of these were aged <15 years and 16% were aged <5 years (Figure 3.7). The population ratio of males to females was 89:100; with fewer men aged between 25 and 69 years (Figure 3.7), a common feature of the KHDSS where men migrate to larger towns in search of employment.

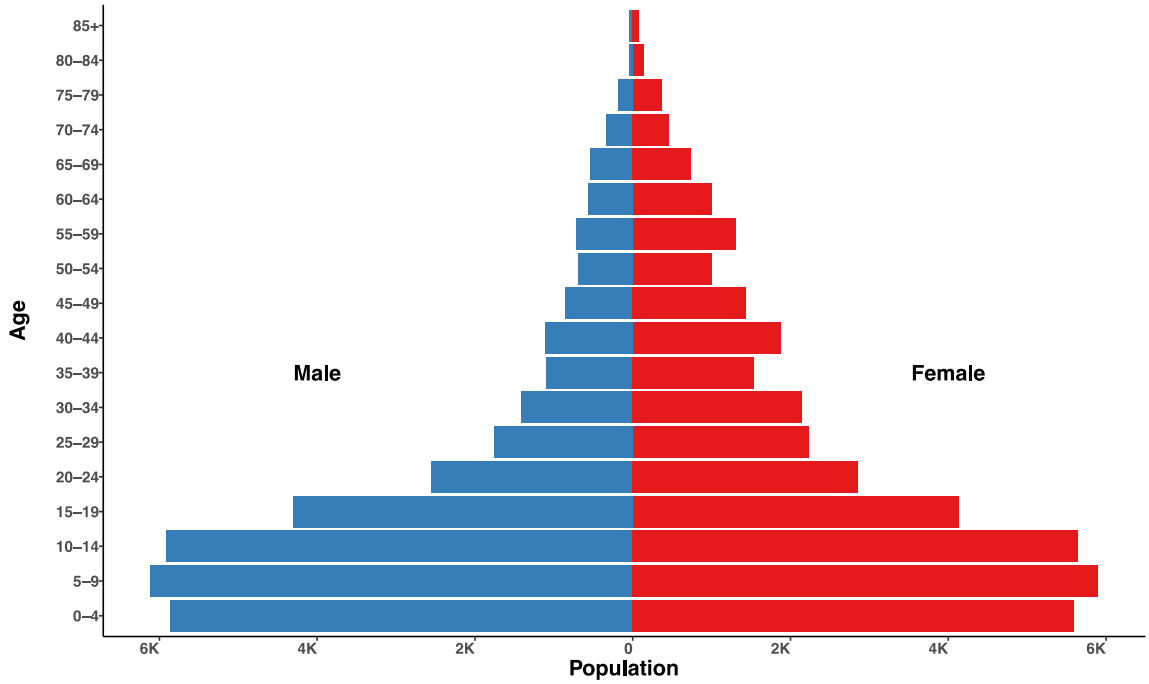


Figure 3.7: Population pyramid of the study area (Section 3.4.2)

3.5.2 The community-based survey

Details of screening and enrolment of participants in the community-based surveys are presented in Figure 3.8. Between May 2018 and January 2019, 7,255 participants ≥6 months of age were approached for enrolment over the four cross-sectional surveys; 425 (5.9%) declined consent and 351 were excluded because they either had been enrolled in the health facility survey within the last 14 days or were pregnant or had missing RDT results (Figure 3.8).

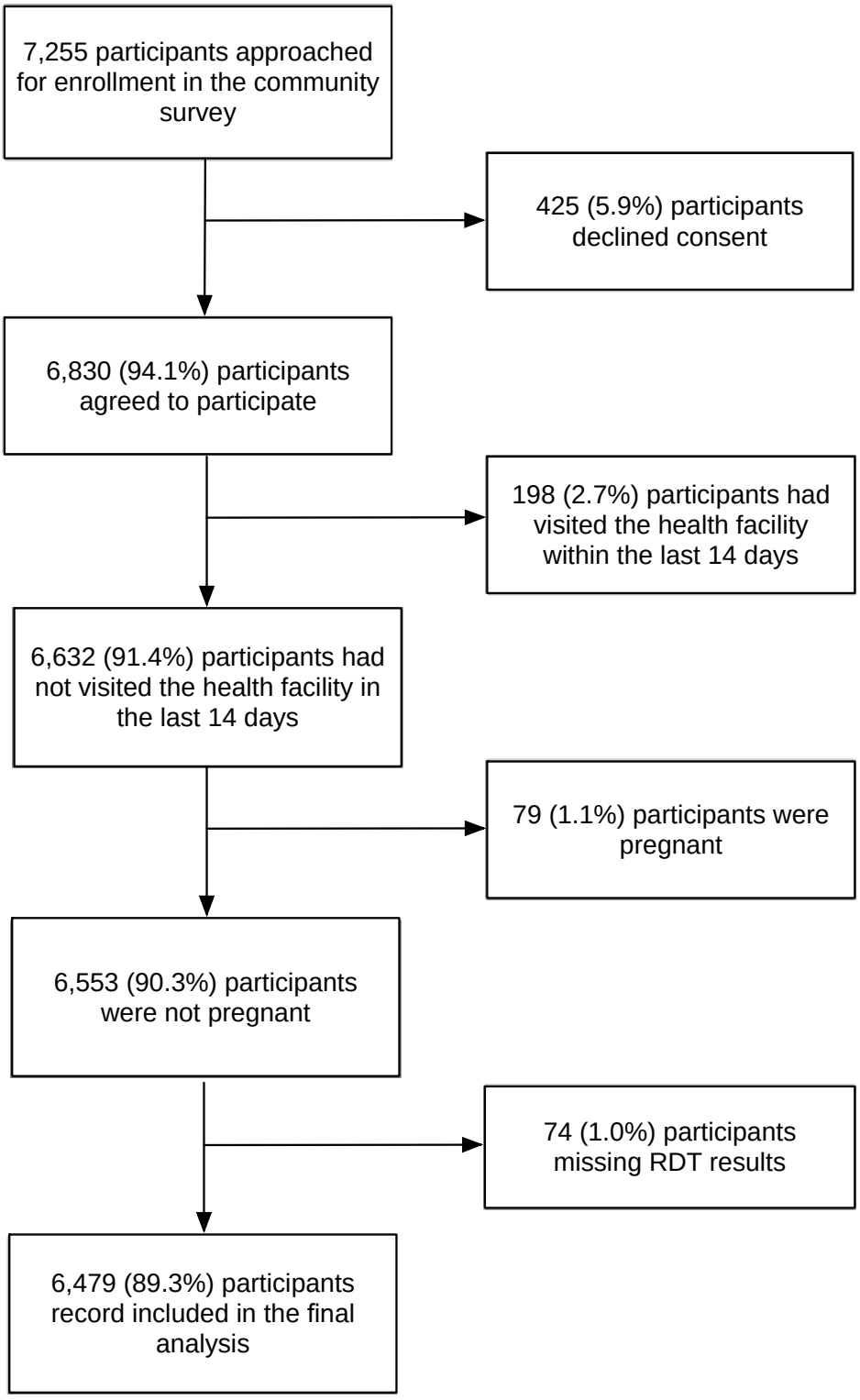


Figure 3.8: Screening and enrolment of participants in the community-based surveys

The spatial distribution of the 6,479 participants enrolled in the six study sites over the four cross-sectional surveys is shown in Figure 3.9a1 & Figure 3.9a2. The participants enrolled in all study sites were equally distributed as shown in Table 3.1. In all study sites, most participants were female (61%). The overall median age of the participants was 12 years (IQR: 6 years, 24 years) and ranged from 11 years in Bomani and Kadzinuni to 14 years in Jaribuni (Table 3.1). The largest number (39%) of participants enrolled were children aged 5-14 years. About 21% of the participants were children aged 6 months-4 years and only 9% were aged 50 years and above. There were no apparent differences in the proportion of participants in age categories between the study sites (Table 3.1). However, there was a significant difference in the age-sex pattern (χ^2=15.95; p=0.001). There were more females (68%) aged 1-9 years and (66%) 30-64 years which reflects the age-sex patterns in Figure 3.7. This, however, did not influence the result of this study as parasite prevalence was not sex-specific (Annex 7).

Of the 6,479 participants, 72% slept under a LLIN the night prior to the survey and this ranged from 55% in Ziani to 91% in Bomani (Table 3.1). Only 4% of the participants had travelled in the last one week and of these 22% had travelled outside the study area (Table 3.1).

Table 3.1: Background characteristics of study participants in the community-based survey

Characteristics	Bomani	Chasimba	Jaribuni	Kadzinuni	Mavueni	Ziani	Overall
Number enrolled, n	1,036	1,105	1,076	1,165	1,020	1,077	6,479
Number of non-pregnant female, n (%)	683 (65.9)	587 (53.1)	617 (57.3)	747 (64.1)	632 (62.0)	688 (63.9)	3,954 (61.0)
Median age in years, (IQR)	11 (16)	12 (20)	14 (23)	11 (17)	12 (17)	12 (17)	12 (18)
Number of participants, n (%)							
6-11 months	16 (1.5)	18 (1.6)	17 (1.5)	23 (2.0)	12 (1.2)	13 (1.2)	99 (1.5)
1-4 years	220 (21.2)	222 (20.1)	178 (16.5)	248 (21.3)	185 (18.1)	190 (17.6)	1,243 (19.2)
5-9 years	205 (19.8)	208 (18.8)	182 (16.9)	249 (21.4)	203 (19.9)	231 (21.5)	1,278 (19.7)
10-14 years	207 (20.0)	222 (20.1)	182 (16.9)	219 (18.8)	197 (19.3)	218 (20.2)	1,245 (19.2)
15-29 years	203 (19.6)	185 (16.7)	244 (22.7)	215 (18.5)	234 (22.9)	208 (19.3)	1,289 (19.9)
30-49 years	126 (12.2)	127 (11.5)	159 (14.8)	134 (11.5)	108 (10.6)	113 (10.5)	767 (11.8)
50-64 years	43 (4.2)	65 (5.9)	72 (6.7)	47 (4.0)	44 (4.3)	62 (5.8)	333 (5.1)
65+ years	16 (1.5)	58 (5.3)	42 (3.9)	30 (2.6)	37 (3.6)	42 (3.9)	225 (3.5)
Mean temperature ºC[¶], (SD)	36.1 (0.73)	36.2 (0.78)	36.4 (0.67)	35.7 (0.91)	35.9 (0.67)	36.2 (0.52)	36.1 (0.76)
Number of participants with temperature ≥ 37.5 ºC[¶], n (%)	10 (1.0)	26 (2.4)	22 (2.0)	8 (0.7)	10 (1.0)	12 (1.1)	88 (1.4)
Reported fever, n (%)	14 (1.4)	20 (1.8)	45 (4.2)	26 (2.2)	126 (12.4)	26 (2.4)	257 (4.0)
Parasite prevalence, n (%)	51 (4.9)	42 (3.8)	124 (11.5)	283 (24.3)	74 (7.3)	69 (6.4)	643 (9.9)
Slept under a LLINs last night, n (%)	938 (90.5)	706 (63.9)	815 (75.7)	821 (70.5)	776 (76.1)	590 (54.8)	4,646 (71.7)
Travelled in the last one week, n (%)	31 (3.0)	36 (3.3)	62 (5.8)	16 (1.4)	75 (7.4)	18 (1.7)	238 (3.7)

[¶] 4 (0.06%) participants had missing data on measured axillary temperature

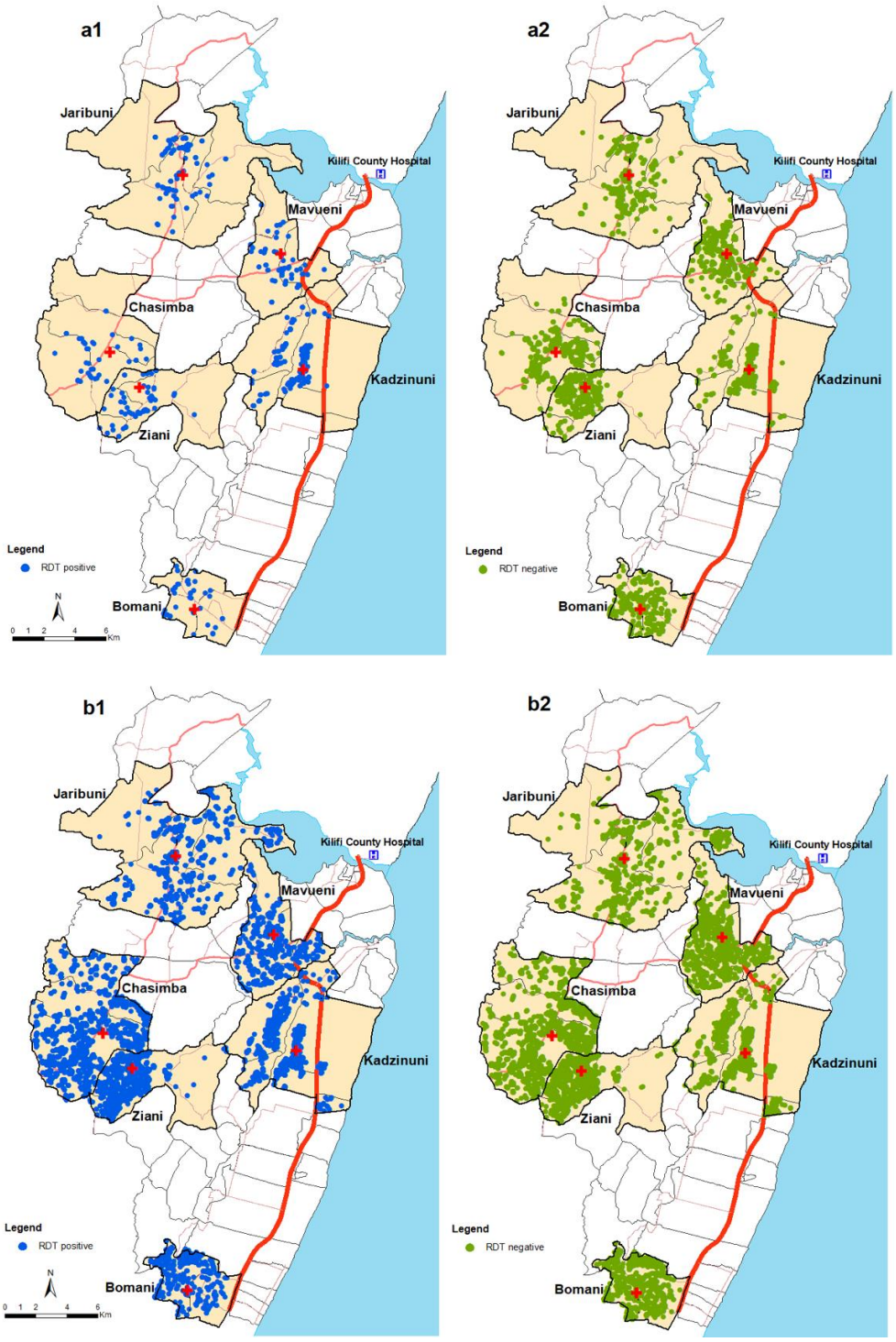


Figure 3.9: Spatial distribution of the participants in the community-based survey and in the health facility-based survey. Panel A1 – the community-based spatial distribution of RDT positive participants; Panel A2 – the community-based spatial distribution of RDT negative participants; Panel B1 – the health facility-based spatial distribution of RDT positive participants; and Panel B2 – the health facility-based spatial distribution of RDT negative participants

The average axillary temperature among study participants recruited during the 4 cross-sectional surveys was 36.1±0.8 ºC with a maximum temperature of 40.1 ºC and a minimum temperature of 32.0 ºC (Table 3.1 & Figure 3.10). However, there was significant variation (F statistics =10.37; p <0.001) across the age groups. Children aged 5-14 years had a slightly higher axillary temperature (36.2±0.7 ºC) compared to children aged 6 months-4 years (36.1±0.8 ºC) (Figure 3.10). The elderly (50 years and above) had the lowest axillary temperature (36.0±0.7 ºC). 5.4% of the enrolled participants (95% CI: 4.8%, 5.9%) had either measured or reported fever; 4% reported fever in the last 24 hours and 1.4% had measured temperature ≥37.5 ºC. Despite there being a higher number (5%) of participants 50 years and above with reported fever in the past 24 hours, <1% had measured axillary temperature ≥37.5 ºC. Prevalence of reported and measured fever (5.2% vs. 2.4%) among children aged 6 months-4 years was higher than that of children aged 5-14 years (3.6% vs. 1.4%) and adults aged 15-49 years (3.3% vs. 0.9%).

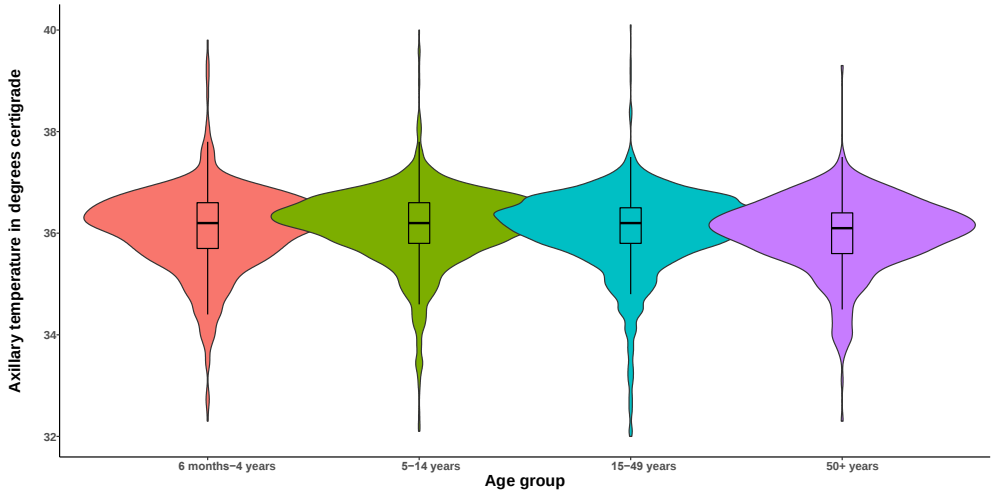


Figure 3.10: The distribution of axillary temperature stratified by age group. The box plots show the median axillary temperature for all six out-patient health facilities. The violin plot visualizing the underlying distribution of the observations

Legend: The median (central line), 25th and 75th percentile (box width), upper and lower limit (T), and outliers (black dots). The shape of the violin represents the density of the observations: the more data points in a specific range, the larger the violin is for that range.

Malaria rapid diagnostic test positivity, herein regarded as parasite prevalence (PR), across all age groups from all four surveys conducted during the wet and dry seasons is shown in Figure 3.11. The spatial distribution of participants that had a positive RDT is shown in Figure 3.9a1. PR did not differ during the wet vs. dry season (9.5% vs. 10.4%; χ^2=1.25; p=0.264). Infection among those who reported to have travelled outside the study area in the last one week was 6% vs. 10% among those who had not travelled (χ^2=4.52; p=0.034). There were differences in PR between sites (χ^2=370.48; p<0.001); the highest PR was observed in Kadzinuni (24%) while the lowest was in Chasimba at 3.8% (Table 3.1). The overall PR for malaria was 9.9% (95% CI: 9.2%, 10.7%) (Table 3.1) and was 13.7%, 10.7%, 7.2% and 9.0% during each cross-sectional survey, respectively. PR was highest among children aged 5-14 years at 13.4% (95% CI: 12.1%, 14.7%) (Figure 3.11). The median age of participants who tested positive for malaria (10; IQR: 5,15) was significantly lower compared to those who tested negative (12; IQR: 6, 26) (χ^2=35.62; p<0.001).

Compared to children aged 6 months-4 years, children aged 5-14 years had a higher prevalence of malaria infection (aOR=1.28; 95% CI: 1.02, 1.61; p<0.001); after adjusting for site, month of enrolment, LLINs use, and sex. However, malaria parasite prevalence was lower in the older age groups compared to children aged 6 months-4 years (15-49 years – aOR=0.63; 95% CI: 0.49, 0.82); with the lowest risk being reported among participants aged 50 years and above (aOR=0.38; 95% CI: 0.24, 0.61).

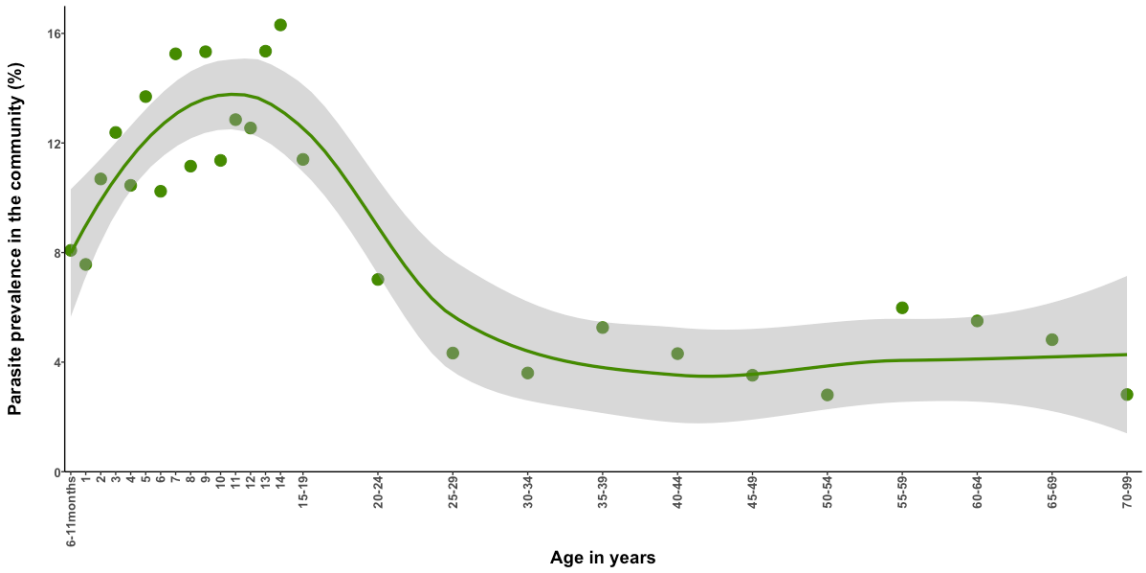


Figure 3.11: The age-specific malaria parasite prevalence. The curve was fitted using locally weighted least squares (loess) regression, with standard errors (shaded grey region) estimated with 1,000 bootstrapping replicates

Among those with reported fever, children aged 5-14 years had the highest parasite prevalence (35.2%) followed by adults aged 15-49 years (29.9%), children aged 6 months-4 years (18.6%), and finally among the elderly at 10.3% (Figure 3.12). PR among those with measured temperature ≥37.5 ºC was 45.7% among children aged 5-14 years, 34.4% among children aged 6 months-4 years, 22.2% among adults aged 15-49 years and drop below detection in the elderly (Figure 3.12). The highest PR among those without fever was still observed among children aged 5-14 years at 12.3%, followed by children aged 6 months-4 years at 9.2%, adults aged 15-49 years at 6.1% and the elderly (50 years and above) had the lowest prevalence at 3.8% (Figure 3.12). There were no age-sex differences among those with reported fever, measured fever, nor among those positive for malaria using RDT i.e. parasite prevalence (Annex 8-10).

Febrile (i.e. measured or reported fever) participants had significantly higher (27.3%; 95% CI: 22.7%, 32.3%) *P. falciparum* prevalence compared to non-febrile participants (8.9%;

95% CI: 8.2%, 9.7%) (p<0.001). Fever was associated with a higher risk of malaria infection (aOR=5.2; 95% CI: 3.9, 7.0; p<0.001) compared to participants without fever; after adjusting for site, month of enrolment, age, and sex.

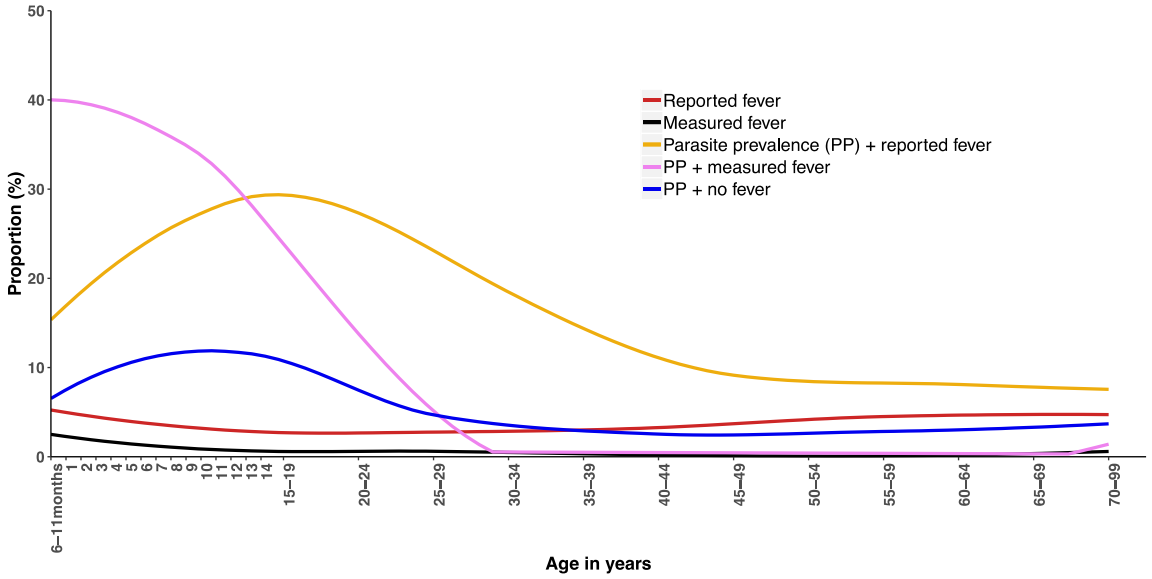


Figure 3.12: The age-specific community-based prevalence of reported fever (red line); prevalence of measured fever i.e. temperature ≥37.5 ºC (black line); parasite prevalence among participants with reported fever (orange line); parasite prevalence among participants with measured fever (purple line); and parasite prevalence among those without fever (blue line) across age. The curves were fitted using locally weighted least squares (loess) regression

3.5.3 Health facility-based passive surveillance of fever infections

Details of screening and enrolment of participants in the health facility survey are presented in Figure 3.13. Between March 2018 and February 2019, 46,567 febrile patients ≥6 months of age sought treatment in one of the six out-patient health facilities (Chasimba health centre, Ziani, Mavueni, Bomani Malde, Jaribuni, or Kadzinuni Kendrick dispensaries). Of the 46,567 febrile patients, 18,433 were excluded because they either lived outside the study area, had been enrolled in the community survey within the last 14 days, were pregnant, or had missing RDT results (Figure 3.13).

The spatial distribution of the included records of 28,134 febrile patients that visited the six out-patient health facilities is shown in Figure 3.9b1 & Figure 3.9b2. The characteristics of the study participants enrolled in each health facility are shown in Table 3.2. The majority (25%) of the febrile patients visited Chasimba health centre while only 10% of the patients visited either Mavueni dispensary or Bomani Malde dispensary. Although there were differences between sites, the majority (65%) of the patients were within a 2 km straight-line distance to the health facility. In Chasimba health centre and Jaribuni dispensary, only a third of the patients were within 2 km; however, 65% and 63% of the patients were within a 3 km straight-line distance from Chasimba health centre and Jaribuni dispensary, respectively (Table 3.2). A more detailed analysis of spatial differences is considered in Chapter 5.

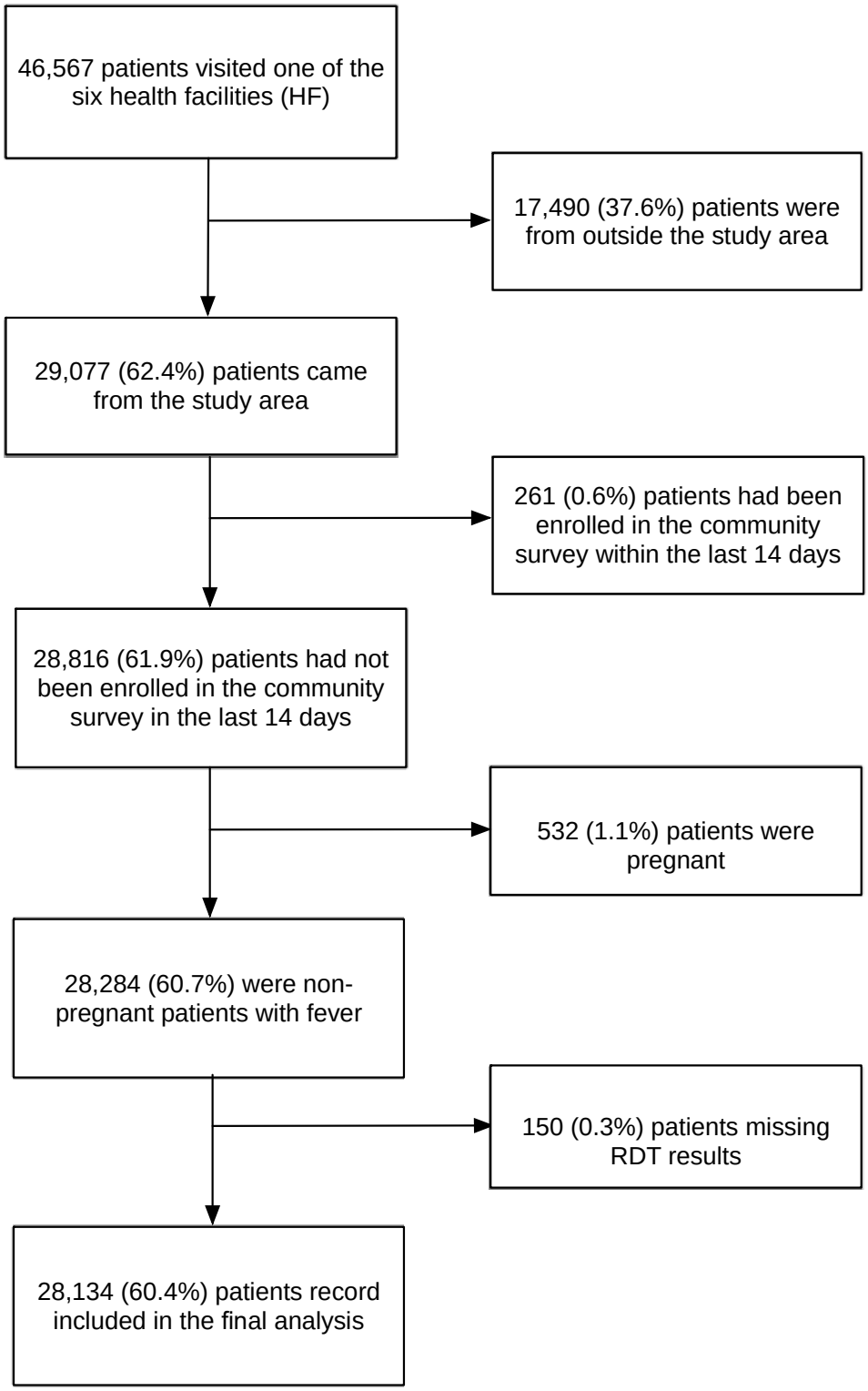


Figure 3.13: Screening and enrolment of participants in the health-facility based surveys

The majority (54%) of the patients were female except in Bomani Malde dispensary where there were more males (56%). Among patients aged 25-69 years, there were more females (81%) compared to male attendance which reflects the age-sex patterns in Figure 3.7. This, however, did not influence the result of this study as prevalence or incidence was not sex specific. The overall median age was 11 years (IQR: 4 years, 19 years) and the largest number of attendees in all six out-patient health facilities was among children aged 5-14 years (39%). About 26% of the attendees were among children aged 6 months-4 years, 28% among patients aged 15-49 years, and only 7% were aged 50 years and above. There were significant differences in the proportion of participants in age categories between the study sites (χ^2=443.3; p<0.001) (Table 3.2) and in the age-sex pattern (χ^2=3104.7; p<0.001) (Annex 11).

Of the 28,134 records of febrile patients, 11,215 (40%) were re-attendances. The number of re-attendances ranged between 2 and 13 times. The majority (62.2%; 10,516/16,919) of the patients presented once, while 22.2% (3,755) presented twice, and 9% (1,529) presented three times. Ten (0.06%) patients presented ten times, five (0.03%) patients presented 11 times, three (0.01%) presented 12 times, and four (0.02%) patients presented 13 times (Annex 12). In all future references, period prevalence is defined as all cases testing RDT positive including re-attendance while the incidence was defined using records of first cases only.

The majority (78%) of the febrile patients slept under LLIN the night prior to the survey and this ranged from 61% in Ziani to 94% in Bomani. Only 2% of the febrile patients had travelled in the last one week and 20% had travelled outside of the study area (Table 3.2).

Table 3.2: Background characteristics of study participants in the health facility survey

Characteristics	Bomani	Chasimba	Jaribuni	Kadzinuni	Mavueni	Ziani	Overall
Number of facility attendees, n	2,906	7,155	4,140	5,732	2,696	5,232	28,134
Distance from household to health facility, n (%)							
<1 km	631 (21.7)	472 (6.6)	392 (9.5)	1,979 (34.5)	602 (20.3)	1,648 (31.5)	5,724 (31.5)
1-1.9 km	1,249 (43.0)	1,685 (23.6)	1,252 (30.2)	1,938 (33.8)	1,187 (40.0)	2,305 (44.1)	9,619 (34.2)
2-2.9 km	1,004 (34.6)	2,399 (33.5)	1,007 (24.3)	1,355 (23.6)	788 (26.5)	1,015 (19.4)	7,568 (26.9)
3-3.9 km	22 (0.8)	1,628 (22.8)	677 (16.4)	355 (6.2)	373 (12.6)	248 (4.7)	3,303 (11.7)
≥4 km	0 (0)	971 (13.6)	812 (19.6)	105 (1.8)	19 (0.6)	16 (0.3)	1,923 (6.8)
Number of non-pregnant female, n (%)	1,291 (44.4)	3,981 (55.6)	2,162 (52.2)	3,212 (56.0)	1,537 (51.8)	2,891 (55.3)	15,074 (53.6)
Median age in years, (IQR)	9 (12)	9 (13)	12 (21)	10 (14)	12 (17)	12 (15)	11 (15)
Number of facility attendees, n (%)							
6-11 months	87 (3.0)	229 (3.2)	111 (2.7)	209 (3.7)	84 (2.8)	120 (2.3)	840 (3.0)
1-4 years	717 (24.7)	1,901 (26.6)	759 (18.3)	1,369 (23.9)	677 (22.8)	1,025 (19.6)	6,448 (22.9)
5-9 years	651 (22.4)	1,572 (22.0)	745 (18.0)	1,142 (19.9)	515 (17.4)	1,035 (19.8)	5,660 (20.1)
10-14 years	572 (19.7)	1,289 (18.0)	810 (19.6)	1,078 (18.8)	505 (17.0)	1,113 (21.3)	5,367 (19.1)
15-29 years	510 (17.6)	997 (13.9)	786 (19.0)	1,017 (17.7)	612 (20.6)	936 (17.9)	4,858 (17.3)
30-49 years	259 (8.9)	651 (9.1)	568 (13.7)	556 (9.7)	326 (11.0)	528 (10.1)	2,888 (10.3)
50-64 years	81 (2.8)	339 (4.7)	259 (6.3)	227 (4.0)	164 (5.5)	302 (5.8)	1,372 (4.9)
≥65 years	29 (1.0)	177 (2.5)	102 (2.5)	134 (2.3)	86 (2.9)	173 (3.3)	701 (2.5)
Mean temperature ºC¶, (SD)	37.5 (0.87)	37.5 (1.02)	37.3 (0.69)	37.2 (0.96)	37.2 (1.06)	37.6 (1.07)	37.4 (0.98)
Number of participants with temperature ≥37.5 ºC¶, n (%)	1,449 (49.9)	3,868 (54.1)	1,162 (28.1)	1,760 (30.7)	1,295 (43.7)	2,978 (56.9)	1,2512 (44.5)
Reported fever, n (%)	2,891 (99.5)	7,023 (98.2)	4,139 (99.9)	5,723 (99.8)	2,917 (98.3)	4,693 (89.7)	2,7386 (97.3)
Test positivity rate (TPR), n (%)	1,018 (35.0)	3,562 (49.8)	1,534 (37.1)	2,615 (45.6)	712 (24.0)	2,702 (51.6)	1,2143 (43.2)
Median age of negative RDT, (IQR)	9 (15)	10 (24)	15 (28)	11 (23)	12 (22)	13 (28)	12 (24)
Median age of TPR, (IQR)	10 (8)	9 (10)	10 (9)	10 (10)	11 (9)	11 (10)	10 (10)
Slept under a LLINs last night, n (%)	2,728 (93.9)	5,577 (78.0)	3,706 (89.5)	4,255 (74.2)	2,498 (84.1)	3,211 (61.4)	21,975 (78.1)
Travelled in the last one week, n (%)	33 (1.1)	302 (4.2)	43 (1.0)	37 (0.7)	128 (4.3)	94 (1.8)	637 (2.3)

Straight-line distance to the health facility from the household was estimated using the ArcGIS point distance tool (ESRI, Inc.) between the centroid point of the household and the coordinate point of the health facility; ¶13 (0.05%) patients had missing data on measured axillary temperature.

The majority 97.3% (95% CI: 97.1%, 97.5%) of the patients had reported fever and only 44.5% (95% CI: 43.9%, 45.1%) had a raised measured axillary temperature ≥37.5 ºC; 13 (0.05%) patients had missing data on axillary temperature. The prevalence of reported and measured fever was 98% vs. 50% among children aged 6 months-4 years, 98% vs. 51% among children aged 5-14 years, 97% vs. 35% among adults aged 15-49 years, and 97% vs. 28% among the elderly (50 years and above). The mean temperature ranged from 37.0 ºC to 37.5 ºC across all age groups with a maximum temperature of 42.4 ºC and a minimum temperature of 32.1 ºC (Figure 3.14). The average axillary temperature among children aged 6 months-4 years was 37.5±1.0 ºC and was significantly higher compared to the rest of the age groups (F statistics = 342.72; p<0.001). Compared to the community-based participants, health facility-based patients had a significantly higher axillary temperature with a mean difference of +1.3 ºC (p<0.001).

The overall RDT test positivity rate (TPR) was 43.2% (95% CI: 42.6%, 43.7%) and the highest TPR was observed among children aged 5-14 years at 57.9% (95% CI: 57.0%, 58.9%) (Figure 3.15). The lowest TPR (19%) was reported among patients aged 50 years and above, while 36% of children aged 6 month-4 years were positive and comparable to patients aged 15-49 years (35%). The median age of febrile patients who tested positive for malaria was significantly lower compared to the non-malaria fevers (χ^2=138.9; p<0.001) (Table 3.2). There was no difference in TPR among those who reported having travelled outside the study area in the last one weeks (41%) and among those who had not travelled (43%) (χ^2=1.66; p = 0.197).

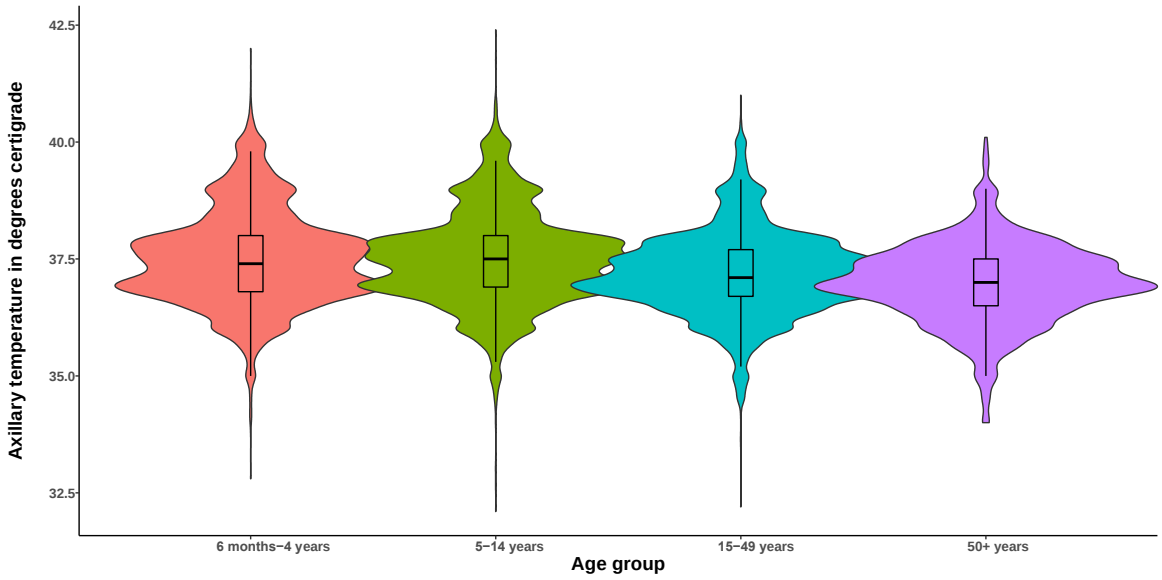


Figure 3.14: The distribution of axillary temperature stratified by age group. The box plots show the median axillary temperature for all six out-patient health facilities. The violin plot visualizing the underlying distribution of the observations

Legend: The median (central line), 25th and 75th percentile (box width), upper and lower limit (T), and outliers (black dots). The shape of the violin represents the density of the observations: the more data points in a specific range, the larger the violin is for that range.

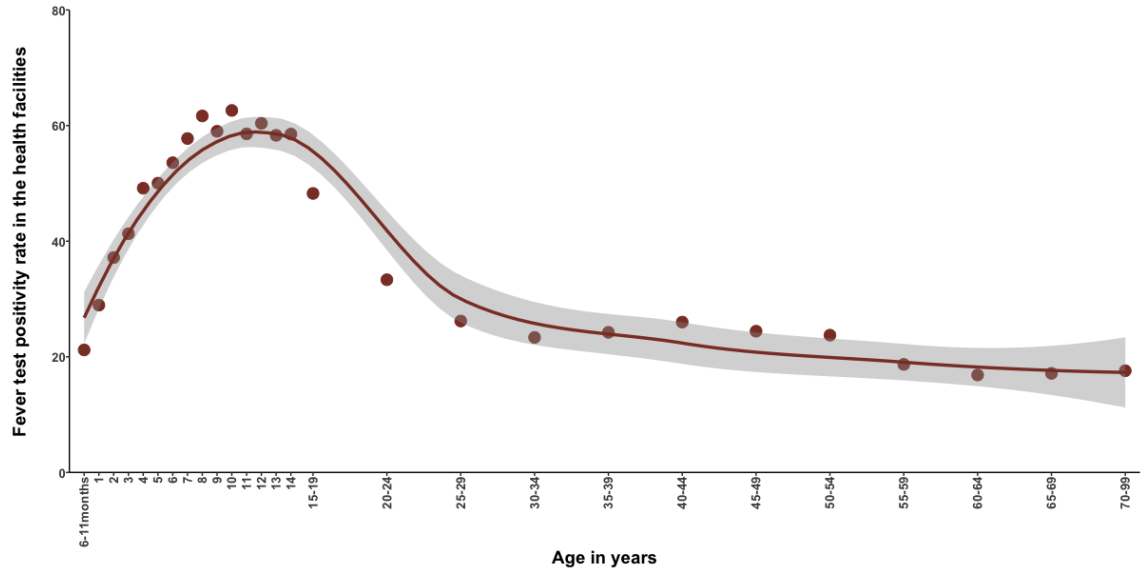


Figure 3.15: The age-specific malaria fever test positivity rate. The curve was fitted using locally weighted least squares (loess) regression, with standard errors (shaded grey region) estimated with 1,000 bootstrapping replicates

Among those with reported fever, 42% (95% CI: 41.4%, 42.6%) tested positive for malaria and was highest among children aged 5-14 years at 57% (95% CI: 55.6%, 57.5%) (Figure 3.16). Among those with a measured axillary temperature ≥37.5 ºC, 26% (95% CI: 25.8%, 26.8%) tested positive for malaria and was also highest among children aged 5-14 years (35%) followed by children aged 6 months-4 years (24%) and adults aged 15-49 years (19%) and finally among the elderly at 10% (Figure 3.16). There were no age-sex differences among patients with either reported fever or measured fever (Annex 13). However, there was significant age-sex differences among patients who tested positive by RDT (χ^2=118.53; p <0.001) (Annex 14).

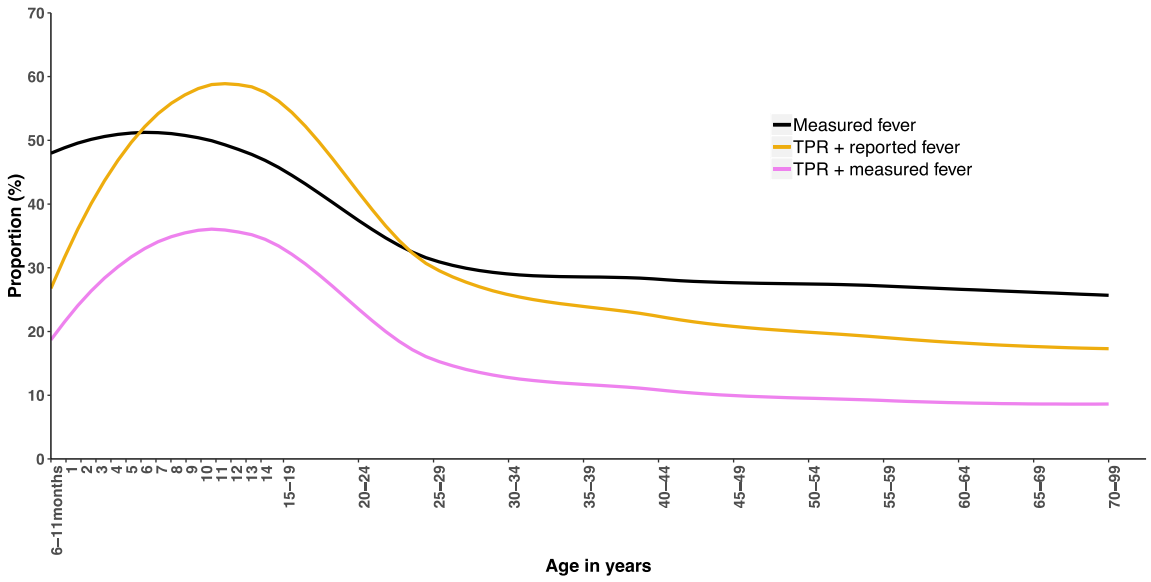


Figure 3.16: The age-specific health facility prevalence of measured fever i.e. temperature ≥37.5 ºC (black line); test positive rate (TPR) among patients with reported fever (orange line); and test positive rate among patients with measured fever (purple line). The curves were fitted using locally weighted least squares (loess) regression

Malaria test positivity rate did not differ during the wet (April, May, June, October, and November) *versus* dry season (i.e. 42.7% vs. 43.5%; χ^2=1.85; p=0.173). To examine rainfall, monthly precipitation was obtained from the nearest meteorological station located

less than 2 km away from Kilifi township at the Kilifi Sisal Plantation (https://doi.org/10.7910/DVN/9VFB1K). The total monthly rainfall collected over the enrolment period was superimposed over the monthly TPR (Figure 3.17). Most of the rainfall was recorded between April and October. Malaria positivity was relatively similar across the enrolment period with a peak being observed in December, which was one month after the rainy season.

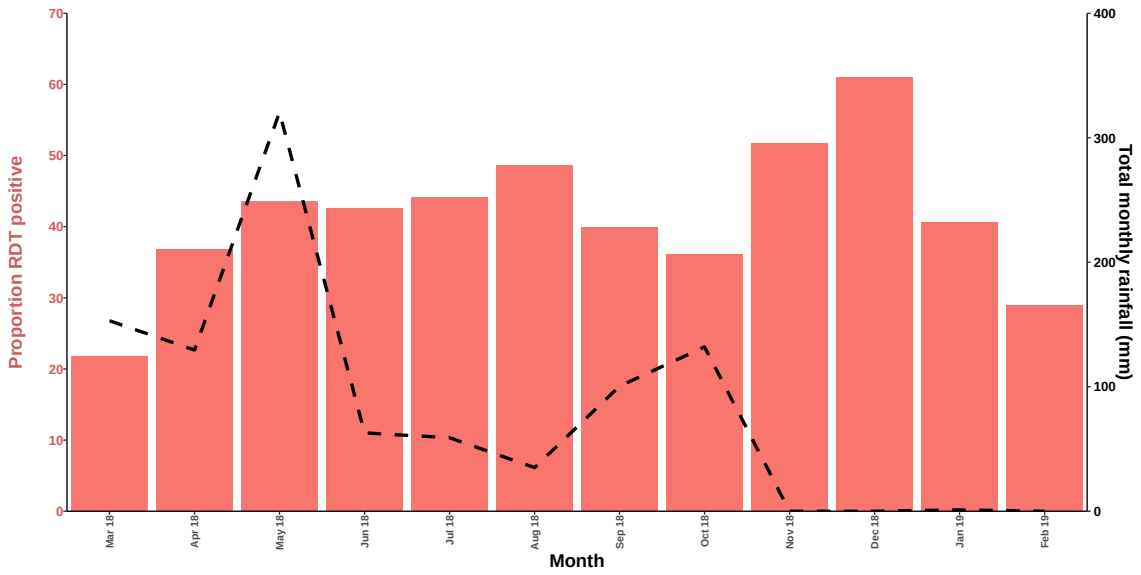


Figure 3.17: Seasonality of confirmed malaria using mRDTs (red bars) among 28,134 febrile patients presenting at one of the six out-patient health facilities during the period between March 2018 and February 2019 and total monthly rainfall in the same time period (black dashed line)

Febrile children aged 5-14 years had a higher risk of testing RDT positive (aOR=2.40; 95% CI: 2.25, 2.56; p<0.001) compared to febrile children aged 6 months-4 years; after adjusting for site, month of enrolment, LLINs use, and sex. Other age groups had a lower risk of RDT positivity (i.e. for 15-49 years, aOR=0.99; 95% CI: 0.92, 1.06; and 50 years and above, aOR=0.40; 95% CI: 0.35, 0.45) compared to febrile children aged 6 months-4 years.

To compute the period prevalence and incidence rate, the study area's person-years of observation from the KHDSS stratified by age was used. During the surveillance period, there were 71,562 person-years of observation in residents of the study area aged ≥6 months. The period prevalence and incidence rate of measured temperature was lower than reported fever across all ages (Figure 3.18). The trend of combined measured and reported fever was very similar to that of reported fever since 97% of the patients had reported fever. Both the measure and reported fever were high in the younger age groups but gradually declined in older children and then remained constant in the older age groups. The period prevalence and incidence rate of RDT positivity gradually increased from 6 months of age and peaked around 13 years before declining thereafter. The period prevalence and incidence rate of non-malaria fever were high among the younger ages, dipped in those aged 14-19 years and a slight resurgence was observed in the older age groups (Figure 3.18).

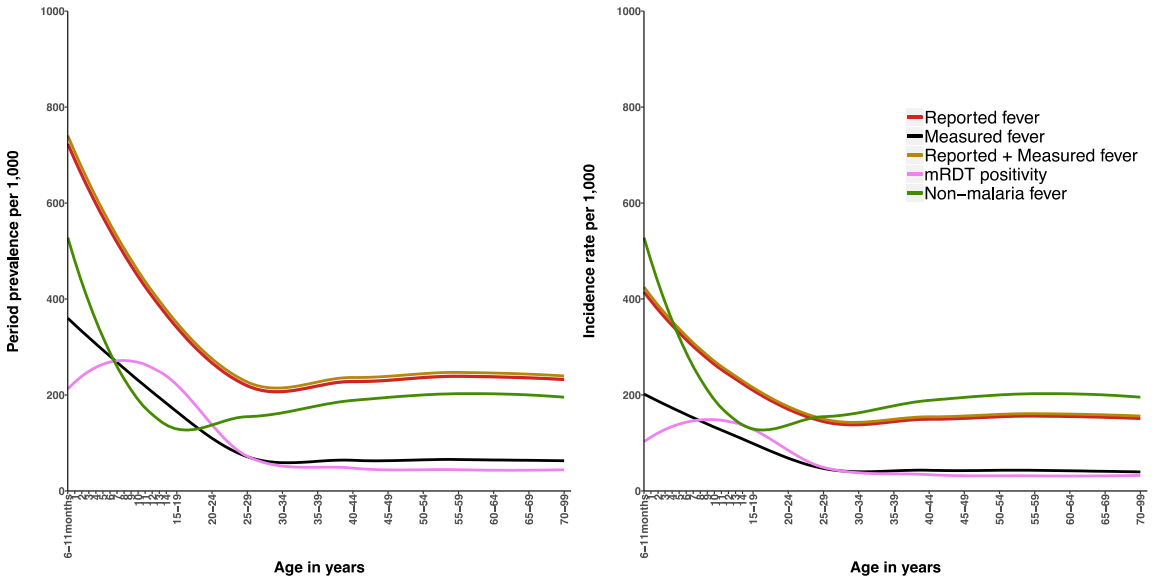


Figure 3.18: The age-specific health facility period prevalence (left) and incidence rates (right) of reported fever (red line); measured fever i.e. temperature ≥37.5 ºC (black line); combination of both reported and measured fever (orange line); RDT positivity (purple line); and non-malaria fevers (green line) expressed per 1,000 person-years of observation. The curves were fitted using locally weighted least squares (loess) regression

3.5.4 In-patient surveillance

After excluding patients who were not residents of the study area and patients who were <6 months of age, there were 597 in-patient admissions to Kilifi county hospital between March 2018 and February 2019 from the study areas (Figure 3.19). The characteristics of patients admitted to Kilifi county hospital are shown in Table 3.3. The majority (28%) of in-patient admissions were from Kadzinuni while only 7% of the patients came from Jaribuni. There were significant differences between sites, however, 50% of the patients were within a 14 km straight-line distance to Kilifi county hospital. Residents of Mavueni were closest to the hospital while Bomani (≥25 km) was the furthest (Table 3.3). The spatial distribution of all in-patient admissions is shown in Figure 3.20c1.

Of the 597 in-patient admissions, 45% (n=268) were female and 13% (n=80) had been admitted in the high dependency unit (HDU). The overall median age of all-cause admission was 12 years (IQR: 2 years, 39 years) and ranged from 9 years in Mavueni to 28 years in Bomani (Table 3.3). The average axillary temperature among in-patient admissions was 37.1±1.1 ºC which was slightly lower than that observed in the health facility-based survey; about 30% of the in-patient admissions had a temperature ≥37.5 ºC (Table 3.3). The median length of hospital stay was 3.3 days (IQR 1.9 days, 6.7 days). Fifty-three (8.9%) deaths occurred during hospital admission at Kilifi county hospital with a median time to death of 30 hours (IQR 15, 74 hours) among paediatric admissions and 5.8 days (IQR 2.8, 8.2 days) among adult admissions; 12 (23%) patients died within the first 24 hours of admission (Table 3.3).

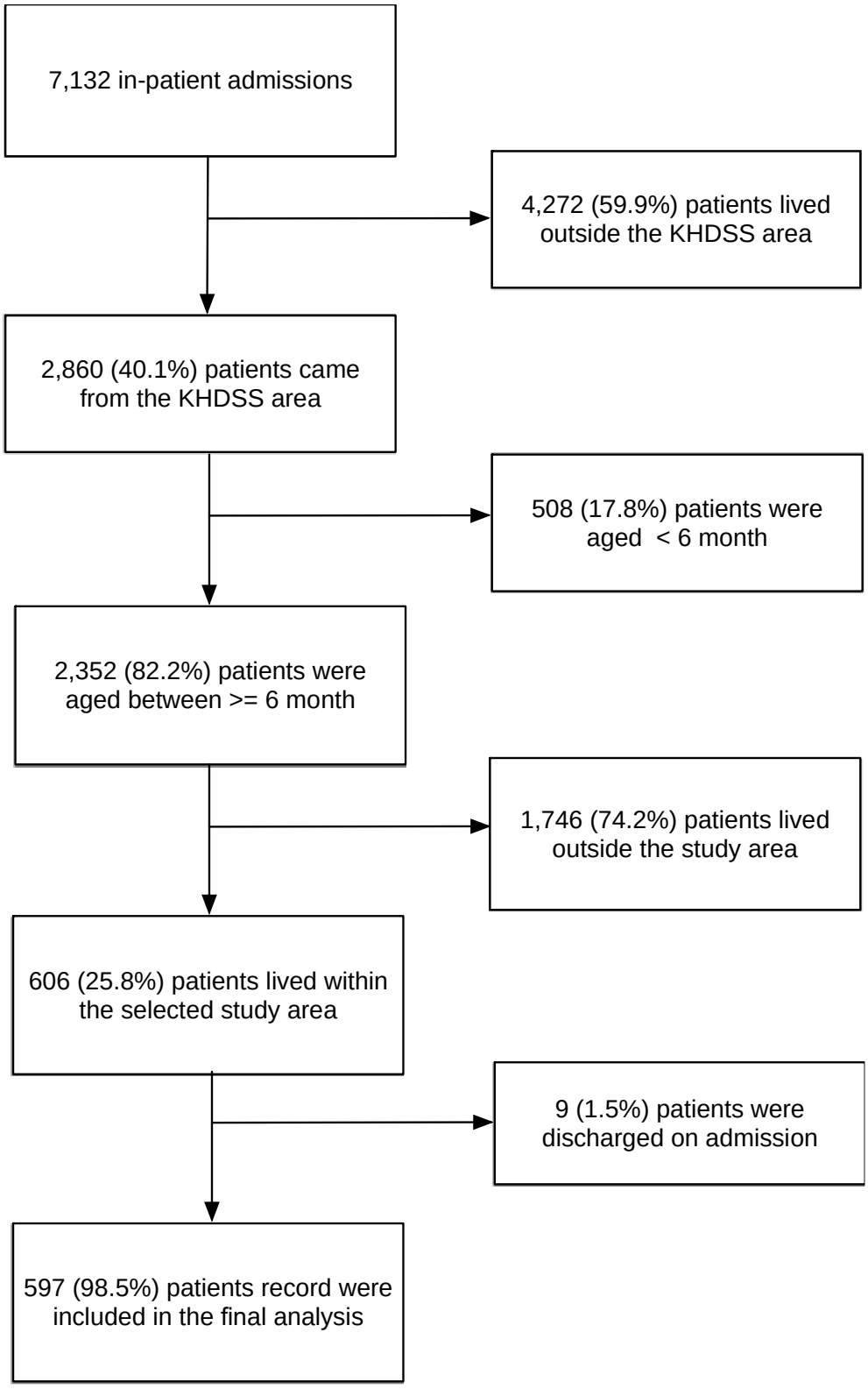


Figure 3.19: Flow of patients included in the final analysis

Table 3.3: Background characteristics of in-patient admission at Kilifi County hospital

Characteristics	Bomani	Chasimba	Jaribuni	Kadzinuni	Mavueni	Ziani	Overall
All-cause admission, n	46	111	44	168	138	90	597
Distance from household to Kilifi County hospital, n (%)							
5-9 km	0 (0)	0 (0)	5 (11.4)	33 (19.7)	114 (82.6)	0 (0)	152 (25.5)
10-14 km	0 (0)	0 (0)	27 (61.4)	96 (57.1)	24 (17.4)	0 (0)	147 (24.6)
15-19 km	0 (0)	42 (37.8)	12 (27.2)	39 (23.2)	0 (0)	20 (22.2)	113 (18.9)
20-24 km	0 (0)	65 (58.6)	0 (0)	0 (0)	0 (0)	70 (77.8)	135 (22.6)
≥25 km	46 (100)	4 (3.6)	0 (0)	0 (0)	0 (0)	0 (0)	50 (8.4)
Median age in years of all-cause admissions, (IQR)	23 (48)	11 (40)	18 (36)	12 (34)	9 (26)	14 (52)	12 (37)
Median length of hospital stay in days, (IQR)	3.1 (7.2)	3.1 (4,4)	3.6 (4.1)	3.8 (4.6)	2.9 (4.5)	4.1 (4.7)	3.3 (4.8)
Number of non-pregnant female, n (%)	23 (50)	51 (46)	19 (43)	74 (44)	51 (37)	50 (56)	268 (45)
Mean temperature $^{o}C^{¶}$, (SD)	37.0 (1.4)	37.2 (1.1)	36.9 (0.8)	37.2 (1.2)	37.0 (1.3)	37.0 (0.9)	37.1 (1.1)
Number of participants with temperature ≥37.5 $^{o}C^{¶}$, n (%)	14 (30.4)	35 (31.5)	11 (25.0)	57 (33.9)	36 (26.1)	27 (30.0)	180 (30.1)
All malaria admissions, n (%)[¶]	2 (4.3)	24 (21.6)	4 (9.1)	22 (13.1)	12 (8.7)	12 (13.3)	76 (12.7)
Median age in years of malaria admissions, (IQR)	7 (2)	4 (4)	1.5 (2)	3 (7)	3 (4)	2 (3)	3 (5)
Severe malaria, n (%)[¶]	2 (4.3)	11 (9.9)	2 (4.5)	11 (6.5)	8 (5.8)	9 (10.0)	43 (7.2)
Median age in years of severe malaria, (IQR)	7 (2)	2 (3)	1 (2)	3 (4)	2.5 (4)	2 (3)	2 (4)
Cerebral malaria, n (%)[¶]	0 (0)	2 (1.8)	2 (4.5)	3 (1.8)	2 (1.4)	6 (6.7)	15 (2.5)
Respiratory distress, n (%)	0 (0)	0 (0)	0 (0)	3 (1.8)	2 (1.4)	1 (1.1)	6 (1.0)
Multiple convulsions, n (%)	1 (2.2)	9 (8.1)	1 (2.3)	8 (4.8)	4 (2.9)	4 (4.4)	27 (4.5)
Severe anaemia, n (%)[¶]	1 (2.2)	1 (0.9)	0 (0)	1 (0.6)	1 (0.7)	2 (2.2)	6 (1.0)
Case fatality, n (%)	5 (10.9)	13 (11.7)	3 (6.8)	12 (7.1)	8 (5.8)	12 (13.3)	53 (8.9)
Malaria related case fatality, n (%)	0 (0)	0 (0)	0 (0)	1 (0.6)	1 (0.7)	1 (1.1)	3 (0.5)
Median time to death in days, (IQR)	5.3 (4.9)	5.8 (6.8)	3.3 (5.5)	2.1 (5.4)	1.3 (14.3)	3.9 (6.0)	3.3 (6.0)

[¶]3/597 (0.5%) patients had missing data on measured axillary temperature; 2/290 (0.7%) had missing data on Glasgow coma score; 30/342 (8.8%) patients had missing data on haemoglobin concentration; 14/342 (4.1%) patients had missing blood film

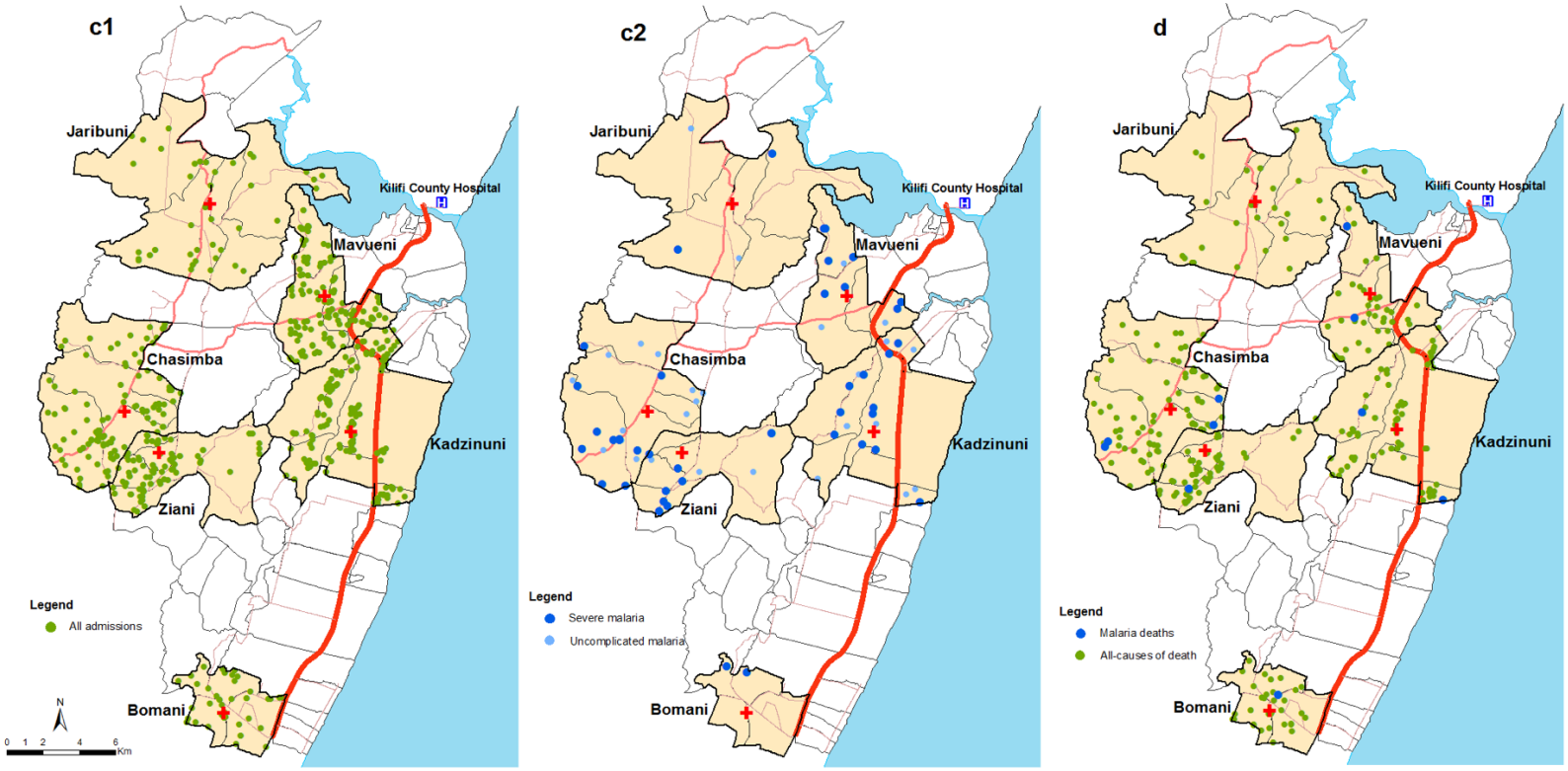


Figure 3.20: Spatial distribution of patients admitted at Kilifi County and people living within the study area that died. Panel C1 – the spatial distribution of all in-patient admissions to Kilifi county hospital between Mar 2018 and Feb 2019; Panel C2 – the spatial distribution of patients admitted with severe (dark blue dots) and uncomplicated malaria (light blue dots); and Panel D – the spatial distribution of people who died in the study area i.e. all-causes of death (green dots) and malaria related deaths (blue dots)

Information on age, sex, multiple convulsions, respiratory distress, and Blantyre Coma Score were available for all admissions. Glasgow Coma Score was available for 99% of the adult admissions (Table 3.3). Of those that were suspected to have an infectious disease or were febrile, a blood film for microscopy was available among 77% of the patients. In addition, complete data on haemoglobin concentration was available among 91% of the patients.

The causes of admission and death among the paediatric and adult patients by the broad categorization of the discharge diagnosis is shown in Table 3.4. The top five causes of admission across all ages, in rank order, were: accidents and injury (19.6%), malaria (12.7%), lower respiratory tract infection (8.5%), obstetric (8.5%), and stroke/hypertension/chronic heart disease (5.5%). Malaria (23%) and lower respiratory tract infection (17%) were the leading causes of admission among children aged 6 months-4 years. The leading causes of admission among those aged 5-14 years were malaria (22%) and accidents and injury (17%) (Table 3.4). Among the 15-49 years old, obstetric (36%) and accidents and injury (29%) were the leading causes of admission. Stroke/hypertension/chronic heart disease (28%) was the leading COD among the elderly followed by accidents and injury (19%). The median age of children admitted with malaria was 37 months (IQR: 22, 71 months) and was higher compared to the median age of children admitted with lower respiratory tract infection i.e. 22 months (IQR: 12, 31 months). Other diagnoses and unknown causes of admissions accounted for 9% and 7% of all the admissions, respectively.

Case fatality across all age groups was highest among patients with lower respiratory tract infection (15%) and stroke/hypertension/chronic heart disease (15%). The second most common cause of death was meningitis (8%). Malaria, anaemia, and malnutrition each

accounted for 5.7% (n=3) of all hospital deaths in the study area (Table 3.4). Other causes of death and unknown causes of death accounted for 11% and 9% of all the hospital deaths, respectively.

Table 3.4: Causes of admission among paediatric and adult patients and inpatient deaths (in parenthesis) between March 2018 and February 2019 at Kilifi county hospital stratified the age group

In-patient cause of admission and death	6 months-4 years	5-14 years	15-49 years	50+ years	Overall cause of admission, n (%)	Overall cause of death, n (%)
Trauma-injury-accident-snake bite	18 (1)	18 (0)	60 (0)	21 (0)	117 (19.6)	1 (1.9)
Malaria	49 (1)	24 (2)	2 (0)	1 (0)	76 (12.7)	3 (5.7)
Lower respiratory tract infection	35 (4)	6 (0)	3 (1)	7 (3)	51 (8.5)	8 (15.1)
Obstetric	0 (0)	0 (0)	49 (0)	2 (0)	51 (8.5)	0 (0)
Stroke/hypertension/chronic heart disease	0 (0)	0 (0)	1 (0)	32 (8)	33 (5.5)	8 (15.1)
Sickle cell disease	11 (0)	18 (1)	3 (0)	0 (0)	32 (5.4)	1 (1.9)
Gastroenteritis	25 (0)	2 (1)	1 (0)	0 (0)	28 (4.7)	1 (1.9)
Epilepsy	7 (0)	6 (0)	4 (0)	1 (0)	18 (3.0)	0 (0)
Hernia	0 (0)	1 (0)	7 (0)	8 (0)	16 (2.7)	0 (0)
Anaemia	5 (1)	5 (1)	3 (0)	1 (1)	14 (2.4)	3 (5.7)
Cancer	0 (0)	0 (0)	0 (0)	14 (3)	14 (2.4)	3 (5.7)
Meningitis	4 (0)	2 (0)	4 (2)	2 (2)	12 (2.0)	4 (7.6)
Skin infections/cellulitis	0 (0)	0 (0)	6 (0)	6 (0)	12 (2.0)	0 (0)
Malnutrition	10 (3)	1 (0)	0 (0)	0 (0)	11 (1.8)	3 (5.7)
Organ infections	0 (0)	1 (0)	1 (0)	4 (3)	6 (1.0)	3 (5.7)
Tuberculosis	0 (0)	0 (0)	3 (1)	3 (1)	6 (1.0)	2 (3.8)
Diabetes	0 (0)	0 (0)	2 (0)	2 (2)	4 (0.7)	2 (3.8)
Mental disorders	0 (0)	0 (0)	3 (0)	0 (0)	3 (0.5)	0 (0)
Other causes of admission	21 (1)	15 (2)	13 (3)	5 (0)	54 (9.0)	6 (11.3)
Unknown causes of admission	25 (1)	8 (2)	2 (0)	4 (2)	39 (6.5)	5 (9.4)
All causes of admission	210 (12)	107 (9)	167 (7)	113 (25)	597 (100)	53 (100)

Discharge diagnoses were amalgamated to form broad categories; other causes of admissions included upper respiratory tract infection, septicaemia/sepsis, urinary tract infection, cerebral palsy, bronchiolitis, acute renal failure, hepatic failure, intestinal obstruction, and neonatal sepsis.

3.5.5 Hospitalised malaria

Of the 76 malaria cases, the majority (57%) presented with one or more criteria for severe malaria; 33 (43%) cases had uncomplicated malaria. Twenty cases (26%) presented with multiple convulsions as the only criteria for severe malaria, six (8%) with cerebral malaria only, two (3%) with respiratory distress, and five (7%) with severe malaria anaemia only. Six cases (8%) presented with signs of both multiple convulsions and cerebral malaria, one case (1%) presented with signs of both multiple convulsions and respiratory distress, one (1%) with both respiratory distress and severe malaria anaemia, and three (4%) with cerebral malaria and respiratory distress, where all three cases died. The ratio of children with cerebral malaria to severe malaria anaemia was 5:2. The spatial distribution of all patients with uncomplicated and severe malaria in the study area is shown in Figure 3.20c2.

The age distribution of features of malaria clinical presentation is shown in Table 3.5. The median age of all malaria admission was 3 years (IQR: 1 year, 6 years). There were no severe cases of malaria among patients aged 9 years and above. There were, however, eight uncomplicated malaria cases reported among patients aged 11, 12, 18, 31 and 88 years: two among females and six among male patients. The highest number of malaria cases were reported among children aged one year with the majority presenting with multiple convulsions (Table 3.5). The median age of patients presenting with cerebral malaria was 57 months (IQR: 28, 97 months) and the median age of those with respiratory distress was higher 71 months (IQR: 57, 84 months). However, the median age among those with severe malaria anaemia was lower at 33 months (IQR: 22, 77 months). There was no obvious association of any form of disease severity and age except for multiple convulsions where the median age was significantly lower (χ^2=9.87; p=0.002).

Additionally, there was no difference in the age-sex pattern among patients with malaria (χ^2=3.68; p=0.72) (Annex 15).

Table 3.5: Clinical presentation of severe forms of malaria and uncomplicated malaria in patients aged 6 months and above

Severity feature	6 months-4 years	5-14 years	15-49 years	>49 years	Overall
All malaria admissions	49	24	2	1	76
Uncomplicated malaria	19	11	2	1	33
Severe malaria	30	13	0	0	43
Cerebral malaria	8	7	0	0	15
Respiratory distress	2	4	0	0	6
Multiple convulsions	22	5	NA	NA	27
Severe anaemia	4	2	0	0	6

The incidence of malaria admissions, computed as the number of episodes of malaria admissions/person-years of observation, was obtained from the in-patient surveillance (Figure 3.21). The incidence of malaria admission was highest, at 7.96 per 1,000 person-years (95% CI: 4.79, 12.43 episode per 1,000 person-years), among children aged 1 year and then declined thereafter. Malaria admission among adults was negligible. A similar trend was observed with the severe malaria cases (Figure 3.21), where severe malaria cases peaked at 5.03 episodes per 1,000 person-years (95% CI: 2.60, 8.78 episodes per 1,000 person-years) and then sharply declined thereafter.

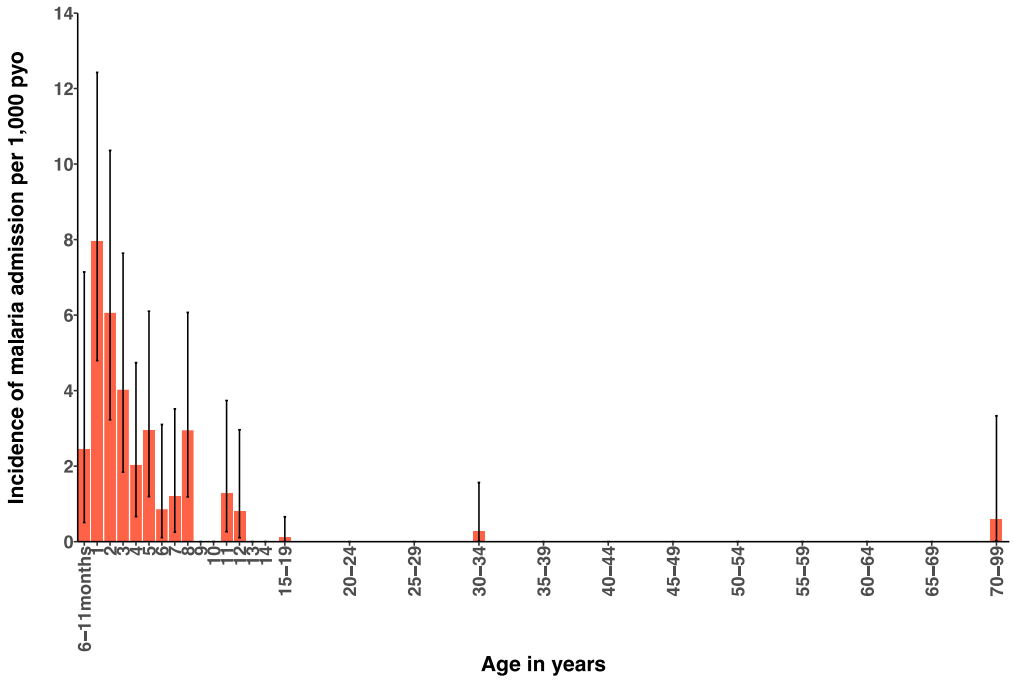


Figure 3.21: Age-specific incidence rate of malaria admission per 1,000 person-years of observation with 95% confidence interval computed using the exact Poisson distribution

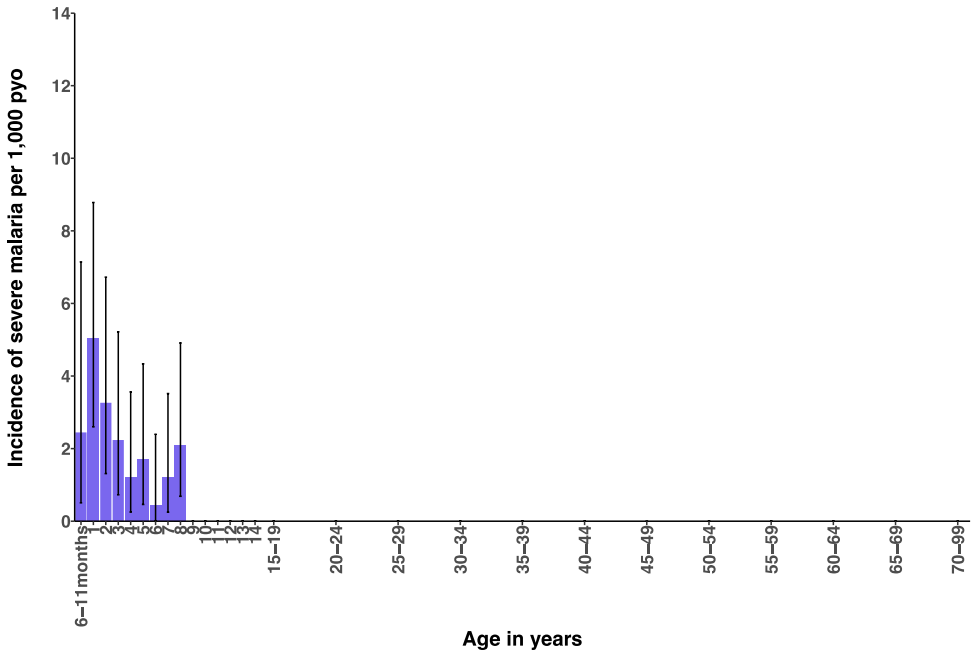


Figure 3.22: Age-specific incidence rate of severe malaria admission per 1,000 person-years of observation with 95% confidence interval computed using the exact Poisson distribution

3.5.6 Cause of deaths in the selected study area

A total of 316 deaths were recorded among the population of the study area between March 2018 and February 2019. The characteristics of the people that died in the study area are shown in Table 3.6. The majority (26%) of deaths occurred in Chasimba while only 9% of deaths occurred in Jaribuni (Table 3.6). Thirty-six deaths (11%) were among children aged 6 months-4 years, 22 (7%) among 5-14 years, 61 (20%) among 15-49 years and 197 (62%) deaths among those aged 50 years and above. Among children aged 6 months-4 years, 10 (28%) deaths occurred before the 1st birthday. Deaths among males were comparable to deaths among females (53% vs. 47%, respectively; χ^2=45.08; p=0.08) (Table 3.6). Of the 316 deaths, 81 (23%) had been admitted at the Kilifi county hospital over the preceding 24 months. 55 (77%) died during hospital admission, 8 (11%) died <30 days post-discharge and only 4/18 (13%) individuals had been admitted over the preceding 24 months, where three had been diagnosed with terminal cancer and one with epilepsy (Table 3.6 & Figure 3.23). Verbal autopsy (VA) interviews were completed for 197 (79%) of 249 deaths without hospital contact. The median time to VA interview was 10.2 weeks (IQR: 6.9 weeks, 14 weeks). 35 deaths were classified as unambiguous causes of death that were not malaria after reviewing the InterVA-4 100% probability assigned cause or available information in the free text fields (Figure 3.23). Among the remaining 162 VA defined deaths, the InterVA-4 model assigned a single cause of death to 141 cases (87.0%), two causes of death to 14 cases (8.6%), three causes of death to one case (0.6%) and 6 cases (3.7%) were indeterminate. The spatial distribution of people that died in the study area and those whose cause of death was attributable to malaria is shown in Figure 3.20d.

Table 3.6: Background characteristics of people living in the study area that died between March 2018 and February 2019

Characteristics	Bomani	Chasimba	Jaribuni	Kadzinuni	Mavueni	Ziani	Overall
All-causes of death, n	38	80	30	70	43	55	316
Median age in years of all-causes of death, (IQR)	53.5 (26)	60.5 (60)	68 (39)	60 (48)	53 (45)	66 (34)	60.5 (41)
Number of female, n (%)	15 (39.5)	39 (48.8)	15 (50)	34 (48.6)	17 (39.5)	28 (50.9)	148 (46.8)
Admitted at Kilifi County hospital, n (%)	10 (18.4)	19 (21.3)	7 (16.7)	16 (21.4)	12 (25.6)	17 (29.1)	81 (22.5)
Died during hospital admission, n (%)	5 (13.2)	13 (16.3)	3 (10.0)	11 (15.7)	9 (20.9)	14 (25.5)	55 (17.4)
Died within 30 days post-discharge, n (%)	1 (2.6)	2 (2.5)	0 (0)	1 (1.4)	2 (4.7)	2 (3.6)	8 (2.5)
Died within 24-month post-discharge, n (%)	4 (10.5)	4 (5.0)	4 (13.3)	4 (5.7)	1 (2.3)	1 (1.8)	18 (5.7)
Unambiguous causes of death, n (%)	4 (10.5)	9 (11.3)	4 (13.3)	7 (10.0)	8 (18.6)	3 (5.5)	35 (11.1)
Verbal autopsy (VA) interviews completed, n (%)	18 (47.4)	41 (51.3)	14 (46.7)	37 (52.9)	18 (41.9)	28 (50.9)	156 (49.4)
Cause of death (COD) completed, n (%) [¶]	29 (76.3)	66 (82.5)	23 (76.7)	59 (84.3)	38 (88.4)	49 (89.1)	264 (83.6)
Missing COD, n (%)	9 (23.7)	14 (17.5)	7 (23.3)	11 (15.7)	5 (11.6)	6 (10.9)	52 (16.4)
Median time to VA interview in weeks, (IQR)	12.4 (8.6)	9.6 (4.7)	9.1 (7.9)	11.4 (7.3)	10.2 (8.8)	8.9 (9.4)	10.2 (7.1)

[¶] Cause of death (COD) was either assigned at the hospital or from the InterVA-model

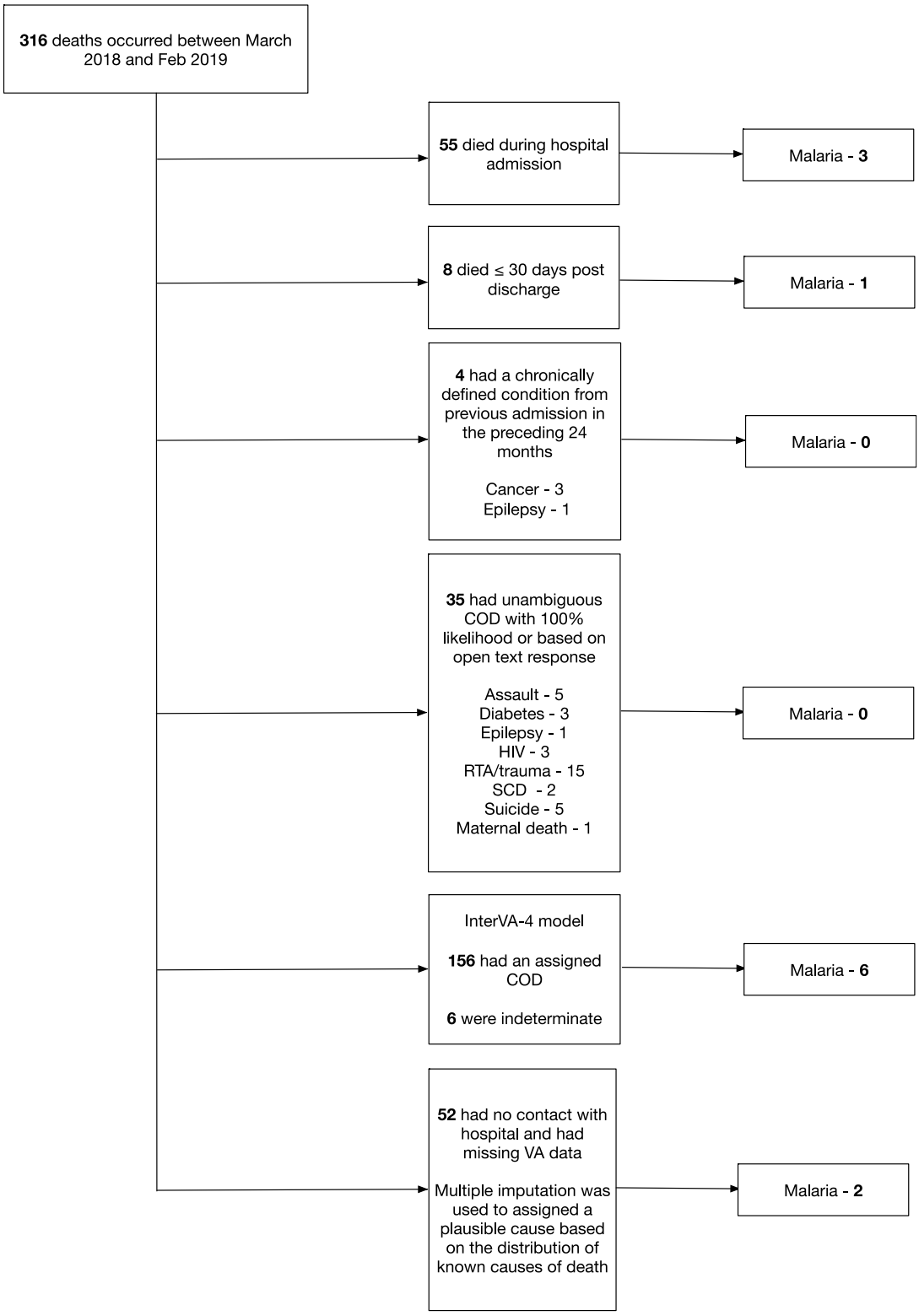


Figure 3.23: Varying confirmatory evidence to attribute deaths with malaria

Cause of death (COD) was available in 84% of the people that died; assigned either at the hospital or from the InterVA-4 model (Table 3.6). The top six causes of death (COD) across all ages, in rank order, were: acute respiratory infections (22.0%), stroke/ hypertension/chronic heart disease (16.3%), cancer (9.1%), accidents and injury (6.8%), malaria, and malnutrition each accounting for 3.8% of the deaths. Respiratory infection (44%) was the leading COD among children aged 6 months-4 years (n=11); malaria accounted for 16% of all deaths in this age group (Table 3.7). The leading CODs among those aged 5-14 years was malaria (28.6%), while HIV/AIDS related death, acute respiratory infection, anaemia, and gastroenteritis each accounted for 4.8% of deaths (Table 3.7). Among the 15-49 years old, accidents and injury (14.3%) and respiratory infections (12.2%) were the leading CODs. Stroke/hypertension/chronic heart disease (25.2%) was the leading COD among the elderly followed by respiratory infection (24.5%) and cancer at 13.5% (Table 3.7). About 49% of children aged <15 years and 25% of all adult deaths in the study area occurred during hospital admission.

Table 3.7: Cause of death assigned at the hospital or from VA stratified by age group, n [x/y where x = hospital death and y = VA death] (% of total deaths in that age group)

Cause of death	6 months-4 years	5-14 years	15-49 years	50+ years	Overall
Pneumonia infections	11 [4/7] (44.0%)	1 [0/1] (4.5%)	6 [1/5] (11.8%)	40 [3/37] (24.1%)	58 [8/50] (22.0%)
Stroke/hypertension/chronic heart disease	0 [0/0] (0%)	1 0/1] (4.5%)	1 [0/1] (2.0%)	41[10/31] (24.7%)	43 [10/33] (16.3%)
Cancer	0 [0/0] (0%)	0 [0/0] (0%)	2 [1/1] (3.9%)	22 [5/17] (13.3%)	24 [6/18] (9.1%)
Trauma/injury/accident/snake bite	2 [1/1] (8.0%)	2 [0/2] (9.1%)	7 [1/6] (13.7%)	7 [1/6] (4.2%)	18 [3/15] (6.8%)
Malaria	4 [1/3] (16.0%)	6 [3/3] (27.3%)	0 [0/0] (0%)	0 [0/0] (0%)	10 [4/6] (3.8%)
Malnutrition	3 [3/0] (12.0%)	0 [0/0] (0%)	1 [0/1] (2.0%)	6 [0/6] (3.6%)	10 [3/7] (3.8%)
HIV/AIDS	0 [0/0] (0%)	1 0/1] (4.5%)	3 [0/3] (5.9%)	3 [0/3] (1.8%)	7 [0/7] (2.7%)
Anaemia	1 [1/0] (4.0%)	1 0/1] (4.5%)	0 [0/0] (0%)	4 [1/3] (2.4%)	6 [3/3] (2.3%)
Assault	0 [0/0] (0%)	0 [0/0] (0%)	3 [0/3] (5.9%)	2 [0/2] (1.2%)	5 [0/5] (1.9%)
Diabetes	0 [0/0] (0%)	0 [0/0] (0%)	0 [0/0] (0%)	5 [2/3] (3.0%)	5 [2/3] (1.9%)
Meningitis	1 [0/1] (4.0%)	0 [0/0] (0%)	1 [0/1] (2.0%)	3 [2/1] (1.8%)	5 [3/2] (1.9%)
Suicide	0 [0/0] (0%)	0 [0/0] (0%)	4 [0/4] (7.8%)	1 [0/1] (0.6%)	5 [0/5] (1.9%)
Tuberculosis	0 [0/0] (0%)	0 [0/0] (0%)	1 [0/1] (2.0%)	4 [1/3] (2.4%)	5 [1/4] (1.9%)
Epilepsy	1 [1/1] (4.0%)	0 [0/0] (0%)	1 [0/1] (2.0%)	2 [0/2] (1.2%)	4 [1/3] (1.5%)
Maternal death	0 [0/0] (0%)	0 [0/0] (0%)	3 [0/3] (5.9%)	0 [0/0] (0%)	3 [0/3] (1.1%)
Organ Infection	0 [0/0] (0%)	0 [0/0] (0%)	0 [0/0] (0%)	3 [3/0] (1.8%)	3 [3/0] (1.1%)
SCD	0 [0/0] (0%)	2 [0/2] (9.1%)	1 [0/1] (2.0%)	0 [0/0] (0%)	3 [1/2] (1.1%)
Other COD	1 [1/0] (4.0%)	3 [3/0] (13.6%)	14 [7/7] (27.5%)	14 [4/10] (8.4%)	32 [15/17] (12.1%)
Unknown	1 [1/0] (4.0%)	5 [2/3] (22.7%)	3 [0/3] (5.9%)	9 [1/8] (5.4%)	18 [4/14] (6.8%)
All-cause mortality, n	25 [13/12]	22 [10/12]	51 [11/40]	166 [33/133]	264 [67/197]

The cause-specific mortality fractions were assigned either at the Kilifi county hospital or by the InterVA-4 model. Other cause of death (COD) included: sickle cell disease, asthma, renal failure, septicaemia/sepsis, epilepsy, gastroenteritis, diabetes, liver cirrhosis, intentional self-harm, abortion-related death, other and unspecified infectious diseases, other and unspecified maternal COD; sepsis (non-obstetric), breast neoplasms, oral neoplasms, digestive neoplasms, other and unspecified neoplasms, and respiratory neoplasms.

Of the 55 individuals who died during hospital admission, only 3 had been diagnosed with malaria. Among the 8 individuals that died <30 days post-discharge, only one was diagnosed with malaria during admission. InterVA-4 model assigned malaria as a primary cause of death to 6 individuals (Figure 3.23). There were two individuals aged 1 year and 98 years that had malaria recorded by the InterVA-4 model as a secondary cause of death. On reviewing the VA questionnaire, the indicators showed that the 1-year-old child had acute fever, acute rapid breathing, chest wall indrawing, vomiting, swollen abdomen, anaemia, and had received antibiotic treatment. In this infant, the primary cause of death, acute abdomen, was replaced with malaria. The female aged 98 years had the following indicators acute fever, acute cough, which was excluded as the primary underlying COD assigned by the InterVA-4 model was acute respiratory infections including pneumonia. One 40-year-old woman had malaria recorded by the InterVA-4 as a tertiary cause of death, which was also excluded as the primary and secondary causes were abortion-related and pregnancy-related sepsis, respectively.

COD data was missing for 52 (16.4%) of 316 deaths; 21% among children aged 6 months-4 years, 19% among adults aged 15-49 years, and 60% among the elderly. There was no difference in the age distribution of complete cases vs. those missing COD (χ^2=6.60; p=0.09). Using the MICE algorithm, there were 2 cases (IQR 1,3 cases) ascribed malaria based on the distribution of deaths among known causes.

Using the composite approach, malaria was attributed as the primary cause of death among 6/36 children aged 6 months-4 years, 6/22 deaths among children aged 5-14 years, and none among the 258 adult deaths above 15 years (Table 3.8 & Figure 3.24). Only 3.7% (12/316) of deaths were attributable to malaria. The overall incidence of malaria related deaths was 0.17 episodes per 1,000 person-years (95% CI: 0.09, 0.29 episode

per 1000 person-years). Malaria mortality rates among children aged 6 months-4 years and 5-14 years, were 0.57 per 1,000 person-years (95% CI: 0.2, 1.2 episode per 1000 person-years) and 0.25 per 1,000 person-years (95% CI: 0.09, 0.56 episode per 1000 person-years), respectively (Table 3.8).

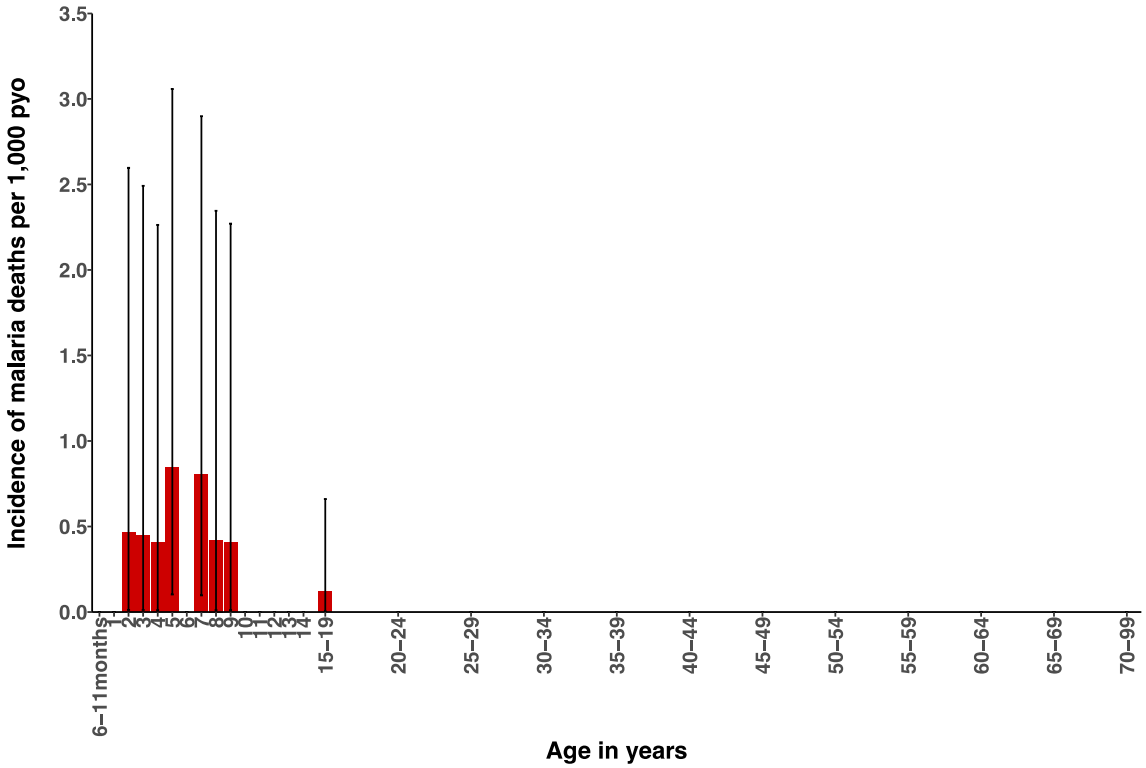


Figure 3.24: Age-specific incidence rate of deaths caused by malaria (derived either from hospital records, by the InterVA-4 model, or by MICE algorithm) per 1,000 person-years of observation with 95% confidence interval computed using the exact Poisson distribution

3.6 Discussion

Paramount to the understanding of the expected impact of interventions that reduce parasite exposure is the relationship between malaria transmission intensity and the ensuing burden of disease, or mortality. The relationship between these measures is certainly governed by the biology of immune acquisition, however, empirical data on the incidence of new infections, mild clinical disease, severe disease and death remain rare.

The focus has been on the relationships of infection and disease risks in childhood, far less is currently known about these relationships in non-pregnant adults.

3.6.1 Malaria infection prevalence

Across four cross-sectional surveys, the overall prevalence of infection was 10%, without significant seasonal variation. The prevalence among children aged 2-10 years was 12.7% and the area is therefore currently best described as meso-endemic [Metselaar & Van, 1959; Table 1.4]. It was not possible to compute the incidence of new infections, as this would require entomological surveillance or oversampling infants during the cross-sectional surveys. However, using a previously developed mathematical model on the relationship between prevalence in children aged 2-10 years and entomological inoculation rates (EIR) [Smith et al., 2005; Gething et al., 2011], it was estimated that individuals in this area might expect to receive one infectious bite every two years.

Despite a low transmission intensity, the age-pattern of infection was consistent with patterns previously described across a wide range of endemicities (Section 1.5.1; Figure 1.5). Infection rose through childhood to peak at 12 years, before declining after 24 years and remained relatively constant, below 5%, throughout adult life (Figure 3.25A). Between 1999-2001, within in a similar geographical range to the present study [Mwangi, 2003; Mwangi et al., 2005; Figure 3.26] and a parasite rate of 43.1%, a similar age-pattern of infection was observed except that it peaked at 10 years and declined after 19 years, showing that the curve had shifted slightly but infection was much lower in adulthood (Figure 3.26). This suggests that a combination of immune acquisition and behavioural protection from infection might continue to operate in the same way over time. While the age of decline may be reliant on the frequencies of new infections, anti-parasitic immunity was acquired during late childhood under different transmission intensities. This was an

interesting observation, and consistent with recent studies in Uganda on the speed of anti-parasitic immunity from birth to the 10th birthday described at three sites, of different starting EIRs (2, 8 and 51) [Rodriguez-Barraquer et al., 2016; Rodriguez-Barraquer et al., 2018]. Despite differences in the acquisition of clinical immunity between sites, the rate of acquired anti-parasitic immunity was broadly similar [Rodriguez-Barraque et al., 2018].

Here RDTs have been used to describe the prevalence of HRP2 antigenemia, to serve as a direct comparison with methods used during surveillance at health facilities. However, RDTs are often described as having a high false positive rate compared to microscopy. In addition, microscopy is known to have false negatives when compared with molecular methods, and the HRP2 antigenemia detected by RDTs may reflect recent infection that has been cleared (Section 1.7.1). An analysis of these imperfect tests using a Bayesian framework applied to data from Kilifi concluded that microscopy and RDT afford high sensitivity and specificity in symptomatic care-seeking children in this low *P. falciparum* prevalence setting [Mweu et al., 2019]. Moreover, no parasites lacking both HRP2 and HRP3 genes have been detected in Kenya [Beshir et al., 2017]. RDTs are now widely used in clinical and survey settings, but it is important to note that comparisons with other data on microscopy (Figure 3.26) are relative, rather than absolute.

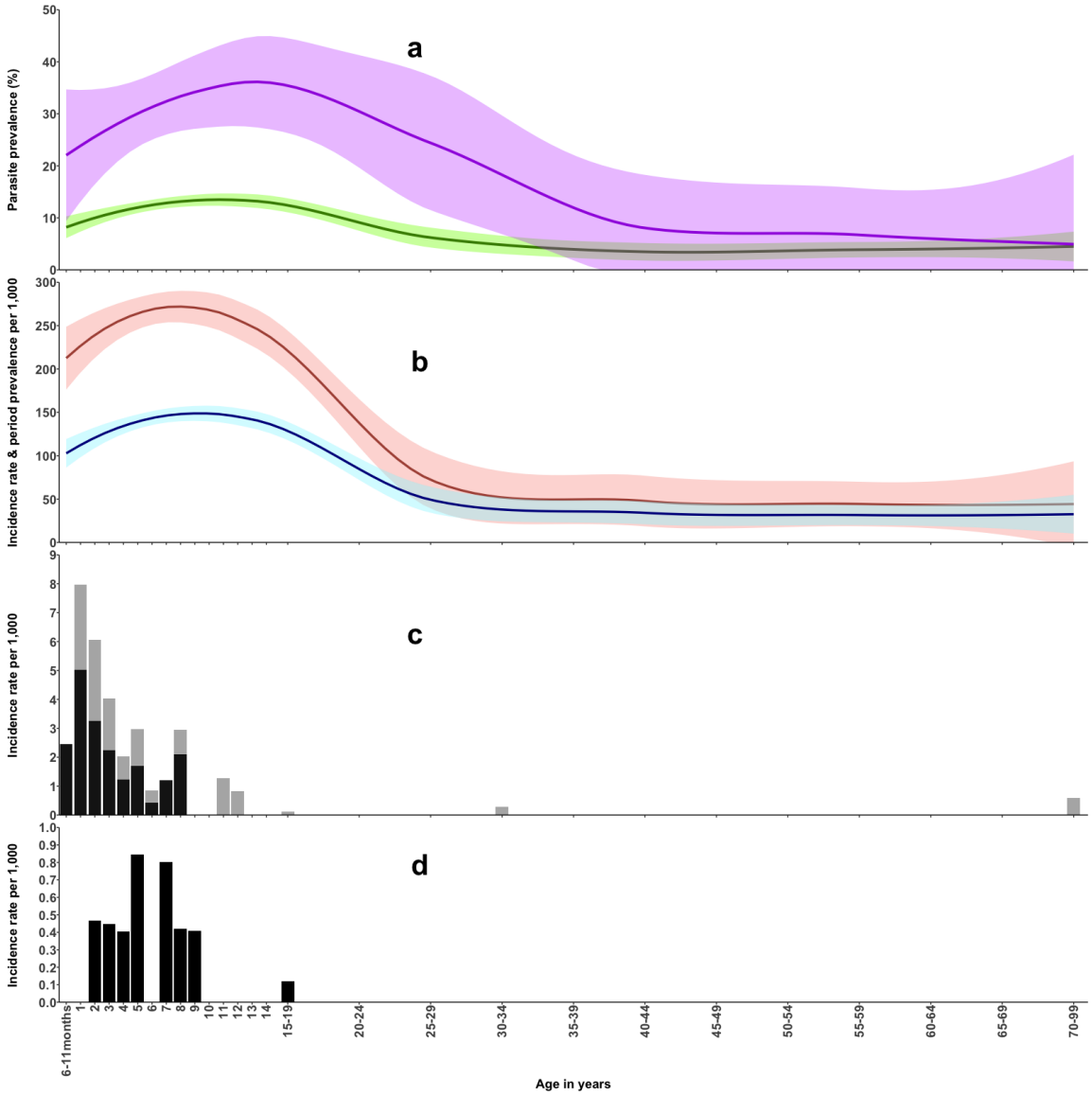


Figure 3.25: Comparison of malaria metrics across all age in the study area. Panel A – the parasite prevalence (green line) and community fever test positive prevalence (purple line). Panel B – the health facility RDT period prevalence (red line) and health facility RDT incidence rate (blue line). Panel C – the incidence of uncomplicated malaria admission (grey bar) and incidence of severe malaria (black bars). Panel D – the incidence of deaths attributable to malaria. Reproduced from Kamau et al., 2020, published CC-BY 4.0

Table 3.8: Likelihood of malaria infection and disease severity by age group. Reproduced from Kamau et al., 2020, published CC-BY 4.0

Measure	6 months - 4 years	5 - 14 years	15 - 49 years	50+ years	Overall
Parasite prevalence (PR)					
%	10.1%	13.4%	7.1%	4.3%	9.9%
(95% CI)	(8.5, 12.0)	(12.0, 14.9)	(6.0, 8.4)	(2.8, 6.4)	(9.2, 10.7)
n/N	136/1342	337/2523	146/2056	24/558	643/6479
Fever test positivity prevalence					
%	22.0%	35.0%	28.9%	11.4%	27.3%
(95% CI)	(13.8, 33.3)	(25.3, 47.1)	(18.9, 42.3)	(3.1, 29.3)	(22.7, 32.3)
n/N	22/200	43/123	26/90	4/35	95/348
Malaria passive period prevalence					
‰	251.3‰	271.0‰	93.3‰	47.8‰	169.7‰
(95% CI)	(241.8, 261.1)	(264.4, 277.7)	(89.8, 96.9)	(43.2, 52.8)	(166.9, 172.5)
n/N	2628/10456	6388/23571	2733/29297	394/8238	12143/71562
Malaria passive incidence rate					
‰	121.5‰	150.1‰	60.0‰	33.4‰	95.6‰
(95% CI)	(114.9, 128.3)	(145.2, 155.2)	(57.3, 62.9)	(29.6, 37.6)	(93.5, 97.8)
n/N	1270/10456	3539/23571	1759/29297	275/8238	6843/71562
Malaria admissions					
‰	4.7‰	1.0‰	0.07‰	0.1‰	1.1‰
(95% CI)	(3.5, 6.2)	(0.7, 1.5)	(0.008, 0.2)	(0.003, 0.7)	(0.8, 1.3)
n/N	49/10456	24/23571	2/29297	1/8283	76/71562
Severe malaria					
‰	2.9‰	0.6‰	0‰	0‰	0.6‰
(95% CI)	(1.9, 4.1)	(0.3, 0.9)	(0, 0.1)	(0, 0.4)	(0.4, 0.8)
n/N	30/10456	13/23571	0/29297	0/8283	43/71562
Hospital malaria Deaths					
‰	0.1‰	0.1‰	0‰	0‰	0.06‰
(95% CI)	(0.002, 0.5)	(0.03, 0.4)	(0, 0.1)	(0, 0.4)	(0.02, 0.1)
n/N	1/10456	3/23571	0/29297	0/8283	4/71562
Hospital + Inter-VA malaria Deaths					
‰	0.4‰	0.3‰	0‰	0‰	0.1‰
(95% CI)	(0.1, 1.0)	(0.1, 0.6)	(0, 0.1)	(0, 0.4)	(0.07, 0.3)
n/N	4/10456	6/23571	0/29297	0/8283	10/71562
Hospital + Inter-VA malaria Deaths + Imputed malaria deaths					
‰	0.6‰	0.3‰	0‰	0‰	0.2‰
(95% CI)	(0.2, 1.2)	(0.1, 0.6)	(0, 0.1)	(0, 0.4)	(0.09, 0.3)
n/N	6/10456	6/23571	0/29297	0/8283	12/71562

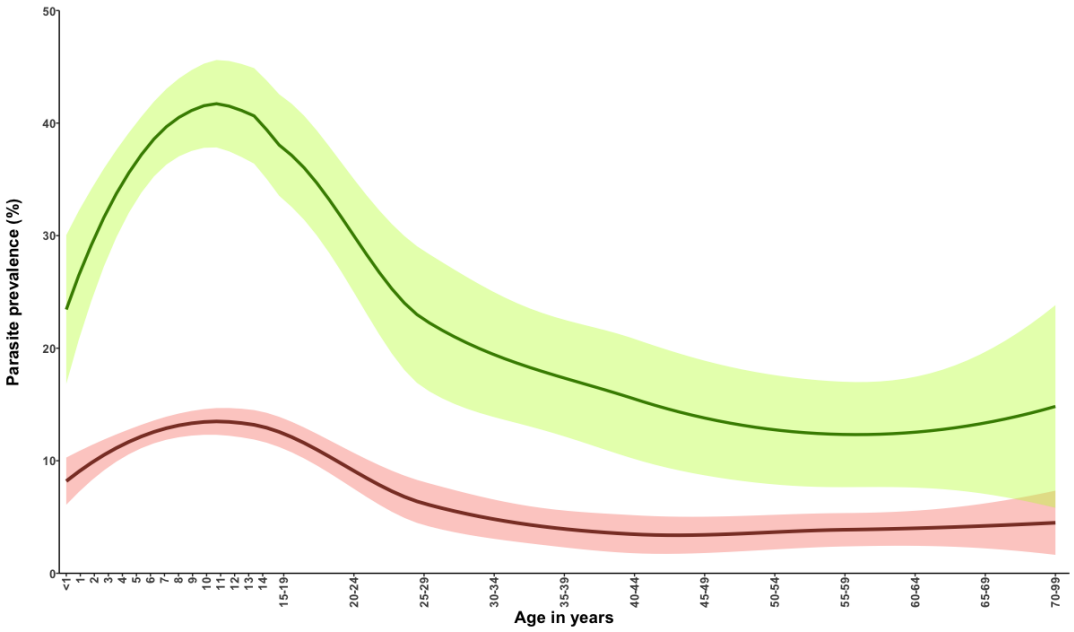


Figure 3.26: Parasite prevalence between 1999 - 2001 (green line) [Mwangi, 2003; Mwangi et al., 2005]. Current parasite prevalence between 2018 – 2019 (red line). Reproduced from Kamau et al., 2020, published CC-BY 4.0

The prevalence of infection was highest among children aged 5-14 years (Table 3.8 & Figure 3.25A). In addition, this age group experienced the highest cross-sectional prevalence of reported/measured fever associated with infection (Figure 3.25A), accounting for 45.3% of all RDT positive fevers detected during the four cross-sectional surveys. School-aged children and adolescents remain a neglected age-group in many strategies for malaria prevention and disease management [Lalloo et al., 2006; Noor et al., 2009d; Cohee et al., 2020]. Insecticide-treated net delivery systems often focus on protecting new-borns through provision to mothers attending antenatal clinics or at maternal and child health clinics. The protection from infection through seasonal malaria chemoprevention is principally aimed at children under-five years. Where the intention is to reduce the parasite burden in a community and hence influence transmission intensity. Children aged 5-14 years should not be ignored since they substantially contribute to the reservoir of *P. falciparum* infection [Walldorf et al., 2015; Cohee et al., 2020].

From the age of 30 years, prevalence steadily decreased to very low level through to old age, suggesting a continued acquisition of non-sterilizing immunity throughout adulthood (Figure 3.25A), similar to what was observed 20 years ago in the same area (Figure 3.26). This pattern was also observed among adults tested with PCR in Mozambique [Mayor et al., 2007]

3.6.2 Incidence of fevers associated with malaria

Over 12 months, 12,143 fevers associated with malaria infection presented to the six health facilities shown in Figure 3.6, among a censused population of 71,562 aged 6 months and above. This corresponded to a 95.6 (95% CI: 93.5, 97.8) annual incidence of passively detected cases of 'malaria' per 1,000 person-years per annum (Table 3.8). Not all events would have been clinical malaria, rather a definition was used that reflects proposed clinical practice to manage malaria among out-patient populations according to guidelines provided by the Ministry of Health [MoPHS, 2010]. Underlying causes of fever were not excluded [D'Acremont et al., 2014], nor was a parasite density threshold used as proposed for clinical trials or age-fever dependent thresholds of parasite density used during Active Case-Detection (ACD) surveys in Africa (Section 1.7.2). The passively detected morbidity burden represents definitions used by WHO for disease burden estimation (Section 1.9.2) and what should be managed by health workers in Kenya.

The age-pattern of the period prevalence and incidence of fevers associated with malaria rose in childhood to peak at 10 years and declined thereafter to low level throughout adulthood (Figure 3.25B). Repeat episodes were more common in younger children as shown in the difference between period prevalence and incidence (Figure 3.25B). The decline in the incidence of fever test-positivity occurred earlier than community-defined

prevalence (Figure 3.25A). The highest risk in children aged 5-14 years was consistent with the background prevalence of infection in this community and may represent a coincidental rather than attributable risk in this age group. However, among all individuals presenting to the health facilities with RDT positive fevers, 52.6% were aged 5-14 years and therefore represents a substantial health system burden requiring malaria treatment according to national guidelines [Guinovart et al., 2008; Ndong et al., 2014; Githinji et al., 2016; Kapesa et al., 2018; Lechthaler et al., 2019; Manego et al., 2019].

Fever test positive period prevalence and incidence were much lower among non-pregnant adults beyond the age of 20 years and was similar to the prevalence of infection in the community (Figure 3.25B), suggesting that infection in this age range was similar and, therefore not an attributable risk of infection. In Southern Mozambique, 50% of adults were infected with *P. falciparum* by PCR, however, using a stricter definition of clinical malaria only 2.3% of fevers could be attributed to infection above 15 years [Mayor et al., 2007].

The burden of clinically defined malaria morbidity as a relative difference between children under-five years and those aged 5-14 years appears to vary between settings and broadly relates to the intensity of transmission between sites. In lower transmission settings, the burden was notably higher among children aged 5-14 years compared to children under-five years, for example, Eastern Sudan [Giha et al., 2000], Sotuba, Mali [Dicko et al., 2007], Ankazobe, Madagascar [Boisier et al., 2002] and Ndiop, Senegal [Trape & Rogier, 1996], but higher among children under-five years relative to children aged 5-14 years in high transmission settings, for example, Ifakara, Tanzania [Smith et al., 1993], Siaya, Kenya [Bloland et al., 1999], Chonyi and Ngerenya, Kenya [Mwangi, 2003; Mwangi et al., 2005], Dielmo, Senegal [Trape et al., 1994; Trape & Rogier, 1996], Baloghin, Burkina Faso

[Nebie et al., 2008], Donéguébougou, Mali [Dicko et al., 2007] Koro, Mali [Dolo et al., 2005], and Brazzaville, Congo [Trape et al., 1987]. Anomalies exist with higher rates among children aged 5-14 year compared to under-five years in a high transmission setting of northern Ghana [Koram et al., 2003], and a low transmission setting in Madagascar where the incidence of clinical malaria was higher among children under-five years compared to children aged 5-14 years [Rabarijaona et al., 2009]. However, in sites where adults were included, the incidence of clinical malaria was considerably lower among adults across all transmission settings [Smith et al., 1993; Trape & Rogier, 1996; Giha et al., 2000; Boisier et al., 2002; Koram et al., 2003; Dolo et al., 2005; Mwangi et al., 2005; Rabarijaona et al., 2009; Nankabirwa et al., 2020].

The precise relationship between the intensity of transmission and the incidence of clinical malaria by age remains uncertain, largely because of variations in the detection methods (ACD, PCD, daily, weekly, fortnightly), case definitions used between sites, and the paucity of data beyond 15 years of age (Section 1.10).

3.6.3 Severe malaria

The age-specific incidence of severe malaria showed a very different age-profile to either community-based or passively detected fever prevalence of malaria infection (Figure 3.25C). The incidence of hospitalised malaria from the same community was concentrated among children aged 6 months to 4 years i.e. 64% and 70% of all hospitalized and severe malaria during the 12 months of surveillance, respectively. Only 25% and 30% of all hospitalised and severe malaria occurred in the age group 5-9 years, respectively. There were three cases of non-severe, hospitalised malaria described in individuals aged, 18, 31, 88 years, none of these presented with severe malaria (Figure 3.25C). This suggests that immunity to the severe consequences of infection is acquired earlier in life than

immune protection to milder forms of febrile disease (Figure 3.25B) and infection (Figure 3.25A). Despite the low numbers of severe malaria cases from the specified study area, cerebral malaria was the most prevalent syndrome compared to severe malaria anaemia. At current levels of low infection prevalence, and presumed EIR, hospitalised malaria continues to be a paediatric problem, with the median age of admission being 37 months among children aged less than 15 years. This was higher than the median age (15 months) of hospitalized malaria reported within the same geographical range between 1992-1996 [Snow et al., 1997].

The concentration of hospitalized and severe malaria among children aged below five, and the rarity of admissions older than 10 years has recently been shown across a wide range of transmission settings in western Kenya [Akech et al., 2019] and Uganda [Mpimbaza et al., 2020a]. The present study area is part of a wider surveillance community, which has been under surveillance since 1990. Across the wider area, the mean age of paediatric malaria admissions to KCH, has been steadily increasing since 1990 from 20.2 months to 45.3 months in 2014 [Mogeni et al., 2016; Njuguna et al., 2019]. This shifting age-pattern of malaria requiring hospitalisation was consistent with a declining parasite exposure on the Kenyan coast [Snow et al., 2015a; Macharia et al., 2018] and infection prevalence among paediatric trauma admissions to KCH [Mogeni et al., 2016] (Figure 3.3). However, most paediatric admissions in the wider Kilifi DSS between 2015-2017 were among children under five (57%) or under 10 (93%) years [Njuguna et al., 2019].

The present study area has also been subject to a transition in the intensity of malaria transmission over the last 20 years (Figure 3.26). This is important when considering risks among adults, who will have been exposed to very different levels of parasite exposure

during their childhood. Nevertheless, the declining incidence over the first five years of life (Figure 3.25C), when transmission intensity is likely to have remained constant, still suggests that immunity to severe disease is still acquired early in life. The rarity of malaria requiring hospitalisation and the absence of severe malaria after 8 years of age suggests that few infections, early in life might confer long-term protection against severe, life-threatening morbidity [Gupta et al., 1999]. As such even when malaria transmission falls significantly, immunity is still acquired.

There are relatively few investigations of severe, clinical malaria in adults living under stable endemic settings in Africa (Section 1.4), and the public health focus remains on children under-five years. Routine diagnosis of severe malaria among adults in hospitals is often poor, a diagnosis of convenience without confirmatory parasitology [Makani et al., 2003]. Detailed descriptions of severe malaria among adults comes largely from south east Asia [Dondorp et al., 2008] or among imported cases to Europe [Bruneel et al., 2010], only a few studies of adult severe malaria exist in Africa [Giha et al., 2005; Eholie et al., 2004; Robinson et al., 2006; Wade et al., 2012; Abdallah et al., 2013]. In one study in Eastern Sudan, an area of unstable *P. falciparum* transmission, the risks of admission declined sharply after 5-19 years among 110 WHO defined severe malaria; 45% were aged 2-4 years and 24% were above 12 years of age [Giha et al., 2005].

3.6.4 Malaria mortality

During the study period, there were 316 deaths recorded within the community aged 6 months and above. A composite approach was considered, with varying levels of confirmatory evidence, to attribute deaths to malaria (Figure 3.23). The overall malaria-specific mortality rate was estimated to be 0.17 per 1,000 population above 6 months p.a. (95% CI: 0.09, 0.29 episode per 1,000 person-years). With this approach, there were no

malaria deaths among children aged 6-11 months, 6 (50%) of the malaria deaths occurred among children aged 1-4 years, 6 (50%) among children aged 5-14 years, and there with no deaths attributed to malaria among the non-pregnant population aged above 15 years (Table 3.8 & Figure 3.25D). Malaria-specific mortality rates were highest among children aged 6 months to 4 years, 0.57 per 1,000 p.a. compared to 0.25 per 1,000 p.a. among children aged 5-14 years. The high mortality rate among children aged 5-14 years, was consistent with data on malaria hospitalization in this age group (Figure 3.25C), and fever test positivity at peripheral clinics (Figure 3.25B) but remains lower than mortality in the 6 months to 4-year age group. This suggests that fatal malaria events are still concentrated in young children. These findings are consistent with the notion of an early acquired immunity to the fatal consequences of malaria infection and an absence of risk in non-pregnant adolescents and adults, even under a low rate of parasite exposure. Furthermore, there was consistency with data on the age-specific incidence of severe malaria presenting to hospital (Figure 3.25C) which lends confirmatory support to the malaria mortality data from the same community. These observations are also consistent with autopsy studies undertaken in Nigeria between 1944-48 [Bruce-Chwatt, 1952] and Ghana 1921-52 [Colbourne & Eddington, 1954] which showed that autopsy findings of malaria were rare among adults (Section 1.5.4).

Conversely, the Global Burden of Disease project, relies entirely on VA data from DSS sites in SSA (Section 1.9.1.3) showing different malaria-specific age patterns [Murray et al., 2012; Murray et al., 2014; Gething et al., 2016]. Between 1980 and 2010 the percentage of deaths attributable to malaria among individuals aged ≥15 years was 58% in SSA, more than those defined among children <5 years of age (24%) reported in 2008 [Murray et al., 2012]. In 2010, among the global malaria mortality, 20% were among those aged 15-49 years, 9% among those aged 50-69 years, and 6% among those aged 70

years or older [Murray et al., 2012]. Furthermore, at nine DSS sites between 1992 and 2012 where malaria was stable endemic, in Burkina Faso, Côte d'Ivoire, The Gambia, Ghana, Kenya, and Senegal, a review of VA defined malaria mortality was undertaken [Streatfield et al., 2014a]. The percentage of all malaria deaths was 65% among children <5 years of age (4,274/6,490) and 26% (1,706/6,490) among individuals aged ≥15 years; with 15% (1,003/6,490) being among individuals aged ≥50 years [Streatfield et al., 2014a].

Previous studies on the validity of the VA for adult deaths in Kilifi, suggested that various VA methods showed reasonable predictive accuracies for the top five causes of death compared to hospital diagnoses, however, malaria was not specifically included [Bauni et al., 2011]. At three malaria endemic sites in Africa during the 1990s, the positive predictive value (PPV) of the VA among adults was 0%, 46% and 68% (Section 1.7.4) [Chandramohan et al., 1998].

Deaths that had contact with diagnostic facilities provide unique information on causes of death. Relying solely upon a computerized algorithm to attribute malaria as a cause of death from VA responses, misses opportunities to review underlying causes available in free-text commentaries, notably in the identification of important unambiguous causes, including HIV and SCD. The approach taken here maximizes the amount of information available, and by comparing with hospital presentations with severe malaria allows a more plausible approach to defining the contribution of malaria mortality by age.

3.6.5 Disease progression

In the present study, the prevalence of infection in the studied population was 10%, 17% of the population presented at least once (period prevalence) with a fever associated with malaria infection to one of the six health facilities, 0.11% were admitted to hospital with a

parasitologically confirmed primary diagnosis of malaria, 0.06% of the population had severe life-threatening events and over the 12 months of surveillance, an estimated 0.02% died from malaria. It was previously assumed that under stable endemic conditions, for every 200 infected children, 100 (50%) would develop a clinical episode attack, two (2%) would evolve to severe disease and with a 50% case-fatality, one would die (1%) [Greenwood et al., 1991]. In the present series, among children aged 6 months-4 years for every 100 clinical events, 0.3% developed severe malaria and 0.04% were presumed to have died of malaria (Table 3.8). Greenwood et al. (1991) used a hypothetical scenario and the present study will not have detected every true clinical attack, few severe malaria events may not have reached hospital and recovered in the community, and there are uncertainties about the precise mortality burden. Nevertheless, the data and the hypothetical hierarchy of events both highlight that while infection and mild disease are common, the severe and fatal consequences of *P. falciparum* are comparatively rare, demonstrating the effects of naturally acquired functional immunity. However, the present data suggest a log-order difference in the magnitude of disease progression to that described by Greenwood et al. (1991). As such disease progression also depends critically upon access to prompt and effective treatment at every stage of the disease. Access to health facilities providing efficacious treatment for all parasitologically diagnosed malaria cases was high during the surveillance period, and paediatric case-fatalities in the hospital (9.3%) were much lower than 50%. While natural age-related patterns of immune acquisition remain an important determinant of disease burden in a community, equally significant will be how disease is managed by the health system. As non-sterilizing vaccines continue to be developed, a health system's ability to manage disease should not be ignored.

3.6.6 Caveats

This study did not include children under 6 months of age because including this age group would be considered as a different study question regarding passive immunity and it would require staff to be trained further on how to collect a blood sample. However, it seems unlikely that measures reported among children under-five years would be significantly different from those reported among children aged 6 months-4 years. During the hospital surveillance, not all adults had a blood slide for malaria performed which could have led to an under-estimation of incidence of hospitalised malaria among the adult population. However, it is unlikely that the general conclusion would have changed significantly since 89% (250/280) of all adult admissions had chronic illnesses or final diagnoses that included skin/organ infections, trauma, hernia or obstetric related problems. Of the remaining 30 infectious disease admissions, 23 (77%) had a blood film to confirm malaria. Although the age pattern of severe disease and mortality are shown in this study, caution should be used in interpreting the patterns observed because these are rare events that would require a larger population to interrogate the finer age-resolved patterns for both outcomes. Additionally, the number of deaths and severe disease reported here may not be representative of all cases of malaria, as an unknown proportion of cases never present to the formal health care system. This study was conducted in a single study site and the results may not be generalizable to other settings.

3.7 Conclusions

Under the current conditions of much lower transmission intensity, one might presume a different age pattern with malaria risks (Section 1.5). It appears that immunity to severe and fatal consequences of *P. falciparum* continues to be acquired in childhood and faster than anti-parasitic immunity, consistent with data over 20 years ago and models of

immune protection (Section 1.5). The delay in the acquisition of anti-parasitic immunity may be due to the reduced exposure in the earlier years of life. Consequently, children aged 5-14 years were the greatest contributors to the persistent pool of malaria transmission. In addition, clinical malaria, defined as either facility-based test positivity or parasite-density attributable incidence, was prevalent among adult populations, but considerably lower compared to children. There is no evidence of an emerging significant burden of severe malaria or malaria mortality among young adults.

Despite a reduction in parasite transmission and hospitalization for malaria over the last 20 years, malaria remains an important cause of under-five mortality in this area. This is contrary to current modelled approaches to disease burden estimation in Africa. The continued absence of precise estimates of the age-specific malaria mortality patterns in the community limits the ability to look at immune protection against fatal outcomes of infection and presents a problem in defining the global and national burdens of malaria mortality (Section 1.5.4).

The results presented here support continued, targeted infection prevention strategies to prevent life-threatening disease among young children in low transmission settings, while reductions in infection prevalence and mild disease would benefit from interventions that reach school-aged children.

Chapter 4 : The relationship between facility-based malaria test positivity rate and community-based parasite prevalence

4.1 Introduction

Monitoring the intensity of malaria transmission in time and space is an important parameter to define the required combinations of intervention to accelerate control and elimination, measure impact and over time repurpose intervention and control ambitions (Sections 1.1. and 1.6). With the rolling out of the WHO's policy on test-treat-track [WHO, 2012b], the universal acceptance and delivery of malaria rapid diagnostic tests (RDTs) across Africa [WHO, 2019a] and the adoption of digital health data capture platform (DHIS2) [Alegana et al., 2020], opportunities exist to use test positivity rates (TPR) as a measurable, temporal quantity of malaria endemicity in more localities across Africa than provided by community prevalence surveys [WHO 2018b; Stresman et al., 2020]. While the detection of all malaria cases represents a core intervention for elimination [GMP, 2017], the use of routine health facility TPR data for malaria endemicity stratification and surveillance at national scale remains underutilised in the high burden areas of SSA due to their imperfections [Alegana et al., 2020]. In this chapter, the relationship between time-space matched community-based prevalence of infection and TPR at health facilities on the Kenyan coast was examined.

4.2 Materials and Methods

4.2.1 Study area

This study was conducted in the southern part of the KHDSS. The surveillance area is described in detail in Section 3.4 that included six public health facilities and the KHDSS enumeration zones (EZ) surrounding each facility within a 2 km radius as shown in Figure 3.6.

Passive surveillance of fever infection and community-based surveillance have been described in detail in Sections 3.4.3-3.4.4. Briefly, the study involved records of all patients ≥6months of age that sought treatment between March 2018 and February 2019 with a history of fever in the last 24 hours as part of presenting illness or a measured axillary temperature ≥37.5°C, hereafter referred to as febrile patients. All febrile patients were tested using malaria rapid diagnostic test (CareStart™) to detect HRP2 specific to *P. falciparum*. If the RDT result was positive the patient received appropriate treatment as per the Government of Kenya guidelines for malaria-case management [MoPHS, 2010]. The patient's residence was documented and matched to the enumerated KHDSS geo-coded homestead register.

Four community-based prevalence surveys were undertaken during the facility surveillance period: May-June 2018, August 2018, October 2018 and December 2018-January 2019. For each consenting homestead member aged ≥ 6 months of age, the fieldworkers obtained information on the participant's demographics. Fever was assessed as an axillary temperature ≥37.5°C; or a history of reported fever in the last 24-hours. A malaria test was performed on all consenting participants using RDT (CareStart™), irrespective of their fever status. All participants with fever and/or a positive rapid test were advised to seek treatment at the nearest health facility.

4.2.2 Data analysis

This analysis included only data for participants identified as residents of the catchment areas shown in Figure 3.6. Pregnant women and participants that had been enrolled in either the health facility or community survey within the last 14 days were excluded. Descriptive statistics included proportions with 95% confidence interval (CI), means with

standard deviation (SD), and medians with interquartile range (IQR). A Chi-square test was used to compare the difference in proportions.

The health facility TPR was defined as the number of positive diagnostic tests as a proportion of the total tests performed among febrile patients. The community parasite prevalence (PR) was defined as the proportion of participants tested found with a positive malaria RDT. To compute the TPR and PR for each EZ, the number of positive participants and total tests performed were aggregated at the EZ level. For each EZ, the facility TPR data were matched to a two-month period around each community-based cross-sectional survey. To explore different temporal matches, the time interval was altered by 1) matching the health facility data to the same four-time periods when the community-based survey was conducted; 2) matching to the subsequent month i.e. lagging the health facility data by one month after the community cross-sectional survey, or 3) by using all the health facility data in each EZ versus all four community-based prevalence surveys in each EZ. TPR and PR values were compared using actual age-groupings and against the traditional $PR_{2–10\ years}$ using data from the entire community age-standardised to the 2-10 age group in each EZ as described elsewhere [Smith et al., 2007]. The association between health facilities TPR and PR (age-matched and age-standardized 2-10 years) was determined using Spearman's rank correlation; and the varying facility time-periods used as a sensitivity analysis.

To explore the functional form of the relationship between TPR and PR in a more formal form, i.e. to define a function (F), that transforms an estimate of PR over any range (x, y), into a TPR over any range (L, U), i.e. F: PR(x, y)→TPR(L, U), various models were considered. The relationship was assessed using a linear relationship and other flexible function forms using the polynomial and exponential transformations. A selection of the

best fitting model was made using the goodness of fit, measured as root mean square error (RMSE), adjusted R^2, and Akaike Information Criteria (AIC). Regression diagnostics were performed including Cook's D to assess for high leverage, which was indicative of influential EZ, and/or large residuals (outliers). To test the variability in the prediction performance of the models, 80% of the data were divided into train and 20% into test datasets and the model was rerun on 100 randomly selected samples. The models developed by the training dataset were validated against the test datasets by comparing the accuracy measures i.e. the correlation between actual and predicted estimates and the error rates (mean absolute percentage error (MAPE), mean square error (MSE) and mean absolute error (MAE)). As a sensitivity analysis, the effects of using varying intervals of TPR in quantifying the relationship between TPR and PR using the best fitting model was explored.

Finally, the predictive ranges of TPR were explored for community PR endemicity risk groups of programmatic value, i.e. cut-offs of low (PR<5%) and high (PR≥30%), used in national malaria stratification in Kenya [DOMC, 2010; Macharia et al., 2018; Noor et al., 2009b] and Tanzania [Thawer et al., 2020] (Section 1.7.1). To serve as a guide to set the appropriate cut-offs for low transmission settings, the upper bound of the 95% confidence interval (CI) of the predictive range of TPR was used as a conservative measure. While the lower bound of the 95% CI of the predictive range of TPR was used in high transmission. Data analysis was performed in Stata, version 13 (Stata Corporation, College Station, TX) and R version 3.6.1 (R Core Team (2019), Vienna, Austria).

4.3 Results

4.3.1 Characteristics of the study participants

Between March 2018 and February 2019, 46,567 febrile patients ≥6 months of age sought treatment in one of the six out-patient health facilities shown in Figure 3.13. Among the 28,134 febrile non-pregnant patients resident within the 36 EZs, 54% were female and the median age was 11 years (IQR: 4, 19 years) (Table 4.1). Among all febrile patients, 12,143 (43%) had a positive RDT and the median age of those with a positive RDT was 10 years (IQR: 5, 15 years). The highest TPR was among children aged 10-14 years and the lowest among adults ≥50 years (Table 4.2).

During the four community-based prevalence surveys, 7,255 participants ≥6 months of age were approached for enrolment (Figure 3.8). A total of 6,479 non-pregnant participants aged 6 months to 98 years were surveyed in the community with an average of 180 per EZ. The median age of those sampled was 12 years (IQR: 6 years, 24 years), 61% were female (Table 4.1) and 348 (5.8%) were febrile. The overall community PR was 9.9% (95% CI: 9.2, 10.7%) (Table 4.1) and was higher (27.3%) among community participants with fever. PR varied significantly across the 36 EZs ($p < 0.001$), ranging between 0% and 41%. There were no clear patterns between seasonality and PR (9.4% in the wet vs. 10.5% in the dry; $p = 0.12$). The community PR was highest among children aged 10-14 years (13.6%: 95% CI: 11.7%, 15.6%) and lowest among adults aged 50 years and above (4.3%: 95% CI: 2.8%, 6.3%) (Table 4.2). The overall age-standardized $PR_{2–10\ years}$ was 12.7% and ranged between 0.01% and 53.2% in the 36 EZs.

Table 4.1: Background characteristics of study participants in the health facility survey and community-based survey. Reproduced from Kamau et al., 2020, published CC-BY 4.0

Characteristics	Health facility-based survey	Community-based survey
Total number of enumeration zones (EZ), n	36	36
Number enrolled, n	28,134	6,479
Average number of participants per EZ, (SD)	781.5 (585.1)	180.0 (161.3)
Average number of participants under-five years per EZ, (SD)	202.4 (161.0)	37.3 (32.3)
Median Euclidean distance (km) from homestead to health facility, (IQR)	1.9 (1.1, 2.7)	-
Number of non-pregnant females, n (%)	15,074 (53.6)	3,954 (61.0)
Median age in years, (IQR)	11 (4, 19)	12 (6, 24)
Malaria RDT positivity, n (%)	12,143 (43.2)	643 (9.9)
Average number of RDT positivity across all ages per EZ, (SD)	337.3 (330.5)	17.9 (30.6)
Average number of RDT positivity among children under-five years per EZ, (SD)	73.0 (86.0)	3.8 (6.1)
Median age in years of RDT positivity, (IQR)	10 (5, 15)	10 (5, 15)

HF = Health Facility; CS = Community Survey; IQR = Interquartile Range; SD = standard deviation

Table 4.2: The relationship between health facility fever test-positivity rate (TPR) (matched to 2 months period around each cross-sectional surveys) and community parasite rate (PR) stratified by age group. Reproduced from Kamau et al., 2020, published CC-BY 4.0

Age group	TPR (n/N, %)	PR (n/N, %)	Correlation TPR vs. community PR (95% CI)	P value	Correlation TPR vs. $PR_{2-10\ years}$ (95% CI)	P value
6-11 months	144/575 (25.0)	8/99 (8.1)	-0.11 (-0.45, 0.25)	0.540	0.27 (-0.07, 0.55)	0.119
1-4 years	1,972/4,830 (40.8)	128/1,243 (10.3)	0.60 (0.33, 0.77)	<0.001	0.66 (0.42, 0.81)	<0.001
5-9 years	2,594/4,434 (58.5)	168/1,278 (13.1)	0.54 (0.26, 0.74)	<0.001	0.69 (0.47, 0.83)	<0.001
10-14 years	2,658/4,269 (62.3)	169/1,245 (13.6)	0.35 (0.02, 0.61)	0.039	0.62 (0.37, 0.79)	<0.001
15-49 years	2,236/6,008 (37.2)	146/2,056 (7.1)	0.03 (-0.31, 0.35)	0.878	0.32 (-0.01, 0.59)	0.055
50+ years	323/1,584 (20.4)	24/558 (4.3)	0.20 (-0.15, 0.51)	0.251	0.13 (-0.21, 0.44)	0.464
Overall	9,927/21,700 (45.8)	643/6,479 (9.9)	0.63 (0.38, 0.79)	<0.001	0.62 (0.37, 0.79)	<0.001

4.3.2 Correlation between TPR and PR

When the health-facility data was matched to two months around the four cross-sectional surveys, there were 21,700 patients aged 6 months to 95 years seen at the facilities from the 36 EZs with an average of 603 (SD = 444.6) attendees per EZ. Among this time-matched series, TPR varied significantly ($p < 0.001$) across the 36 enumeration zones ranging between 17% and 73% and significantly differed across age groups (Table 4.2). The correlation between facility-based fever TPR and community PR across all age groups was 0.63 (95% CI: 0.38, 0.79; $p < 0.001$) and was comparable to the age-standardized $PR_{2\text{-}10\ years}$ (Table 4.2). The correlations were weakest among age groups 6-11 months, 15-49 years, and adults ≥50 years (Table 4.2 & Figure 4.1). Stronger correlations were shown in the age groups 1-4 years (*rho*=0.60; 95% CI: 0.33, 0.77; $p<0.001$) and 5-9 years (*rho*=0.54; 95% CI: 0.26, 0.74) (Table 4.2 & Figure 4.1). These comparisons were comparable across the different temporal matches of TPR data (Table 4.3).

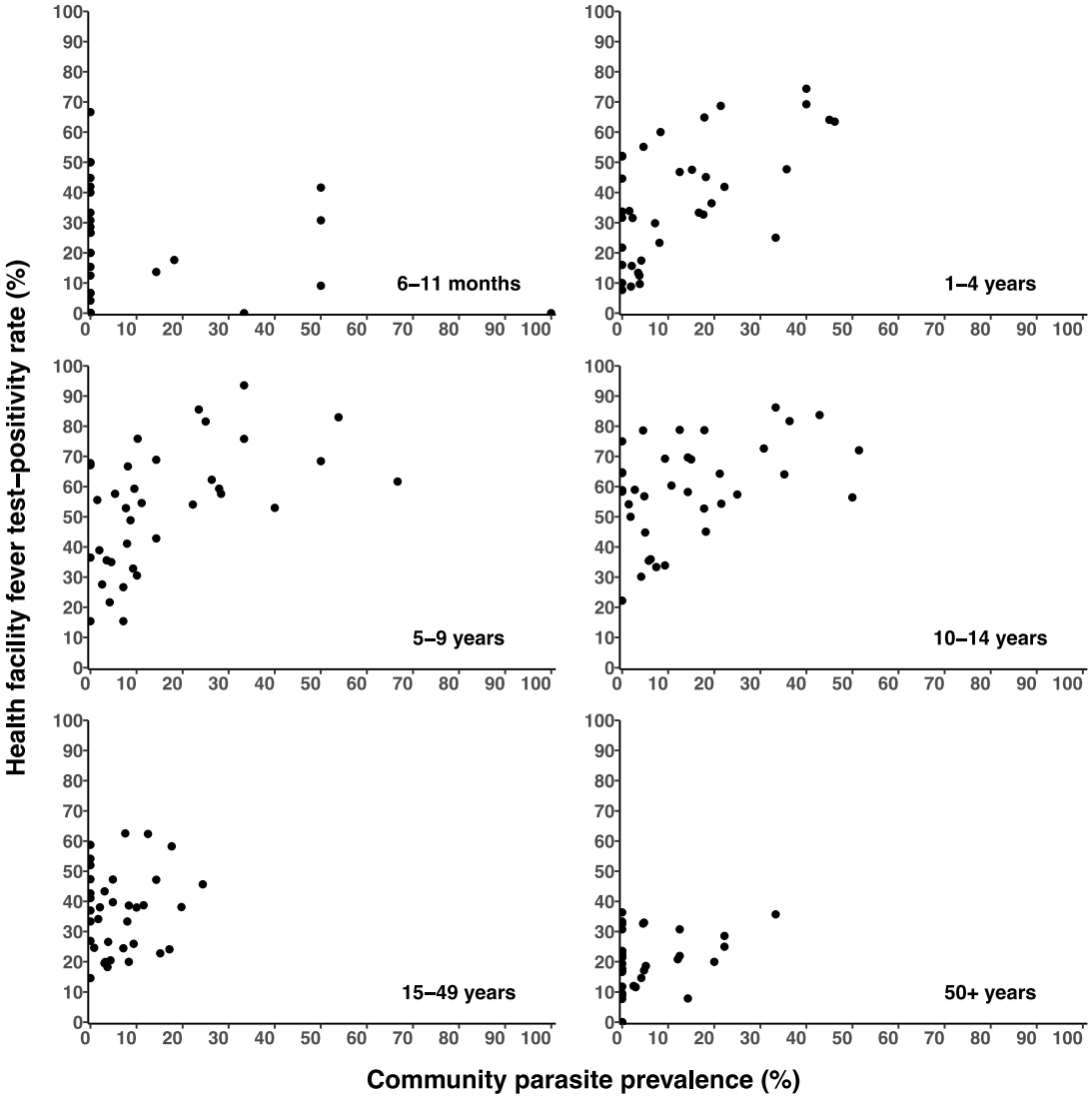


Figure 4.1: Scatter plot of health facility fever test-positivity rate (TPR) (matched to 2 months period around each cross-sectional surveys) *versus* community parasite prevalence (PR) stratified by age group. Reproduced from Kamau et al., 2020, published CC-BY 4.0

Table 4.3: The correlation between health facility fever test-positivity rate (TPR) and community parasite rate (PR) stratified by age group and varying the intervals of TPR as described in the methods section

	All time points		Matched to 4 time-periods during cross-sectional surveys		Matched to subsequent month i.e. lagged by 1 month		Matched to 2 months period around cross-sectional surveys	
Age group	**Correlation (95% CI)**	**P value**	**Correlation (95% CI)**	**P value**	**Correlation (95% CI)**	**P value**	**Correlation (95% CI)**	**P value**
6-11 months	-0.10 (-0.44, 0.26)	0.581	-0.16 (-0.48, 0.21)	0.399	0.05 (-0.32, 0.41)	0.793	-0.11 (-0.45, 0.25)	0.540
1-4 years	0.62 (0.37, 0.79)	<0.001	0.64 (0.40, 0.80)	<0.001	0.50 (0.21, 0.71)	0.002	0.60 (0.33, 0.77)	<0.001
5-9 years	0.56 (0.28, 0.75)	<0.001	0.49 (0.20, 0.71)	0.002	0.54 (0.26, 0.74)	<0.001	0.54 (0.26, 0.74)	<0.001
10-14 years	0.37 (0.05, 0.62)	0.026	0.32 (-0.01, 0.59)	0.056	0.33 (-0.003, 0.59)	0.053	0.35 (0.02, 0.61)	0.039
15-49 years	0.06 (-0.27, 0.38)	0.721	0.12 (-0.21, 0.44)	0.470	0.13 (-0.21, 0.44)	0.445	0.03 (-0.31, 0.35)	0.878
50+ years	0.16 (-0.19, 0.48)	0.359	0.16 (-0.19, 0.48)	0.358	0.12 (-0.22, 0.44)	0.487	0.20 (-0.15, 0.51)	0.251
All ages	0.65 (0.41, 081)	<0.001	0.61 (0.35, 0.78)	<0.001	0.60 (0.33, 0.77)	<0.001	0.63 (0.38, 0.79)	<0.001

4.3.3 The algebraic relationship between TPR and PR

The subsequent analysis focuses on three age comparisons: 1) children aged <5 years, as DHIS2 data is aggregated over the age groups below and above five years and household surveys measure malaria infection mostly in children aged 6 months to five years; 2) all ages, as this is also available from existing national DHIS2 platforms; and 3) TPR comparisons to age-standardized $PR_{2 - 10 \text{ years}}$, currently used to map malaria transmission in Africa (Section 1.9.1.1).

To examine the functional form of the relationship between matched TPR and PR, four models were explored (Table 4.4). The polynomial model of order 2 was the best fitting model, based on goodness of fit measures (RMSE, AIC and R2), in all comparisons, except $TPR_{0.5\text{-}4 \text{ years}}$ vs. $PR_{0.5\text{-}4 \text{ years}}$, where the linear model was the best fitting model (Table 4.4 & Figure 4.2). The selection of the age-specific models was also supported by the measures of predictive performance (MSE, MAE and MAPE) (Table 4.4). Changing the temporal matches of TPR data did not alter the selection of the models (Table 4.5). There were significant differences in the predictive ranges of TPR using the programmatic cut-offs of PR <5% and ≥30% in all the models (Table 4.6).

Table 4.4: Regression models of diagnostic test positivity rates (TPR) as predictors of parasite prevalence (PR) stratified by age

Model	Formula	RMSE	Adjusted R^2	AIC	*rho*[¶]	MAE	MSE	MAPE
$TPR_{0.5\text{-}4\ years}$ vs. $PR_{0.5\text{-}4\ years}$								
Linear	**y = b0 + b1x**	**0.149**	**0.387**	**-32.74**	**0.61**	**0.13**	**0.02**	**0.50**
Exponential	$y = b0 * b1^x$	0.561	0.298	62.46	0.61	0.14	0.03	0.47
Cubic	$y = b0 + b1x + b2x^2 + b3x^3$	0.152	0.364	-29.59	0.55	0.14	0.03	0.55
Polynomial order 2	$y = b0 + b1x + b2x^2$	0.151	0.372	-30.97	0.6	0.13	0.02	0.52
$TPR_{all\ ages}$ vs. $PR_{all\ ages}$								
Linear	y = b0 + b1x	0.127	0.36	-44.74	0.62	0.11	0.01	0.28
Exponential	$y = b0 * b1^x$	0.333	0.324	24.89	0.62	0.11	0.02	0.28
Cubic	$y = b0 + b1x + b2x^2 + b3x^3$	0.128	0.344	-42.02	0.56	0.11	0.02	0.29
Polynomial order 2	**$y = b0 + b1x + b2x^2$**	**0.126**	**0.364**	**-44.00**	**0.60**	**0.11**	**0.02**	**0.28**
$TPR_{0.5\text{-}4\ years}$ vs. $PR_{2\text{-}10\ years}$								
Linear	y = b0 + b1x	0.152	0.365	-31.49	0.62	0.13	0.02	0.54
Exponential	$y = b0 * b1^x$	0.564	0.29	62.87	0.59	0.15	0.03	0.51
Cubic	$y = b0 + b1x + b2x^2 + b3x^3$	0.153	0.354	-29.04	0.59	0.13	0.02	0.56
Polynomial order 2	**$y = b0 + b1x + b2x^2$**	**0.151**	**0.373**	**-31.04**	**0.61**	**0.13**	**0.02**	**0.53**
$TPR_{all\ ages}$ vs. $PR_{2\text{-}10\ years}$								
Linear	y = b0 + b1x	0.128	0.341	-43.65	0.59	0.11	0.02	0.29
Exponential	$y = b0 * b1^x$	0.336	0.313	25.50	0.59	0.12	0.02	0.29
Cubic	$y = b0 + b1x + b2x^2 + b3x^3$	0.129	0.336	-41.56	0.56	0.11	0.02	0.30
Polynomial order 2	**$y = b0 + b1x + b2x^2$**	**0.127**	**0.356**	**-43.55**	**0.58**	**0.11**	**0.02**	**0.29**

[¶] ***rho* =** Correlation between actual and predicted TPR; root mean square error (RMSE); mean absolute error (MAE); mean square error (MSE); mean absolute percentage error (MAPE). The linear regression model in some age groupings predicted values for TPR that were outside the (0, 1) interval. For example, a standardized $PR_{2\text{-}10\ years}$ beyond 85% corresponds to a predicted $TPR_{0.5\text{-}4\ years}$ >100%. Similarly, a community $PR_{all\ ages}$ beyond 72% corresponds to a predicted $TPR_{all\ ages}$ >100%.

Table 4.5: Sensitivity analysis exploring the quantitative relationship between health facility fever test-positivity rate (TPR) and community parasite prevalence (PR) stratified by age-specific comparisons and temporal match. Reproduced from Kamau et al., 2020, published CC-BY 4.0

Model	Coefficients			Goodness of fit		
	PR (95% CI)	PR^2 (95% CI)	P-value	RMSE	Adjusted R^2	AIC
$TPR_{0.5\text{-}4\ years}$ vs $PR_{0.5\text{-}4\ years}$						
TPR matched to 2 months period around cross-sectional surveys	0.87 (0.50, 1.23)	-	<0.001	0.149	0.387	-32.74
TPR matched to 4 time-periods during cross-sectional surveys	0.89 (0.54, 1.24)	-	<0.001	0.142	0.426	-36.25
TPR matched to subsequent month i.e. lagged by 1 month	0.84 (0.44, 1.25)	-	<0.001	0.165	0.324	-25.55
All time points	0.87 (0.54, 1.21)	-	<0.001	0.137	0.433	-38.80
$TPR_{all\ ages}$ vs $PR_{all\ ages}$						
TPR matched to 2 months period around cross-sectional surveys	1.62 (0.28, 2.96)	-1.88 (-5.42, 1.66)	<0.001	0.126	0.364	-44.00
TPR matched to 4 time-periods during cross-sectional surveys	1.56 (0.23, 2.88)	-1.82 (-5.32, 1.69)	<0.001	0.125	0.347	-44.73
TPR matched to subsequent month i.e. lagged by 1 month	1.98 (0.43, 3.52)	-2.63 (-6.70, 1.44)	<0.001	0.145	0.345	-33.9
All time points	1.74 (0.41, 3.07)	-2.19 (-5.70, 1.31)	<0.001	0.125	0.379	-44.69

Community parasite prevalence (PR); PR^2 is a function of the polynomial equation; health facility fever test-positivity rate (TPR)

Table 4.5 continued…

Model	Polynomial coefficients			Goodness of fit		
	PR (95% CI)	PR^2 (95% CI)	P-value	RMSE	Adjusted R^2	AIC
$TPR_{0.5\text{-}4\ years}$ vs $PR_{2\text{-}10\ years}$						
TPR matched to 2 months period around cross-sectional surveys	1.59 (0.37, 2.80)	-1.48 (-3.97, 1.01)	<0.001	0.151	0.373	-31.04
TPR matched to 4 time-periods during cross-sectional surveys	1.61 (0.40, 2.81)	-1.58 (-4.05, 0.89)	<0.001	0.150	0.365	-31.69
TPR matched to subsequent month i.e. lagged by 1 month	1.70 (0.37, 3.02)	-1.75 (-4.47, 0.96)	<0.001	0.165	0.327	-24.77
All time points	1.66 (0.53, 2.80)	-1.68 (-4.00, 0.64)	<0.001	0.141	0.404	-36.09
$TPR_{all\ ages}$ vs $PR_{2\text{-}10\ years}$						
TPR matched to 2 months period around cross-sectional surveys	1.36 (0.34, 2.39)	-1.38 (-3.47, 0.71)	<0.001	0.127	0.356	-43.55
TPR matched to 4 time-periods during cross-sectional surveys	1.32 (0.31, 2.34)	-1.37 (-3.44, 0.71)	<0.001	0.126	0.338	-44.25
TPR matched to subsequent month i.e. lagged by 1 month	1.65 (0.47, 2.83)	-1.88 (-4.29, 0.53)	<0.001	0.146	0.334	-33.34
All time points	1.45 (0.44, 2.47)	-1.56 (-3.63, 0.52)	<0.001	0.126	0.370	-44.19

Community parasite prevalence (PR); PR^2 is a function of the polynomial equation; health facility fever test-positivity rate (TPR)

Table 4.6: The predictive ranges of test positivity rates (TPR) for three endemicity classes of parasite prevalence (PR) stratified by age-specific comparisons. Reproduced from Kamau et al., 2020, published CC-BY 4.0

	PR cut-offs	
	<5%	**≥30%**
$TPR_{0.5\text{-}4\ years}$ vs $PR_{0.5\text{-}4\ years}$		
Actual predicted TPR	30%	51%
95% CI	24%, **35%**¶	**43%**†, 59%
$TPR_{all\ ages}$ vs $PR_{all\ ages}$		
Actual predicted TPR	35%	60%
95% CI	31%, **41%**¶	**52%**†, 69%
$TPR_{0.5\text{-}4\ years}$ vs $PR_{2\text{-}10\ years}$		
Actual predicted TPR	26%	53%
95% CI	19%, **32%**¶	**44%**†, 62%
$TPR_{all\ ages}$ vs $PR_{2\text{-}10\ years}$		
Actual predicted TPR	35%	57%
95% CI	29%, **40%**¶	**49%**†, 64%

¶For low transmission settings, the upper confidence limit of predicted TPR range was used as the conservative allocation of the maximum probable TPR as a proxy measure for PR <5%, † while for high transmission settings, the lower confidence limit of the predicted TPR range was used as a conservative allocation of the minimum probable TPR as a proxy measure for PR ≥30%.

4.3.4 Comparison among children aged <5 years

The linear model among children aged 6 months-4 years between the facility and community surveys suggested that only a fraction of infections in the community ($PR_{0.5\text{-}4\ years}$) developed symptoms that required treatment in an out-patient health facility (ß = 0.87; 95% CI: 0.50, 1.23; p<0.001) (Table 4.1 *&* Figure 4.2). The linear model estimated that a $PR_{0.5\text{-}4\ years}$ <5% corresponded to a maximum 95% CI predicted $TPR_{0.5\text{-}4\ years}$ of <35%; and a $PR_{0.5\text{-}4\ years}$ ≥30% corresponded to a minimum 95% CI predicted $TPR_{0.5\text{-}4\ years}$ of ≥43% (Table 4.6). However, the linear model performed poorly when $PR_{0.5\text{-}4\ years}$ was >85% leading to predicted values for $TPR_{0.5\text{-}4\ years}$ greater than 100% if the linear model holds true outside of the observed values.

4.3.5 Comparison across all ages

A polynomial model was used for all age-groups from facility and community surveys (Table 4.5 & Figure 4.2). The model signified slightly larger changes in the predicted $TPR_{all\ ages}$ when $PR_{all\ ages}$ was below 10%, but smaller changes in the predicted $TPR_{all\ ages}$ when $PR_{all\ ages}$ was above 30% (Figure 4.2). The polynomial model estimated that a $PR_{all\ ages}$ <5% corresponded to a maximum 95% CI predicted $TPR_{all\ ages}$ of approximately <41%; and a $PR_{all\ ages}$ ≥30% corresponded to a minimum 95% CI predicted $TPR_{all\ ages}$ ≥52% (Table 4.6). Beyond a $PR_{all\ ages}$ of 45%, the polynomial model predictions of $TPR_{all\ ages}$ saturates, if the polynomial model holds true outside of the observed values.

4.3.6 Comparison to age-standardized $PR_{2\text{-}10\ years}$

The analysis was repeated using age-standardized $PR_{2\text{-}10\ year}$ data. Here a polynomial model best described the relationships between $TPR_{0.5\text{-}4\ years}$ vs. $PR_{2\text{-}10\ year}$ and $TPR_{all\ ages}$ vs. $PR_{2\text{-}10\ year}$ (Table 4.5 *&* Figure 4.2). The polynomial model estimates that an age-standardized $PR_{2\text{-}10\ year}$ <5% corresponded to a maximum 95% CI predicted $TPR_{0.5\text{-}4\ years}$ of <32%, which was lower than that estimated using the linear model. The age-standardized $PR_{2\text{-}10\ year}$ ≥30% corresponded to a similar minimum 95% CI predicted $TPR_{0.5\text{-}4\ years}$ of ≥44%. When the standardized $PR_{2\text{-}10\ year}$ was beyond 65%, the polynomial model saturated. For $TPR_{all\ ages}$ the predictive accuracies of the endemicity classes of the age-standardized $PR_{2\text{-}10\ year}$ were similar to those predicted using the actual $PR_{all\ ages}$ data (Table 4.6).

In summary, although the polynomial model might not be discriminatory enough, it was the best fitting model for the data that described the algebraic relationship between TPR and PR. In this setting, a TPR of ≥49% in all age groups would correspond to $PR_{2\text{-}10\ years}$ of ≥30%, while a $TPR_{all\ ages}$ of <40% would correspond to age-standardized $PR_{2\text{-}10\ years}$ of <5%.

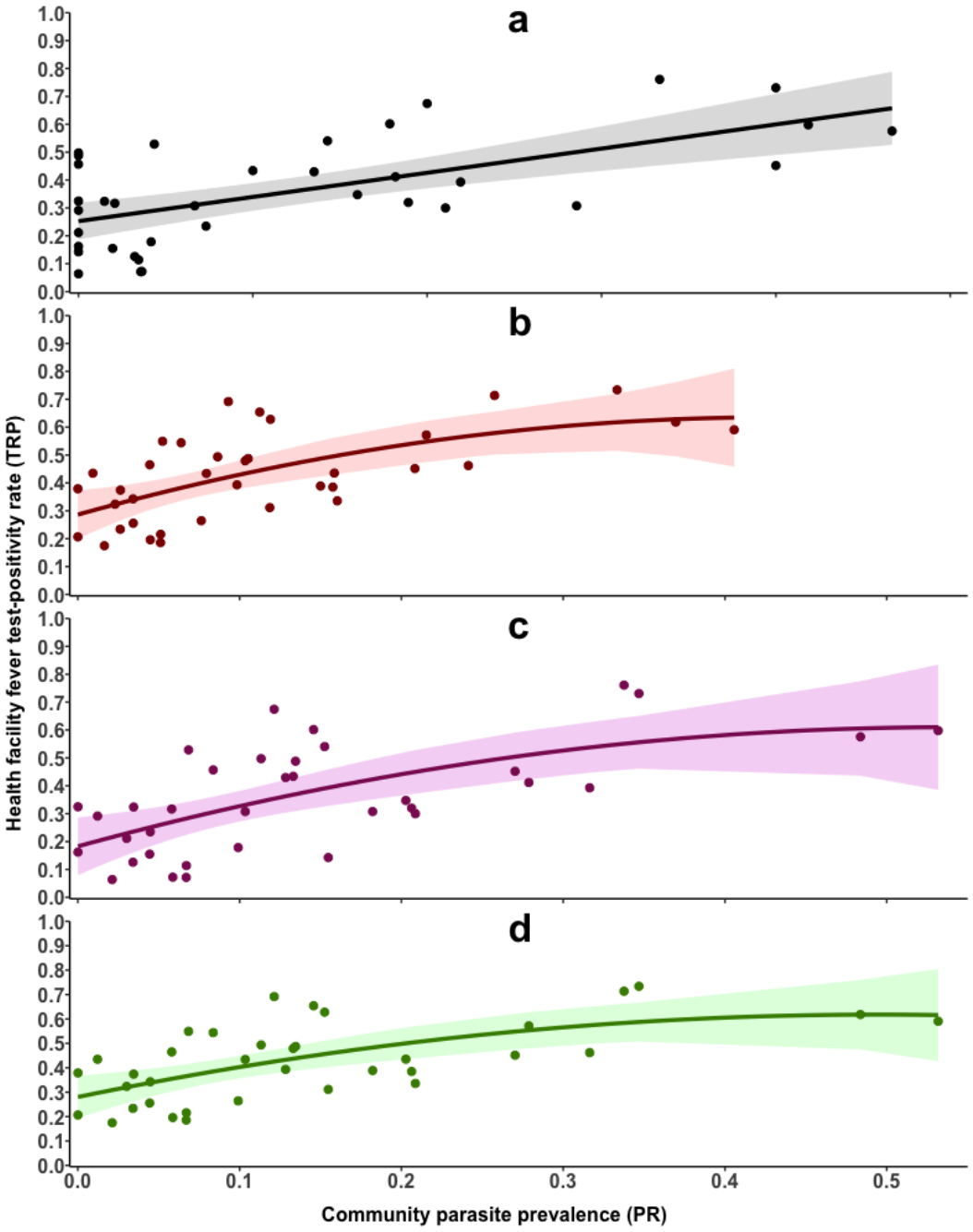


Figure 4.2: The relationship between health facility fever test-positivity rate (TPR) and community parasite prevalence (PR). Panel A – shows the relationship between $TPR_{0.5\text{-}4\ years}$ and $PR_{0.5\text{-}4\ years}$ (black line). Panel B - shows the relationship between $TPR_{all\ ages}$ and $PR_{all\ ages}$ (red line). Panel C - shows the relationship between $TPR_{0.5\text{-}4\ years}$ and standardized $PR_{2\text{-}10\ years}$ (purple line). Panel D - shows the relationship $TPR_{all\ ages}$ and standardized $PR_{2\text{-}10\ years}$ (green line). Reproduced from Kamau et al., 2020, published CC-BY 4.0

4.4 Discussion

The utility of malaria surveillance passively collected at health facilities as a surrogate to community infection prevalence remains poorly defined (Section 1.7.3). To characterise this relationship, 36 paired facility-based fever TPR and community PR were examined over a 12-month period on the Kenyan coast. The community-based malaria infection prevalence was 10% among residents aged ≥6 months, however, 43% of patients of the same age, from the same communities presenting with fever to a health facility were infected. In this low-moderate transmission area, there was a strong positive correlation (*rho* = 0.63) between facility-based fever TPR and community PR reported across all ages (Table 4.2). The association between TPR and PR was higher in children aged 6 months-14 years than in adults aged ≥15 years since in this low-moderate transmission setting, children were more likely to become symptomatic leading to prompt care-seeking. However, the association could also represent opportunistically detected malaria infections in children, meaning, fevers seen in the facilities might not be causally related to malaria infection. A direct non-linear, polynomial relationship was observed between the relative change in TPR and changes in the PR (Table 4.5), suggesting a statistical relationship between TPR as a proxy for traditional community-based measures of malaria transmission. The complex relationship between TPR and PR in this setting may be explained by age and immunological protection (Chapter 3). However, the polynomial model fitting of routine data might not lend itself easily to programmatic use for malaria stratification by NMCP, where simpler cut-offs are required.

NMCPs must make strategic policy decisions for intervention based on data [WHO, 2018d]. Decisions to-date have relied heavily on interpolated, infrequent and incomplete community-based infection prevalence maps (Section 1.9.1.1). Within the study area, a maximum probable TPR of <40% would correspond to areas with a PR

of <5%, while a corresponding minimum probable TPR of approximately ≥49% would identify high transmission areas (PR≥30%) in need of addition malaria prevention (Table 4.6). These two predictive ranges of TPR, defined through testing all fevers, were significantly different in all the models (Table 4.6), however, the actual differences in the upper and lower bounds of the conservative values 40% *versus* 49% TPR might not provide NMCPs adequate discriminatory power when using data collected under routine conditions. Electing to migrate from one vector control strategy to another to promote sub-county policy decisions on a pathway to elimination, based on these narrow discriminatory cut-offs seems unlikely. Larger, more spatially diverse data series using routinely collected TPR matched to community-based infection prevalence data are required to explore the more practical implications of using TPR as a replacement for community PR. The aim here was to show that a statistical relationship does exist using carefully controlled data.

The relationships between TPR and PR shown here are consistent with other studies undertaken using similar designs. In three separate transmission settings in western Kenya, the correlation between malaria positivity rate among suspected patients from the health facilities and asymptomatic malaria positivity among school children was 0.78, 0.61, and -0.039 in the low, moderate, and high transmission settings, respectively [Kapesa et al., 2018]. As with the present study, the weakest correlation was also reported for TPR among individuals aged ≥15 years in the moderate (*rho* = 0.32) and high transmission areas (*rho* = 0.01) [Kapesa et al., 2018]. A much earlier study, outside of Africa, in the Punjab, Pakistan, found a stronger positive correlation (*rho*=0.97) between clinic slide positivity data and community survey data from four villages compared at three different timepoints [Fox et al., 1987].

An important observation is that using TPR among all age groups did correspond to $PR_{all\text{-}ages}$ and $PR_{2\text{-}10\ years}$ (Table 4.6) or $PR_{school\ children}$ [Kapesa et al. 2018]. The

comparative value of TPR in older individuals was less than that of children under 15 years of age. However, data through the current routine health information systems is only available above and below five years of age. This suggests that using the universe of all testing data from all age groups as a proxy to community infection prevalence would not require changes to existing data reporting DHIS2 architecture.

Routinely collected TPR has several advantages as a surrogate measure of malaria transmission. There are obvious opportunity costs of using routine, rather than expensive survey data; data are spatially cosmopolitan rather than opportunistically sampled; available at continuous temporal resolutions; and provide granular data at district levels for district level decision making. In the present study, national guidelines [MoPHS, 2010] on test-treat among all age groups were followed, to this end, all fevers were tested, RDTs were supplied by the research team and careful documentation of all events formed the basis of the study. Under normal health facility conditions, the reality is likely to be very different. Studies have shown that not all fevers presenting to clinics are tested and reporting rates are often incomplete [Oduro et al., 2016; Boyce & O'Meara, 2017; Namuyinga et al., 2017; Plucinski et al., 2018a; WHO, 2019a; Alegana et al., 2020; Amboko et al., 2020; Colborn et al., 2020]. Although TPR is a useful measure in the reflection of infection transmission dynamics in the communities [Fox et al., 1987; Kapesa et al., 2018], there are several important considerations. First, despite its low cost and simplicity, the use of TPR is hugely dependent on coverage, completeness, quality of information [Githinji et al, 2016; Maina et al., 2017; Okello et al., 2019], and may be affected by health seeking behaviours, and diagnostic test utilization [WHO, 2019a]. Variations in the testing rates have been associated with levels of endemicity, staffing or workload, inadequate training and lack of supervision of health care workers, shortages and stock-outs of RDTs, and patient-level factors [Alegana et al., 2020]. In Kenya, there is increasing evidence that coverage,

completeness, and quality of routine reliable malaria information remains inadequate [Githinji et al., 2017; Maina et al., 2017; Okello et al., 2019] but is improving in high transmission areas.

To explore what was reported nationally from the six facilities during the period of investigation, the national DHIS2 platform was accessed in 2020. Data were available for the six health facilities, reporting on 23,975 positive cases, more than those defined during the observation period by the study (19,761). The number of RDTs performed were, however, inconsistent: data was missing completely for all 12 months in Bomani, Mavueni and Ziani but available for 2 months in Jaribuni, 8 months in Chasimba, and 10 months in Kadzinuni. Where data was available on the number of RDT tests performed over a combined 20 months at Jaribuni, Chasimba and Kadzinuni, the mean monthly $TPR_{all\ ages}$ was 33% (range 21-94%) which compared to a matched mean $TPR_{all\ ages}$ during the study period from the same facilities of 43% (range 17%-63%). This highlights the incompleteness of data, where TPR could only be computed in 20/72 possible facility months and the inaccuracies of data when reported, a TPR difference of 10%.

Because of the vagaries of current routine data in Africa, the default position for measuring the risk and disease across 36 high burden countries in SSA is the fine resolution maps generated by MAP in support of the WHO (Section 1.9.1.1-1.9.1.2). The assumption is that these are more accurate than routine data. It is therefore interesting to compare the actual and all-age standardized $PR_{2\text{-}10\ years}$ measured across the 36 EZs in the present study combined for all four surveys 2018-19 with estimates of *Pf*$PR_{2\text{-}10}$ predicted by MAP in 2015 [Bhatt et al., 2015b] and 2017 [Weiss et al., 2019] (Figure 4.3). The mean MAP predicted *Pf*$PR_{2\text{-}10}$ in 2015 across the 36 EZs was 23% (range 19%-25%) [Bhatt et al., 2015b], different to 2015 predicted mean *Pf*$PR_{2\text{-}10}$

provided in the revised model of 8% (range 5%-11%) [Weiss et al., 2019]. In 2017, this corresponded to a predicted mean *Pf*PR_{2-10} of 9% (range: 6%-12%) (Figure 4.3). The actual mean PR among children aged 2-10 years (14%: range 0%-52%) and age-standardized mean PR_{2-10} based on data from all age groups (15%: range 0.01%-53%) in 2018-19 were broadly similar with MAP predictions. However, the fine spatial resolution predictive modelling used by MAP is unable to capture the wide variation in PR between sites, over-estimating low transmission sites and under-estimating high transmission sites (Figure 4.3). This is shown here to highlight that while there remains a reluctance to use routine data, the default modelled predictions of PR have huge margins of prediction error at the spatial scales they presume accuracy.

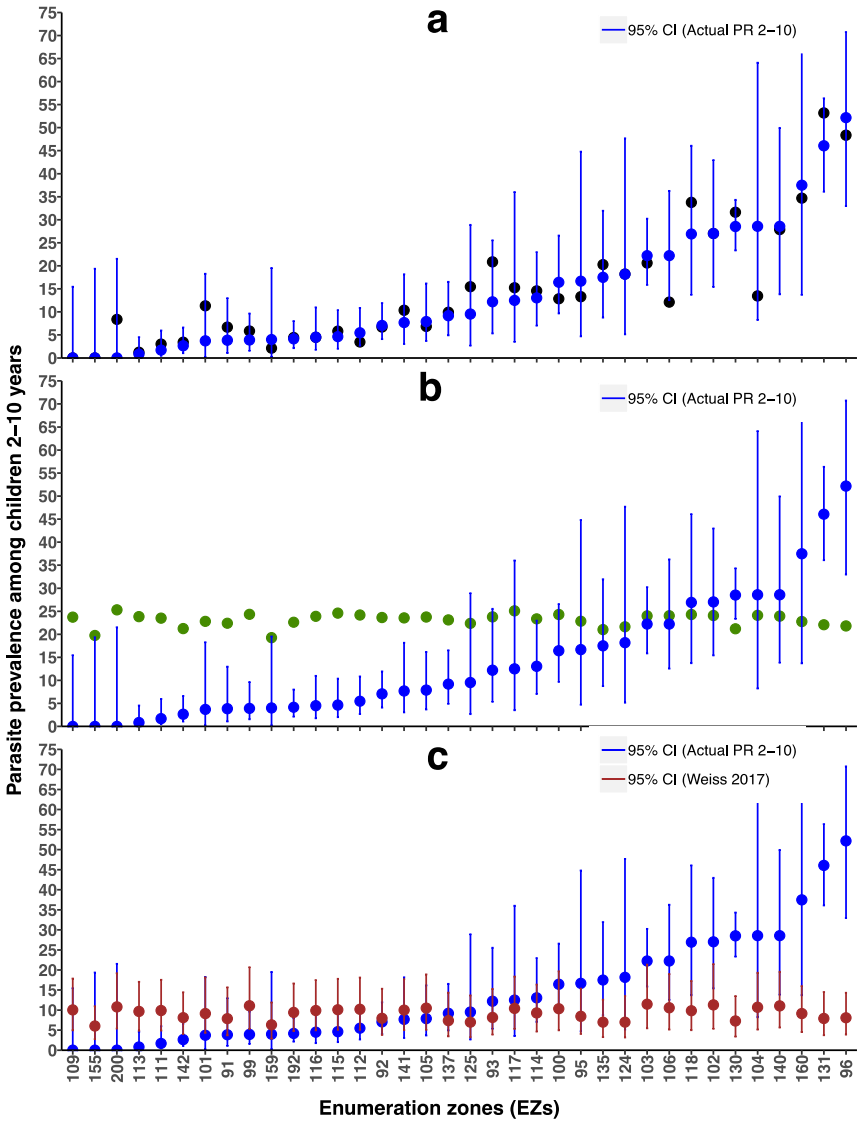


Figure 4.3: Comparison of empirically collected parasite prevalence against MAP modelled predictions in 2015 and 2017 across the 36 enumerations zones

Legend: Panel A - shows the actual parasite prevalence among children aged 2-10 years (blue points) with their 95% CI (vertical blue line) and age-standardized $PR_{2\text{-}10\ years}$ computed for the study area (black points). Panel B - shows the actual parasite prevalence among children aged 2-10 years (blue points) against mean MAP predicted *Pf*$PR_{2\text{-}10}$ in 2015 (green points) [Bhatt et al., 2015b]. Panel C - shows the actual parasite prevalence among children aged 2-10 years (blue points) mean MAP predicted *Pf*$PR_{2\text{-}10}$ in 2017 (red points) with their 95% CI (vertical red line) [Weiss et al., 2019] for each enumeration zone.

It is striking that in the present study, less than 10% of people were harbouring malaria infections at any point in time, however, more than 40% of those with a fever attending a facility had infection. In this low-moderate transmission setting, fever might be a good predictor of infection. During the community-based surveys, 22% of children aged 6 months-4 years reporting fever were RDT positive, compared to 9% of afebrile

children, i.e. three times more likely to be infected. This has also been shown across a range of endemicities [Okiro & Snow, 2010]. Conversely, 60% of fevers are not associated with malaria infections when they present to clinics, highlighting the importance of the test-treat policy.

4.4.1 Caveats

Although RDTs are now widely used in clinical and survey settings, it is important to note they are often less sensitive in low parasitaemia (<100 parasites/ul of blood) and they lack specificity as the antigen can persist in the patient's blood for weeks after successful antimalarial treatment [Plucinski et al., 2018b]. However, it was decided to mimic national malaria case-management and diagnosis guidelines for facilities without functioning laboratories, where RDTs are recommended. Similarly, to ensure comparability RDTs were used during the community surveys, often used during national household surveys for measuring infection prevalence. It is also important to note that case-management policy and routine data in Kenya includes all children under five years, however, this study did not include children under 6 months of age though it seems unlikely that TPR reports among children under-five years would be significantly different from TPR reported among children aged 6 months-4 years. Although an out-of-sample validation was performed, the confidence in the generalizability of the results is reinforced if it is validated in an external population. Furthermore, caution should be used in interpreting the function of best-fit regression. Noise in the estimation of either variable will lead to not just uncertainty in the estimate, but also to a slope that is biased towards zero because of regression dilution bias. Noise can be introduced by completely random errors (minimized by sample size) and other errors introduced by heterogeneity in transmission. In addition, although a TPR <40% may be compatible with a PR<5% it is also compatible with PRs > 5%. It is possible that larger datasets would lead to the estimation of a steeper function linking PR to TPR, which would then lead to a more favourable impression of

the utility of TPR in determining endemicity. Finally, it should be acknowledged that not all fevers occurring in a community will seek treatment at health facilities [McCombie,1996; Baume et al., 2000]. The results presented in this chapter only reflect data that would theoretically be available routinely through DHIS2 of patients who seek care at a diagnostic centre. Much less is known about the relationships between TPR and PR among those who seek care in the informal sector, private clinics or among those who seek treatment from community health workers.

4.5 Conclusion

Health facility-based surveillance with indicators like TPR remains an attractive measure which might be a crude reflection of transmission dynamics while at the same time, they are more operationally attractive compared with community-based surveys in terms of time and cost. However, a better understanding is required of the biological, clinical, social and epidemiological relationships between malaria infection and fever across all ages, and all health systems. Importantly, these studies must be undertaken across a wide range of endemicities to develop more pragmatic usable criteria for NMCPs to use effectively in a stratified response to malaria control. While inadequacies continue to exist for the accurate and complete collection of routine data these problems are surmountable. They represent a reality that requires health systems investments to change. Moreover, surveillance data is a key pillar of intervention necessary for future national malaria control in Africa [WHO, 2015].

Chapter 5 : Spatial-temporal clustering of malaria test positivity rate using routinely collected health facility data

5.1 Introduction

Malaria is a spatially and temporally heterogeneous disease. As transmission declines, malaria risk becomes increasingly clustered in specific localities or populations (Section 1.8). Identifying areas experiencing significantly more malaria cases than would be expected by chance might be important to target increased control efforts to localities contributing the highest burden. The use of spatial tools to detect malaria hotspots (i.e. single villages or groups of households within villages with increased risk of malaria transmission) using routinely collected data would increase the value of local health information systems at district levels. There have been very few examples of "hotspot" detection under stable transmission settings using passively detected cases reported through routine health information systems (Table 1.7). This chapter explores the spatial and temporal dynamics of fever positive RDT malaria cases routinely collected in six health facilities.

5.2 Materials and Methods

5.2.1 Study outline

The study area and included health facilities have been described in detail in Sections 3.4.2-3.4.3. Briefly, the data used in this chapter was obtained from Mavueni dispensary, Jaribuni dispensary, Kadzinuni Kendrick dispensary, Bomani Malde dispensary, Ziani dispensary, and Chasimba health centre between March 2018 to February 2019 (Figure 3.6).

To quantify spatial clustering of passively detected cases, two spatial resolutions were considered. All health facility attendees included in this study were linked to the KHDSS homestead level geospatial coordinates to assess heterogeneity at a very fine spatial scale (i.e. the gold standard methodology). However, geospatial data at this level would not be available routinely in health facilities. Since patient records generally

do not include actual residential addresses, homesteads level data was aggregated at enumeration zone (EZ) (equivalent to a village) to explore the feasibility of hotspots detection using village-level information likely to be recorded routinely in health facilities. The geographic coordinate of the centroid of each EZ was used.

5.2.2 Statistical analysis

The focus of the analysis was across all ages (≥6 months) as these data are available from existing DHIS2 platforms and because TPR across all ages was strongly associated with infection prevalence in the community, suggesting that passive surveillance does provide a reflection of infection prevalence in the community (Section 4.3.2). Since geospatial coordinates (longitude and latitude) of homesteads tended to have a small number of patients resulting in higher standard errors and therefore less precise TPR, smoothing was performed. TPR was calculated as a simple proportion of RDT positive homestead members within a radius of <1 km around each index patient. To explore different smoothed estimates of TPR, the radius was also altered at <0.2 km and <0.5 km. TPR for each EZ was calculated as the number of positive diagnostic tests as a proportion of the total tests performed among febrile patients aggregated at the EZ level.

5.2.2.1 Local spatial cluster detection

Local clustering detection was performed using Martin Kulldorff 's spatial scan statistic (SaTScan) [Kulldorff, 1997]. SaTScan imposes an infinite number of circular scanning windows across a study area with radius varying from zero to a maximum of 50% of the population in the sampling frame. Each scanning window is evaluated as a potential cluster by the calculation of a log-likelihood ratio (LLR) test statistic based on the observed, expected and total number of cases. To test the null hypothesis of complete spatial randomness, SaTScan employs Monte Carlo simulations where for each simulation run, the observed cases are randomly permuted in space across the

entire set of data locations. The observed log-likelihood is then compared with the simulated log-likelihoods to determine significance. The statistical significance of a cluster (or ‘‘hotspot’’) is then evaluated taking into account the multiple tests for the many potential cluster locations and sizes assessed.

Spatial analyses using Kulldorff ’s spatial scan statistic has predominately been used in malaria epidemiology to demonstrate spatial heterogeneity (Table 1.7). Therefore, in this analysis, spatial scan statistics using the Bernoulli probability model was used to detect hotspots of fever positive RDTs across all ages using actual data rather than the smoothed estimates, where cases were febrile individuals with a positive test and controls were individuals with a negative test. The maximum spatial cluster size was set at a radius of 3 km. Two assumptions guided the choice of the threshold distance: i) the effective flight range of malaria vector mosquitoes and ii) the estimated travel distance of patients from their homesteads to the health facilities (Table 3.2). For each detected hotspot, a relative risk (RR) was computed. The RR is the magnitude of the risk of malaria for individuals residing within the hotspot compared to the estimated risk in the surrounding area. The spatial analysis was restricted to circular windows for hotspot detection with the maximum window size set to 50% so that both small and large clusters could be detected. The circular windows were used in line with common practice. They are computationally efficient, and it is easier to determine hotspot properties that are of interest (Radius, RR and significance).

SaTScan was applied since results from previous studies indicated that it maintains a reasonably high power compared to other methods such as LISA which are influenced by neighbours [Jackson et al., 2009] and higher sensitivity compared to Getis-Ord Gi* statistic [Barro et al., 2015]. Furthermore, Getis also suffer from multiple testing which is inherently accounted for in SaTScan [Kulldorff, 1997]. In this way, SaTScan

combines both exploratory and confirmatory capabilities which enable explicit statistical assessment of spatial patterns across the study area [Kulldorff, 1997].

5.2.2.2 Temporal stability of hotspots

As shown earlier, there were no clear patterns between seasonality and TPR (Figure 3.17). Therefore, to test for temporal stability of spatial clusters, the data was sub-divided into quarterly intervals i.e. March to May 2018 (Q1), June to August 2018 (Q2), September to November 2018 (Q3) and December 2018 to February 2019 (Q4). The spatial analysis, described above, was repeated for each interval rather than a spatial-temporal model to enable comparison of hotspots of fever positive RDT with data from four cross-sectional surveys of infection prevalence in the same community (described in detail in Section 3.4.4). The most likely cluster (hereafter referred to as primary cluster) was identified based on the maximum log-likelihood ratio. In addition, other clusters with statistically significant log-likelihood values were defined as secondary clusters.

Spatial cluster analysis was performed using SaTScan™ software version 9.6 (Information Management Services Inc, Silver Spring, Maryland, USA). All other statistical analyses were performed in Stata, version 13 (Stata Corporation, College Station, TX) and R version 3.6.1 (R Core Team (2019), Vienna, Austria). Maps of hotspots were produced in R.

5.3 Results

5.3.1 Description of the spatial data

Overall, the study comprised of 28,134 febrile health facility attendees of all ages in 5,323 geocoded homesteads between March 2018 and February 2019. Among all febrile patients, 12,143 (43%) tested positive for malaria using RDT. The number of febrile health facilities attendees varied across the quarterly intervals ranging between

4,284 and 9,119 (Table 5.1). The RDT fever test positivity rate was lowest between March and May 2018 at 39% (1,651 cases) and highest between June and August 2018 at 45% (4,096 cases) (Table 5.1). A similar test positivity rate (45%) was observed between December 2018 to February 2019 (Table 5.1). The overall smoothed 1 km mean TPR was 38.8% and ranged between 0% and 89.3% in an average of 680 febrile health facilities attendees and 289 RDT positive cases in 5,323 geocoded homesteads located in 36 EZs (Figure 5.1 & Annex 16). The smoothed mean TPR was comparable when the radial distance was altered which was 38.7% for both 0.2 km and 0.5 km (Annex 16). The 1 km radius was chosen over other radial distances as 'noise' was minimised with greater stability.

Table 5.1: Summary of data routinely collected at six health facilities stratified by quarterly intervals

Summary measures	March-May 2018 (Q1)	June-August 2018 (Q2)	September-November 2018 (Q3)	December 2018-February 2019 (Q4)	Overall
Number of geo-coded homesteads	2,290	3,532	3,368	2,890	5,323
Number of attendees (N)	4,284	9,119	8,396	6,335	28,134
Number of cases (n)	1,651	4,096	3,554	2,842	12,143
TPR, (95% CI)	38.5% (37.1%, 40.0%)	44.9% (43.9%, 45.9%)	42.3% (41.3%, 43.4%)	44.9% (43.6%, 46.1%)	43.2% (42.6%, 43.7%)

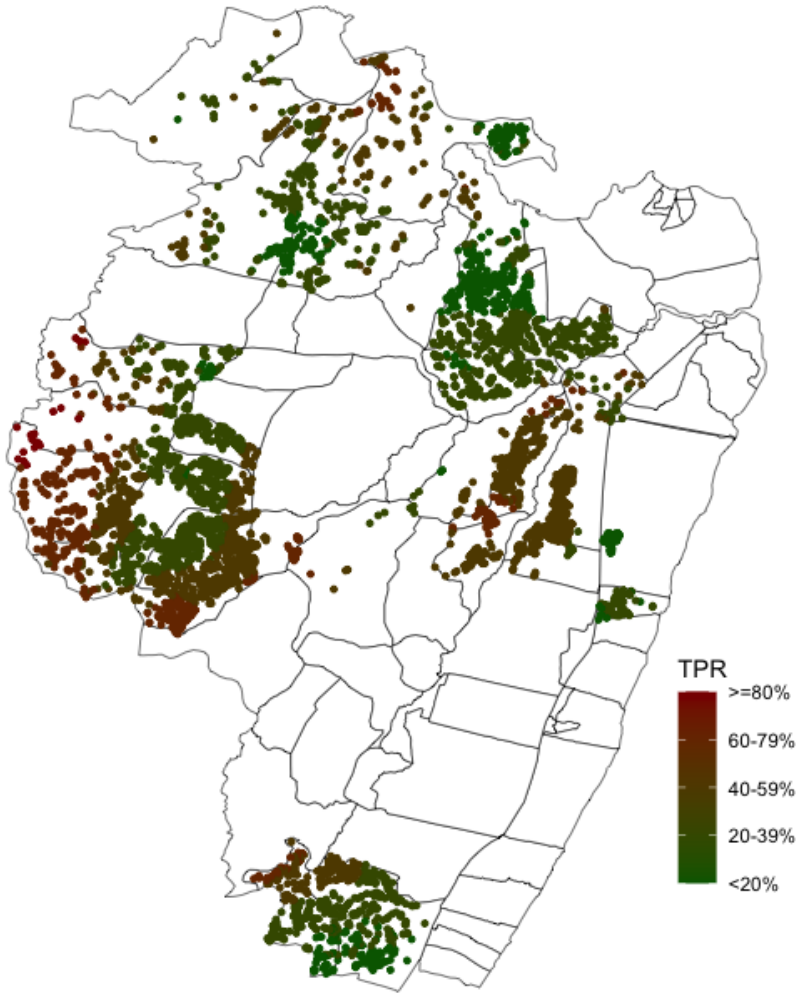


Figure 5.1: The spatial distribution of yearly smoothed mean TPR at homestead level aggregated at a 1 km radius

Legend: Each plotted point represents an individual homestead, where the colour shading indicates TPR, with red shading indicating high TPR and green shading indicating lower TPR**.**

5.3.2 Spatial hotspot detection

Across 12 months of surveillance, nine significant clusters were identified using the purely spatial scan statistics among RDT positive fevers of all age groups (Figure 5.2). The primary cluster with a radius of 3.0 km was detected among patients attending Chasimba health centre, composed of 289 (5.4%) homesteads accounting for 16.0% (1,939) of all fever test positive cases detected (cluster 1 in Figure 5.2). The homesteads within this cluster were 1.75 ($p<0.001$) times more at risk of testing positive for malaria than homesteads outside the cluster. In addition, secondary

hotspots were identified among patients attending Ziani (cluster 2, 3, and 9), Kadzinuni (cluster 4), Bomani (cluster 5) and Jaribuni (cluster 6 and 7) dispensaries (Figure 5.2). Cumulatively, in both the primary and secondary hotspots, there were 1,520/5,323 (28.6%) homesteads that accounted for 51.8% (6,293/12,143) of all fever test positive cases detected in the study area. When data were aggregated at EZ level, a spatial resolution equivalent to what might be available through routine health information systems, the primary and secondary hotspots identified were generally located in the same areas as those identified using the homestead level data (Figure 5.3).

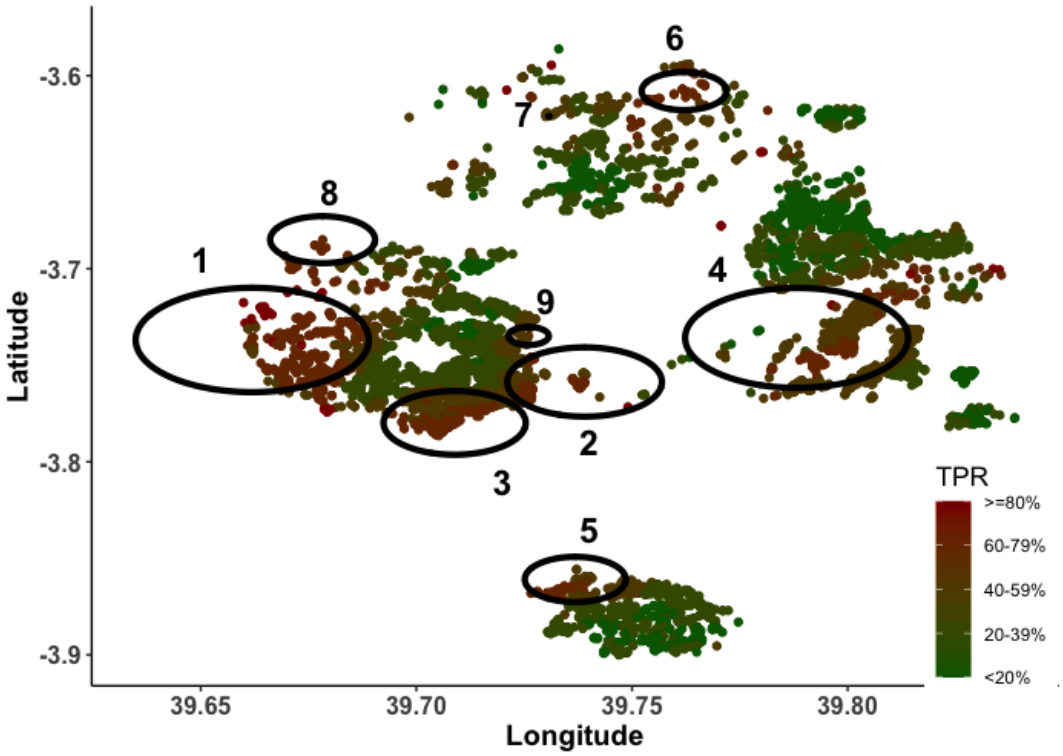


Figure 5.2: Spatial distribution of smoothed mean TPR across 12 months of surveillance at homesteads level aggregated at 1 km radius and the spatial hotspots of fever positive RDT cases, analysed without smoothing

Legend: Each plotted point represents an individual homestead, where red shading indicates high TPR and green shading indicates lower TPR. The large black circles indicate the significant hotspots (analysed without smoothing) where 1 indicates the primary cluster located in Chasimba health centre and clusters 2-9 are the secondary hotspots located in Ziani, Kadzinuni, Bomani and Jaribuni dispensaries.

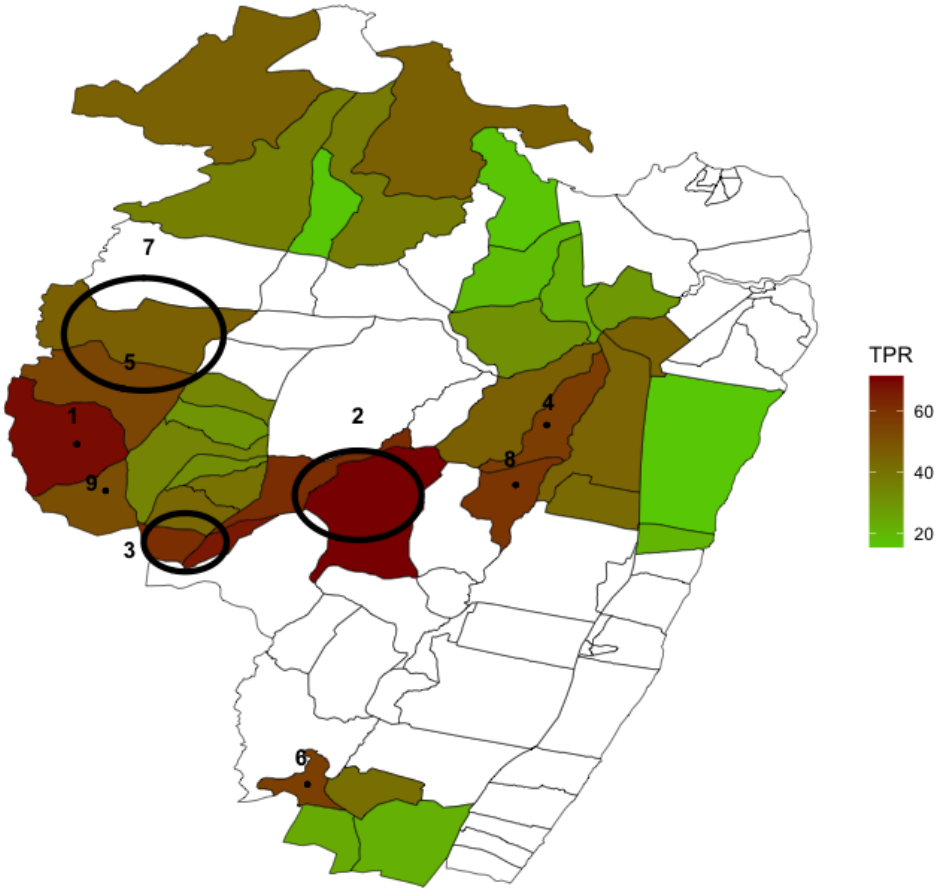


Figure 5.3: Spatial pattern of annual malaria RDT positivity rate by enumeration zones and spatial hotspots of fever test positive cases

Legend: The red shading in the choropleth map indicates very high TPR (≥ 60%), brown indicated high TPR (40-59%), dark green is low-moderate TPR regions (20-39%) and light green shading indicating lower TPR (<20%). The large black circles indicate the location of high-risk clusters detected by purely spatial scan statistics using geographic coordinates of the centroid of each EZ. Cluster 1 indicates the primary cluster located in Chasimba health centre and clusters 2-9 are the secondary hotspots located in Ziani (clusters 2 and 3), Kadzinuni (clusters 4 and 8) and Bomani (cluster 6) dispensaries. The additional secondary clusters 5, 7 and 9 were located in Chasimba health centre.

5.3.3 Temporal stability of hotspot detection

To test for temporal stability of spatial clusters, the data was sub-divided into quarterly intervals. When the spatial analysis was repeated for each quarter, several hotspots were detected. The relative risk of infection within these clusters was significantly higher in comparison to the population outside of these clusters (Table 5.2). The radius of the spanning windows ranged from 0.66 km to 3.0 km and four, six, four and five clusters were detected in the first, second, third and four quarters, respectively (Table 5.2). These spatial clusters represented between 17.7% (405) and 32.6% (1,098) of

all the geocoded homesteads (Table 5.2). Only two clusters seemed temporally stable across the quarterly intervals (Figure 5.4).

Table 5.2: Spatial clusters of fever positive RDT cases detected by SaTScan, ordered from the cluster with the highest LLR, stratified by quarterly intervals

Period	Cluster order	Radius (Km)	Number of cases in cluster (n)	Cumulative cases/Total cases	Expected cases	Number of HMs in cluster (n)	Cumulative HMs/Total HMs	RR	P-value
Q1	1	2.90	287	287/1,651	139.12	106	106/2,290	2.29	<0.001
	2	2.31	270	557/1,651	174.58	216	322/2,290	1.65	<0.001
	3	1.13	44	601/1,651	21.2	23	345/2,290	2.11	<0.001
	4	0.66	88	689/1,651	59.74	60	405/2,290	1.50	0.03
Q2	1	3.00	583	583/4,096	371.51	220	220/3,532	1.66	<0.001
	2	1.72	289	872/4,096	197.21	143	363/3,532	1.50	<0.001
	3	2.09	363	1,235/4,096	270.88	227	590/3,532	1.37	<0.001
	4	2.52	103	1,338/4,096	64.69	40	630/3,532	1.61	<0.001
	5	2.49	222	1,560/4,096	163.97	84	714/3,532	1.37	<0.001
	6	2.32	283	1,843/4,096	229.1	251	965/3,532	1.25	0.02
Q3	1	2.28	815	815/3,554	550.29	546	546/3,368	1.62	<0.001
	2	2.78	503	1,318/3,554	306.47	177	723/3,368	1.75	<0.001
	3	2.97	537	1,855/3,554	400.44	306	1,029/3,368	1.40	<0.001
	4	1.24	133	1,988/3,554	89.74	69	1,098/3,368	1.50	<0.001
Q4	1	2.75	538	538/2,842	334.22	216	216/2,890	1.75	<0.001
	2	1.51	226	764/2,842	157.47	188	404/2,890	1.47	<0.001
	3	1.74	134	898/2,842	84.34	74	478/2,890	1.62	<0.001
	4	1.82	247	1,145/2,842	183.04	178	656/2,890	1.38	<0.001
	5	2.70	114	1,259/2,842	73.12	76	732/2,890	1.58	<0.001

The primary cluster in the first quarter was a 2.9 km radius west of the study area, composed of 106 (4.6%) homesteads accounting for 17.3% (287) of all fever test positive cases identified in that period. The homesteads within this cluster attended Chasimba health centre and were 2.29 ($p<0.001$) times more at risk of testing positive for malaria than homesteads outside the cluster. In the second quarter, the primary cluster had the highest-risk (1.66; $p<0.001$) and overlapped with the cluster detected in the first quarters. This cluster represented 8.5% of the homesteads accounting for

14.2% of all fever test positive cases (Table 5.2). The primary cluster detected in the third quarter had a radius of 2.28 km with a risk of 1.62 ($p<0.001$) but was located in the central part of the study area among patients attending Ziani dispensary. This cluster represented 15.9% of the homesteads and 22.9% of all fever test positive cases detected in that period (Table 5.2). The cluster with the highest risk (RR=1.75; $p<0.001$) in the third quarter was in a similar location as the primary clusters detected in the first and second quarter. The fourth quarter showed a similar pattern to what was observed in the first and second quarter. The highest-risk hotspot was detected in the same location with a RR of 1.75 ($p<0.001$) and represented 7.4% of the homesteads and accounted for 18.9% of all fever test positive cases in that period (Figure 5.4).

There were several secondary hotspots identified across all the quarterly intervals (Table 5.2 & Figure 5.4). The secondary clusters were characterized in Jaribuni, Kadzinuni and Bomani dispensaries. However, the spatial location and size varied across the intervals. There were neither primary nor secondary clusters detected using data obtained from Mavueni dispensary. Cumulatively, all the hotspots detected in the first quarter represented 17.7% (405/2,290) of all the homesteads accounting for 41.7% (689/1,651) of all fever test positive cases detected. In the second quarter, 27.3% (965/3,532) of the homesteads accounted for 45.0% (1,843/4,096) of the case, in the third quarter 32.6% (1,098/3,368) of the homesteads accounted for 56.0% (1,988/3,554) of the cases and in the fourth quarter, 25.3% (732/2,890) of the homesteads accounted for 44.3% (1,259/2,842) of the cases detected (Table 5.2).

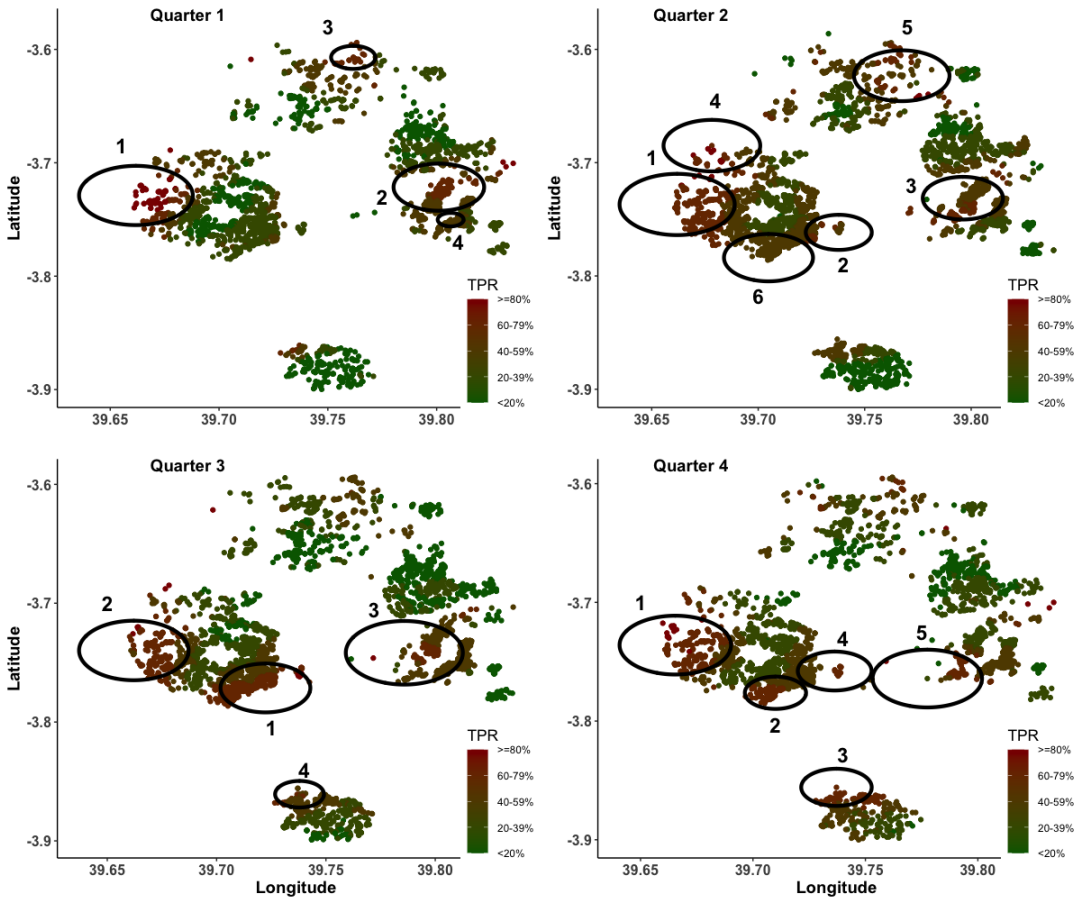


Figure 5.4: Spatial distribution of smoothed mean TPR across all ages at homesteads level aggregated at 1 km radius and the spatial hotspots of fever positive RDT cases stratified by quarterly monthly periods, analyzed without smoothing

Legend: Each plotted point represents an individual homestead, where red shading indicating high TPR and green shading indicating lower TPR. The large black circles indicate the significant hotspots (analysed without smoothing) where 1 indicates the primary cluster and clusters 2 - 6 are the secondary hotspots.

In the two temporally stable hotspots, 142/5,323 (2.7%) homesteads were consistently identified in these hotspots across the four-time intervals accounting for 10.8% (1,311/12,143) of all fever test positive cases detected, 353 (6.6%) were identified three times and accounted for 17.5% (2,122) of the cases, 218 (4.1%) were identified twice accounting for 5.3% (643) of the cases and 306 (5.8%) were identified once accounting for 9.0% (1,095) of the cases while 4,304 (80.9%) homesteads were in the unstable hotspots or were never identified in a hotspot area. Again, when data was aggregated at EZ (village) level, the primary and secondary hotspots identified across the quarterly intervals (Figure 5.5) were roughly located in the same areas as those identified using the homestead level data (Figure 5.4).

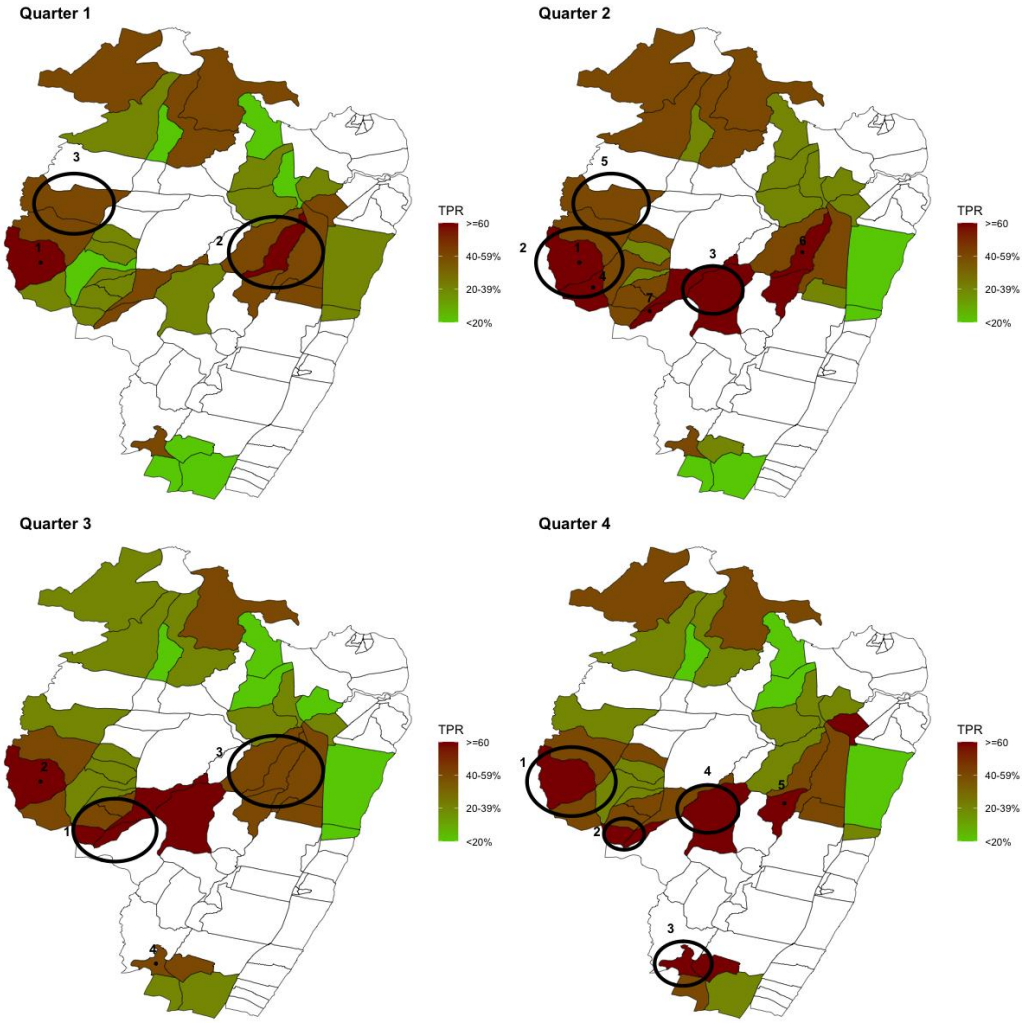


Figure 5.5: Spatial pattern of annual malaria RDT positivity rate by enumeration zones and spatial hotspots of fever test positive cases stratified by quarterly monthly periods

Legend: The red shading in the choropleth map indicates very high TPR (≥60%), brown indicated high TPR (40-59%), dark green is low-moderate TPR regions (20-39%) and light green shading indicating lower TPR (<20%). The large black circles indicate the location of high-risk clusters detected by purely spatial scan statistics using geographic coordinates of the centroid of each EZ. Cluster 1 indicates the primary cluster located and clusters 2-7 are the secondary hotspots.

5.4 Discussion

The results presented in this chapter demonstrate that information obtained through routine testing of febrile patients for malaria can identify spatial and temporal heterogeneities of malaria risk at very fine spatial scales, where homestead coordinates are available and importantly at lower resolutions where village names might be available (Figure 5.2 & Figure 5.3).

Fever positive RDTs cases exhibited spatial heterogeneity as evidenced by the existence of statistically significant ($P<0.05$) spatial clusters in groups of homesteads among residence of six catchment areas of six health facilities. Across the 12-month surveillance period, these clusters included 52% of all fever positive RDT cases detected in 29% of the geocoded homesteads in the study area. In addition, the power to detect clusters of fever positive RDT cases did not diminish when data were spatially aggregated at EZ (village) level (Figure 5.3) as demonstrated previously [Jones & Kulldorff, 2012]. However, aggregations negatively impacted the ability to more accurately determine the exact spatial location of the clusters. These results support the hypothesis that malaria tends to significantly cluster within certain geographic units [Woolhouse et al., 1997; Gaudart et al., 2006; Mirghani et al., 2010; Bousema et al., 2010, 2012; Stresman et al., 2018; Bejon et al., 2014; Rouamba et al., 2019; Hamre et al., 2020].

When the temporal stability of the hotspots was examined, the hotspots varied greatly across the intervals (Figure 5.4). The clusters of fever positive RDT cases moved in space across the quarterly intervals and rarely reoccurred in the same location. This has also been noted in other clustering studies [Bejon et al., 2014; Rouamba et al., 2019; Hamre et al., 2020]. Only two temporally stable hotspots were identified with 2.7% of the homesteads consistently located in these areas across all the intervals and included 10.8% of all fever positive RDT cases detected.

Among these two stable hotspots, data on infection prevalence across four cross-sectional surveys conducted in the same community (the methods are described in detail in section 3.4.4, and the results of community prevalence from these surveys are given in Table 3.1) were re-analysed to explore differences in transmission. When the community infection prevalence data was linked to the homesteads within these two temporally stable hotspots, there were significant differences in the parasite

prevalence within these hotspot radii (27.3%, 245/897) compared to outside the radii (7.3%, 343/4,712) (p<0.001). Homesteads in these stable hotspots were 4.9 (95% CI: 4.1, 6.0; p<0.001) times more likely to have asymptomatic infection compared to homesteads outside of these clusters. This data demonstrates that there appears to be a higher level of malaria transmission in the stable, passively detected hotspots relative to the wider community. This highlights an added value of using routine data to identify areas that might require additional control efforts.

Most studies that have mapped the spatial distribution of malaria burden have relied upon surveys of well-defined demographic and spatial distributions of the at-risk population [Clark et al., 2008; Bejon et al., 2010; Bousema et al., 2010; Bejon et al., 2014; Kangoye et al., 2016; Mogeni et al., 2017b; Rouamba et al., 2019; Hamre et al., 2020] (Section 1.8). Few studies have examined the use of routine PCD data in defining clusters of disease risks (Table 1.7). Of these PCD studies, variable patterns of spatial clustering have been reported. Some studies support consistent hotspots [Ernst et al., 2006; Ouedrago et al., 2018] while others suggest greater variability [Bejon et al., 2014; Rouamba et al., 2019; Hamre et al., 2020] (Section 1.8). For example, in a highland area in Kenya the risk of malaria was consistently higher between 2001 and 2004 among individuals living in hotspot area however, the number of households within the cluster varied and included between 29.3% and 49.3% of all cases detected [Ernst et al., 2006]. In Ouagadougou, Burkina Faso the location of clusters identified as high risk varied little across three transmission periods [Ouedrago et al., 2018]. In areas of moderate malaria transmission in coastal Kenya [Bejon et al., 2014], very low transmission in a highland area of Kenya [Hamre et al., 2020] and Nanoro DSS, Burkina Faso [Rouamba et al., 2019], hotspots of malaria were not consistently identified over time.

The use of passively collected routine health facility data does offer opportunities to detect clusters down to the village level at an affordable cost. However, appropriately structured and defined health facility data will be needed. To tap the full potential of these data, it is of strategic importance to refine the current surveillance tools such that they have the potential of collecting information at sufficiently precise scales (at individual level and 'village' scales). Closing these gaps could result in health information systems that have the potential of becoming scalable, integral, and sustainable components of control programmes, which can then target interventions to clusters of elevated risk [Mlacha et al., 2017; Hamre et al., 2020].

Hotspot-targeted interventions have been hypothesized to be a highly efficient method of reducing malaria transmission not only inside these hotspots but also in adjacent areas [Bousema et al., 2012; Bejon et al., 2014]. While biologically plausible, there has been mixed evidence to support this concept. For example, a trial conducted in western Kenya failed to observe any sustained reduction in transmission [Bousema et al., 2016]. Despite achieving high coverage of interventions in hotspot areas, the interventions resulted in a modest and transient reduction in transmission inside targeted hotspots and failed to influence malaria transmission dynamics outside the targeted areas [Bousema et al., 2016]. In a more recent study in Rufiji District, southern Tanzania, the implementation of a locally tailored surveillance-response strategy contributed convincingly to the reduction of malaria burden in hotspot villages (with the highest malaria incidence ratio) using health facility-based data [Mlacha et al., 2020]. This study offered the first attempt of implementing surveillance as an intervention in areas with high malaria burden, which is in line with the current WHO recommended strategy [WHO, 2015; WHO, 2019a; Mlacha et al., 2020].

5.4.1 Caveats

Although only six health facilities were included in this study, they are not the universe of all health service providers in the study area, as such febrile patients may have elected to use retail or private facilities or formal health services more distal to their home. In addition, this study was limited in terms of spatial and temporal coverage as it was only conducted in the southern part of the KHDSS for 1 year. Nonetheless, spatial and temporal clusters were still detected which was the objective of this chapter. It is possible that the spatial heterogeneity observed may have been due to measurement bias of how fever positive RDTs cases are defined. For example, there is a possibility that some of the fever test positive case was from a single infectious bite or repeated inoculations within the same individual because all cases testing RDT positive including re-attendance were used. To evaluate the degree of potential measurement bias as an alternative explanation, SaTScan analysis was rerun using records of first cases only of RDT positive patients. Fortunately, the results were generally similar to the results obtained using records of all cases (Annex 17). Although Kulldorff's scan statistic was successfully used to detect circular clusters, it may have ignored irregularly shaped clusters. An elliptic window shape can be used as an alternative to the circular window, which may provide higher power for true clusters that are elliptical in shape, but lower power for circular or other very compact clusters and comes with extra computational cost. Despite these potential limitations, the results of this study are still important and suggest that routine data might be useful for planning local disease control. However, the value of hotspot detection would need to be contextualised, discussed in the next section.

5.5 Conclusion and programme implications

In this study, approximately a third of the homesteads in the study area fell within identified hotspots and accounted for half of all health facility fever positive RDTs

cases. These hotspots varied over time, but two stable hotspots showed higher community-based infection prevalence, suggesting they were different from surrounding areas. The operational question is whether these areas are ‘hot enough’ to re-design district level control strategies from one of universal coverage of interventions, assuming no heterogeneity, to one of a more tailored, nuanced approach based on local data. The temporal instability of the hotspots suggests that the use of local data would require real-time analysis and intervention. The complexity of these analyses in time and space, suggests that hotspot-targeted interventions may at this stage be unnecessary in this part of Kilifi county.

Chapter 6 : Concluding remarks

6.1 Introduction

Malaria in Africa has witnessed cycles of declining transmission intensity since 1900. The impact of changing malaria prevalence, however, remains poorly defined. Our current understanding of the malaria disease burden across much of Africa continues to rely on geo-spatial epidemiological models based on multiple assumptions as well as incomplete and opportunistic data. The WHO's Global Malaria Programme recognises the significance of investing in better quality routine national malaria surveillance, which now forms an important pillar of the Global Technical Strategy for malaria.

This thesis explored the precision of existing geo-spatial models to define malaria trends at a continental scale accompanied by detailed, prospective investigations of the epidemiology of malaria at one community on the Kenyan Coast. Prospective studies used combinations of routinely available health facility data and community defined events to better define the age patterns of morbidity and mortality, explored alternative facility-based metrics of transmission and how routine data might define the heterogeneous nature of malaria in a community.

6.2 How well do modelled predictions of malaria burden compare to empirical evidence?

In 36 high burden countries in SSA (86% of SSAs at-risk population), considered to have unreliable reporting systems, GBD/MAP modelled predictions currently provide the only source of information on the public health impact of malaria burden [Murray et al., 2012; Murray et al., 2014; Bhatt et al., 2015b; Gething et al., 2016; Weiss et al., 2019]. While these models provide broad approximations of malaria disease burden, they are rarely tested or validated against empirical data. Chapter 2 compared empirical data from 93 time-series sites in SSA on the yearly burden of malaria

presentation with those predicted by MAP at the same space-time. Despite an overall broad congruence in the trend of clinical malaria between the modelled predictions and empirical data, the modelled predictions were less accurate at sites where progress in burden reduction was stalling or where resurgence was documented. This has been the first attempt to triangulate empirical data with modelled temporal disease trends. Although models offer some guide to the overall temporal trends at regional levels, they have limited usefulness at local scales, necessary for national malaria control programmes to define sub-national strategies and progress.

One collateral observation from the systematic review of empirical evidence was the paucity of quality, long-term disease burden surveillance across Africa since 2000. There were only a handful of studies that included hospital surveillance data from Central and West Africa. Another key conclusion from Chapter 2's review was that there is need for increased investment in hospital-based surveillance to triangulate with model predictions in data sparse areas. This should be viewed as a public health priority: high quality, temporally and spatially representative data to empower confidence in disease burden transitions and claims of resurging or stalling progress. Models cannot, and should not, replace empirical evidence.

6.3 The age-patterns of malaria under declining transmission intensity

The GBD/MAP estimation of malaria morbidity and mortality burdens are based on scanty, historical data. For mortality, these are estimated across all age groups using notoriously insensitive verbal autopsies. For example, in SSA between 1980 and 2010, 58% of all malaria deaths were reported among individuals aged ≥15 years [Murray et al., 2012]. The precise relationship between malaria infection rate, clinical disease and mortality remains poorly defined, especially in non-pregnant adults. The absence of a complete understanding of infection-disease progression hinders all attempts to model

malaria burden in the absence of empirical data in SSA. To explore the age-related patterns of infection, severe disease and death attributed to malaria, a 12-month prospective study was established involving repeat active surveillance of the community linked to passive fever detection at six proximal health facilities and the paediatric and adult admission facilities at the nearest county hospital. The selected area has been subject to a long-term decline in malaria transmission intensity from a community infection prevalence of 43% to 10% during the study period.

During the 12-months of observation, 17% of the population presented at least once (period prevalence) with a fever associated with malaria infection to one of the six health facilities, 0.11% were admitted to hospital with a parasitologically confirmed primary diagnosis of malaria, 0.06% of the population had severe life-threatening events and an estimated 0.02% died from malaria (Table 3.8).

Despite a reduction in transmission intensity to low levels over the study period, the severe consequences of malaria infection continued to be concentrated in young children and an important cause of death in this age group. There was no evidence of an emerging significant burden of severe malaria or malaria mortality among young and older adults. Infection prevalence and fevers associated with infection rose through childhood to young adolescence. The implications of these findings support continued disease prevention efforts in young children, but attention should be given to infection control in the school-aged population of 5-14 years. Schools offer unique opportunities for direct chemoprevention strategies and the school-aged population serves as the greatest reservoir of infection in this community. From a biological perspective, the findings support the notion that immunity to disease and mortality are acquired in childhood, even when infection exposure is low, and occurs faster than anti-parasitic immunity. The implications of these observations are that relatively few parasite exposures appear to continue to protect against severe disease and death.

There remains a group of malaria burden modellers who maintain that malaria continues to serve as a direct cause of death in adult populations in SSA [Gelband et al., 2020]. Severe consequences of malaria in adults were negligible in the present study, however, there remains a paucity of detailed investigations of the morbid and fatal consequences of malaria in non-pregnant adults across the range of transmission settings that characterise SSA. Contemporary malaria epidemiological studies across all age groups such as those presented in Chapter 3, are rare. The epidemiological focus remains on under-fives and pregnant women, leaving important information gaps among those age >5 years. Further detailed epidemiological studies, that combine post-mortem interviews with minimal invasive autopsy methods linked to clinical surveillance of hospitalisation will provide a better understanding of the malaria risks in the non-pregnant adult population of SSA.

6.4 Is there a relationship between routinely measured fever infection test positivity (TPR) and community-based infection prevalence (PR)?

Parasite prevalence serves as the default entry point for estimating disease burden in all models of malaria burden [Bhatt et al., 2015b; Gething et al., 2016; Weiss et al., 2019]. However, the sparsity of community-based prevalence surveys remains an important source of error in the predictions of malaria endemicity and disease burden in time and space across SSA. As we move towards improving the use of routine data, alternatives to expensive community-based infection prevalence studies need to be explored. A more continuous and spatially ubiquitous source of information is the prevalence of malaria infection among patients examined in health facilities.

The value of routine health facility TPR data for malaria endemicity stratification and surveillance remains underutilised in the high burden areas of SSA. Chapter 4 describes the comparisons between 36 matched community-facility PR/TPR estimates

over 12 months among the studied population on the Kenyan coast. A direct non-linear polynomial relationship was observed between the relative change in TPR and changes in the PR, which is likely to have important implications for malaria surveillance programs. NMCPs must make strategic policy decisions for intervention based on data to either sustain and accelerate existing disease control efforts or migrate to more efficient systems of case-detection on a pathway to elimination [WHO, 2018d]. There are no guidelines on the cut-offs based on community-based PR in relation to the selection of specific interventions, except for seasonal malaria chemoprevention. Several countries have elected to use pragmatic cut-offs of <5% PR to consider revising policies on vector control and prevention of malaria in pregnancy; while identifying areas ≥30% PR that demand improved coverage of all prevention strategies and increased sub-national malaria control investment. The present study area demonstrated that a maximum probable TPR of <40% would correspond to areas with a PR of <5%, while a corresponding minimum probable TPR of ≥49% would identify high transmission areas (PR ≥30%). These narrow cut-offs may not provide NMCPs adequate discriminatory power to promote sub-county policy decisions. The study highlighted the need to consider a much larger range of endemicities than those covered within the study area before making a national set of recommendations. Importantly, for the value of routinely recorded TPR, there is a statistical relationship with traditional community-based measures of malaria transmission and hence TPR could be used as a proxy.

Opportunities exist to use TPR as a measurable, temporal quantity of malaria endemicity in more localities across Africa than provided by community prevalence surveys. While there are inadequacies in the accuracy and completeness of routinely collected data, these problems are surmountable with increased health system investments. Future sub-national micro-risk stratification should begin to explore using hybrids of routinely assembled malaria metrics, such as fever TPR, and traditional

existing PR maps [Alegana et al., 2020]. Such approaches of integrating different data sources have started in Tanzania [Thawer et al., 2020] and Madagascar [Arembepola et al., 2020].

Future work should also exploit the use of other routinely assembled data to serve as proxies, or integrated measures to the expensive single time-stamped community-based parasite prevalence surveys. These include prevalence of infection among antenatal attendees [van Eijk et al., 2015; Brunner et al., 2019], testing of replacement blood donors [WHO, 2010; Rocha et al. 2020], or exploiting the relationships between low-birthweight records in primigravid vs multigravida deliveries and endemicity [Brabin et al., 1999].

6.5 Can routine health facility data be used to identify localised malaria hotspots?

Malaria infection and disease are temporally and spatially heterogeneous. The concept that malaria is over-distributed in space has led to attempts to define “hotspots” in more stable endemic areas of Africa. Many of these studies have used actively detected infection and disease events. Far fewer studies have investigated the use of routine health facility data as a low-cost strategy to identify hotspots. Routine passively detected fevers associated with malaria infection over 12-months presenting to six health facilities were used to explore the heterogeneity of malaria in the study area. Using established clustering statistical tools, only two temporally stable hotspots of fever RDT positive cases were identified. These two hotspots coincidentally had higher community-based infection prevalence, suggesting that areas inside these hotspots were different from surrounding areas. Furthermore, when the resolution of the data was changed from homestead surveillance using GPS (not available to local planners) to village names (could be included in routine DHIS2 data) the same two hotspots emerged. The other detected clusters showed temporal instability and it seems unlikely

that systematic detection by county health management teams of these hotspots from their data would be easy, requiring a real-time analysis and intervention. Furthermore, resources and interventions to target the two stable hotspots remain unclear. In the present study area, under the current level of endemicity, it might remain pragmatic to sustain blanket control coverage of LLINs, prompt treatment and prevention of malaria in pregnant women rather than new, targeted interventions in two sub-communities that are not 'hot enough' to warrant a re-design in sub-county control strategies.

The results presented continue to demonstrate that information obtained through routine testing of febrile patients for malaria can describe local malaria epidemiology at fine spatial scales. When communities, or districts, are at exceptionally low parasite prevalence and are moving toward elimination, the detection of malaria hotspots using routinely collected data would prove more valuable.

6.6 Conclusion

The results presented in this thesis provide additional evidence to the ongoing global discussions on the feasibility of using routinely collected data as an independent intervention necessary for future malaria control. Notably, the results will add to the dialogue on the use of models and how to improve the important malaria surveillance pillar of the WHO. Additionally, these results emphasize on the need for national malaria control programmes to define sub-national strategies and progress based on local data.

The continued absence of precise estimates of the age-specific malaria mortality patterns in the community limits the ability to look at immune protection against fatal outcomes of infection and presents a problem in defining the global and national burdens of malaria mortality and discussions on target populations for control.

The actual number of morbid and fatal events across all age-groups recorded through fully functioning, accurate health and civil registration systems remains the holy grail. This remains an immediate, crucial requirement for those countries aiming for elimination. Most of the high burden countries in Africa, however, require the capacity to use multiple data layers to define the levels of risk sub-nationally to tailor combinations of appropriate interventions. The absence of credible data has been an unfortunate, but striking feature of malaria since the launch of the RBM strategy 20 years ago. The same is true with respect to reliable data on the COVID-19 pandemic, globally. As with COVID-19, relying on modelled predictions of sparse data will not serve a future of malaria control in Africa. The improved use of empirical data should replace models. On this surveillance pathway, interrogating multiple forms of routine data under varying malaria transmission intensities, exploiting data from sentinel health facilities data and increased comparisons/triangulation with community-based survey data will provide ongoing, iterative support to the Global Technical Strategy.

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