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Chuma, Victoria Mathew Mwakalinga

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Integrated geographical tools can enable selectively targeted urban planning interventions to control risk of malaria transmission in Dar es Salaam, Tanzania

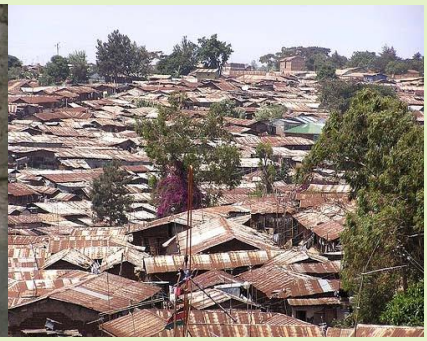
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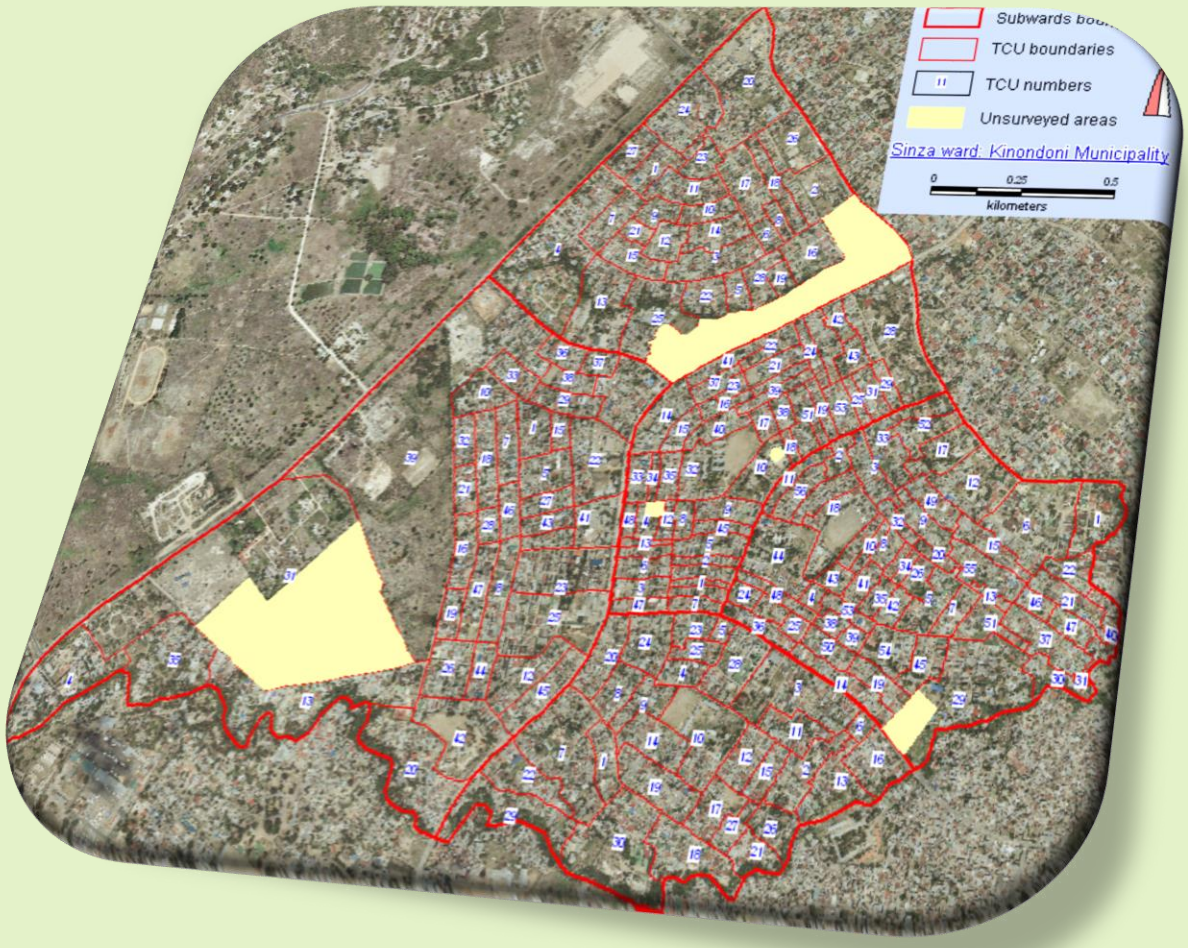
A thesis submitted to the School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Doctor of Philosophy

Johannesburg, 2017








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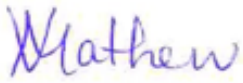






Candidate declaration

I VICTORIA MATHEW MWAKALINGA CHUMA do solemnly declare, in accordance with Rule G27 that this thesis is my own work. This thesis is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg, and has not been used as a submission for any other degree or submitted at any other university.



_____ __ 28th October, 2017___

Victoria Mathew Mwakalinga Chuma **Date**

Dedication

To my husband Beatus for your constant support during the PhD period, and for your endurance during the lonely moments. I am indebted for your love and care to our children Catherine, Beatus Jr, Seraphine and Lisabeth during the long periods of my absence.

Thanks to almighty God for His grace and mercy.

Abstract

Rationale: Although public health and urban planning share the common goal of preventing urban outbreaks of infectious diseases, there is little operational overlap between these disciplines today. The separation of the fields has contributed to uncoordinated efforts to address the health of urban populations. Recently, infectious diseases like malaria are posing a great health hazard, particularly to developing countries. On one hand, almost all current research focuses on tackling this issue through public health programmes with little direct influence on the root causes of risk. On the other hand, urban planning is guiding infrastructure development/upgrading and delivery of adequate housing programmes which essentially can provide the basis of complementary interventions for malaria if appropriately and selectively targeted to high-risk areas. Integration of such public health considerations into this larger development agenda is often neglected, but could help target the areas of highest risk of malaria transmission with far more effective mitigation and intervention measures than are possible through the health sector alone. However, a greater challenge remains in how to identify areas for spatial targeting of interventions at finer geographic scales, because in cities malaria risk is highly heterogeneous, dynamic and unpredictable at finer spatial resolution.

Aim: Firstly, to identify and characterize risk of malaria at finer scales; by calibrating a comprehensive range of high resolution topographic predictors of risk using entomological and epidemiological field surveys. Secondly, to provide evidence-based guidelines for optimal design and spatial targeting of interventions that can be integrated into public health, infrastructure and settlement development programmes to effectively prevent urban malaria transmission.

Methods: The study was conducted in Dar es Salaam city (Tanzania), located along the shores of Indian Ocean; with an area of 148km^2 and 3.6 million residents. Longitudinal and household cross-sectional surveys; were conducted to monitor entomological (adult mosquitoes using tent traps) and epidemiological (positivity obtained using Rapid Diagnostic Tests (RDTs)) indicators in 2,013 and 430 survey locations respectively, between March 2010 to February 2013. Indicators of city's resilience were obtained from existing maps of land uses and infrastructure. Topographical predictors of local water accumulation potential were extracted from a 20m grid of a Digital Elevation Model (DEM). The spatial locations of study sites were collected using global positioning system (GPS) receivers at 5m accuracy. Spatial autocorrelations in the outcome variables were assessed using Global Moran's I statistics (MI) and Variance Inflation Factor (VIF) was used to assess multi-collinearity among geographic predictors. Proximity analysis was used to compute the distance metrics from households to various infrastructures. Hotspots based on entomological and parasitological indicators were detected using Flexible spatial scan statistics. Boosted regression trees (BRT) accounting for spatial effects and generalized linear mixed models (GLMMs) were separately fitted to evaluate the influence of resilience indicators upon malaria transmission risk. Multivariable - Conditional Autoregressive Models (M-CARs) using Markov chain Monte Carlo (MCMC) simulation were used to predict hazard (M-CAR-Poisson) and risk (M-CAR-Binomial) of malaria using local topographic predictors of water accumulation potential and factors for population resilience.

Key findings: A total of 12,170 catches per person per trap night were conducted. Out of these nights, 382 (mean 0.02 per catch) female *An. gambiae s.l.* were caught; of which 328 were *An. gambiae sensu stricto*, 40 were *Anopheles arabiensis*, 4 were *Anopheles funestus* and 10 were other *Anopheles* as confirmed by PCR. Similarly, out of 11,187 individuals tested for malaria positivity 11.1% were positive and 88.9% were negative, though 88% of the positive cases were afebrile and only 0.37% of these chronic carriers had been treated for malaria. Persistence of unresponsive malaria prevalence (mean

10%) was noted from 2011, disregard scale up of interventions towards the end of the study. However, only a third of survey locations with detectable *An. gambiae s.l.* and one half of human malaria infections were spatially aggregated in statistically identifiable hotspots while the remaining adult mosquitoes and human infections were haphazardly distributed across the city in many small, scattered loci[1] of transmission hazard and risk. Hotspots of *An. gambiae s.l.* and those of human infections were only very loosely associated with each other (Odds ratio (OR) [95% Confidence Interval (CI)] = 1.56 [0.89, 1.78], P = 0.52) even though malaria was transmitted locally within the city. Scale up of larviciding and LLINs to universal coverage in 2011 reduced densities of *An. gambiae s.l.* but not human prevalence which persistently remained at a 10% average regardless of the interventions in place, this was further confirmed using M-CAR model (which accounts for spatial autocorrelations occurring in the city). This remaining portion of unresponsive, persistent malaria infection appears to arise from pre-existing, chronic, long-term infections that could not be cleared using preventive measures such as larviciding and LLINs. Interestingly, 90% of this chronic infection occurred outside of upgraded and serviced informal settlements. As expected, indicators of topographic wetness are predictive of both vector densities and human infection prevalence. The surprise, however is that indicators of well drained locations, specifically steep slopes and the tops of steep slopes are also positively associated with high vector densities and high infection prevalence. The distribution of malaria vector densities is very heterogeneous and topographically predictable: 85% of all malaria vectors caught were trapped in the 15% of surveyed locations with highest predicted hazard. The distribution of human infection prevalence is only weakly predictable based on topography: 40% of the survey locations with highest predicted risk would need to be targeted to cover only 60% of the detected infections. However, inclusion of population resilience and hazard in the model improved the performance of malaria risk model by 31%.

[1] Refers to >0 mean catches of *An. gambiae* per trap night (hazard) or >10% prevalence of malaria infections (risk)

Implications: Selective spatial targeting based directly on clustering patterns within data obtainable at geographic resolution of the existing survey methods is clearly insufficient to achieve sufficient coverage of interventions against either mosquitoes or human infections in Dar es Salaam city. Vector control with larviciding together with high coverage of window screening and LLINs, was sufficient to reduce malaria transmission down to lower levels but active mass screening and treatment (MSAT) or mass drug administration (MDA) will be required to accelerate clearing of infectious reservoirs. The best predictors of human infection prevalence are indicative of local water accumulation in valley bottoms, where no or relatively few people live. Therefore, they are really not particularly useful for targeting anti-parasitic measures like MDA and MSAT but are ideal for larval source management to kill immature mosquitoes; and also for urban planning measures to provide drainage systems and upgrading of human settlements where necessary. The densities of *An. gambiae* were clearly mapped to steep slopes and the tops of steep slopes on the edges of valleys, where IRS, spatial repellents or space spraying could be readily targeted as barrier interventions at the periphery of populated human settlements, where people are disproportionately exposed to host seeking vectors dispersing from the valleys. Complementary urban planning measures such as house screening, promotion of land tenure and provision of social services such as healthcare facilities, enhanced access to diagnostic and treatment centres are required to control malaria risk in these zones.

Keywords: malaria, *Anopheles gambiae*, hazard, risk, resilience, spatially selectively targeted interventions, spatial analysis, spatial epidemiology, urban, topography – malaria risk, hydrology – malaria risk, Tanzania

Original papers

The thesis is based on the following papers:

I. Mwakalinga, V.M., Sartorius, B., Mlacha, P., Msellemu, D., Chaki, P., Govella, N., Coetzee, Killeen, G. and M. Dongus, S. (2016). "Spatially aggregated clusters and scattered smaller loci of elevated malaria vector density and human infection prevalence in urban Dar es Salaam, Tanzania." *Malar J* **15**: 135 (Annexure Ia).

Student's contribution to the paper: Lead spatial data collection, extraction, analysis and writing of the manuscript.

II. Msellemu, D., I. Namango, **V. Mwakalinga**, A. Ntamatungiro, Y. Mlacha, Z. J. Mtema, S. Kiware, N. F. Lobo, S. Majambere, S. Dongus, C. J. Drakeley, N. J. Govella, P. P. Chaki and G. F. Killeen (2016). "The epidemiology of residual Plasmodium falciparum malaria transmission and infection burden in an African city with high coverage of multiple vector control measures." *Malar J* **15**:288 (Annexure Ib).

Student's contribution to the paper: Spatial data collection, design of the study, training and supervising field workers, data management, analysis and writing of the manuscript.

III. Mwakalinga, V. M., M. Burra, B. K. D. Sartorius, Y. P. Mlacha, D. F. Msellemu, N. J. Govella, M. Coetzee, S. Dongus and G. F. Killeen. *(In manuscript)* "Upgrading of informal settlements and house screening provide effective urban planning interventions against malaria transmission hazard and risk to complement bed nets and microbial larviciding in Dar es Salaam Tanzania " (Annexure Ic)

Student's contribution to the paper: Design of the study, data extraction, training and supervising field workers, data management, analysis and writing of the manuscript

IV. Mwakalinga, V.M., Sartorius, B., Mlacha, P., Msellemu, D., Chaki, P., Govella, N., Coetzee, M. Dongus, S. and Killeen, G. *(Re-submitted to Journal of Royal Society Open Science)* "Topographic mapping of the interfaces between settled human habitats and aquatic habitats for immature mosquitoes, to enable barrier-targeting of interventions against adult mosquitoes" (Annexure Id)

Student's contribution to the paper: Design of the study, data extraction, seeking additional research funds, data management, analysis and writing of the manuscript

Conference Proceedings

Mwakalinga, V.M., Msellemu, D., Namango, I.H., Sartorius, B., Dongus, S., Mlacha, P., Limwagu, A., Mageni, Z., Paliga, J., Coetzee, M., Ntamatungiro, A., Mtema, Z., Kiware, S., Lobo, N.F., Majambere, S., Drakeley, C.J., Govella, N., Chaki, P. and Gerry Killeen. Programmatic blanket-coverage roll out of microbial larvicide application by local government in urban Dar es Salaam, Tanzania. Oral presentation at Salford Manchester, June 6-8, 2016.

Mwakalinga, V.M., Sartorius, B., Mlacha, P., Msellemu, D., Chaki, P., Govella, N., Coetzee, M. Dongus, S. and Killeen, G. Topographic predictability of locations for targeting complementary interventions to eliminate residual malaria transmission in urban Dar es Salaam, Tanzania. Oral presentation at the 13th International Conference on Urban Health, San Francisco, April 1-4, 2016.

Mwakalinga, V.M., Sartorius, B., Mlacha, P., Msellemu, D., Chaki, P., Govella, N., Coetzee, M., Killeen, G. and Dongus, S. Predicting hotspots of vector mosquito densities and malaria positivity rates using hydrology and topography in Dar es Salaam, Tanzania. Oral presentation at the 8th International Symposium on Geospatial Health to be held in New Orleans, Louisiana, October 31-November 2, 2014

Mwakalinga, V.M., Sartorius, B., Mlacha, P., Msellemu, D., Chaki, P., Govella, N., Coetzee, M., Killeen, G. and Dongus, S. (2013). Modelling malaria hazard hotspots using local hydrology and topography to sustain detection of transmission residuals in highly urbanizing cities in Tanzania. Poster presentation at the 6th MIM Pan Africa Malaria Conference (October 2013)

Awards/Fellowships

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CARTA (Consortium for Research Training in Africa), 2014 to facilitate training in spatial modelling at ITC in Netherlands

CARTA (Consortium for Research Training in Africa), 2016 three months Internship at Wits University to enable write up of the integrating narrative

List of abbreviations

	African Population and Health Research Center
Bti	*Bacillus thuringiensis var. israelensis*
CARTA	Consortium of Advanced Research Training in Africa
CORPs	Community Resource Persons
DEM	Digital Elevation Model
FSAT	Focal screening and treatment
GIS	Geographic Information System
GoT	Central Government of Tanzania
GPS	Global Positioning System
HLC	Human landing catches
ITT	Ifakara Tent Traps
JAS	Joint Advanced Seminar
LA	Larvicide Application
LLINs	Long Lasting Treated Nets
MDA	Mass Drug Administration
MoHSW	Ministry of Health and Social Welfare
MSAT	Mass Screening and Treatment
NMCP	National Maria Control Programme
RBM	Roll Back Malaria
RS	Remote Sensing
RTI	Research Triangle Initiative
SSA	Sub-Saharan Africa
TCU	Ten Cell Unit
UMCP	Urban Malaria Control Programme
UN	United Nations
UNFPA	United Nations Population Fund
UN-HABITAT	The UN Human Settlements Programme
UNICEF	United Nations Children Education Fund
VIF r	Variance Inflation Facto
WHO	World Health Organization
WITS	University of the Witwatersrand

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Chapter One: Background

1.1 Study overview

This thesis deals with spatial prediction of malaria transmission at fine spatial scales based on entomological, epidemiological, local topography and population resilience in urban areas of Dar es Salaam. It further presents factors for high transmission hazard and risk. This subject is important because to our knowledge there is no other work in Dar es Salaam that has previously mapped risk of malaria transmission extensively to such a high spatial resolution. Prior literature has not predicted risk while taking into account hazard and population resilience altogether. Most importantly, the consideration to integrate interventions for controlling malaria in sectors such as urban planning and housing development other than health sector is new and of high significance to public health if urban malaria is to be eliminated in Sub-Saharan African cities/urban settings.

Malaria is posing great health hazards, particularly in developing countries due to poor urban planning. Poor urban planning has increased the number of slums in cities which leads to poor housing and poverty, and provides potential mosquito breeding habitats. Due to rapid urbanization, recent public health literature emphasizes the importance of urban planning in tackling the causes behind the sources of ill-health in the urban settings (WHO and UN-Habitat, 2010). Although the fields of urban planning, public health and house development share the common goal of preventing urban outbreaks of infectious diseases, there is little operational overlap between these disciplines today. The separation of these disciplines has contributed to uncoordinated efforts to address the health of urban populations. For instance, in malaria control, almost all current research focuses on tackling this issue through public health programmes with little direct influence on the root causes of risk. While

urban planning is guiding infrastructure upgrading and adequate housing provision programmes, integration of such public health considerations into this larger development agenda is often neglected (Corburn, 2004, Smit et al., 2010, WHO, 2010b, GRNUHE, 2010). But, could help target the areas of high risk with far more effective mitigation and intervention measures than are possible through the health sector. Using malaria as a case study, this study demonstrates how public health needs in urban areas can often be addressed more effectively through integrated approach.

1.2 Urban Health

The importance of urban health in population and public health disciplines is increasingly important recently due to unprecedented global demographic growth, in the past fifty years (UN, 2015, UNFPA, 2007). Currently, more than half of humanity lives in urban areas and it is projected that by 2050, seven out of every ten people will live in towns and cities (UN, 2008, WHO, 2015a, UN, 2014). Thus the prospects for a better future are tied to living conditions in towns and cities; highlighting the need for a successful urban planning agenda to prepare cities for sustainable adaptation to mega influx of populations spatial adjustments (UNFPA, 2007, UN-Habitat, 2016). Much of this growth is expected to be in low-income countries (LDC's) of which Africa will host nearly a quarter of the world's urban population (UN-Habitat, 2013, UN-Habitat, 2016). Unfortunately, these regions are least equipped to deal with the problems of urbanization (UN-Habitat, 2011) and governments already cannot deal with the scale of city expansion and infrastructure provision with limited investments in urban planning (WHO, 2010b, Castro et al., 2010, Rietveld et al., 2016). Consequently, the pace of urbanization is not proportional to economic growth and is highly characterized by extreme poverty (UN-Habitat, 2016).

Urbanization has increased population density in deteriorating environments with increased risks of exposure which brings new control challenges for infectious, non-infectious and emerging chronic

diseases (Donnelly et al., 2005). More than 2 billion of the world population is projected to be living in slum conditions (informal and un-serviced settlements) by 2030 (WHO and UN-Habitat, 2010, UN-Habitat, 2016). The urban poor are forced to live in marginal lands where nobody else wants to live, such as in polluted and dangerous neighbourhoods and in crowded and precarious housing with no security of tenure (WHO, 2010d, Freudenberg et al., 2005, UN-Habitat, 2003). Studies highlight that these areas provide potential breeding habitats for mosquito vectors including those of the *Anopheles gambiae* complex (Castro et al., 2007, Castro et al., 2010, De Silva and Marshall, 2012).

While urbanization is the driving engine for modernization, economic growth and development (Chaolin et al., 2012), there is increasing concern for the effects of expanding cities on human health (Redman and Jones, 2005, Neiderud, 2015). Different studies show a substantial impact of urbanization on the epidemiological characteristics of infectious diseases, including malaria (Norris, 2004, Siri et al., 2008, WHO, 2010c, Donnelly et al., 2005, Alirol et al., 2011, Neiderud, 2015). Cities are projected to become incubators of infectious and concentrators for chronic diseases (WHO, 2010a). The health sector will therefore have to deal with a dual burden of existing and emerging infectious diseases such as cholera, malaria, HIV and filariasis but also cope with emerging acute and chronic diseases (WHO, 2010d, WHO, 2010a).

Nevertheless, cities are engines of growth; they are places of hope and better healthcare (Vlahov et al., 2007). Urban living is likely to offer higher chances of employment, increased access to health care services and better education (Alirol et al., 2011). Child survival rates are better and maternal deaths are lower in cities than in rural areas (Mulholland et al., 2008). The population density and economies of agglomeration in urban areas attract entrepreneurs and investors to urban health systems. Higher Gross Domestic Product (GDP) is associated with urbanization which in turn empowers governments to provide better services, including healthcare and improved human wellbeing (IHC, 2010).

Furthermore, urban settings offer more options for mosquito vector control due to relatively good transport infrastructure, wide coverage of health service infrastructure and advanced communication technologies. High population densities offer a quite narrow spectrum of focal breeding sites, which can thus provide opportunities for spatially targeted interventions. Strong institutional capacity and political will in urban areas encourage vector control activities through community awareness and mobilization (Geissbühler et al., 2009, Chaki et al., 2009, Fillinger et al., 2008, Keiser et al., 2004). As such, cities require enabling capacities to respond positively to urbanization pressure by creating new paradigms, new technologies, innovative public services and new economic models that will support healthy and resilient growth (UN-Habitat, 2016). Effective and healthy urban planning is highly associated with population wellbeing and recommended for greater capacity for future resilience in cities (Leon, 2008, Swanstrom, 2008, Vale and Campanella, 2005, UN-Habitat, 2016).

Urban health issues are complex and multifaceted; and the health sector alone cannot effectively tackle these issues (Harpham and Molyneux, 2001). This is because major drivers and determinants of health in the urban settings reach beyond the health sector alone (WHO and UN-Habitat, 2010). Successful interventions rely upon inter-sectoral and multi-disciplinary collaborative approach (WHO, 1995, Rietveld et al., 2016). Take the example of "Healthy Cities" Approach, which initiated healthy urban planning in rapidly growing cities to accommodate health issues in urban designs (WHO, 1995, Harpham and Molyneux, 2001). It is apparently potential and timely for public health discipline to broaden its research focus to enable understanding of urban health complexities in cities (Breslow, 2002). This understanding will enable proper utilization of existing capacity/infrastructure to facilitate appropriate and informed public health interventions. Informed and appropriate intervention measures can only be achieved where there is routine and reliable information on urban factors that are risks or protective (resilience) of human health (Vlahov and Galea, 2002). However, successful implementation of these measures will require integrated approach across disciplines (WHO, 1995).

1.3 Mosquito-borne diseases in sub-Saharan African (SSA) cities

Mosquito-borne diseases are viral and parasitic infectious diseases transmitted to humans through the bites of infected female mosquitoes (Gillett, 1971, Norris, 2004, Tolle, 2009). In Sub-Saharan Africa (SSA), these diseases cause significant public health burdens. It is thought that about ten different anopheline species are responsible for malaria transmission in SSA, while only three namely *Anopheles gambiae*, *Anopheles arabiensis* which belong to the *An. gambiae* complex and *Anopheles funestu*s are central for urban malaria (Robert et al., 2003). Although urban areas have limited aquatic habitats for mosquito breeding particularly *An. gambiae* due to high population density and drainage systems, yet urban malaria is increasingly significant (Keiser et al., 2005). Nearly half of the world's population is infected with at least one type of mosquito-borne pathogen (WHO, 2008, Tolle, 2009). Despite impressive coverage of control programmes, improved healthcare services and available treatments in the urban settings, mosquito-borne diseases especially malaria have and will continue to pose a major health threat (Tolle, 2009, Murray et al., 2012b, WHO, 2015c).

Malaria

Human malaria is an infectious mosquito borne disease caused by protozoan blood parasites of the genus *Plasmodium* that is transmitted through bites of infected female mosquitoes of the genus *Anopheles. Anopheles* mosquitoes mainly bite at dusk and dawn (WHO, 2011). Malaria has been known to be caused by four species of *Plasmodium* parasites namely; *P. falciparum, P. vivax, P. malariae* and *P. ovale* (Gillies and De Meillon, 1968, WHO, 2011). Recent studies identify *Plasmodium knowlesi,* a simian malaria parasite in Asia, as the fifth cause of human malaria, similar to *P. falciparum* malaria, but not known to occur in Africa. P*lasmodium falciparum* remains the most severe strain of malaria, is life threatening and responsible for 86% of morbidity and mortality cases, predominantly in Sub-Saharan Africa (WHO, 2015c). *Plasmodium knowlesi* can also be fatal (Singh and Daneshvar,

2010, WHO, 2011, Kantele and Jokiranta, 2011) and can lead to severe cases that are more than those caused by *P. vivax* and *P. malariae* (Kantele and Jokiranta, 2011).

Malaria remains endemic in 95 countries, and half of the world's population is at risk of acquiring new infections (WHO, 2015c). However, between 2000 and 2015 the global rate of new cases fell by 37% and mortality by 60% and 65% among all age groups and children under 5 respectively. About 90% of all malaria deaths occur in SSA, of these 78% are children under five years (WHO, 2015c). In addition to that, malaria reduces Gross Domestic Product (GDP) of many endemic countries. As reported by the World Bank, malaria is one of the diseases which discourages foreign investment in SSA, leading to almost 1.3% reduction in economic growth (World Bank, 2015). The risk of malaria transmission is across all population groups, although some groups are considered to be at an higher risk, such as pregnant women, HIV patients, non/semi-immune migrants, mobile populations or travellers and children under five years of age in high transmission areas (WHO, 2015c, Thimasarn, 2011).

Tanzania is among the endemic African countries that are heavily affected by malaria (Murray et al., 2012b). This disease remains a major public health threat to the country and about 95% of the population are at risk of malaria infections (NMCP, 2014). According to the 2013 update of the Global Burden of Disease (GDB) project, it was estimated that 44% of the disease burden was due to infectious and parasitic diseases (Murray et al., 2012b). Among these, malaria was responsible for 20%, and it was the largest burden (responsible for between 100,000 to 125,000 deaths per year) (WHO, 2016b, NMCP, 2014). This situation underlines the need for public health research and appropriate interventions to reduce the burden of malaria in Tanzania (Mboera et al., 2008).

1.4 Public health importance of urban malaria

Urban malaria control is increasingly relevant because of demographic changes (WHO, 2015). Despite being preventable and curable, malaria still ranks among the world's most prevalent tropical infectious diseases (Murray et al., 2012b). WHO places malaria as one of the top deadly infectious diseases in the world and among the ten tropical diseases targeted by the WHO special programme for research and training in tropical settings because of its overall health significance and social burden (Tolle, 2009).

Cities may perhaps offer ideal settings for malaria elimination due to high human population densities surrounding aquatic larval habitats which allows mosquitoes to feed nearby and then return to oviposit (Sattler et al., 2005). This, however, potentially limits their dispersal and the diffusion of malaria transmission across the landscape (Keiser et al., 2004, Killeen et al., 2003, Menach et al., 2005), hence making it potentially easy to target vector control activities. In addition to that, urban settings have lower transmission intensity than rural areas, because high population density dilutes out vector biting burden (Killeen et al., 2000, Smith and Mckenzie, 2004) and urban planning can reduce this even further (Keiser et al., 2004, Robert et al., 2003). Therefore, urban transmission may be more vulnerable to control with effective interventions generally and targeted interventions specifically. Furthermore, infrastructure, institutional capacity and governance systems are often better developed than in rural areas. Moreover, greater numbers of people can be protected per unit of surface area covered, so several intervention strategies may be viable in towns and cities than would otherwise be considered infeasible in more disseminated rural settings (Fillinger and Lindsay, 2011, Keiser et al., 2004, Robert et al., 2003, WHO, 2013, Hay et al., 2005). Urban dwellers widely access diverse sources of media and communication resources, which again provides great opportunities for public health education and health campaigns on prevention, diagnosis and

treatments (Geissbuhler et al., 2007). Moreover, in cities there are incredible opportunities for diseases surveillance, control and prevention measures (Alirol et al., 2011).

However, one of the greatest challenges to malaria elimination in the urban setting is the very fine scales that heterogeneity of malaria risk occurs at (Bousema et al., 2012a, Bejon et al., 2014, Gaudart et al., 2006, Carter et al., 2000, Bejon et al., 2010). Lack of physical and social infrastructure to support public health interventions make it difficult to reach all area with higher risk of malaria transmission in slums/informal settlements (De Silva and Marshall, 2012).

The amount of funding for controlling malaria vectors, is unprecedented and has resulted in considerable successes (Geissbühler et al., 2009, O'Meara et al., 2008, Roberts and Enserink, 2007, WHO, 2015c), however this still falls vastly short of what is required to deliver even with the most basic interventions throughout the public health sector (Kiszewski et al., 2007, Snow et al., 2008). Vector control is one of the strongest interventions for Roll Back Malaria (RBM) (WHO, 2015b, RBM, 2015). These initiatives have triggered political commitments and financial support towards elimination of the disease. But in order to support the transition from control to elimination and further eradication, there is a need to improve existing tools and discover new ones (GHP, 2011, RBM, 2015). The achievement of this transition will depend on improved data and an ability to generate additional information, knowledge and evidence from such data (Marsh, 2010).

1.5 Public health interventions against malaria transmission

Lately, public health interventions against malaria include indoor residual spraying (IRS), long lasting insecticide-treated bed nets (LLINs), reliable diagnosis and timely treatment with artemisinin-based combination drugs (WHO, 2015c). LLINs and IRS are the most important and widespread measures,

but their effectiveness can only be realized in areas where transmission occurs indoors (Russell et al., 2011). Increased outdoor biting rates and early peaking behaviour of mosquitoes in big cities such as Dar es Salaam, nullify the efficacy of LLINs and IRS because they confer less protection than in rural areas (Geissbuhler et al., 2007). LLINs and IRS alone are not sufficient to eliminate transmission in the urban settings (Ferguson et al., 2010). Other complementary vector control measures that can tackle mosquitoes at the source including environmental management (reduction of standing water bodies, for example by drainage) and larviciding (application of biological or synthetic insecticides in standing water bodies in order to kill mosquito larvae) are critical (Geissbuhler et al., 2007), as there will always be a portion of mosquitoes that escapes indoor control measures and will thus have to be tackled at source. Furthermore, studies suggest that mosquito-proof housing has a great impact in providing personal protection and reduce transmission risks (Ogoma et al., 2010, Msellemu et al., 2016). However, spatial information on breeding sites location can increase the efficiency through tackling mosquitoes at the source (Dongus et al., 2009, Dongus et al., 2007). In Dar es Salaam, participatory mapping was adopted by the Urban Malaria Control Programme (UMCP) to ensure total spatial coverage of breeding sites and hence facilitate targeted operational larval source management (Dongus et al., 2007). Above all, there is a need to exploit fully spatial information technologies such as Geographical Information Systems (GIS) and spatial modelling in public health to understand hotspots for transmission and ensure that available limited resources are targeted to foci of transmissions and to the most vulnerable and least resilient sub-populations.

Effective control measures in the urban settings

Due to heterogeneity and localized transmission of malaria in the urban settings, targeted interventions are more likely to succeed. Nevertheless, identification of the population at risk as well as total spatial coverage of risky areas are paramount for successful interventions (Keiser et al., 2004). Targeted control measures will have direct benefits not just for the individuals who are included in the

control effort but also the community as a whole. Individuals who are bitten most often are very likely to be infected and can amplify transmission by conveying the parasites to a large number of mosquitoes (Bousema et al., 2010). Such targeted interventions enhance community protection by simply eliminating transmission among human hosts. In low transmission areas, targeted interventions for hotspots can pave the way to elimination of malaria unlike other wider coverage that reduces transmission intensities but does not eliminate malaria (Bousema et al., 2010).

Controlled and thoughtful urbanization can produce substantive economic and health returns at all community levels. Studies show that certain spatial patterns of urban development can increase resilience towards mosquito-borne diseases. Furthermore, infrastructure developments can provide physical protection (UN-Habitat, 2011). Whenever possible local governments and ministries should incorporate health concerns into urban development schemes, including city's master and strategic planning, detailed urban designs, resettlement plans, informal settlements upgrading, infrastructure provision/maintenance, housing and sanitation programmes (Alirol et al., 2011). In the 20th century, good urban planning and public health collaborations largely contributed to elimination of many infectious diseases in the cities of developed countries (PHAC, 2008).

Generally, integrated urban planning is increasingly recognized as a tool to promote resilience for population health in urban areas that includes: targeted location of pharmacies, clinics, hospitals, emergency ambulance routes; promoting safety and reduced occupational hazards in the city; preventing noise pollution for mental health benefits; promoting healthy buildings and settlements that are vector sensitive, hygienic and clean (UN-Habitat, 2009, Malhotra, 2011). It is hence necessary to explore the use of urban planning as a tool that can promote improved urban public health, including reduction of disease vector productivity within a wider context of sustainable development

(Malhotra, 2011). Further collaborative approach is required for a sharp decrease of vector borne diseases in growing cities such as Dar es Salaam.

1.6 Epidemiology, distribution and determinants of urban malaria

Like any other disease, the epidemiology of malaria consists of three basic elements including person, place and time (Snow, 1855). The focus in epidemiologic researches has been on person and time; even though the importance of place or space in disease outbreaks is realized and documented historically (Moore and Carpenter, 1999, Snow, 1855). However, in the last decade numerous studies have shown that spatial distribution in measuring disease risk may provide etiologic insight into diseases (Moore and Carpenter, 1999) and guide targeted interventions planning (Carter et al, 2000).

In Sub-Saharan Africa, urban malaria is transmitted by *Anopheles gambiae*, *An. coluzzii, An. arabiensis* and *An. funestus* (Sinka et al., 2010, Coetzee et al., 2013). All four species are highly efficient vectors (Sinka et al., 2010). Basically, *Anopheles* mosquitoes breed in temporary sun-lit small ponds, pools and puddles, and in more permanent habitats such as marshes and rice fields (Gillies and De Meillon, 1968). Common habitats in the urban settings include pools left as a result of overflowing rivers, hoof prints around ponds, discarded tins/containers, tyres and rainwater collecting in natural depressions (De Silva and Marshall, 2012). Recent studies indicate that malaria vectors have been readily adapting to features of fast-growing cities by ovipositing and developing larval habitats in domestic containers, water storage tanks, flower pots, discarded tyres, car tracks, cans, drains, gutters, brackish and polluted water (Brieger, 2011, Geissbuhler et al., 2007, Castro et al., 2010).

Distribution

The tropics and subtropics parts of the world have higher malaria risk due to high temperatures which facilitate rapid development of the sporogonic parasite stages that infect mosquitoes (Feachem *et al.* 2010, Snow *et al.* 2005). Primarily, malaria has been considered a rural disease because the process of urbanization limits suitability of breeding environments for the *An. gambiae* complex (Donnelly et al., 2005, Machault et al., 2010, Hay et al., 2005). However, recent studies show substantial malaria transmission occurring in cities and towns, contributing up to 28% of global malaria cases (Brieger, 2011, Lines et al., 1994, Keiser et al., 2004); of this urban areas in SSA contribute almost 90% (Byrne, 2007). Malaria risk exposure is typically lower in the urban settings leading to low immunity levels among children and older age groups, making them more vulnerable to malaria (Geissbuhler et al., 2007). Furthermore, malaria mosquito densities are lower in planned cities while unplanned urbanization/growth of informal settlements is often associated with changing vector composition and transmission dynamics as well as increasing density of nuisance mosquitoes such as *Culex* (Warren, 1999). Peri-urban areas are more prone to higher densities of *Anopheles* mosquitoes because they have sparse settlement developments and urban agriculture activities are likely practiced (Mahon et al., 1981, Njenga et al., 2011).

Active transmission contains human habitation within its boundaries because mosquitoes feed on a restricted range of available hosts (Sinka et al., 2016). This means that, adult mosquitoes and risk of malaria exposure will be heterogeneous regardless a uniform distribution of aquatic larval sources in settings with heterogeneous patterns of human habitations (Smith et al., 2004). Increased number of cases will occur within households living near larval habitats, though risk of exposure will depend on structural features, economic factors, cultural experience, human behaviour and genetic characteristics of the dwellers (Carter et al., 2000, Sinka et al., 2016). This further includes availability of services such as drainage, solid waste management and water supply. Poor drainage has been

reported as among potential sources of urban malaria vectors, particularly in situations where drains are not routinely cleaned (Castro et al., 2010, Carter et al., 2000).

In urban settings, risk of malaria transmission is highly focalized depending on distribution of urban aquatic habitats of *An. gambiae s.l* which tend to be heterogeneously distributed and unpredictable because of their dependency on rainfall (Carter et al., 2000). Risk of contracting malaria in urban areas can differ even within a population living in the same vicinity of larval habitats due to differences in human resilience (Thimasarn, 2011, Keiser et al., 2004). This heterogeneity of malaria risk in urban areas is not captured in continental malaria risk mapping initiatives. Mapping malaria risk at finer spatial resolution is therefore necessary to enable control or elimination of malaria at local scales.

Determinants for transmission risks

Apart from very rare blood transfusion risk; malaria transmission involves three main determinants namely; the parasite, the vector and the human host (WHO, 2011). The composition, sensitivity, behaviour and adaptive capacity of these components together determine risks of transmission. These determinants are influenced by a complex interplay of environmental, biological, social, economic and institutional factors (Lieshout, 2006). For instance, spending time outdoors during peak hours when vectors are most active may increase the risk of exposure. Nevertheless, use of personal protection such as spatial repellents (individual uses of repellents to reduce encounters between humans and mosquitoes in a broad area at home or other outdoor activities), can minimize risk of exposure even if densities of infected mosquitoes are high (Eisen and Eisen, 2008).

The burden of malaria is higher among the poorest countries and poorest sub-sectors within a country (WHO, 2010c). In cities, poor households and residents in informal settlements are at higher risk of contracting malaria due substandard living i.e. poor housing, poor drainage, lack of water supply and

poor waste collection system (Vlahov et al., 2007). Additionally, these areas have limited access to healthcare (effective diagnosis and treatment) and public health intervention measures such as LLINs and IRS due to low financial abilities.

Environmental variables contribute about 70-90 percent of all risk factors for malaria (Gilioli and Mariani, 2011, Pascual et al., 2006, Rogers and Randolph, 2000, Smith et al., 1999). These include *climate* which affects development, behaviour and survival of mosquitoes (De Souza et al., 2010), *topography and hydrology* that determines the presence of breeding habitats, abundance and distribution of mosquito vectors and the rate at which vectors develop and survive (Stresman, 2010). High elevation slows the development of mosquito vectors and risk of malaria transmission (Cohen et al., 2008). The proximity of houses to saturated areas such as swamps, wetlands, streams and dams may be an important contributor to malaria risk (Sorensen et al., 2006). Malaria control strategies need to consider how changes in topography and hydrological features affect transmission dynamics (Eisen and Eisen, 2011). *Land use and land cover* substantially influence larval habitat availability, productivity and adult survival (Zhou et al., 2010). H*ousing typology* which includes density, house location and house structures constitute to another important factor for malaria transmission (Zhou et al., 2010). Lastly, high transmission occurs only within certain distances (range) from breeding habitats. In Africa, this range lies between a few hundred meters to a kilometre in the urban settings due to high population densities, while in rural areas, mosquitoes disperse over several kilometres (Carter et al., 2000, Comber et al., 2011).

1.7 Spatial information tools and malaria risk mapping

The importance of spatial information technologies in epidemiology and public health is now widely realized. In epidemiology, spatial information tools such as Geographic Information Systems (GIS), Global Positioning Systems (GPS) and Remote Sensing (RS) have been used as methods for connecting socio-economic, environmental and demographic information with the spatial location of diseases (Comber et al., 2011, Machault et al., 2010, Riedel et al., 2010, Stensgaard et al., 2009, Kazembe, 2007). Spatial analysis and risk maps have been used widely for decision-making and advocacy (Kaiser et al., 2003). At a regional/global level, spatial information techniques have assisted with understanding the spatial variations of malaria and have been used to predict high risk areas. At local levels, these techniques have been used to answer questions regarding mosquito ecology, behaviour, productivity and risk areas in relation to foci of transmission (Gimnig et al., 2006). Moss et al., identified risk factors for malaria in areas with declining transmission using RS (Moss et al., 2011). Castro et al., identified spatial patterns of high malaria risk in the Amazon to guide targeted interventions to the foci of transmission (Castro et al., 2007). In Sri-Lanka, GIS was used to investigate the spatial relationship between malaria and distance from breeding sites and identification of key malaria risk factors at household level. Generated maps of disease risk demonstrating hotspots with associated risk factors, have made it easier to make operational decisions of where to selectively target interventions and identify suitable intervention strategies (Dolgin, 2010, Elliott and Best, 1998, Hassan et al., 1998, Pfeiffer et al., 2008, Schur et al., 2011, Stensgaard et al., 2011).

1.8 Study justification

As described earlier, the risk of malaria transmission in urban settings is highly heterogeneous and geographically restricted (Bousema et al., 2016), due to a number of factors such as vicinity of breeding habitats, urban topography, drainage, access to healthcare for diagnosis and treatment,

housing, use of protection measures and human behaviour (Baragatti et al., 2009). Successful targeted intervention programmes need reliable and accurate information about spatial distribution of high risk clusters and their driving factors (Carter et al., 2000). Spatial information technologies including disease mapping, clustering and ecological analysis have been used in different settings to provide maps and spatial models to identify high risk areas in numerous settings (Alegana et al., 2016). Despite being a valuable tool in diseases control, high risk mapping has not been fully incorporated in operational public health programmes in Sub Saharan Africa.

In recent decades, use of high resolution, accurate and reliable spatial information tools for vector control is gaining unprecedented momentum. For example, MARA maps (Craig et al., 1999) have been produced to describe global and continental risk distribution of malaria. However, the scale of these maps are too small to be useful at the local level (Bejon et al., 2014) and have limited information on local risk factors contributing to disease heterogeneities. Thus the need to produce risk maps at fine spatial scales (Bejon et al., 2014), using cost effective, appropriate and recently available spatial information technologies such as Geographic Information Systems (GIS) and Remote Sensing (RS) in order to unravel local risk factors and identify foci of transmission to facilitate appropriate targets of interventions and proper use of scarce resources. Empirical risk maps to identify these risk foci and clusters are needed to generate valid estimates of population at risk and identify potential 'hotspot' to pave the way for successful interventions. In this study, advanced spatial information tools, mainly Geographic Information Systems (GIS) and spatial modelling, provide empirical evidence of high risk housing-clusters for malaria transmission in Dar es Salaam. These clusters are identified based on both *hazard* and population *resilience*. This subject is important because prior work has identified high risk clusters using environmental factors, parasite carriage and incidence (Bejon et al., 2014, Bousema et al., 2016, Bejon et al., 2010, Kabaria et al., 2016) which basically provide *high hazards* (measures for entomological indicators) and not *high risks* (combines both measures of entomology, human

resilience and human infections). Fundamentally, a place can only be at high risk where high hazard and low resilience are observed in tandem (Obrist et al., 2011). Thus, this study will incorporate *resilience* status in the analysis of high risk clusters to contribute further knowledge in mapping malaria risk. The results provide a basis for interdisciplinary design of selective intervention programmes to control urban malaria risk.

Chapter Two: Aim and objectives

2.1. Overall aims

This study covers two overall aims which are 1) To identify and characterize risk of malaria at finer scales by calibrating a comprehensive range of high resolution topographic predictors of risk using field surveys of human resilience, entomological and epidemiological indicators 2) To provide evidence-based guidelines for optimal design and spatial targeting of interventions that can be integrated into public health, infrastructure and settlement development programmes to effectively prevent urban malaria transmission.

In order to achieve these aims, the following four specific objectives were defined:

2.2. Specific objectives

1. To describe the patterns and local spatial clustering of malaria transmission hazard in terms of mosquito vector densities and human infection prevalence.

2. To analyse the associations between local spatial patterns and topographic indicators of local water accumulation potential and map predicted hazard and risk areas based on these indicators.

3. To examine the influence of the city's population resilience in terms of larviciding application, human behaviour, housing, drainage infrastructure and utilization of health-sector interventions such as bed nets, timely diagnosis and treatment on the distribution of malaria hazard and risk.

4. To develop malaria risk maps based on topography, hazard and population resilience in order to provide a basis for transdisciplinary spatially targeted intervention programmes, such as settlements upgrading and designation of health infrastructure to facilitate health sector interventions and improve access to diagnostic and treatment services.

Chapter Three: Conceptual framework and thesis themes

This chapter covers the main terms and concepts applied in this study. It also introduces the thesis themes emerging from literature review and results of this study. The themes will further be used to guide synthesis of the four papers of this study into a one cover story.

3.1 Conceptual framework

The conceptual framework for this study adapts three main elements (Fig. 3.1) which are *inputs* (datasets from entomological, epidemiological indicators and human resilience), *processes* (methodology – spatial epidemiology) and *outputs* (in terms of the four manuscripts of the thesis). The framework consists of three key concepts namely **malaria risk** (hazard and human resilience), **spatial epidemiology** and **integrated targeted interventions**. Spatial epidemiology is the main concept of the thesis, as it provides ways to link the remaining two concepts and enable identification of geographic areas (spots) which needs integrated interventions. The relationship of these concepts is presented in the conceptual framework below (Fig. 3.1).

Predominantly, **spatial epidemiology** techniques for public health include *disease mapping* which aims at revealing geographical variation of disease risk (Lawson et al., 1999), *disease clustering* which is used to identify spatial anomalies or hotspots and describe their patterns (Baker, 2004), *ecological analysis* which measures explanatory variables and relates them to disease incidence (Wakefield, 2001, Bejon et al., 2010) and *disease monitoring or disease early-warning systems* (Gesler, 1986) which is designed to detect outbreaks very early on their progress (Kulldorff, 2001) rather than studying outbreaks retrospectively (Baker, 2004). Essentially, this study employs disease mapping, clustering and ecological analysis methods of spatial epidemiology.

High **risk** areas (hotspots) in this study refer to geographic locations with spatial coincidence of low human **resilience** and high **hazard**. Hazard is an important determinant of risk but should not be equally regarded as risk (Granger, 1998). It refers to factors or conditions which have the potential to pose a threat to human wellbeing (Briggs, 2000). In mosquito-borne diseases, hazard areas can basically be breeding habitats, i.e. saturated areas such as valleys, marshy land, swampy land and low lying areas. Such hazard areas can be verified using routinely collected mosquito densities. Persistency of higher entomological indicators at similar locations over time indicate a transmission hazard hotspot (Bejon et al., 2010).

The term **"resilience"** was first used in physics and mathematics to describe a material's ability to regain equilibrium following displacement (Norris et al., 2008). The concept has been expanded to be used in many other disciplines. For instance, in the 2000's the term '*resilient city*' emerged in urban planning in connection with rising awareness of climate change (Swanstrom, 2008). Public health is now taking up the concept, especially for diseases which are highly associated with urbanization and climate change (Swanstrom, 2008). Due to its complex nature, resilience has been defined differently by different authors. Broadly, all these authors agree on the capacity of individuals, groups, organization/institutions or environment to withstand loss/damage or to recover from the impact of an emergency/hazard (Obrist et al., 2011). This study considers different aspects of resilience including physical, social and economic resilience of the human population in cities (Fig. 3.1). The physical aspect of resilience refers to the ability of an environment (at community level in particular for this study) to respond and recover from hazard. It includes those essential conditions that allow the built environments to absorb impacts and cope with the hazard (Cutter SL et al., 2008). Physical resilience can be assessed from settlements typology and geographic location, buildings (housing features, quality and uses), access to land, access to health care facilities, security of tenure and infrastructure (Vale and Campanella, 2005).

The social aspect of resilience in this study is considered in terms of human behaviour (which includes health seeking behaviour and preference to spend evening housing outdoors see Annex 1b) and the ability of the city dwellers to afford and utilize health sector interventions. The institutional part of resilience reflects the ability (in terms of spatial coverage) of governments and development partners in providing health interventions (such as larviciding, LLINs) and urban planning programmes (such as upgrading, urban rehabilitation, renewal, regularization). This study analyses all these factors with regards to risk of malaria transmission to determine whether they provide protection against malaria transmission prior (proactive) or post (adaptive) hazard.

Integrated targeted spatial interventions refer to interventions that combine public health and physical planning/urban design practices which are spatially directed to the most vulnerable communities in terms of *An. gambiae* density, malaria prevalence, informal settlement developments and hazardous living environment (such as flooding areas). These interventions may include housing modifications, improved access to appropriate housing, improved access to surveyed land, drainage provision/maintenance, provision/improved waste collection services and provision/improved access to health facilities, improved healthcare, change of human behaviour, community wide LLINs and scale up of larviciding activities. At higher risk levels, urban planning interventions (going along with selective public health interventions) may involve resettlements, settlement segregation and urban renewal/redevelopment.

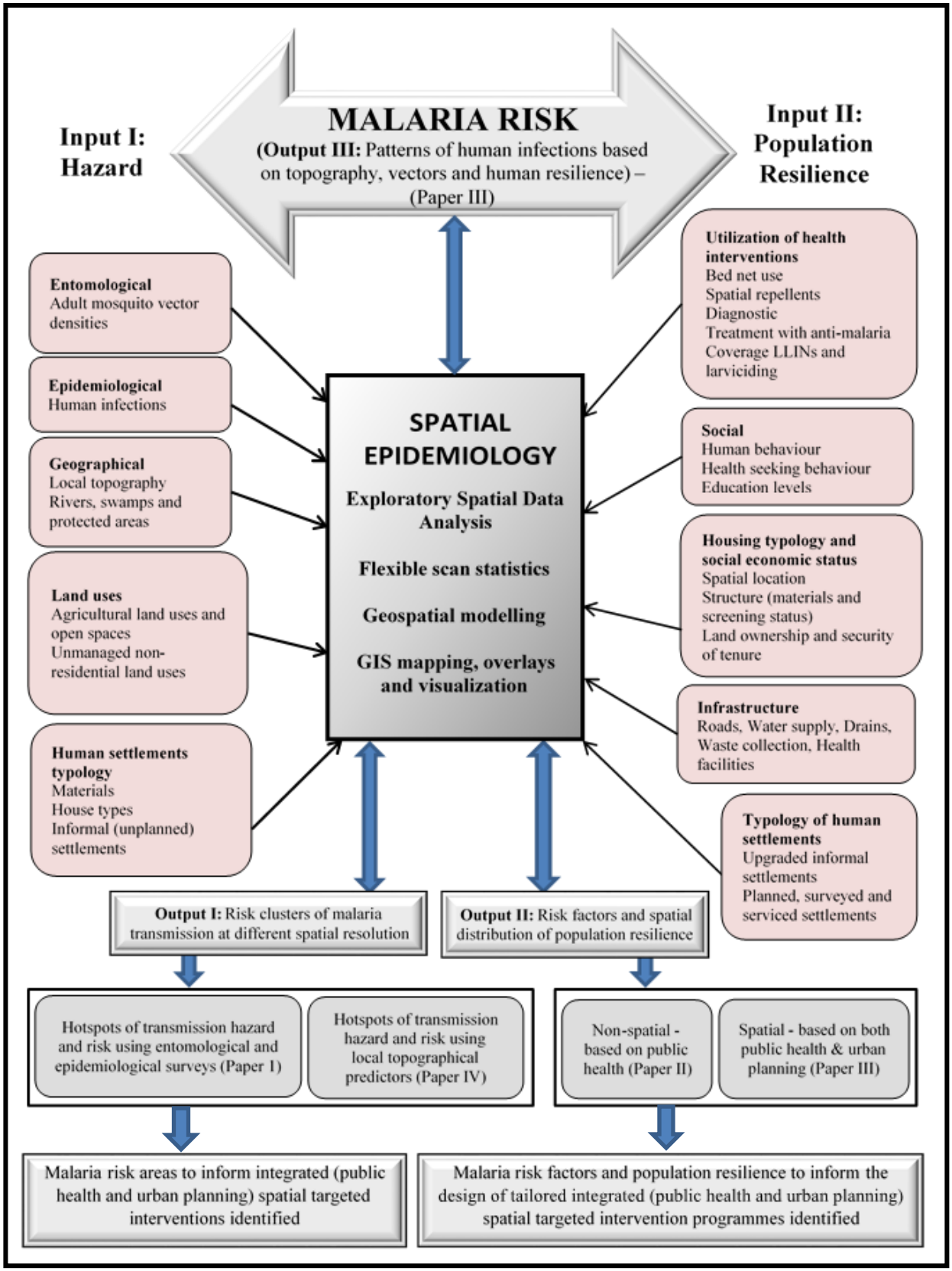


Figure 3.1: Conceptual framework to spatially track malaria hotspots for operational targeted interventions: adapted from (Balls et al., 2004, Cohen et al., 2008, Kelly et al., 2012) and modified to suite the requirements of this study

3.2 Thesis themes

3.2.1 Overall theme

The overarching theme for this thesis is the spatial scalability of malaria risk mapping for selective targeted interventions.

3.2.2 Specific themes

The specific thesis themes (Table 3.1) and their relation to the four thesis papers and objectives are highlighted below (Table 3.2)

1. Patterns of malaria hazard and risk are highly heterogeneous and unpredictable at higher geographic resolutions (Theme 1)
2. Heterogeneous and sporadic patterns of malaria transmission hazard and risk are caused by differences in exposures to local risk factors (Theme 2)
3. Geographic resolutions of malaria hazard and risk predictors are important for optimum design of integrated spatial targeted intervention programmes (Theme 3)
4. Mapping of malaria risk areas in cities needs to be informed by the local levels of population resilience (Theme 4)
5. Control/elimination of malaria risk in cities of SSA needs integrated approach to be adapted in the urban development agenda (Theme 5).

   Theme five provides a conceptual model on how integrated intervention programmes to control and eliminate malaria hazard and risk can be streamlined in the existing urban development agenda (See Fig. 6.1)

Table 3.1: A summary of the five thesis themes

Theme	Key components and description
THEME I: Patterns of malaria hazard and risk are highly heterogeneous and unpredictable at higher geographic resolutions: *Objectives 1 & 2*	Mapping epidemiological and spatial structure of malaria transmission using different predictors is important to reveal the suitable scale for selective spatial targeting of interventions in Dar es Salaam, a typical city in SSA. Noteworthy these patterns are highly sporadic and not easily predictable using the traditional entomological and epidemiological survey methods with large spatial scale particularly in cities where malaria transmission is reduced.
THEME II: Heterogeneous and sporadic patterns of malaria transmission hazard and risk are caused by differences in exposures to local risk factors	Typical breeding habitats for *An. gambiae*, a malaria vector in Dar es Salaam, are small, dynamic and unpredictable. Accounting for spatial effect confirms that topographic indicators of water accumulation potentials mapped at higher resolution are powerful predictors of malaria transmission hazard. Resilience of local population is highly heterogeneous and highly important in determining the risk of malaria transmission at finer scales; and could provide a good basis for setting interventions strategies.
THEME III: Geographic resolutions of malaria hazard and risk predictors are important for optimum design of integrated spatial targeted intervention programmes: *Objectives 2 & 3*	Higher resolution predictors of both hazard and risk of malaria transmission is required in cities to enable adequately informed targeted interventions against mosquito vectors and human infections if urban malaria has to be eliminated.
THEME IV: Mapping of malaria risk areas in cities needs to be informed by the local levels of population resilience: *Objectives 1 & 2*	Local human resilience of city dwellers is a key issue in urban malaria transmission. Successful interventions for urban malaria elimination need to understand this aspect and see how it affects local/heterogeneous patterns of malaria hazard and risk. Most of resilience measures are either preventive, curative or associated with human behaviour; hence they can be incorporated in interventions targeted to high risk areas in order to control transmission.
THEME V: Control/elimination of malaria risk in cities of SSA needs integrated approach to be adapted in the urban development agenda: *Objectives 2*, 3 & 4	The process of mapping hazard and risk of malaria transmission and areas for operational overlap (inter sectoral) is required to guide selective integrated targeted interventions.

Table 3.2: Thesis themes covered by the research and a summary of findings of the related original papers

THEMES	COVER STORY	PAPER I	PAPER II	PAPER III	PAPER IV
	The cover story (cross cutting themes) will be submitted to Global Health Action	Published in Malaria Journal, 2016	Published in Malaria Journal, 2016	Under review by Journal of the Royal Society Open Science	In manuscript draft (To be submitted to PLoS One)
THEME I: Patterns of malaria hazard and risk are highly heterogeneous and unpredictable at higher geographic resolutions: *Objectives 1 & 2*	Epidemiological and spatial patterns of transmission hazard and risk	X		X	
THEME II: Heterogeneous and sporadic patterns of malaria transmission hazard and risk are caused by differences in exposures to local risk factors	Factors contributing to the observed epidemiological and spatial patterns of urban malaria transmission hazard and risk		X		X
THEME III: Geographic resolutions of malaria hazard and risk predictors are important for optimum design of integrated spatial targeted intervention programmes: *Objectives 2 & 3*	The role of spatial resolution of predictors of malaria transmission hazard and risk; and its implications for selective spatial targeting of interventions against mosquito vectors and human infections.	X		X	
THEME IV: Mapping of malaria risk areas in cities needs to be informed by the local levels of population resilience: *Objectives 1 & 2*	Components of malaria transmission risk at fine spatial scale				X
THEME V: Control/elimination of malaria risk in cities of SSA needs integrated approach to be adapted in the urban development agenda: *Objectives 2*, 3 & 4	Overall contribution of the study (points to new ways of researching risk of urban malaria transmission and design of selective spatial targeting of inter-disciplinary interventions against localized malaria risk, conceptual diagram – towards a new approach to 1) mapping of malaria risk and 2) selective spatial targeting of inter sectoral interventions in cities and towns of the SSA		X	X	X

See list of papers on page vii above

Chapter Four: Material and methods

The following section describes the study area and population, study design, the data collected and analyses performed in this thesis.

4.1. Study area and population

This study was conducted in Dar es Salaam (translated as "*the residence of peace*" or "*bandari ya salama*" in Swahili), the biggest economically and politically most important city in Tanzania. The city is situated in Eastern Africa along the shores of the Indian Ocean (Fig 4.1). Dar es Salaam has a total of 4.36 million inhabitants and is expected to expand by more than 85% spatially and population wise by the year 2025 (NBS, 2013). The annual growth rate of 5.6% places Dar es Salaam amongst the ten fastest growing cities worldwide (UN-Habitat, 2016, UN-Habitat, 2013). Unfortunately, 80% of its growth is informal, non- or partially-serviced settlements (Magembe-Mushi and Lupala, 2015, UN-Habitat, 2010b). However, the central government of Tanzania and development partners such as World Bank and UN-Habitat have been collaboratively upgrading informal settlements within the central and crowded parts of the city by providing them with basic infrastructure services and land tenure. The first phase of upgrading was done in 16 sub-wards between 2004 and 2008, covering 200,000 inhabitants. The second phase involved 15 communities between 2009 and 2011, consisting of 220,000 inhabitants.

Dar es Salaam has a hot and humid tropical climate with two rainy seasons which provide ideal conditions for mosquito propagation and malaria transmission. The intense, long rainy season begins in March through to May and a milder, shorter rain season which is erratic, occurring between October and December. The mean temperature ranges from 19°C to 32°C, and the mean annual rainfall is

1,100 mm; both providing satisfying climatic requirements for stable malaria transmission (Craig et al., 1999).

The topography of Dar es Salaam is divided into three distinct zones (RCO and NBS, 2014), *the upland zones* (>100m above mean sea level (AMSL)) consisting of hilly areas, with plains dissected by many well drained streams to the West and Northern sides of the city; *the middle plateau* (62-100m AMSL) which is characterized by gently, undulating plateaus with isolated hills, rock outcrops, dissected by many streams in the central parts of the city; *and the lowlands* (0-62m AMSL) consisting of uniform relief slopes invariably less than 3%, except along the immediate margins of the two big river valley systems, the Msimbazi river in the central and the Mzinga river in the southern parts of the city. This zone consists of the coastal belt extending from northern to southern parts of the city (RCO and NBS, 2014).

Administratively, the city comprises three municipalities namely Ilala, Kinondoni and Temeke (Fig 4.1), which are collectively divided into 90 wards (URT, 2013b) which are further divided into smaller neighbourhood units called *mitaa* (Dongus et al., 2011b). Each *mtaa* is subdivided into Ten Cell Units (TCUs), comprising clusters of approximately 10 to 20 houses, although some TCUs contain a much larger number of houses (Dongus et al., 2011b). In total, the study area covered 498 km^2, consisting of 71 wards, of which 15 are original wards under the UMCP (Fig. 4.1). The study area encompasses an overall population of 3.6 million inhabitants living in 12,000 TCUs with 543,000 enumerated households. The TCUs represent the sampling geographic units that were allocated to individual community resource persons (CORP) for mosquito trapping and implementation of larviciding (Msellemu et al., 2016), and were also the main spatial units of analysis in this study.

Following the outset of this study in 2010, larviciding was applied using a coated granule larvicide formulation (VectoBac®, Valent BioSciences Corporation) of *Bacillus thuringiensis* var. *israelensis* (*Bti*) under temporal management of a foreign contractor, Research Triangle Institute (RTI). In January 2011 the Central Government of Tanzania (GoT) through the Ministry of Health and Social Welfare (MoHSW) took over direct management and financial responsibilities of all larviciding activities, using similar granular *Bti* products from January to July 2011, before moving to a pre-diluted aqueous suspension formulation (Bactivec®, Labiofam®) of *Bti* from September 2011 through end of this study in January 2013 (Msellemu et al., 2016).

4.2. Study design, data collection and timeline

This study uses data collected from two different complementary studies. A longitudinal study was performed to monitor mosquito vector population dynamics and a cross-sectional study was conducted to monitor human infections. However, the sampling frames for these studies were different; the longitudinal surveys being larger than that of cross-sectional household surveys. For comparative purposes, a few of the study locations were co-surveyed.

4.2.1 Longitudinal entomological surveys of mosquito vector densities and behaviour

Densities of adult *Anopheles gambiae* complex mosquitoes were routinely collected using monthly surveys. The mosquitoes were sampled using Ifakara Tent Traps (ITT) (Govella et al., 2010) which were distributed through a community-based surveillance platform (Chaki et al., 2011) with a total of 2,013 sampling locations across the entire city (Fig. 4.1c) which were deliberately chosen by TCU leaders and the CORPs in order to promote a sense of community ownership (Chaki et al., 2012b). These surveys were conducted in two different phases. The first phase was conducted from March - October 2010, consisting of 615 distinct sampling locations (Chaki et al., 2012b) which were set up within the

original 15 wards of the UMCP (Dongus et al., 2011b). The second scaled up phase of the survey was conducted in 1,398 different sampling locations from May 2011 to January 2013 (see (Msellemu et al., 2016, Mwakalinga et al., 2016) for further details of the surveys).

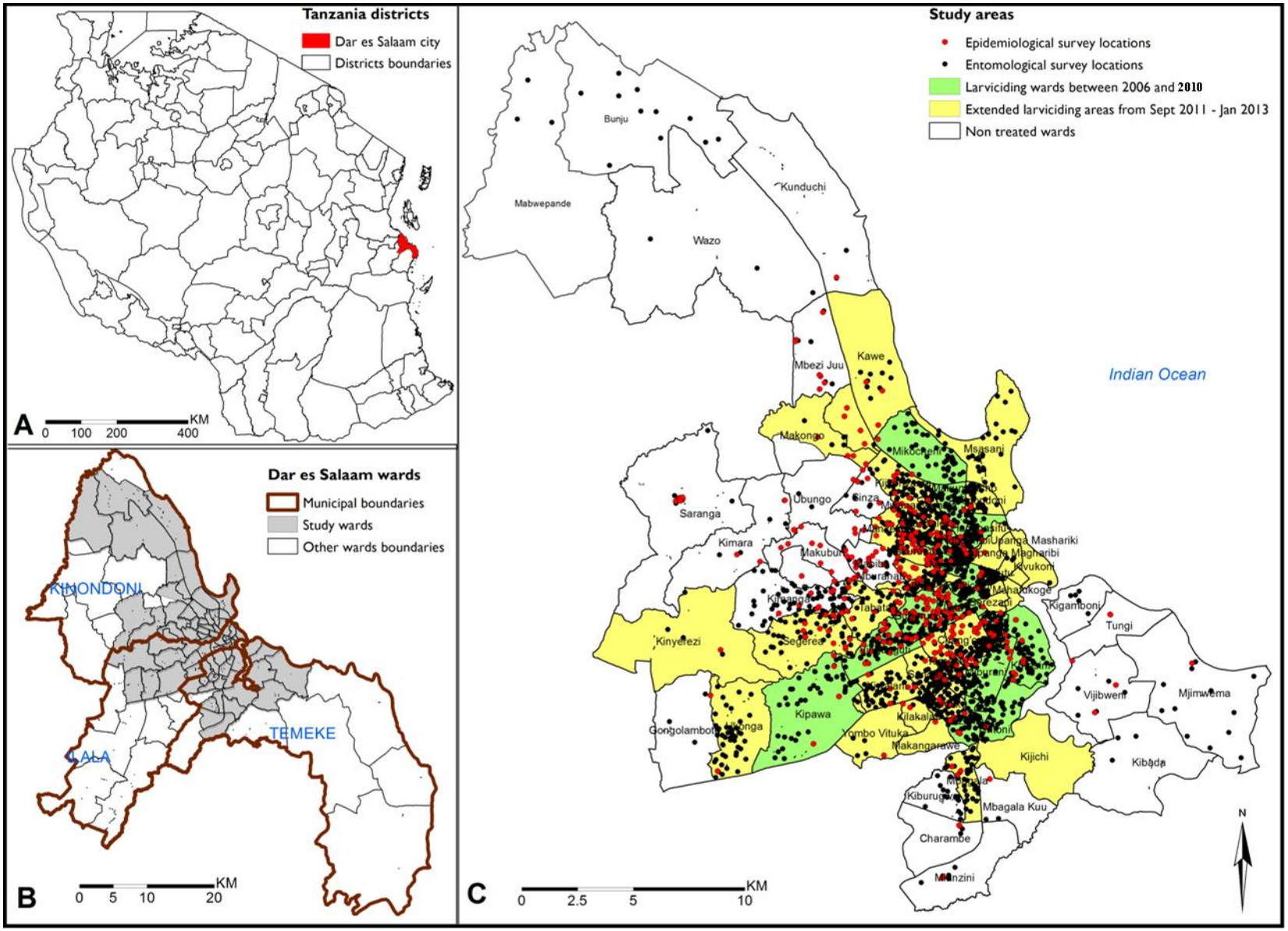


Figure 4.1: A map showing sampling locations of longitudinal and cross-sectional surveys and wards under larviciding over the course of this study.

A Dar es Salaam in the country setting. **B** the study area within the city and its three municipalities **C** and the survey locations and wards in which larvicides were applied. The original map is published in Fig. 1 of Annex 1b (Msellemu et al., 2016).

During both phases, quality assurance was conducted using both human landing catches (HLC) and ITT by a carefully supervised team of specialist technicians. All *Anopheles* mosquitoes captured were tested for the presence of *P. falciparum* circumsporozoite protein by enzyme-linked immunosorbent assay [ELISA] (Burkot et al., 1984), including confirmation by re-assay after heating homogenates of apparently positive samples (Durnez et al., 2011). Laboratory analysis of morphologically-identified specimens of *An. gambiae sensu lato* by polymerase chain reaction (PCR) (Scott et al., 1993) confirmed that this complex was predominantly composed of the nominate sibling species *An. gambiae s.s.*, with the small remainder being *An. arabiensis* (Msellemu et al., 2016). *Anopheles gambiae s.s.* is one of the most anthropophagic members of the complex and is a highly efficient malaria vector while *An. arabiensis* is more variable in its host preferences but is also, nevertheless, an efficient vector. Very few other vectors, e.g. *Anopheles funestus,* or indeed other *Anopheles,* were collected (Msellemu et al., 2016). Vector density was expressed in terms of total numbers of *An. gambiae* complex specimens caught per trap night per TCU for subsequent analyses, and considered representative of this dominant, nominate sibling species (Msellemu et al., 2016).

4.2.2 Epidemiological cross-sectional household surveys of malaria positivity

Two different phases of cross-sectional household surveys were conducted in three different rounds to monitor human malaria infection positivity. Households for the surveys were randomly selected using a multistage cluster sampling approach. The primary sampling clusters were TCU housing clusters (*mashina*), which were weighted according to their population size and selected with probability proportion to size (PPS). Twenty households were randomly selected and surveyed within each TCU sampled. If a TCU had fewer than 20 households, additional households were randomly picked from immediate neighbouring TCUs (Msellemu et al, 2016). The total number of households in each TCU within the mapped area (Dongus et al., 2011b) was enumerated by census between January 2008 and May 2010 (12,000 TCUs and 543,209 households were enumerated). Phase I of the

surveys was carried out from March through September 2010; involving 2,754 individuals who were tested for malaria parasites from 696 households in 302 TCUs. The second phase involved random selection of much smaller numbers of larger population clusters termed as index TCUs. Between October 2010 and May 2012, a second phase of cross sectional surveys was completed, encompassing a total of 8,433 individuals tested from 2,671 households and 86 Index TCU clusters (see (Msellemu et al., 2016) for further details on how these cross sectional surveys were conducted).

Notably, 156 TCUs were included in both the longitudinal and cross-sectional household surveys to enable evaluation of community based platforms for monitoring vector densities at high levels of spatial resolution in terms of its epidemiological predictive power (Chaki et al., 2012b). Human malaria infections in both phases were tested using Rapid Diagnostic Tests (mRDT) (MAL-Pf, ICT Diagnostics, Cape Town, South Africa). Household information was collected through a detailed structured questionnaire which was administered to the heads of households (See household questionnaires in Annex VI).

4.2.3 Data on hazard, risk and resilience factors

Data on risk indicators and human resilience were collected during the two phases of household epidemiological cross-sectional surveys. These include information on population characteristics (sex, age, number of household members, education level of household head); housing structure (wall type, roof type, ceiling type, type of window screening and floor materials, eaves condition, ceiling quality, condition of window air brick gap); utilization of health sectors interventions (bed net use, sprayed in last 12 months, use of insecticide aerosols, use of repellents, bed nets soaked/dipped/long-lasting, treatment seeking behaviour, if they had fever in the past two weeks, use of any drugs in the last two weeks); travel patterns (if they had travelled within or outside the city in the past two weeks) and human behaviour (time they went indoors last night, time they went to bed last night, time they

got out of bed and time they went out that morning). Additional data on population resilience that were not covered during cross-sectional surveys, such as wards under larviciding and provision of urban infrastructures (mainly health facilities, roads, drainage and solid waste collection services), were obtained from the respective municipal councils. Information on land use and settlement typology (referring to building types, materials and physical location of the house, whether in a planned and surveyed, unplanned, upgraded or regularized settlement) were obtained from existing city maps and municipal urban planners.

Finally, topographic data were extracted from a 20m resolution Digital Elevation Model (DEM) using SAGA GIS, a free and open source software (www.saga-gis.org). The DEM was freely obtained from the Faculty of Geo-Information Science and Earth Observation, University of Twente (ITC). Weighted averages of each topographic predictor were computed based on TCU boundaries, which were obtained through a participatory mapping approach (Dongus et al., 2007, Dongus et al., 2011b). The centroids of each TCU were computed and their enumeration locational codes used to link topographic predictors and those of mosquito vectors and malaria infections. The spatial references for ITTs and households for cross-sectional surveys were collected using a hand held global positioning system (GPS) set at 2m accuracy. These spatial references were the basis for calculating the centroids of the sampling clusters. Distances from households to nearest infrastructures or amenities were calculated using proximity spatial analysis in ArcGIS version 10.

4.3 Study variables

The outcome variables of this study were: 1) density of female adult *An. gambiae* which were expressed as total numbers of *An. gambiae* complex specimens caught per trap night per TCU; and 2) *Plasmodium falciparum* malaria infection prevalence per TCU. The explanatory variables differ according to study objectives and the models fitted. Table 4.1 below provides a full list of all explanatory variables and how they were used in this study.

4.4. Data analysis

4.4.1 Descriptive analysis

Descriptive summaries in terms of total number of trap nights conducted over the study period and associated means of adult mosquitoes collected per person nights were created. Trends and averages of *P. falciparum* malaria infection prevalence over different phases of the study were also prepared. All summaries were made using Stata version 13.0 (StataCorp, 2013). Maps describing the distribution of mean catches per trap night of adult *An. gambiae* and human infection prevalence in relation to larvicide application at ward level were set using ArcGIS version 10 to visualize the spatial patterns of the outcome variables.

4.4.2 Spatial clustering and hotspots[2] mapping

Existence of global clustering (spatial autocorrelation) in the spatial arrangement of mean catches of *An. gambiae* and malaria infection prevalence was assessed using Moran's I (MI) statistics (Moran, 1948) in Arc GIS version 10. Spatial autocorrelation occurs when there is clustering (+ve Z-score) or dispersion (–ve Z-score) and this is significant at $p \leq 0.05$ (Moran, 1948). A p value > 0.05 suggests a

[2]Hotspots were defined as spatially aggregated TCUs with significantly higher than average (12.05 % for phase 1 and 8.49 % for phase 2) levels of malaria infection prevalence or *An. gambiae* mosquito densities (any location with detectable *An. gambiae*)

homogeneous spatial pattern (random). The details of this analysis are presented elsewhere (Mwakalinga et al., 2016).

Local clustering (hotspots) of both hazard and risk was detected using a flexibly shaped spatial scan statistic, developed by Tango and Takahashi (Tango and Takahashi, 2005) Flexible scan statistics create both circular and irregular shaped clusters. This method identifies clusters based on a spatial weight matrix in which the detected cluster is allowed to be flexible in shape while at the same time confined within relatively small neighbourhoods of each sampling unit (Tango and Takahashi, 2005). In developing the matrix file, spatial relationships were conceptualized using Delaunay Triangulation, with Euclidian distance. The analysis was done in FleXScan software which uses an irregularly shaped window for each location by connecting its adjacent locations (Tango and Takahashi, 2005). In this study, purely spatial analysis, i.e. scanning for spatial clusters with high rates of malaria prevalence or mosquito vector density irrespective of time was performed. Hotspots of mosquito vector densities were detected based on a Poisson model, the numerator being aggregated counts of female *An. gambiae* per TCU and the denominator being expected population of *An. gambiae* per TCU. Hotspots of malaria infection prevalence were detected using a binomial model. Primary and secondary clusters were explored by means of Monte Carlo replications under the null hypothesis with at least 9999 replications to ensure adequate power for defining those clusters at $p < 0.05$ significance level. The number of adjacent nodes to scan was set to at least 30. ArcGIS was used to make spatial adjacency matrices (which this method uses to allow flexibility and detection of irregular shaped hotspots) and produce final hotspots maps.

4.4.3 Hazard, risk and resilience factors analyses

Individual and household risk factors for malaria transmission were analysed using generalized linear mixed models (GLMMs) with a logit link function and binomial distribution (Msellemu et al., 2016). The dates in which malaria infection data were collected; and the household nested within sample cluster as independent variables with random effects, were included in the models and fitted using the *lme4* package version 1.1-12 (Bates et al., 2015) in R software. In order to account for dispersion in mosquito data, the impact factors for malaria hazard were estimated using the *lme4* package by fitting GLMMs with negative binomial distributions to the counts of mosquitoes caught by each catcher on each night at a given location with an ITT as the dependent variable. In this model, larvicide application for at least two weeks before the night of survey was included as a fixed effect, while TCU nested within ward was treated as a random effect.

Subsequent analysis (see Annex 1c) was performed taking into account the spatial effect of the predictor variables. This analysis used a multilevel modelling approach, including all risk factors (Table 4.1) at individual, household, community, sectoral and institutional levels. However, only non-collinear variables with a Polychoric correlation coefficient (ρ) <0.7 were retained for the final model. The analysis was performed using boosted regression trees (BRT) (Friedman et al., 2000b) in R software version 3.0.2, using package "*dismo*" version 0.8-17 (Cheong et al., 2014a) and package "*gbm*" version 2.1 (Ridgeway, 2013a). The BRT is a machine learning algorithm developed by (Friedman et al., 2000b). This model was preferred in this study because of its capability in dealing with complex relationships including nonlinearities, interactions and adaptation of predictor variables of any type including numeric, binary, categorical and spatial (Cheong et al., 2014a, Elith et al., 2008b). In this study, BRT was fitted with a "Bernoulli" function assuming a binomial distribution of malaria positivity. The steps forward function (Elith et al., 2008b), which is an alternative to Ridgeway cross-validation function (Ridgeway, 2013a) was opted with a bagging factor of 0.5 (Friedman, 2001b). This

means that the first regression tree was fitted to the dependent variable while randomly selecting 50% of the training data (Cheong et al., 2014a).

In BRT models, a slower learning rate (*lr*) usually suggested (and also opted for this study) for a better model building process (Elith et al., 2008b). The number of splits levels of each tree i.e. tree complexity (*tc*), determines the degree to which predictors may interact with each other in relation to the response. More levels of interactions are explained with a higher *tc* (Cheong et al., 2014a). The maximum number of trees was not set to allow identification of the optimal number of trees (*nt*) (Elith et al., 2008b). Three different combination of *lr* (0.0002, 0.001 and 0.05) and four *tc* (3, 5, 7 and 10) parameters were tested. The model with the highest cross-validated Receiver Operating Characteristic Area Under the Curve (ROC AUC) score was selected (Hastie et al., 2009).

The BRT provides relative importance of each predictor variable based on the number of times a variable is selected for splitting, weighted by the squared improvement and averaged over all trees (Friedman and Meulman, 2003). The relative importance of each variable is then scaled to sum up to 100 percent and a variable with highest relative percentage has a stronger effect on the outcome (Elith et al., 2008b). Only variables above the randomness threshold i.e. **100%/Total number of predictors** are considered to be more influential than others. Partial dependence plots were used to visualize and interpret the effect of most influential predictors on risk of malaria transmission. The spatial prediction of BRT model results was done using package "*raster*" version 2.2-30 and package "*rgdal*" version 0.8-16 (Elith et al., 2008b) and mapped using ArcGIS version 10 for consistency with other maps prepared in this study.

Finally, high hazard and risk areas where interventions could be selectively targeted were mapped at increased geographic resolution (see Annex 1d) compared to entomological and epidemiological

predictors used to map malaria hotspots in Annex 1a (Mwakalinga et al., 2016). This analysis further revealed both hazard and risk factors at very fine spatial scales using all topographic indicators of local hydrology, which were extracted from the DEM (see Annex 1d). Two distinct Multivariable Conditional autoregressive models (MCAR), adjusted for larvicide application regimes, were fitted to better understand the spatial interactions that arise between topography, densities of *An. gambiae* and malaria infection prevalence. The model for densities of *An. gambiae* was fitted using a Poisson-lognormal MCAR model (Wany and Kockelman, 2013) and malaria infection prevalence was fitted using Binomial logit MCAR (Gelfand and Vounatsou, 2003). The autoregression parameters and confidence intervals for each model were obtained using Markov chain Monte Carlo (MCMC) simulations (Gelfand and Vounatsou, 2003, Waller and Gotway, 2004). Coefficients for mosquito models were transformed to Odds Ratios / Relative Rates (RR) i.e. exponents of β (exp(β) to guide interpretation of the size of variables effects. Back wise elimination was used in the fitting process, starting with a large model with all topographical covariates as described in Table 4.1 for each outcome. We excluded AAC because when included in the models it failed to solve due to its perfect collinearity with elevation, AACHN and TPI. The succeeding model was then re-fitted after removing one variable with the highest *p-value* observed in the preceding model. This process was repeated until when a reduced model with all significant covariates was attained. Spatial modelling was performed using CrimeStat IV® (Levine, 2013) and SAGA GIS®, both open source GIS software. Final model results were mapped and visualized using ArcGIS v10®. The maps of predicted hazard and risk; and their associated driving factors (including those of local population resilience) were used to develop a framework for integrated targeted intervention programmes in Fig. 6.1.

Table 4.1: List of outcome and predictor variables for each theme

Theme	Outcome variables	Predictor variables	Analysis	Output
I		Counts of female *An. gambiae* complex caught by each catcher on each night at a given TCU	Global Moran's I statistic	Spatial autocorrelation (global clustering) of malaria hazard
			Flexible spatial scan statistic (Poisson)	Hotspots of malaria hazard (local clustering)
		Human infection prevalence at TCU level	Global Moran's I statistic	Spatial autocorrelation (global clustering) of malaria risk
			Flexible spatial scan statistic (Binomial)	Hotspots of malaria risk (local clustering)
II (a) Health sector	Counts of female *An. gambiae* complex caught by each catcher on each night at a given TCU	Community coverage of LLINs Larviciding Individual use of bed nets	Generalized linear mixed model (GLMM) with negative binomial distributions	Hazard factors
	Malaria positivity	Sex Age categories Education status Human behaviour Travel history Window screening Individual use of bed nets Community coverage of LLINs Larviciding Mean catches of *An. gambiae*	Generalized linear mixed model (GLMM) with a logit link function and binomial distribution	Risk factors
II (b) Non-health sector	Malaria positivity	Human behaviour Window screening Education status Individual use of bed nets Community coverage of LLINs Larviciding Mean catches of *An. gambiae* Topographic indicators Land uses Infrastructure Urban planning programmes Settlements typology	Bernoulli Boosted Regression Tree fitted with step forward function using *dismo* and *gbm* packages	Spatial patterns of risk and risk factors

Theme	Outcome variables	Predictor variables	Analysis	Output
III.	Counts of female *An. gambiae* complex caught by each catcher on each night at a given TCU	Altitude above channel network (AACN) Aspect Channel network (CHN) Elevation Hills shading Planform curvature (PLC) Profile curvature (PRC) Slope Topographic Convergence Index (TCI) Topographic Position Index (TPI) Topographic Ruggedness Index (TRI) Topographic Wetness Index (TWI)	Multivariable conditional autoregressive model with Poisson lognormal function	Local spatial patterns of hazard and associated hazard factors
	Malaria positivity		Multivariable conditional autoregressive model with Binomial logit function	Local spatial patterns of risk and associated risk factors
IV.	Malaria positivity	Local human resilience status Mean catches of *An. gambiae (hazard)* Topographic indicators	Bernoulli Boosted Regression Tree fitted with step forward function using *dismo* and *gbm* packages	Spatial patterns of risk based on resilience, hazard and topography
V	Study contribution			

4.4.4 Multicollinearity analysis

This analysis was done using exploratory regression (Rosenshein et al., 2011) in Arc GIS version 10. In human resilience variables, multi collinearity was assessed using Polychoric correlation analysis and only variables with Polychoric correlation coefficient (ρ) of <0.7 were included in the BRT models. However, assessment of multi-collinearity among topographic predictor variables was done using Variance Inflation Factors (VIF) (Liao and Valliant, 2012). Variables with VIF > 10 (Stewart, 1987, O'brien, 2007) were not included in the MCAR models. All these were done to preserve uniqueness of each predictor variable and also to avoid the effects of multi-collinearity such as over predictions or instability of the coefficients (Liao and Valliant, 2012).

4.5. Ethical considerations

Only participants giving informed written consent were included in the study, including the mosquito catchers and the house owners where the catches took place, as well as the participants in the epidemiological cross-sectional parasite surveys. Participants found to be infected with malaria parasites during the surveys were treated with artemether-lumefantrine (Coartem®; Novartis Pharma AG, Basel, Switzerland) following national treatment policies and guidelines. Ethical approval for all procedures involved in this study was obtained from the Institutional Review Board of the Ifakara Health Institute (Approval A.50), the Medical Research Coordination Committee of the Tanzanian National Institute of Medical Research (Approval NIMR/HQ/R.8a/Vol.IX/801), the Research Ethics Committee of the Liverpool School of Tropical Medicine (09.60) and the Human Research Ethics Committee (HREC) at University of the Witwatersrand (M120835).

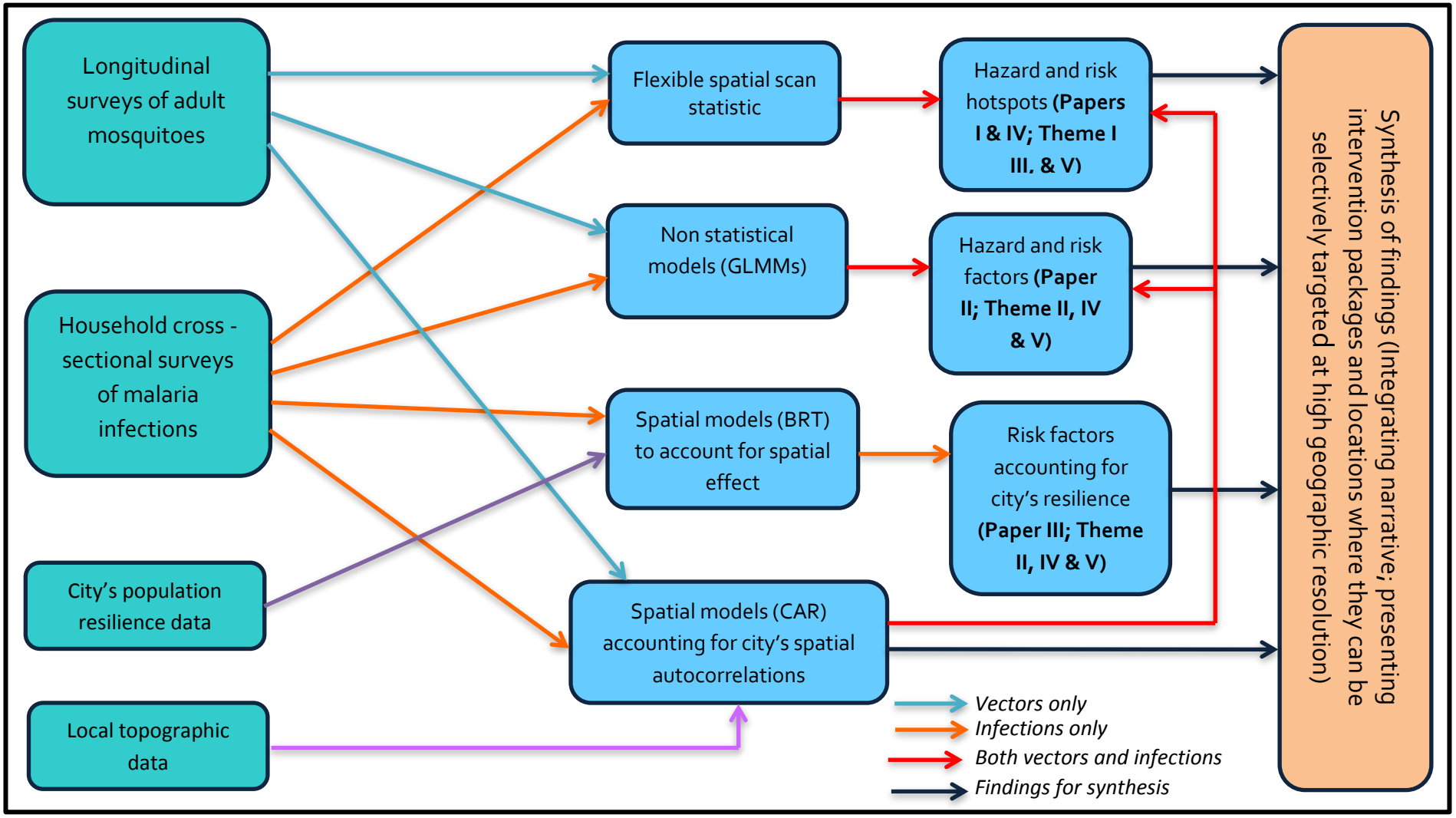


Figure 4.2: Flow chart showing the linkages between the different data sets used in this study, methods of analysis and their associated papers.
Full references for each paper is given at the beginning of the thesis on page viii and the papers themselves are included in Annexures 1a - d

Chapter Five: Results

This chapter provides an overview of the descriptive statistics for the study population (by way of background) and the results of the study in accordance with the research themes (introduced above in Tables 3.1 and 3.2) in reference to the original four papers (Annex 1a – d) which contain the details of the study findings. The inter linkages of the research themes and the study designs, papers and the integrating narrative as a whole have been presented in the methods chapter (Fig. 4.2). Notably, relative rate (RR) and odds ratio (OR) are interchangeably used in this chapter for Poisson regression models which were fitted on mosquito density and logistic regression models which were fitted on human infection respectively to aid interpretation of malaria transmission hazard and risk.

5.1. Synthesizing the four components of the study

This section is divided in two sections. The first section (5.1.1 and 5.1.2) presents quantitative summaries of entomological (densities of *An. gambiae* and indicator of malaria hazard) and epidemiological (human infection prevalence and indicator of malaria risk) data sets used in this study. While the second section provides a synthesis of all data from longitudinal entomological and household cross-sectional epidemiological surveys; and those collected from the city councils as well as topographical data. The identified locations with highest hazard and risk of malaria transmission are presented, along with factors driving hazard and risk of malaria transmission and local population resilience factors with high influence on focalized patterns of urban malaria. Altogether these factors could be used to design tailor-made geographically targeted interventions against urban malaria hazard and risk (see Fig. 6.1). The emerging themes have already been introduced in chapters 3 and

4. Notably, only key findings are presented here with references provided to the original papers (Annex 1a – d) where detailed findings of this study are presented.

5.1.1 Densities of adult *Anopheles gambiae* complex (malaria hazard)

A total of 12,170 person nights (number of traps per night per TCU) of community-based ITT capture were conducted from March 2010 to January 2013. Out of these nights, a total of 382 female *An. gambiae s.l.* were caught with an overall average (including standard deviation (SD)) catch per trap night of 0.024, SD = 0.068 (0.064, SD =0.187 in phase I and 0.012, SD =0.068 in phase II). Results of PCR tests confirm that of the caught malaria vectors; 328 (86%) were *An. gambiae sensu stricto*, 40 (10%) were *Anopheles arabiensis*, 4 (3%) were *Anopheles funestus* and 10 (1%) were other *Anopheles.* However, distribution of these mosquitoes was sporadic (Fig. 5.1b): most of the sampling locations caught no *An. gambiae* throughout the study period (Figs. 5.2a, c & 5.3a). Hence for this thesis, a sampling location with any detectable *An. gambiae* (Figs. 5.2a & 5.3b) is considered a higher transmission hazard area as is described elsewhere (Chaki et al., 2012b).

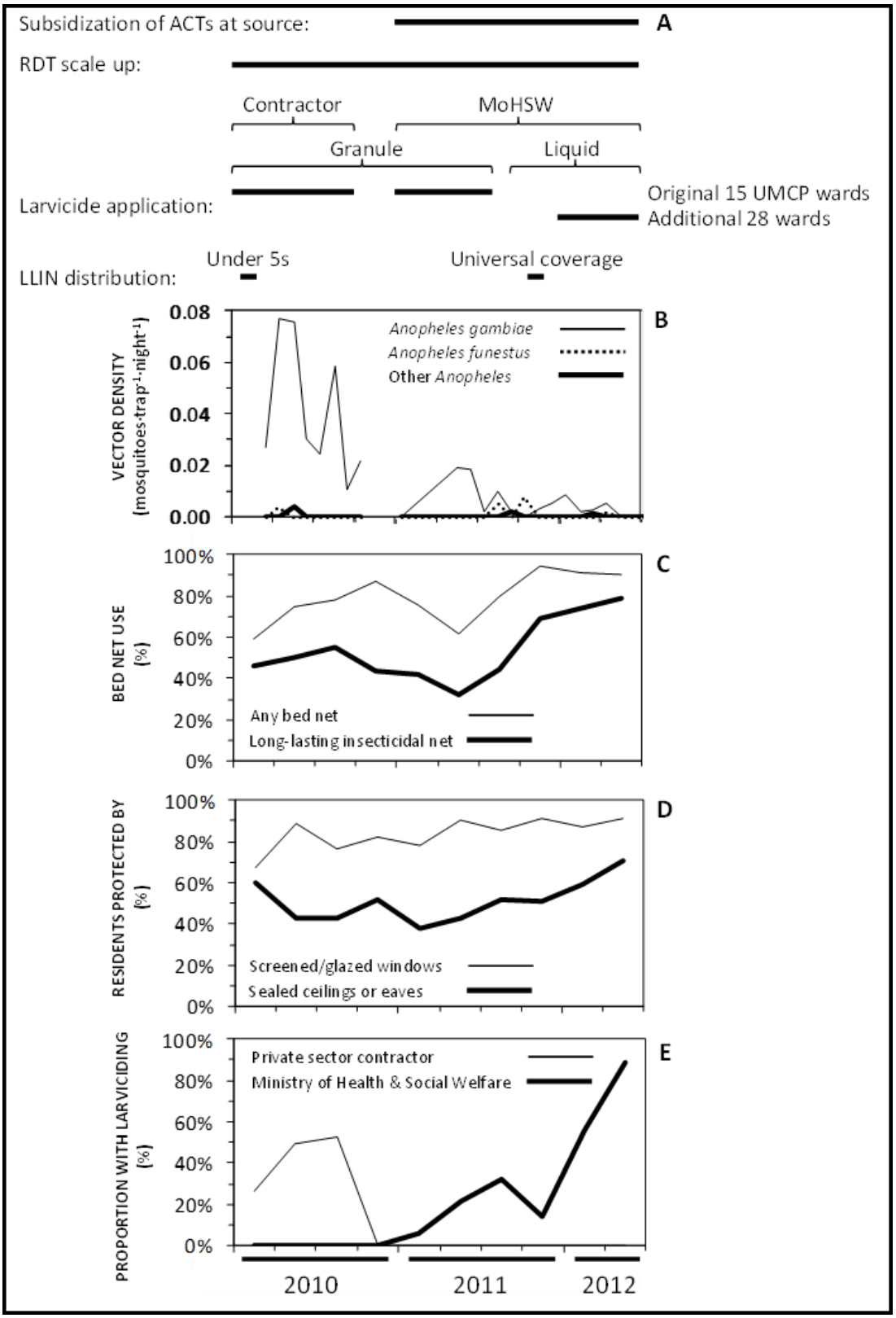


Figure 5.1: Temporal coverage of interventions against malaria infections during the time of cross sectional surveys. a) Schematic summary of specific intervention introductions; **b** Vector densities; **c** Prevalence of *Plasmodium falciparum* infection and recollection of fever; **d** Anti-malarial drug use and **e** Bed net use the previous night (Msellemu et al., 2016).

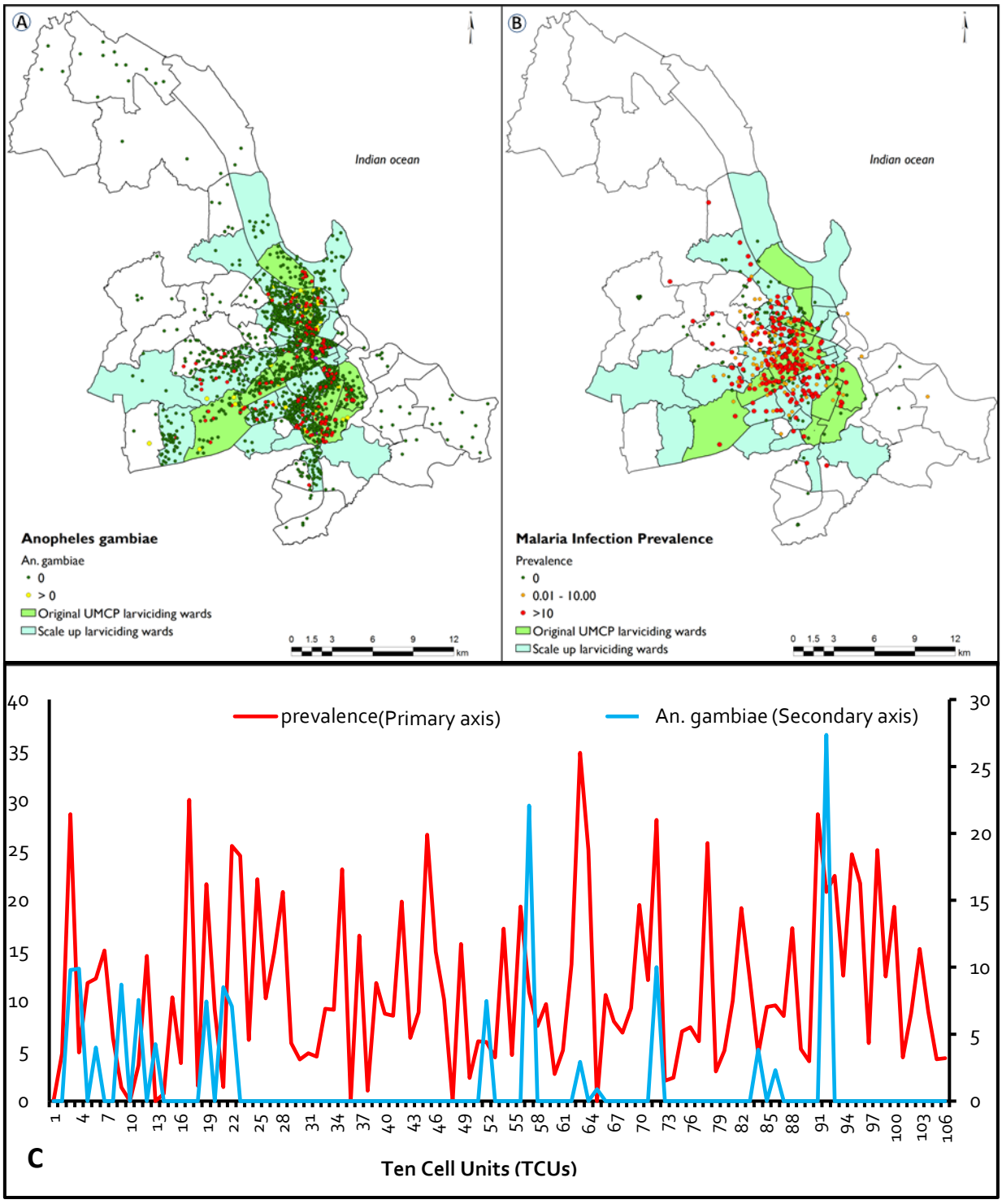


Figure 5.2: Spatial distribution of *An. gambiae* and human infection prevalence in Dar es Salaam: **A** surveyed locations with detectable populations of Anopheles gambiae vectors; **B** *Plasmodium falciparum* infection prevalence and **C** detectable *An. gambiae* and infection prevalence > 10% per TCU

5.1.2 *Plasmodium falciparum* malaria infection prevalence

In total 11,187 individuals were tested for malaria positivity *(Plasmodium falciparum)*. Of these, only 1,237 (11.1%) were positive. Males tested positive more frequently than females (Table 2 in Annex 1b) and there were no differences in risk of infections across the age groups (Fig. 7b in Annex 1b). Of the infected individuals, 88% (1090/1237) had not experienced fever recently (Msellemu et al., 2016). Over the study period, the overall prevalence was 11%; 12.7% (381/2,754) being the average prevalence in phase I and 10.8% (854/8,433) in phase II. Despite wider coverage of interventions such as larviciding (Fig. 5.1e), scale up of LLINs from the end of 2011 onwards (Fig. 5.1c) and increased community uptake of window screening (Fig. 5.1d) dramatically reduced vector population density (Fig. 5.1b), malaria infection prevalence persisted at an average of 10% from phase II through to the end of the study. This unresponsive and persisting average coincides with what is reported as the city's overall prevalence in the new malaria strategy (NMCP, 2014). Therefore, for subsequent parts of this integrating narrative, any sampling location with prevalence greater than or equal to 10% (Figs. 5.2 & 5.3d) is considered a high risk area and vice versa.

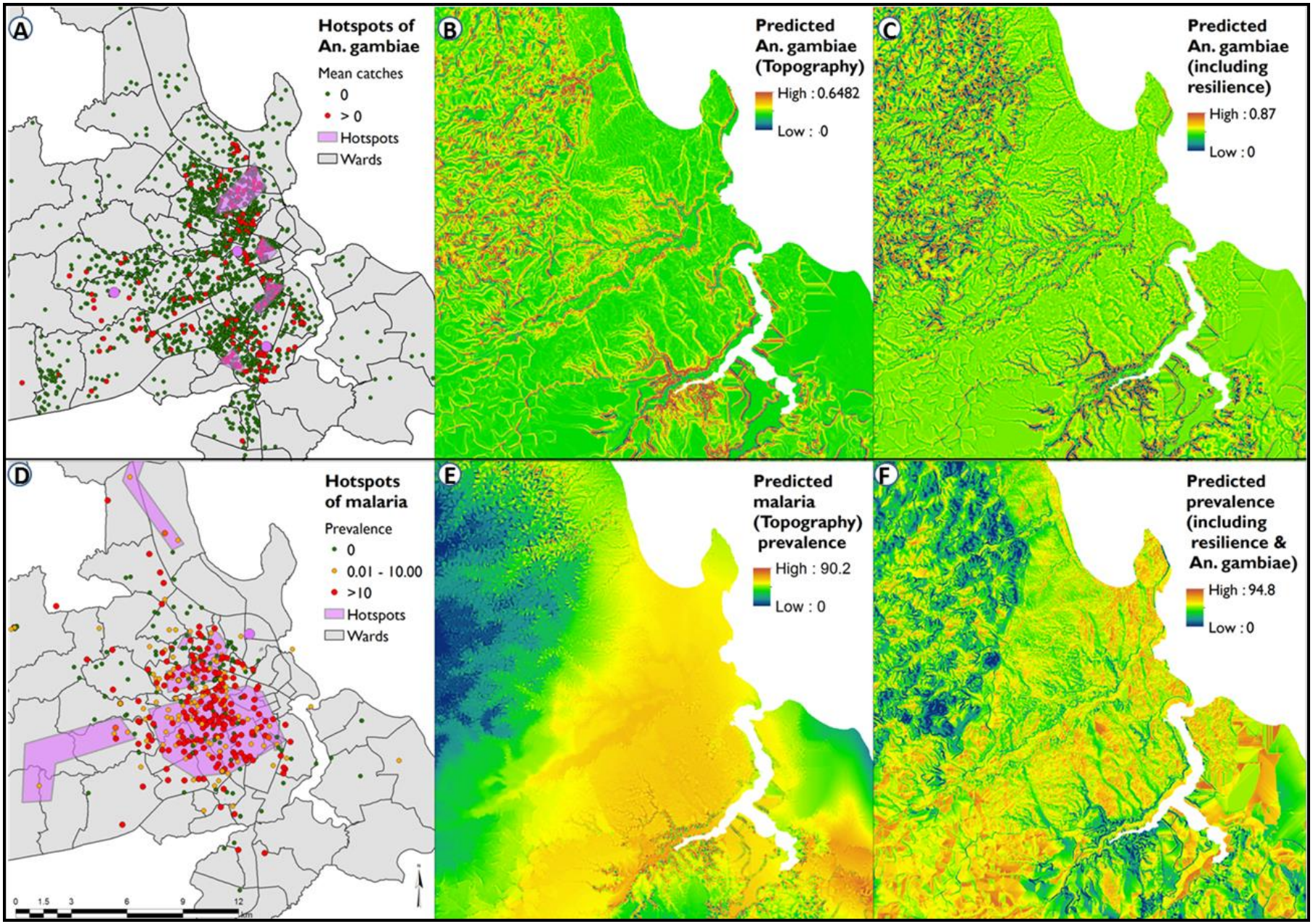


Figure 5.3: Mapping of location with high hazard and risk using different spatial resolution of predictors to determine areas for selective spatial targeted interventions: Panel **a** was mapped based on entomological surveys (slightly high resolution), **d** based on epidemiological surveys (low resolution), **b** & **e** based on topography (high resolution), **c** based on topography controlling for resilience and **f** based on topography controlling for hazard and resilience.

5.1.3 Patterns of malaria hazard and risk are highly heterogeneous and unpredictable at higher geographic resolutions (Theme 1)

At global scales (Mwakalinga et al., 2016) , the spatial patterns of *An. gambiae* and malaria infections showed a tendency towards clustering (Fig. 5.2). Nevertheless, this tendency was much stronger (more spatially constrained) for densities of *An. gambiae* (Moran's I (MI) = 0.15, P=0.002, mean distance between points [3] of 174 m in phase I; MI = 0.11, P=0.005, mean distance between points of 210m in phase II) but slightly weaker in human prevalence (MI = 0.17, P=0.018, mean distance between points 208 m in phase I; MI = 0.34, P=0.011, mean distance between points 799m in phase II). Shorter distance between points among mosquito sampling locations indicates higher spatial resolution of the data compared to those of malaria infection which had lower resolution (sampling locations were fewer and far from each other).

At local scales (Mwakalinga et al., 2016) only a few locations with higher vector densities (hazard) and infection prevalence (risk) were spatially aggregated in hotspots (Fig. 5.3d) while the remaining majority were scattered all over the city in small loci of both hazard and risk of transmission (Fig 5.3a). In both phases of the entomological surveys, only a third of locations with detectable *An. gambiae* were included in the hotspots (Table 5.1). The remaining majority (76%; 95/125 in phase I and 74%; 42/57 in phase II) of locations where any *An. gambiae* were caught were haphazardly scattered outside of the hotspots (Table 5.1). Similarly, in the phases of epidemiological surveys, the detected hotspots encompassed slightly more than half of all detected cases of malaria infection (Table 5.1); but just like *An. gambiae*, the majority (60% in phase I and 54.3% in phase II) of locations with elevated prevalence

[3] mean distance between points is the average distance on space which identify the propensity for nearby locations to influence each other and to possess similar attributes. This distance is used in spatial auto correlation to measure the similarity of points.

(>10%) occurred outside of these clusters, haphazardly distributed across disparate parts of the city (Fig 5.3d; Table 5.1).

The areas with the highest hazard and risk of malaria transmission at local scales were further mapped using explicit topographic indicators (Figs. 5.3b & e), and with addition of resilience status index (RSI) for hazard (Fig. 5.3c) as well as topographic indicators with RSI and hazard for infection risk (Fig. 5.3f). Based on explicit topographic indicators, 85% of densities of *An. gambiae* caught were mapped in only 15% of the sampling locations with detectable vectors (Fig 5.3b). However, similar to previous analyses with epidemiological indicators (see Annex 1a), topography mapped only 60% of highest risk in almost half (40%) of sampling locations, meaning that only 40% of locations with predicted highest risk will need to be targeted in order to cover 60% of malaria infections (see Annex 1d). Interestingly, hazard of malaria infections was again clearly mapped on the edges of steep slopes (Fig. 5.3c) when RSI was accounted for (see Annex 1c). In this case, 89% of predicted densities of *An. gambiae* were confined in only 11% of locations with highest hazard. With regards to risk, 81% of elevated infections were mapped in only 19% of locations (heterogeneously distributed in the lowlands towards the edges of elevated areas) with predicted highest infection risk (Fig.5.3f) when both hazard and RSI were added in the models along with topographic predictors (see Annex 1c).

Table 5.1: Hotspots (local spatial clustering) of *An. gambiae* and malaria infection prevalence

		Phase 1: March – September 2010						Phase 2: October 2010 – February 2013					
Outcome variable	Hotspot clusters	Proportion of all mosquitoes or detected infections (%(n/N))	Proportion of all survey locations in clusters (%(n/N))	Proportion of survey locations under larviciding (%(n/N))	Expected mosquitoes or prevalent infections	RR	P	Proportion of all mosquitoes or detected infections (%(n/N))	Proportion of all survey locations in clusters (%(n/N))	Proportion of survey locations under larviciding in (%(n/N)	Expected mosquitoes or prevalent infections	RR	P
Mean catches per trap night of female *An. gambiae*	Primary cluster	13.6(52/382)	3.7(23/615)	34.8(8/23)	12.89	4.58	0.0001	32.9(23/70)	4.8(67/1398)	67.2(45/67)	6.10	5.22	0.0003
	Secondary cluster 1	6(23/382)	3.6(22/615)	68.2(15/22)	2.32	10.54	0.0001						
	Secondary cluster 2	3.9(15/382)	1.5(9/615)	33.3(3/9)	1.27	12.33	0.0001						
	Secondary cluster 3	2.4(9/382)	0.2(1/615)	100(1/1)	1.06	8.72	0.0104						
	Secondary cluster 4	2.1(8/382)	0.2(1/615)	100(1/1)	0.85	9.67	0.0150						
	Secondary cluster 5	1.6(6/382)	0.2(1/615)	0	0.56	10.82	0.0464						
Total		29.6%(113/382)	9.3 (57/615)	49.1 (28/57)				32.9 (23/70)	4.8 (67/1398)	67.2 (45/67)			
Human malaria infection prevalence	Primary cluster	39.4(148/376)	29.8(78/261)	46.2(36/78)	124.31	1.82	0.0000	13.4(114/852)	5.8(5/86)	0.6(3/5)	53.98	2.28	0.0001
	Secondary cluster 1	15.7(59/376)	10.0 (26/261)	50(13/26)	18.73	2.40	0.0013	5.9(50/852	3.5(3/86)	100(3/3)	21.15	2.45	0.0003
	Secondary cluster 2							7.9(67/852)	3.5(3/86)	0	35.04	1.99	0.0003
	Secondary cluster 3							7.3(62/852)	4.7(4/86)	0	33.33	1.93	0.0010
	Secondary cluster 4							9.9(84/852)	2.3(2/86)	0	46.22	1.91	0.0015
	Secondary cluster 5							3.2(27/852)	1.2(1/86)	0	10.57	2.60	0.0030
Total		55.1(207/376)	39.8(104/261	47.1 (49/104)				47.4 (404/852)	20.9 (18/86)	33.3 (6/18)			

Hotspots of *An. gambiae* were identified using Poisson statistical model while those of infection prevalence were detected using binomial statistical model. RR stands for relative risk which refers to the standardized risk ratio of observed mean catches of mosquitoes or prevalent infections (indicated by 'n' in a third column) over the expected mean or prevalent infections (Mwakalinga et al., 2016).

Despite the major differences in spatial and temporal resolution of the entomological and parasitological data, it was nevertheless possible to examine their mutual association in survey locations where both types of surveys were conducted (Fig 4.1). Interestingly, vector propagation hazard (exposure to *An. gambiae*) and malaria infection risk were only not associated (see Fig. 5.2c) with each other (OR [95% CI] = 1.56 [0.89, 1.78], P = 0.056); although malaria was probably locally acquired within the city. The analysis in Annex 1b shows no significant difference in risk between travel within and outside the city was apparent (OR [95% CI] = 1.25 [0.98, 1.61], P = 0.071), and travel history, therefore, seems unlikely to be a major contributor to ongoing transmission in Dar es Salaam. Conversely, only a minority of co-surveyed locations (26.8% (11/42) in phase I and 37.5% (3/8) in phase II) where *An. gambiae* were detected had human infection prevalence of more than 10%.

5.1.4 Heterogeneous and sporadic patterns of malaria transmission hazard and risk are caused by differences in exposure to local risk factors (Theme 2)

Factors governing both spatial and epidemiological structures of hazard and risk of malaria transmission in this study are complex, multifaceted and most important, highly interacting. In this theme, the factors emerging are grouped into three categories, namely: 1) factors related to health sector (some increase hazard, others are preventive/resilient and curative factors); 2) social, inter-sectoral and governance factors (some are preventive or resilience while others increase vulnerabilities of city dwellers to malaria risk); and 3) natural environmental factors (these influence biological distribution of malaria vectors and they increase hazard and vulnerability to malaria risk in cases of low population resilience). The correlation plots relating these features and malaria transmission hazard and risk are presented in Fig.6 in Annex 1c.

Factors related to health sector

i) Vectors

Risk of malaria transmission was higher in certain locations with detectable *An. gambiae s.l.* than those without any *An. gambiae s.l.* caught over the study period. However, these vectors were only predictive [RR (95% CI) = 22.5 (20.7, 186.2), P = 0.004] of malaria risk in only a small portion (14%) of city dwellers residing in houses lacking window screening[4] (See Figs. 6c & d and Table 2 in Annex 1b) and those in unscreened houses whose human behaviour indicators (πi[5]) belong to the lowest tercile of indoor transmission exposure (See Fig. 8 and Table 2 in Annex 1b). The distribution of biting activity of *An. gambiae s.l.* across different times of the night remained consistent with those observed previously (Fillinger et al., 2008, Geissbuhler et al., 2007), except perhaps for a slight shift to later hours of the night, between mid-night and dawn (See Fig. 4c in Annex 1b).

ii) Bed net uses

Increased community-wide coverage of LLINs significantly reduced both malaria infection hazard (Table 5.2) and risk (Table 5.3). The effect of individual use of treated bed nets was also associated with decreased (as indicated by a negative step function in Annex 1c Fig. 4j) densities of *An. gambiae s.l.* In stark contrast, results from both GLLM (see Table 2 in Annex 1b) and BRT (see Table 5.3 and Fig. 4f in Annex 1c) models show positive association of malaria infections and individual use of bed nets rather than vice versa. More interestingly, this variable was among the most influential indicators of malaria risk (Table 5.3). This counter-intuitive association was however rationalized through focus group discussions and revealed that bed net usage behaviour was elicited by past experience of malaria infections rather than immediately active cases but presumably chronic infection at the time of the survey (Msellemu et al, unpublished). This

[4]Based on exploratory analysis as described in the main text, with glass, completely screened with no holes and completely screened with holes classified as adequately-screened and protective, whereas unscreened, torn or only partially screened were all classified as inadequately screened

[5]Πi is a measure of human behaviour which is calculated based on the time spent indoors and outdoors during mosquito peak hours (Msellemu et al, 2016).

observation was further confirmed by a serological test on >1000 serum samples which provided evidence of a history of previous exposure to malaria (detected via AMA antigen), suggesting that use of a bed net the previous night was positively associated with AMA-reactive serum [OR (95% CI) = 1.67 (1.04, 2.69), P = 0.034] but not with infection at the time of the survey [OR (95% CI) = 1.01 (0.81, 1.26), P = 0.901].

iii) Larvicide application (LA)

Larviciding did not have any detectable effect on either hazard [OR (95% CI) = 0.89 (0.72, 1.09), P=0.247] or risk [OR (95% CI) = 0.68 (0.38, 1.21), P=0.187] of malaria transmission when its activities were managed and financed by an external contractor (RTI) (See Annex 1b for detailed analysis). Its effect was intensely noticed in 2011 when the GoT, through the NMCP, took over all the management and financial responsibilities of larvicide application using a granular *Bti* product similar to what RTI used in 2010. During this period, malaria hazard was reduced by 69% and risk by 74%. Further reduction of malaria hazard (85% reduction) was observed in 2012, when the government started using a pre-diluted liquid suspension product of *Bti*. However, malaria risk did not reduce any further following continuation with the liquid *Bti* product (see Table 2, Figs. 3c & 5f in Annex 1b; and Table 3 in Annex 1d). Further results of BRT models indicate that, residing in wards under larviciding had collective effects on reducing hazard (See Fig. 4d in Annex 1c) as well as risk (See Fig. 5i in Annex 1c) of malaria transmission. For *An. gambiae*, larviciding was among the four most important predictors of malaria hazard in the city.

iv) Diagnostics and treatment

Multivariable adjusted findings of a BRT model (Table 5.3) showed that health seeking behaviour was positively associated with risk of malaria transmission [OR (95% CI) = 1.23 (1.07, 1.40), P = 0.003]. Presumably this was due to the fact that people seek health advice when they have fever or other symptoms of malaria infections, hence those who went to health facilities for diagnosis and treatment were more likely infected. However, almost 100% of infected individuals had

afebrile malaria and only a tiny portion [0.37% (4/1090)] of these chronic carriers had been treated. Nonetheless, a slightly increased rate of treatment of fevers with anti-malaria drugs in the final round of the cross - sectional surveys (see Annex 1b Table 2) was noted.

Table 5.2: Factors underlying hazard of malaria transmission and their relative contributions

Variable	Relative rate [95 % CI]	P	Relative importance (%)	Interpretation (variable indication)
Indicators of human and city resilience/vulnerability				
Residing in upgraded settlements (CIUP)	0.528 [0.421, 0.662]	< 0.001	11.2	Resilience, community†
Distance to rivers	2.287 [2.2673.634]	< 0.001	9.3	Hazard, household
Security of tenure (right of occupancy)	0.522 [0.397, 0.685]	< 0.001	8.6	Resilience, household†
Residing in larviciding wards	0.318 [0.157, 0.644]	0.001	8.4	Resilience, community†
Housing quality (highest quantiles)	0.188 [.129, 0.273]	< 0.001	7.6	Resilience, household†
Distance to main roads	0.329 [0.202, 0.536]	< 0.001	7.3	Resilience, household†
Distance to protected/hazard areas	3.258 [2.558, 4.148]	< 0.001	7.2	Hazard, household
Distance to water pipes	4.234 [3.364, 5.329]	< 0.001	6.9	Hazard, household
Residing in regularized informal settlements	0.709 [0.563, 0.894]	0.004	6.7	Resilience, community†
Bed net uses	0.714 [0.586, 0.870]	0.001	6.1	Resilience, household†
Distance to agricultural area	4.101 [2.701, 6.227]	< 0.001	5.2	Hazard, household
Distance to waste collection/dump sites	4.721 [3.856, 5.779]	< 0.001	5.1	Hazard, household
Distance to storm water drains	3.841 [2.571, 5.740]	< 0.001	5.0	Hazard, household
Distance to garages	1.628 [1.204, 2.205]	0.002	2.1	Hazard, household
House screening (highest quantiles)	0.659,[0.510, 0.852]	0.001	1.3	Resilience, household†
Distance to markets	1.735 [1.182, 2.548]	0.005	0.8	Hazard, household
Distance to open spaces	1.606 [1.228, 2.101]	0.001	0.6	Hazard, household
Distance to commercial areas	3.004 [2.228, 4.0510	0.007	0.4	Hazard, household
Distance to industrial areas*	1.297 [1.022, 1.645]	0.032	0.1	Hazard, household
Designated areas for informal sector activities	3.493 [2.176, 5.610]	< 0.001	0.1	Hazard, household
Natural landscapes				
Slope	2.076 [1.2-3.7]	0.013	60.1	Hazard, household
Topographic wetness index	7.111 [6.2-8.2]	0.010	27.2	Hazard, household
Topographic ruggedness index	2.051 [1.7-2.5	< 0.001	22.0	Hazard, household
Profile curvature	9.9 [8.3-11.5]	< 0.001	15.3	Hazard, household

Note: The parameters and relative influence of indicators of human and city resilience were estimated using multivariable Boosted Regression Trees (with Poisson function). For natural landscape predictors, multivariable Poisson - CAR was used to estimate the parameters. Resilience Status Index (RSI) for malaria hazard was thereafter computed for further analysis using factor analysis based on variables marked with †) and adjusted for multiple testing of variables using Bonferroni correlation.

Social, inter-sectoral and governance factors

i) Human and social

Travel history

History of travel within (sleeping elsewhere within the city) and outside (sleeping elsewhere outside the city) Dar es Salaam did not show any apparent difference in risk of malaria transmission (see Annex 1b Table 2). Further results of BRT models indicated no difference in hazard [OR (95% CI) = 1.08 (0.95, 1.22), P = 0.242] or infection risk [OR (95% CI) = 1.18 (0.91, 1.51), P = 0.208] between households residing within 500m radius of train/bus/taxi/lorry terminals and those living elsewhere, outside these catchments in the city (see Annex 1c). Travel history, therefore, seems unlikely to be a major contributor to ongoing exposure and persistent high and chronic prevalence in this study area, so most malaria cases were probably locally acquired within the city.

Human behaviour

Of all the contributing human behaviour variables used to estimate the proportion of exposure to *An. gambiae s.l.* bites that would occur indoors in the absence of a bed net or window screening (π_i), none were predictive of malaria risk in their own right (See Table 2 in Annex 1b). Neither the time at which residents went indoors [OR (95% CI) = 0.37 (0.11, 1.18), P = 0.413] and then went to bed in the evening [OR (95% CI) = 0.46 (0.15, 1.39), P = 0.583), or got out of bed [OR (95% CI) = 1.78 (0.87, 3.67), P = 0.198) and then left the house in the morning [OR (95% CI) = 1.05 (0.49, 2.25), P = 0.121] had any obvious association with malaria infection risk. However, examining the distribution of values reported for all these variables reveals remarkably subtle differences between these epidemiologically-relevant behavioural strata. Few participants stayed outdoors beyond 23.00 h or left the house before 05.00 h (see Fig. 8 in Annex 1b) had more malaria similar to those sleeping in unscreened houses. So, it seems that even a few extra hours of outdoor exposure in the evenings or mornings resulted in comparable malaria risk to spending all night in a house with no window screens.

ii) Housing and security of tenure

Housing

House screening (Msellemu et al., 2016) reduced risk of malaria transmission [OR (95% CI) = 0.74 (0.57, 0.97), P = 0.028 for partial window screening and OR (95% CI) = 22.5 (2.7, 186.2), P = 0.0039, for complete window screening). No effect of local vector density was observed [OR (95 % CI) = 0.79 (0.53, 1.16), P = 0.428] among the majority of participants (86%) staying in houses with window screens (See Fig. 6c & d in Annex 1b). Together with window screening, simple features such as closed eaves[6] and/or ceilings were also associated with reduced malaria risk [OR (95% CI) = 0.36 (0.14-0.89), P = 0.028] because these features limit the entry of mosquito vectors in the house. Notably, house screening only reduced risk of infections [OR (95% CI) = 0.71 (0.62, 0.82), P = <0.001]; and Fig. 5d in Annex 1c) if the evenings and mornings were spent indoors (among individuals belonging to highest and middle tercile of human behaviour). Both hazard and risk were significantly lower among individuals whose houses were built with higher quality building materials (See Tables 5.2 & 5.3; and Figs. 4d & 5b in Annex 1c). Better-quality housing appeared to be amongst the most influential factors underlying the variations on malaria hazard (see Table 5.2) and infections risk (see Table 5.3) probably because higher quality building is an indication of higher social economic status (SES) and people with higher SES are able to purchase protection measures against mosquito bites and treatment of malaria infections.

Security of tenure

Unexpectedly, having a right of occupancy (security of tenure) was a leading protective factor against risk (See Table 5.3) and the third against hazard (See Table 5.2) of malaria transmission in Dar es Salaam. Security of tenure had a very strong negative association with both malaria hazard (See Fig. 4c in Annex 1c) and risk (See Fig. 5a in Annex 1c). More remarkably, 93% of perfectly screened houses (windows, airbrick gaps and roof) and 96% of houses built with high quality building materials had title deeds. This implies that security of tenure motivated residents to build

[6]the gap between the top of the wall and the over-hanging roof

standard houses which in other ways lessens human contact with mosquito vectors and hence reduced risk of malaria transmission.

iii) Informal settlements licensing and infrastructure upgrading programmes

Informal settlements licensing programme (under the Ministry of Lands through MKURABITA) did not show any detectable effect on both hazard [OR (95% CI) = 0.82 (0.18, 3.64), P = 0.794] and risk [OR (95% CI) = 0.76 (0.28, 2.05), P = 0.583] of malaria transmission. This observation was similar to informal wards which were not covered by any urban planning program. Dramatic reduction of malaria transmission hazard and risk (See Tables 5.2 & 5.3; and Figs. 4a & i; 5c & h in Annex 1c) was noted in the wards which were under housing and infrastructure upgrading (under CIUP financed by the GoT/World Bank) as well as informal settlements regularization programmes (under supervision of local governments but financed by local communities themselves). In both cases the two programmes were among the most influential factors for malaria hazard (Table 5.2) and risk (Table 5.3). This is presumably because apart from legalizing the plots/houses by offering long term (33, 66 and 99 years) title deeds, the programmes involved systematic spatial organization and surveying of all settlements under the project areas. The CIUP for instance, went further to financing and constructing roads, drainage networks, sanitation, sewerage and garbage collection facilities. The settlement plans under these programmes designated and allocated plots for all other urban amenities such as health facilities. Although these projects were intended for upgrading of informal settlements, their impact went further to reduction of breeding habitats within the project areas through constructed drains. They also contributed to improved accessibility to effective diagnostic and treatment services through bringing social services including health closer to individuals, among other elements of the programmes to empower the urban poor.

iv) Thresholds and catchments of urban infrastructure and services

Surprisingly, living at shorter distance (within 500m) from major roads and drainage (Annex 1c Fig. 2a) was positively associated with malaria hazard (Table 5.2) and risk (Table 5.3). Closer proximity to roads have been reported elsewhere (Kazembe, 2007) to enhance access to diagnostic and treatment facilities. Both of these factors were among the most influential determinants of hazard (Table 5.2) and only distance to roads for transmission risk (Table 5.3). Nevertheless, shorter distances to these roads and drainage had no detectable effects [OR (95% CI) = 2.17 (0.49, 9.61), P = 0.309] for hazard and for risk [OR (95% CI) = 1.75 (0.67, 4.59), P = 0.254] among the households who were living in upgraded settlements and those with security of tenure (see Annex 1c). In addition to roads and drainage, hazard and risk of malaria transmission was also high among households residing within shorter distances (up to 500m) from main water pipes (See Fig. 2a in Annex 1c) and waste collection/dump sites (Table 5.2 & 5.3) particularly in informal settlements. Access to informal structure however is a reflection of lower SES which influence affordability to protection and treatment measures. Living within 500m radius from any health facility (dispensary, hospital, health centre and medical shops) reduced malaria risk but did not have any detectable effect [OR (95% CI) = 0.43 (0.02, 10.95), P= 0.613] on hazard of transmission.

v) Urban land uses

Similar to findings from elsewhere (Klinkenberg et al., 2003, Klinkenberg et al., 2008, Leon, 2008), diversity of urban land use types is strongly associated with the presence of multiple distinct aquatic larval habitat types of *An. gambiae*, diverse proliferation of adult mosquitoes and malaria infections at different spatial scales. In Dar es Salaam, foci (Carter et al., 2000) of malaria transmission occurred within a 500m radius from agricultural, open spaces, commercial and industrial uses (See Fig. 2 in Annex 1c). This finding suggests that households residing within these catchments experienced higher hazard and risk of malaria transmission (Table 5.2 & 5.3) than those living elsewhere in the city, unless the resilience of these households is high enough to reduce risk of exposure. Moreover, densities of *An. gambiae* correlated with shorter distances to

garages, markets and areas designated for petty trading (Table 5.2) while malaria risk was lower in households living closer to institutional land uses (Table 5.3).

Table 5.3: Factors underlying risk of malaria transmission and their relative contributions

Variable	Odds ratio [95 % CI]	P	Relative importance (%)	Interpretation (variable indication, effect level)
Indicators of human and city resilience/vulnerability				
Security of tenure (right of occupancy)	0.247 [0.105, 0.581]	0.001	32.5	Resilience, household†
Housing quality (highest quantiles)	0.068 [0.010, 0.467]	0.006	11.2	Resilience, household†
Residing in upgraded settlements (CIUP)	0.175 [0.073, 0.419]	< 0.001	8.1	Resilience, community†
House screening (highest quantiles)	0.436 [0.228, 0.831]	0.012	6.6	Resilience, household†
Distance to main roads	5.242 [1.471, 18.678]	0.011	6.3	Vulnerability, household
Bed net uses	3.360 [1.316, 8.576]	0.011	6.1	Resilience, household†
Human behaviour (highest/middle tercile)	0.329 [0.132, 0.819]	0.017	6.0	Resilience, household†
Residing in regularized informal settlements	0.086 [0.015, 0.475]	0.005	5.9	Resilience, community†
Residing in larviciding wards	0.352 [0.136, 0.915]	0.032	5.9	Resilience, community†
Distance to water pipes	2.162 [1.017, 4.598]	0.042	3.5	Vulnerability, household
Distance to agricultural area	3.916[1.714, 8.945]	0.001	1.8	Vulnerability, household
Distance to protected/hazard areas	3.026 [1.541, 5.940]	0.001	1.4	Vulnerability, household
Distance to rivers	2.256 [1.081, 4.705]	0.030	1.4	Vulnerability, household
Distance to health facilities	0.135 [0.019, 0.936]	0.043	1.3	Resilience, household†
Distance to storm water drains	0.818 [0.674, 0.995]	0.044	1.1	Resilience, household†
Distance to waste collection/dump sites	2.576 [1.454, 4.562]	0.001	0.5	Vulnerability, household
Distance to institutional areas*	0.323 [0.123, 0.848]	0.022	0.4	Resilience, household†
Natural landscapes				
Elevation	0.98 [0.97-0.99]	0.008	60.4	Vulnerability, household
Planform curvature	1.66 [1.64-1.67][b]	0.002	26.2	Vulnerability, household

Note: The parameters and relative influence of indicators of human and city resilience were estimated using multivariable Boosted Regression trees (with Bernoulli function). For natural landscape predictors, multivariable Binomial - CAR was used to estimate the parameters. Resilience Status Index (RSI) for malaria risk was thereafter computed for subsequent analyses using factor analysis based on variables marked with †) and adjusted for multiple testing of variables using Bonferroni correlation.

Natural environmental factors

i) Rivers and hazard (protected) areas

As expected living within 500m from rivers and protected areas (flood plains, swamps and marshy areas) strongly increased hazard (see Table 5.2 and Annex 1c Figs. 4b & g) and risk (Table 5.3) of malaria transmission. Although these factors were significant for risk of transmission, they did not rank among the most influential determinants of malaria risk in the city (Table 5.2).

ii) Local topography and hydrology

As expected, hazard and risk of malaria infection were associated with topographic predictors of aquatic habitat suitability, such as lower elevation for increased malaria risk along with higher topographic wetness index and concave profile curvature for malaria hazard (Tables 5.2 & 5.3; and Annex 1d Table 3). Surprisingly, these outcomes were also associated with very well drained locations on the periphery of valleys and depressions with high TWI (See in Fig. 1e in Annex 1d), such as edges of elevated areas with convex planform curvature (See Fig. 1c in Annex 1d) for infection risk; steep slopes (See Fig. 1b in Annex 1d) and the edges of steep slopes with high terrain ruggedness (See Fig. 1f in Annex 1d) for infection hazard. Interestingly, these counter-intuitive indicators of elevated hazard and risk define the fringes of human settlements (See Fig. 2 d & e in Annex 1d), where residents are disproportionately exposed to mosquitoes dispersing from wet areas where they emerge and oviposit.

5.1.5 Geographic resolutions of malaria hazard and risk predictors are important for optimum design of integrated spatial targeted intervention programmes (Theme 3)

The justification for spatially integrated targeted interventions programmes in cities depends on the level of geographic aggregation of malaria risk. In this study, predictors of malaria risk and hazard based on the existing entomological and epidemiological survey methods respectively, predicted only a third (33%) of the hazard and about half (47%) of the risk (Fig.5.3a & d). Essentially, this level of aggregation was not justifiable enough to provide a basis for spatially targeted interventions because the majority of locations with higher mosquito vector densities (77%) as well as infected humans (53%) would not be covered, and hence elimination would not be achieved.

Noteworthy, 88% of detectable *An. gambiae* (See Table 3 in Annex 1d) was predicted when topographic predictors with increased spatial resolution than that of entomological surveys was used (Fig. 5.3 b & e). However, even with increased spatial resolution of predictors, only 55% (See Table 3 in Annex 1d) of malaria risk could be predicted using topography. These findings suggest that with increased spatial resolution of solely environmental predictors, densities of *An. gambiae* could be spatially targeted through integrated approach but may not adequately define human risk to guide interventions to target human infections. The explanation for this finding could be due to the fact that malaria risk is driven by diverse factors as described in Theme 2, and local resilience plays a big role for heterogeneities in malaria risk as described in Theme 1, hence topography alone cannot adequately predict human risk. The impact of scale and resolution of these and other predictors need to be clearly assessed for appropriate design of any selective spatially targeted intervention programmes, to enable of optimum impact upon malaria control or elimination in cities.

5.1.6 Mapping of malaria risk areas in cities needs to be informed by the local levels of population resilience (Theme 4)

This theme highlights the importance of local population resilience when mapping risk of malaria transmission. Inclusion of RSI in the CAR models improved performance in hazard prediction (R^2 = 0.88) when only topography was included and improved by a further 3% (R^2 = 0.91) when RSI was accounted for (See Table 5 in Annex 1c). Correspondingly, very high performance of the CAR risk model was found when hazard and resilience were included as predictors together with topography (R^2 was only 0.55 when topography alone was used and it improved by a further 31%, R^2 = 0.86, when RSI and hazard were added). More interestingly, in the risk model RSI accounted for more than half of the contribution of model performance, while topography and hazard accounted for less than a third of the contribution (See Table 5 in Annex 1c).

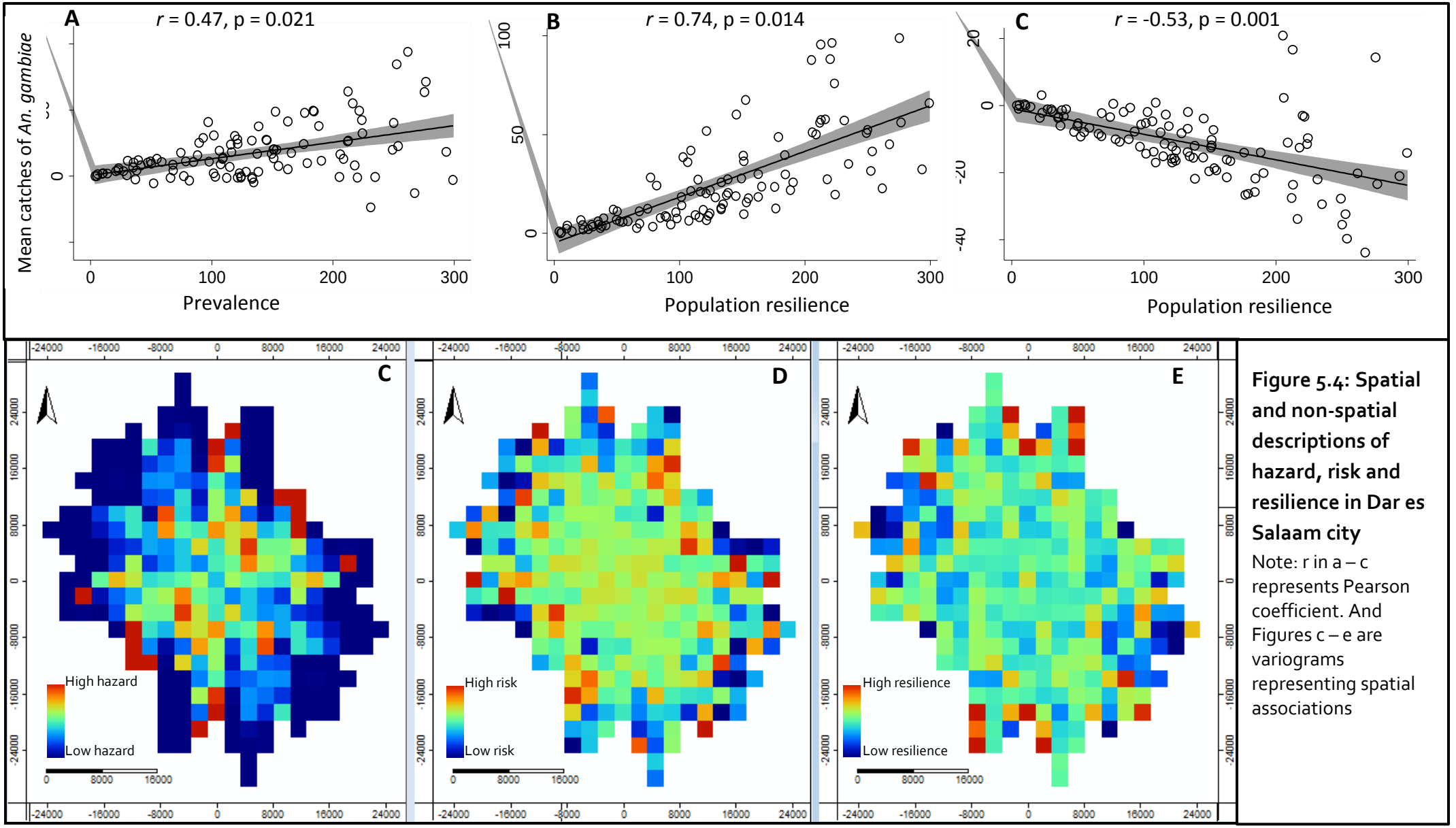


Figure 5.4: Spatial and non-spatial descriptions of hazard, risk and resilience in Dar es Salaam city

Note: r in a – c represents Pearson coefficient. And Figures c – e are variograms representing spatial associations

The differences in population resilience could be the reason for why malaria risk is highly sporadic and focalized in Dar es Salaam (Mwakalinga et al., 2016). Simple correlation plots in Figure 5.4a shows a positive correlation (r = 0.47, p = 0.021) between transmission hazard and risk while resilience of human population is negatively correlated (r = 0.53, p = 0.001) to risk of malaria transmission (Fig. 5.4c), indicating that local residents with higher resilience has less malaria infections. Nonetheless, the positive correlation (r = 0.74, p = 0.014) between densities of *An. gambiae* and human resilience in Fig. 5.4b was contradictory meaning that higher densities of malaria vectors were amongst inhabitants whose resilience was higher. However, this suggests that city dwellers with higher transmission exposure (due to higher densities of *An. gambiae*) are forced to use more protection against mosquito bites, such as repellents, bed nets and house screening, and not vice versa. The explanation for this relationship is similar to that of bed nets and malaria infections presented in Theme 2.

Spatially, the variograms in Figure 5.4c - e show that locations with higher malaria risk tend to coincide with those whose population resilience is lower regardless of higher densities of mosquito vectors in place (hazard). For instance, the central parts of the city depicted in Fig 5.4e suggest low to moderate resilience. Consequently, this pattern had implications on the pattern of transmission hazard in the city [Fig 5.4c (very high hazard in locations with very low resilience)]. Similarly, risk in Fig 5.4d appeared low to moderate regardless of the higher densities of *An. gambiae* (confirming the spatial inconsistency of risk and hazard described in theme 1 and the influence of local resilience in these inconsistencies).

Chapter Six: Discussion

Hotspots of malaria transmission hazard and risk have been mapped and characterised using different geographical analysis tools, predictors and spatial resolutions, which can be used to inform geographic targeting of interventions against local malaria transmission at fine spatial scales (Mwakalinga et al., 2016, Bejon et al., 2014, Bousema et al., 2016, Robert et al., 2003, Hay et al., 2005, Bejon et al., 2010). This study provides detailed analysis of potential factors associated with the occurrence and distribution of these hotspots such as use and coverage of interventions, vector exposure, population resilience and topography that would be useful in informing tailored design of packages for spatially targeted interventions in specific hotspots or loci of transmission. Urban planning factors which were considered in this study (among those increasing human resilience), such as housing upgrades and settlement regularization programmes, could provide dramatic preventive effects of both transmission hazard and risk. This study has shown how some aspects of urban planning, such as land tenure, improvement of housing structure, sustained maintenance of drainage systems by providing improved solid waste collection systems and disposal services (which were all provided in upgrading programmes) in Dar es Salaam wards under community upgrading initiatives (Fig. 4.1), provide effective complementary interventions for local transmission.

The results presented in this thesis further suggest that adequate impact of geographically targeted interventions in Dar es Salaam city would be achieved when exclusive topographic predictors (Fig. 5.3b and c) or topographic predictors accounting for hazard of exposure and population resilience (Fig. 5.3f) are used to derive highest hazard and risk of malaria transmission respectively. Inadequate impact would be expected if targeted interventions programmes are designed based on the spatial clustering patterns of mapped hazard and risk using the existing spatial resolution of entomological and epidemiological survey methods (Bejon et al., 2014, Bousema et al., 2016, Mwakalinga et al., 2016). This observation confirms that the municipal

councils and the MoHSW through the NMCP were correct to choose blanket coverage of larvicide application and LLINs rather than targeted coverage of interventions (Msellemu et al., 2016). This is based on their knowledge of local geography and the known highly unpredictable larval ecology of the main local vectors, namely members of the *Anopheles gambiae* complex (Sattler et al., 2005, Fillinger et al., 2008). Notably, regardless of this wider coverage of health sector's interventions, hazard and risk of malaria would not sufficiently decrease to unstable, eliminable levels, entailing the need for improving existing tools or establishing new supplementary interventions (Killeen, 2014, Owens, 2015) to accelerate clearance of local vectors and the infectious reservoir in the city in order to achieve the ambitious goal of malaria elimination (WHO, 2014, WHO, 2015b, WHO, 2016a).

The following section discusses key findings of the study in relation to the literature. The discussion is organized according to the five themes of the thesis: (1) patterns of malaria hazard and risk vary epidemiologically and spatially at different scales; (2) underlying factors for heterogeneous and sporadic patterns of malaria hazard and risk; (3) importance of spatial resolution of predictors in depicting areas for geographically targeted interventions; (4) the need to assess local population resilience when mapping malaria risk areas and (5) adoption of interdisciplinary spatially selective targeted interventions for malaria control/elimination in the urban development agenda. The last theme provides the key contributions of the thesis, together with a conceptual model for transdisciplinary, geographically targeted interventions for malaria control and elimination that would be applicable in the urban development agenda of typical African cities. Finally, the last part of this chapter discusses limitations of the study.

6.1 Patterns of malaria hazard and risk are highly heterogeneous and unpredictable at higher geographic resolutions (Theme 1)

Epidemiological patterns of malaria risk

Key findings

- Men were more at risk of malaria than women, but no difference in risk was observed across age groups
- Majority of infected individuals had afebrile, long term chronic and untreated malaria infections
- Malaria infections were probably locally acquired within the city and not imported

Implications for targeted interventions

- Design of strategic interventions sensitive to all genders and age groups
- Urgent need for active mass screening and treatment (MSAT) and mass drug administration (MDA) are required to clear chronic infections among the population
- Interventions should be geographically targeted within the city unless otherwise confirmed through research and routine surveillance to monitor indicators of urban malaria including travel patterns

Future studies

Extensive research on the travel behaviour in relation to malaria is still required to understand the malaria transmission in Dar es Salaam city

The finding that there was no significant variation in malaria risk across the age groups is different from previous studies (Geissbuhler et al., 2007, Geissbühler et al., 2009, Castro et al., 2004, Fillinger et al., 2008) conducted in Dar es Salaam before scale up of larviciding and community wide coverage of LLINs was fully achieved in 2011 (Msellemu et al., 2016). These results imply that control measures should now focus on all age groups and not be restricted to children less than five years old (Mboera et al., 2008). Consequently, apart from focusing most malaria interventions to pregnant women (Eze et al., 2014), additional intervention programmes designed specifically for the male population are required (WHO and RBM, 2015, Diiro et al., 2016). The persistence of chronic infections (88% of positive cases were afebrile and only 0.4% of these were treated with anti-malarials) was surprising because of decreasing *An. gambiae* numbers (Msellemu et al., 2016), scale up of larvicide application, universal coverage of LLINs and community-wide uptake of window screening in place (NMCP, 2014, Msellemu et al., 2016). However, these infections were presumably acquired before this study was conducted as confirmed by serological markers, hence

these preventive intervention measures could not avert pre-existing infections, despite wide coverage. Complementary population-wide campaigns and parasitic measures such as MSAT and MDA (Chaki et al, unpublished) would be required in the identified locations with high risk to actively treat all local residents who are already infected (Bousema et al., 2014, WHO, 2014, WHO, 2015b, Msellemu et al., 2016). However, reacting to the unpredictable occurrence of unstable hotspots of largely asymptomatic malaria in such settings (Nourein et al., 2011, Bejon et al., 2010) will require further scale up of routine surveillance for both entomological and epidemiological indicators at an increased spatial resolution. Dynamic mapping of high resolution hotspots of persistent transmission needs to be done in order to enable well-timed (Bejon et al., 2014) spatially selective targeted interventions that would accelerate clearance of local transmission in the city (Snow, 1855, Bejon et al., 2010).

Spatial patterns of malaria hazard and risk

Key findings

- Only a third of hazard and one fifth of risk were accounted for in spatially aggregated hotspots while the remaining majorities were unpredictable and haphazardly distributed across the city outside of the hotspots when entomological and epidemiological surveys were used as predictors of hazard and risk respectively.
- 85% of all *An. gambiae* caught were trapped in only 15% of sampling locations (clearly mapped along the edges and tops of steep slopes) with highest predicted hazard when topographic indicators were solely used.
- 81% of elevated infection prevalence was mapped in only 19% of sampling locations in the lowlands with highest predicted risk when topography, population resilience and hazard were used as predictors.
- Spatial inconsistencies occurred between the patterns of highest hazard and highest risk, even though transmission was confirmed to be acquired locally within the city.

Implications for targeted interventions and research

- Selective geographic targeting of interventions based directly on clustering patterns within the current entomological and epidemiological survey methods is clearly insufficient to achieve adequate coverage against either hazard or risk of infections.
- The patterns derived by exclusive topography predictors would be sufficient for geographic targeting of highest hazard while highest risk areas would be sufficiently targeted based on the patterns predicted using topography, population resilience and hazard.
- Further research is required to clearly understand factors behind spatial inconsistencies of local malaria hazard and infection risk in the city

Further research

Further research to understand factors behind the counterintuitive relationship between patterns of local vector proliferation and local malaria transmission risk is required.

The results for this theme suggest feasibility of spatially selective targeted interventions on hotspots of malaria transmission hazard and risk only if sufficient levels of aggregation to satisfy the "80–20 rule" (Woolhouse et al., 1997) would have been achieved. This rule was preferred in this study because it is a robust justification for targeting interventions to high-risk groups in public health (Alan Dever, 1997, Woolhouse et al., 1997). Hotspots mapped using the current entomological and epidemiological survey methods represent useful initial priority areas for spatially targeting new or improved interventions against malaria hazard and risk respectively. Nevertheless, they may have limited impact because they encompass only a relatively small fraction of detectable *An. gambiae* and elevated infection prevalence in spatially aggregated clusters (hotspots) while the majority were haphazardly distributed across the city outside of these hotspots in small loci of hazard and risk of malaria transmission (Mwakalinga et al., 2016). Of course, targeting only the spatially aggregated hotspots of detectable hazard or elevated risk

of malaria could slightly reduce malaria transmission in Dar es Salaam. Besides, in order to achieve the ambitious goal of malaria elimination (WHO, 2016a, WHO, 2007, WHO, 2014), or even the vectors of malaria transmission (WHO, 2013), would also require targeting of all the additional loci because this is where local transmission persists (Mwakalinga et al., 2016). However, spatial patterns predicted using topography (hazard) as explicitly covariates and topography accounting for hazard and population resilience (risk) provide sufficient spatial aggregation for both hazard and risk. In this case, 85% of all malaria vectors caught were trapped in the 15% of surveyed locations with highest predicted hazard (Annex 1d). Similarly, only 19% of the surveyed locations with highest predicted risk would need to be targeted to clear 81% of all detected infections (Annex 1c). The hotspots mapped here could provide a suitable basis for spatially selective targeted interventions against local malaria transmission hazard and risk in the city.

In congruence with previous studies elsewhere (Gillies and De Meillon, 1968, Holsein, 1954) and also in Dar es Salaam (Vanek et al., 2006, Sattler et al., 2005, Fillinger and Lindsay, 2011), spatial patterns of malaria hazard (regardless of the predictors used) were consistent with the known breeding and oviposition habitats of *An. gambiae* in urban settings (Staedke et al., 2003). Hence in order to control or eliminate transmission hazard in this city, larval source management or other complementary vector control measures (WHO, 2015b, Killeen, 2014) will be required. However, these measures need to selectively target not only the obvious larger hotspots of high *An. gambiae* density but also in sporadic, smaller scattered pockets of high malaria vector abundance in the loci of transmission hazard (Mwakalinga et al., 2016).

Importantly, hotspots as well as loci of hazard and risk of malaria transmission in Dar es Salaam were loosely associated with each other and spatially inconsistent (Mwakalinga et al., 2016) despite the fact that malaria was locally acquired (Msellemu et al., 2016). These results coincide with those of a study conducted in a coastal district in north-eastern Tanzania (Bousema et al., 2010) which showed higher malaria risk in locations with lower densities of mosquito vectors. As

demonstrated in theme 3 and supported by previous studies elsewhere (Bizimana et al., 2015, Dongus et al., 2010, Konradsen et al., 2003, Ogoma et al., 2012, Ogoma et al., 2010), these inconsistencies are argued to be the result of differences in local human resilience such as bed net use, access to diagnostic and treatment facilities, house screening, access to land tenure and human behaviour. Yet, research to understand factors behind this surprising relationship between patterns of local vector proliferation and local malaria transmission risk is required.

6.2 Heterogeneous and sporadic patterns of malaria transmission hazard and risk are caused by differences in exposure to local risk factors (Theme 2)

Factors for malaria transmission hazard and risk

Key findings

- Hazard and risk of malaria were lower in parts of the city with wider community coverage of health sector's interventions such as larviciding and LLINs; but unexpectedly personal use of nets was associated with increased malaria risk.
- Local vector densities of *An. gambiae* increased risk of exposure only to residents living in *poor-houses*[7] with insecurity of tenure and those whose evenings and mornings were spent outdoors
- Urban planning programmes (licensing/upgrading) and city fabrications (land uses and infrastructure) strongly influenced the patterns of hazard and risk of malaria transmission at both local and community levels
- As expected indicators of wetness were predictive of both hazard and risk; surprisingly indicators of dryness, specifically steep slopes and the tops of steep slopes were also positively associated with high hazard and high risk of malaria transmission

Implications for designs of strategic interventions and further research

- To achieve elimination there is a need to further scale up health sector's interventions at all levels
- Need for strategic housing programmes as supplementary interventions against malaria transmission
- Further research is required to understand interactions between health sectors and urban planning in order to inform designs of tailored inter-sectoral interventions against malaria
- Indicators of wetness map out to the bottoms of valleys where no one lives, hence they can be ideal targets for larval source management but are not suitable for parasitic measures; while those of dryness map out to the fringes of those valleys, where mosquitoes first encounter and can attack humans after emerging or ovipositing in the valley bottoms, hence barrier interventions to reduce adult densities, such as nocturnal space spraying, can be suitably targeted to these landscape features

Further research

Further research is required to disentangle the intricate set of urban planning programmes that can be used to complement health sector's interventions in urban areas

[7] Unscreened, and poorly built (in terms of building material) houses

The observation that individual use of bed nets increases malaria risk was surprising (Table 5.3) (Msellemu et al., 2016). This counter-intuitive association can partially be explained by human behavioural responses to experience of malaria episodes, as shown by results of a qualitative study (Msellemu et al., Unpublished) conducted within the sampling frame of this study. As noted earlier, the striking impact of community-wide uptake of LLINs on reducing both hazard and risk strongly indicates that individual-level protection of net use did occur but had possibly been disguised by this contradicting causality (Msellemu et al., 2016).

The finding that higher local vector densities do not dramatically increase risk of malaria transmission among the households whose windows, eaves and ceilings were completely screened and built with better materials, was in line with other studies done elsewhere (Dongus et al., 2010, Ogoma et al., 2009b, Ogoma et al., 2010, Bizimana et al., 2015, Kienberger and Hagenlocher, 2014). However, in this study, improved housing could not solely provide protection against mosquito exposure among individuals who spent a long time outdoors at night for example staying outdoors beyond 23.00 h. Spending the whole night in unscreened houses results in comparable risk to spending time outdoors during hours of exposure (peak hours) in the evenings and mornings (Msellemu et al., 2016).

Interestingly, apart from factors with direct effect on transmission risk, security of tenure, also observed in Ouagadougou city (Baragatti et al., 2009), strongly reduced both hazard and risk of malaria among households with land titles. A previous study in informal settlements in Dar es Salaam confirmed that land ownership and access to right of occupancy, among other factors, motivated the residents to invest in building more higher quality housing (Kyessi, 2010). The strong protective effect that good housing can provide in reducing risk of malaria transmission has been demonstrated in Dar es Salaam (See Annex 1c) (Msellemu et al., 2016) and elsewhere (Mosha et al., 2014, Atieli et al., 2009, Yé et al., 2006, Kirby et al., 2009). These key aspects of

urban planning should be exploited further to provide complementary health sector interventions in identified hotspots and loci of transmission.

To achieve elimination of local malaria transmission in this city, there is need a to reduce or eliminate the hazard represented by local vector propagation, probably with new or improved vector population abatement measures. There is also a need to empower the most vulnerable inhabitants through different human resilience interventions including bed nets (Augustincic et al., 2015), house screening, (Tusting et al., 2015) spatial repellents (Achee et al., 2012, Govella et al., 2015) or good governance programmes to promote equity in access to land and security of tenure (which indirectly is a social economic status indicator) in the city (Baragatti et al., 2009). These interventions would nevertheless require transdisciplinary and multi-stakeholder approaches, involvement and investment to succeed (WHO, 1995, WHO, 2005, WHO, 2010d, WHO, 2010b, WHO, 2016a, WHO and UN-Habitat, 2010).

Furthermore, the effect of land use diversities in increasing densities of *An. gambiae s.l.* (transmission hazard) and risk of malaria infection has been demonstrated. In line with findings from Ghana (Klinkenberg et al., 2008), Cote d'Ivoire (Matthys et al., 2006) and Dar es Salaam previously (Dongus et al., 2009, Castro et al., 2004), households living closer (<500m) to agricultural areas are more vulnerable to mosquito exposure and risk to acquire new malaria infections. Other land uses such as open spaces, industrial and commercial areas are also positively associated with hazard and risk presumably since most of them are underutilized or undeveloped (UN-Habitat and UNEP, 2005, Kyessi and Mwakalinga, 2009). As a result, they have been informally used as dumping sites for domestic waste and discarded vehicle tyres for example, which both could provide potential artificial breeding habitats for *An. gambiae s.l.* as reported elsewhere (Kling et al., 2007, Sattler et al., 2005, De Silva and Marshall, 2012).

Another expected but interesting observation on land use was the strong relationship between transmission hazard and proximity (< 500m) to large natural habitats such as rivers, swamps and protected/hazard areas. Because of severe water pollution, which has been frequently reported to take place in these habitats (Bryceson, 1982, Ak'habuhaya and Lodenius, 1988, Mbuligwe and Kaseva, 2005, URT, 2013a) due to industrial, agriculture and domestic untreated effluents. This observation confirms findings from previous studies, which show behavioural change of *An. gambiae* to cope with trends of urbanization in cities by breeding and ovipositing in polluted water (Geissbühler et al., 2009, Robert et al., 2003, Keiser et al., 2004, Castro et al., 2004, Dongus et al., 2009, Sattler et al., 2005). To protect households living closer to land use types which increase human vulnerability to malaria, scaling up of larval source management (WHO, 2013) within large natural habitats and also small/large artificial habitats will be required, which would need to be identified in agricultural, commercial, industrial and open spaces. Supplementary preventive measures to interrupt human-vector interaction (Killeen, 2014, WHO, 2014, Hemingway et al., 2016, Yé et al., 2006, Karunamoorthi, 2011) such as house screening and treated bed nets (which also interrupt the lifespan of adult vectors that are still susceptible to the insecticides used to treat bed nets) will be required to target households living within the flight range of adult mosquitoes from high risk land use areas types (Carter et al., 2000).

Furthermore, living within shorter distance to either roads or drainage has been associated with increased hazard and risk of local malaria transmission in different studies in endemic cities in Africa (De Silva and Marshall, 2012, Castro et al., 2010, Alimi et al., 2016, Pinchoff et al., 2015). For instance, in Kenya the positive association with roads specifically, was argued to be indicative of travel and imported malaria (Omukunda et al., 2012). Conversely, this was not the case in Dar es Salaam city where malaria was transmitted locally as shown by history of travel (Msellemu et al., 2016) and lack of any detectable effect of nearness to bus/lorry and train terminals with neither hazard nor risk of malaria (see Annex 1c). In Dar es Salaam, this is presumably due to insecurity of tenure, simply because most of the residents living closer to the main roads have illegally built

their houses within road reserves and are expecting unpaid resettlements at any time when the government decides to use these reserves for road expansion or installation of other line infrastructure such as water and electricity (Magembe-Mushi and Lupala, 2015, Swai, 2016). Apart from roads, pools of water in blocked drains due to haphazard waste disposal have been described to be among productive larval habitats for *An. gambiae s.l.* by previous studies in Dar es Salaam (Dongus et al., 2009, Sattler et al., 2005, Castro et al., 2010). Identification of mosquito habitats within the drainage network in the city would be required to enable geographic targeting of larval source management to eliminate malaria vectors (WHO, 2013). However, elimination of transmission risk would need interventions with curative drugs to treat all infected individuals and most importantly to increase local population resilience such as increased access to land, bed net use and house screening with affordable cost of materials suitable for this vulnerable group. Additionally, urban planning measures to enable sustained maintenance of drainage systems by providing improved solid waste collection systems and disposal services would be required (Kasala, 2013, Tumpale et al., 2014, Sakijege et al., 2012).

The distribution of malaria hazard and risk was further associated with local topography. In accordance with other study findings from Kenya (Atieli et al., 2011, Minakawa et al., 2005, Minakawa et al., 1999, Munga et al., 2006) and Tanzania (Balls et al., 2004, Mboera et al., 2002, Mboera et al., 2008) topographic indicators of water accumulation (primarily in the main river valleys, drainage lines and local depressions of the city landscape) were expectedly associated with increased hazard of malaria transmission (Dongus et al., 2007). However, in contrast to these studies, local topographic indicators of dryness (convex curvature, slopes and tops of steep slopes) were also associated with increased hazard of malaria in the city. This surprising observation indicates that apart from the primary role of topography to predict aquatic habitats of immature *An. gambiae s.l.*, the variable can also map the interfaces between human and mosquito habitats where malaria vectors first encounter human hosts after emerging or ovipositing (see Annex 1d). Geographic zones for barrier interventions to kill dispersing mosquitoes (such as residual surface

spraying (Perich et al., 1993), or alternatives such as vapour-phase insecticide emanators, or even nocturnal space spraying (Killeen, 2014)) can be defined within these interfaces. Apart from protecting the local residents within these interfaces, barrier interventions shield the rest of the population in other parts of the city further away from these wet valleys (Perich et al., 1993, Charlwood et al., 1998) and maximize community benefits to all residents through mass suppression of vector populations.

Similarly, topographic indicators of abundant larval habitats, and the steep banks of these valleys, were also predictive of human infection prevalence but had far less predictive power (See Table 5.2). The weaker predictive value may well be explained by variations in human resilience factors, such as window screening, bed net use and human behaviour (Msellemu et al., 2016) all of which could weaken the dependence of infection risk on exposure to hazard (Mwakalinga et al., Submitted). For example, human infection prevalence is known to be highly dependent upon local vector density near households lacking window screens but essentially unaffected by it (distance to breeding habitat) in well-screened houses (Msellemu et al., 2016). Furthermore, many of the human infections detected in these surveys appear to have long-standing chronic infections (Msellemu et al., 2016) that might not necessarily be directly related to ongoing transmission exposure. In addition, to a little contrast that can be seen in maps of model-predicted malaria infection risk (See Fig. 3b in Annex 1d), higher risk is depicted in the wet valley bottoms where very few people actually live (See Figs 3h and 4b in Annex 1d). Such topographic indicators of likely infection burden in valleys are therefore far less useful for targeting interventions to increase human resilience against exposure hazard, than they are for targeting vector population suppression against adult vectors.

Finally, this study affirmed the typology of settlements (planned, unplanned, serviced or not serviced) where individuals live as important factors influencing both hazard and risk of malaria transmission. For instance in line with the findings in Ouagadougou (Baragatti et al., 2009), living

in informal settlements was strongly associated with increased hazard and risk of malaria transmission. However, it was engrossing to find that modification of these informal settlements through urban planning measures such as infrastructure upgrading programmes reduces both hazard and risk of malaria transmission. In Dar es Salaam, a slight modification of the built environments in 22 informal sub-wards and introduction of basic services such as roads and drainage, designation of plots for health facilities, improving sanitation and waste disposal facilities; all provided through upgrading programmes reduced the risk of malaria. Apart from improving the functional and aesthetic environment in informal settlements, urban planning could be used to mitigate adverse health outcomes in cities (UN-Habitat, 2010a). But only if it is strategically used as long term and effective supplementary-preventive measures for larviciding, LLINs and IRS (WHO, 2010b, WHO, 2014, WHO and UN-Habitat, 2010) which could also work in informal settlements to control malaria hazard and risk. Although this study provides a conceptual snapshot on how urban planning and health sectors could bring their efforts together in tackling local malaria transmission (Fig. 6.1), further research is required to disentangle the intricate set of urban planning programmes that can be used to complement health sector's interventions. These kinds of programmatic researches will accelerate elimination of malaria hazard and risk in Dar es Salaam and other endemic cities in Sub Saharan Africa.

6.3 Geographic resolutions of malaria hazard and risk predictors are important for optimum design of integrated spatial targeted intervention programmes (Theme 3)

Spatial resolution of predictors

Key findings

- Increased spatial resolution of hotspot predictors of hazard and risk in Figs. 5.3b, c, e & f had much greater contrast and specificity than those in Figs. 5.3 a & d to allow far more selective identification of high priority locations for targeting supplementary interventions.
  - Entomological and epidemiological surveys (low resolution); the hotspots identified were not sufficient for targeted interventions
  - Solely topographic indicators (high resolution); the hotspots identified were particularly sufficient for targeting highest hazards but not risk
  - Topographic indicators with human modification factors (high resolution); the hotspots identified were sufficient for targeting both hazard and risk

Implications for selective targeted interventions and policy

- Selective spatial targeting needs to be adopted only when predictors with high resolution are used and their clustering patterns provide enough impact on suppressing hazard and risk if spatially targeted.
- The policy of intervention will need to be developed based on the scale in which hotspots are presented

The findings in this theme present different levels of spatial resolution (Fig. 5.3) to derive hotspots of malaria transmission that could provide useful guidance for geographically targeted interventions. The results show how decisions on choosing geographically targeted interventions relies upon the impact an intervention would provide to the majority of most vulnerable populations while covering the minority of locations with highest predicted risk. Regardless, only a few of the existing studies in malaria risk mapping have highlighted this concern (Hagenlocher et al., 2014, Rincón-Romero and Londoño, 2009, Sturrock et al., 2014, Alegana et al., 2016, Morris et al., 2013, Sturrock et al., 2016). These studies show how the spatial scales used in deriving malaria hotspots particularly in the urban areas where malaria is highly heterogeneous, could influence the decisions and policy for effective targeted interventions.

In this study for instance, different spatial resolutions of hotspot predictors provided different clustering patterns of both hazard and risk of transmission (Fig. 5.3), hence each would provide

different expected impacts from targeted interventions. This observation implies that any setup of targeted interventions for malaria would depend on the resolution employed in mapping and characterising the hotspots of transmission. As reported elsewhere (Hagenlocher et al., 2014, Bousema et al., 2012a, Mwakalinga et al., 2016) targeted interventions need to be focused at a scale where hotspots occur e.g. in cities this tend to be finer scale. Specifically, for Dar es Salaam city this requires very high resolution to achieve high impact, similar to that of topography when used to predict hazard and the one with population resilience when predicting risk. As reported above, transmission hazard and risk tend to be haphazardly scattered all over the city in very small loci and sporadic when spatial resolution of the predictors was increased. As a result, they could not be sufficiently detected as hotspots when lower resolution predictors were used (Mwakalinga et al., 2016, Bejon et al., 2014). Higher contrast of hazard in Figs. 5.3a & c would allow setup of larval source management (to kill immature mosquitoes) to be geographically targeted in the river valleys but also inform/target other vector control measures for adult vectors along the edges of river valleys using a barrier intervention approach. Despite the low contrast in Fig. 5.3d, malaria infection risk was identified in the wet valley bottoms where very few people actually live (Mwakalinga et al., Submitted) and therefore far less useful for targeting interventions to increase human resilience against exposure hazard. However, higher contrast of malaria risk in Fig. 5.3f enables geographic targeting of parasitic measures and other complementary preventive measures against malaria risk. Public health interventions such as spatial repellents and treated bed nets to control risk of malaria within the most vulnerable populations identified within the lowlands, lacking capacity to anticipate mosquito bites and non-resilient enough to cope with malaria infections (Hagenlocher and Castro, 2015, Bizimana et al., 2016) are required. Additional urban planning programmes to provide suitable complementary measures within these areas include modification of house structures with affordable and acceptable materials, improving waste management services and provision of drainage network. Notably, to achieve elimination of hazard and risk with geographically targeted interventions in this city based on the clustering patterns within entomological and epidemiological survey methods; routine, spatially

comprehensive, longitudinal surveillance systems, with adequate sensitivity and spatial resolution to enable detection of small and scattered loci of elevated transmission would be required.

6.4 Mapping of malaria risk areas in cities needs to be informed by the local levels of population resilience (Theme 4)

Population resilience

Key findings

- Malaria risk did not affect all people equally neither is the propagation of local vector densities; the most vulnerable were those with lowest resilience
- Accounting for human resilience in the model enabled capturing local heterogeneities of malaria risk within a single largely homogeneous landscape feature (lowlands)
- Inclusion of human resilience as predictor variable improved the performance of the malaria risk model by 31%

Implications for selective targeted interventions and policy

- The findings may be useful for improving surveillance programmes for urban malaria
- They are salient for designing intervention programmes which need to prioritize and address specific level vulnerability to reduce the population susceptibility while increasing their resilience to risk of malaria transmission
- Further research is required to decompose malaria risk into its actual aspects namely hazard and vulnerability (susceptibility + resilience).

Future research

Further programmatic research and high resolution routine surveillance systems to understand the association between hazard, resilience and risk in the urban context is required in order to enable suitable and more informed design of interventions that can enable elimination of malaria in Dar es Salaam city.

Risk of malaria transmission in this study was not equally shared by all residents in the city, and therefore targeted interventions would be required to protect the most vulnerable groups (González et al., 2016, WHO, 2016a, Bates et al., 2004). The detailed analyses conducted in this study confirm that high malaria risk at local scales appears to be composed by both hazard and resilience as shown elsewhere (Hagenlocher and Castro, 2015, Hagenlocher et al., 2016, Bizimana et al., 2016, Bizimana et al., 2015). Human resilience in this study attenuates the dependence of infection risk on exposure hazard (See Annex 1c). As described above, human infection prevalence is highly dependent upon local vector density among households lacking window screens but essentially unaffected by risk of exposure in well-screened houses (See Annex 1c and (Msellemu

et al., 2016)). It is, therefore, likely that interventions targeted to hotspots of malaria transmission will need to not only eliminate transmission hazard represented by proliferation of local vectors, but also need to vigorously treat all local residents who are already infected with malaria (WHO, 2014, WHO, 2015b). Additionally, it will be important to improve the resilience of the most vulnerable residents such as those in the informal settlements, in the lowlands and edges of river valleys (See Annex 1c and (Mwakalinga et al., Submitted)) by providing them with protective measures such as bed nets, window screening or spatial repellents.

In this study, topographic indicators – apart from their resolution, which enabled convincing prediction of adult *An. gambiae s.l.* – could far less predict malaria risk accurately. Densities of *An. gambiae s.l.* were clearly identified on the edges and tops of steep slopes with sufficient contrast to guide selective spatial targeting of interventions to kill dispersing adult as well as immature mosquitoes in valleys. On the contrary, malaria risk was predicted with lower contrast in the lowlands with almost uniform levels of risk across the landscape (Mwakalinga et al., Submitted), making it far less useful for targeting interventions to increase human resilience against exposure hazard. Inclusion of population resilience in the models improved the contrast of malaria risk dramatically (see Annex 1c).

Even though risk of malaria was consistently mapped within the lowlands, unlike the former which was explicitly based on topography, the latter (which included human resilience) clearly distinguished locations with higher vulnerability (81 % of prevalence in only 19% of location with predicted highest risk) against those with lower vulnerability (Fig. 5.3 f). This would, therefore, provide useful guidance for spatial targeting of measures to reduce exposure hazard such as bed nets, mosquito-proofed housing or repellents, as well as testing and treatment or mass administration of curative drugs to tackle chronic morbidity burden (Chen et al., 2016) and to clear infectious reservoirs (Bousema et al., 2014), than they are for targeting vector population suppression interventions against adult vectors. More importantly further programmatic research

and high resolution routine surveillance systems to understand the association between hazard, resilience and risk in the urban context is required in order to enable suitable and more informed design of interventions that can enable elimination of malaria in Dar es Salaam city.

6.5 Study limitations

The sampling frames used in this study (entomological and epidemiological surveys) were incomparable due to differences in geographic and temporal resolution. Likewise, the differences in sampling frames across the two study phases made it impossible to compare and track temporal/spatial trends within the same outcome variables. However, efforts were made to make comparisons in a few sampling locations which were co-surveyed (156 TCUs with both entomological and epidemiological data). In addition to that, urban planning data on land uses and infrastructure were not collected parallel to entomological and epidemiological surveys. However, for consistency, it was ensured that the maps used to derive data on infrastructure and land uses were produced in the same years when the surveys were conducted.

It is possible that better predictive models of malaria infection risk could be developed using richer sets of independent indicator variables, ranging from environmental, biological, social and economic factors (Leonardo et al., 2005, Donnelly et al., 1997). The spatial models presented in this study relied mostly on geographic parameters, coverage and utilization of intervention programmes, without including factors such as socio - economic status (SES), which has been reported as a potential resilience factor. However, proxy indicators of SES such as quality of building materials and education levels were used. Inclusion of human behaviour, land use and infrastructure allowed having more diversified factors for malaria risk (Bates et al., 2004, Castro et al., 2004).

Most importantly, this study was purely observational in nature; no effort was made to experimentally control routine, programmatic delivery of any malaria control measure. Observational studies are inevitably prone to biases (Wilson et al., 2015). However, observational studies also have the advantage of being highly relevant to policy and practice if they are conducted by an independent evaluation team and the interventions themselves are delivered under representative conditions of routine programmatic practice (Habicht et al., 1999). All entomological and epidemiological surveys were conducted by an independently funded research team at the Ifakara Health Institute, completely independent of the UMCP staff based at either the municipal councils of Dar es Salaam or at the NMCP of the MoHSW (Chaki et al., 2014).

6.6 Key contributions

To our knowledge this is the first time in Dar es Salaam city, malaria transmission hazard and risk have been mapped extensively at high-resolution with associated predictors. It remains the only example in which such comprehensive, high-resolution coverage of an entire region has been achieved. More importantly, the study mapped risk of local malaria transmission by taking into account human resilience. The existing studies which have also accounted for resilience in depicting risk have been conducted at large scale (Hagenlocher and Castro, 2015, Bizimana et al., 2016) which may not be useful for local malaria elimination. While the majority of studies have mapped malaria risk by considering either entomological or epidemiological indicators alone (Noor et al., 2009, Guerra et al., 2006, Sturrock et al., 2014) without taking resilience into consideration.

For the first time, this study reveals that topography, apart from its conventional use in mapping aquatic habitats for mosquito larvae, can also be used to map the borders of human and mosquito habitats where barrier interventions can be spatially targeted to control malaria risk. Importantly, selectively targeted interventions based on topography not only protect residents within local

areas close to rivers, lowlands or marshes but also shield the rest of the population living far away from these wetter topographic areas in the uplands.

Apart from that, the study has indicated how critical urban planning programmes can provide complementary intervention measures that would accelerate achievement of malaria elimination goals in cities when integrated with preventive and curative public health measures.

Finally, the study contributes to the framework (Fig. 6.1) that interdisciplinary intervention programmes could be adapted to spatially target key urban planning and public health measures against hazard and risk of malaria transmission.

6.7 Control/elimination of malaria risk in cities of SSA needs integrated approach to be adapted in the urban development agenda (Theme 5)

This study has shown that selective targeted interventions in Dar es Salaam may be possible and is encouraged in situations where identified areas for targeting provide enough basis for adequate reduction of either malaria transmission hazard, risk or both. Moreover, it is likely that the driving factors for malaria risk are highly inter-sectorally dependent, hence they require inter-sectoral intervention approaches to have a greater impact. Yet, one big challenge remains regarding how interventions from different sectors can be integrated and operationalized to accelerate malaria control and elimination. Based on the results and literature reviewed for this study, a revised conceptual framework is provided (Fig. 6.1) to highlight some basics for inter-disciplinary intervention approaches that can be used in Dar es Salaam and other cities to limit urban malaria risk.

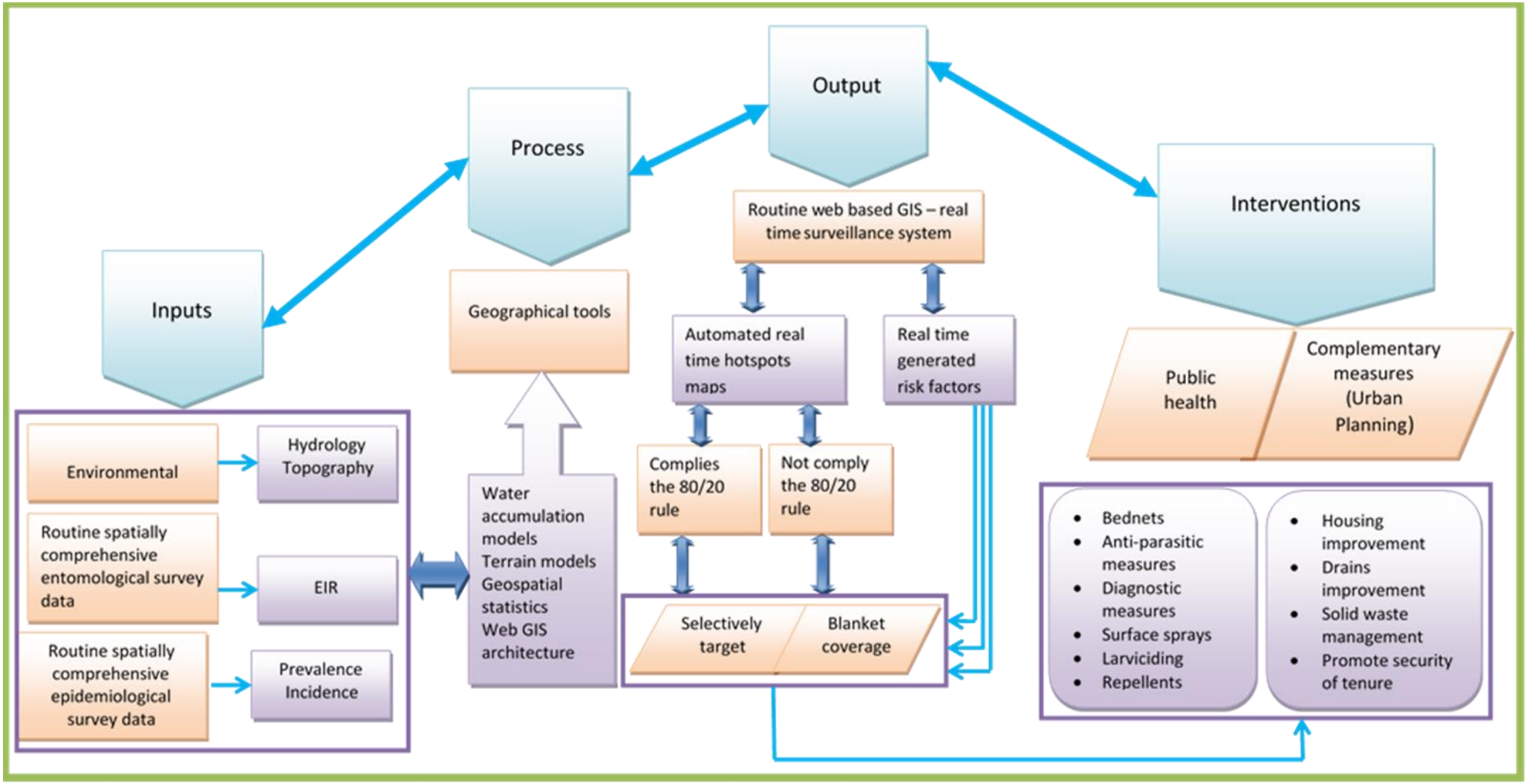


Figure 6.1: The model for integrated approach to enable spatial targeting of interventions to control residual urban malaria transmission

Chapter Seven: Conclusions

The spatial distribution of malaria transmission in Dar es Salaam, a typical African city, is highly heterogeneous, geographically predictable and spatially targetable. This is critical in Dar es Salaam city because persistence of chronic, unresponsive infection is evident despite universal coverage of effective health sector interventions like rapid diagnostic tests, artemisinin-based combination therapy, LLINs, IRS and larviciding. This signifies the need for new or improved strategies for controlling malaria vectors and parasites in order to achieve elimination, delivered to locations where residual transmission persists. Freely available and scalable geographic indicators of malaria distribution provide effective tools for identifying these locations at high spatial resolution possible to equip sufficient geographic targeting of interventions than what the obvious expensive, large-scale entomological and epidemiological survey methods in the city could provide. However, to achieve acceptable levels of impact, geographical indicators should account for population resilience in predicting locations with residual human infections.

Geographic tools such as remote sensing can be valuable for mapping hazard and risk of malaria in places with limited data (particularly in rural areas). Process-based hydrological models can not only map aquatic areas for immature mosquitoes in the urban settings but also map areas where mosquitoes encounter human hosts for blood meals immediately after emerging or ovipositing. By estimating the actual spatial distribution of where malaria residual transmission occurs in Dar es Salaam, this study reveals sporadic and enigmatic distribution of hazard and risk across the city, being driven by a set of complex and interacting factors. The patterns of local transmission hazard and risk disentangled at high spatial resolution provide adequate guidance for decisions towards different approaches of geographically targeted interventions against malaria transmission.

Spatial clustering and geostatistical modelling techniques were employed to identify and characterize the spatial distribution of malaria transmission at different levels of spatial resolution. The findings indicate that spatial hotspots of hazard and risk of malaria in the city are small, scattered and haphazardly distributed across the city. These observations suggest that high resolution predictors which are capable of capturing the pattern of residual transmission in the city, are needed to enable adequate and effective geographically targeted interventions. Topographic predictors of malaria vectors clearly restrict highest transmission hazard within the steep slopes and the tops of steep slopes on the edges of valleys where humans are disproportionately exposed to host seeking vectors dispersing from the valleys. These findings provide useful information on where exactly interventions to kill mosquitoes at immature stages with regular microbial larvicides as well as dispersing adult mosquitoes with surface spraying can be geographically targeted.

Notably, geographically targeted interventions are not sufficient in attacking densities of *An. gambiae* when mean spatial resolution entomological surveys were used to map hotspots of malaria transmission hazard. Here, the results showed inadequate detectable *An. gambiae* that were accounted within the hotspots while the majority were undetectable and scattered all over the city outside of the hotspots. In such a scenario, effective interventions will be those designed to tackle vectors in both identifiable hotspots and the remaining locations with detectable *An. gambiae* (meaning all locations where *An. gambiae* have been caught)

Accounting for population resilience in high resolution topographic predictors maps out high risk areas in the lowlands. These areas should thus be targeted with local bed net distributions, campaigns on preventive human behaviour, MSAT and MDA to clear the infection reservoirs among infected humans. Key urban planning interventions to be selectively targeted within these landscapes include

house screening with affordable and acceptable materials together with sustained drainage systems to drain stagnant water, which not only increases population resilience but also provides effective complementary preventive measures against malaria risk.

The need for spatially targeted interventions is high in parts of the city where residents are most vulnerable. These include residents living in informal settlements, households living within close proximity to roads and lacking security of tenure, communities within low-lying areas with lower human resilience and those along the peripheries of valleys. Essential interventions include enforcement of urban development control and policy in effective management of non-residential land uses such as agriculture, open spaces and commercial zones, upgrading of informal settlements similar to CIUP through improvement of housing structures, provision of infrastructures, improving access to land and promotion of security of tenure. However, these interventions are only preventive. For the case of Dar es Salaam, where many individuals are infected already, policies to guide appropriate and highly effective health sector's interventions to detect and clear infections are of great importance. Other highly effective policies are those promoting preventive human behaviour like encouraging people to spend their evening and morning hours inside screened houses and to sleep under treated bed nets and use spatial repellents when they are outside houses during peak hours. All these transdisciplinary efforts would ultimately increase the resilience of the population in the city and their capacity to better anticipate, cope with, and recover from possible infection.

Geographical targeting of interventions specifically for Dar es Salaam will need to not only tackle vectors and human infections among the most vulnerable populations and locations, but will also need to promote human resilience. Malaria risk should not be considered separately from hazard and human resilience. Inconsistencies of malaria hazard and risk in Dar es Salaam, apart from being due to long term chronic infections were driven by local population resilience. There is therefore need to

further assess malaria risk in its component at local scales to include economic factors as part of population resilience.

Geographical tools and associated spatial statistical methods have considerable potential for mapping malaria risk at high spatial resolution, particularly in areas where barrier interventions to target adult mosquito vectors can be geographically targeted. These maps are particularly helpful in identifying high hazard and risk areas to guide efficient allocation of limited resources and set up of additional (further scale up of existing) or new complementary interventions to further reduce local burden of malaria in Dar es Salaam. Results of hazard and risk factors can contribute to policies to address health inequalities and improve access to health services by enabling rational design of urban development plans to include intervention and mitigation packages designed specifically for informal settlements and in other areas where residents are most vulnerable.

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Annexures

Annexure Ia: Original paper I

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Spatially aggregated clusters and scattered smaller loci of elevated malaria vector density and human infection prevalence in urban Dar es Salaam, Tanzania

Victoria M. Mwakalinga[1,2,3*], Benn K. D. Sartorius[4], Yeromin P. Mlacha[3], Daniel F. Msellemu[3], Alex J. Limwagu[3], Zawadi D. Mageni[3], John M. Paliga[3], Nicodem J. Govella[3], Maureen Coetzee[5], Gerry F. Killeen[3,6] and Stefan Dongus[3,6,7,8]

Abstract

Background: Malaria transmission, primarily mediated by *Anopheles gambiae*, persists in Dar es Salaam (DSM) despite high coverage with bed nets, mosquito-proofed housing and larviciding. New or improved vector control strategies are required to eliminate malaria from DSM, but these will only succeed if they are delivered to the minority of locations where residual transmission actually persists. Hotspots of spatially clustered locations with elevated malaria infection prevalence or vector densities were, therefore, mapped across the city in an attempt to provide a basis for targeting supplementary interventions.

Methods: Two phases of a city-wide population-weighted random sample of cross-sectional household surveys of malaria infections were complemented by two matching phases of geographically overlapping, high-resolution, longitudinal vector density surveys; spanning 2010–2013. Spatial autocorrelations were explored using Moran's I and hotspots were detected using flexible spatial scan statistics.

Results: Seven hotspots of spatially clustered elevated vector density and eight of malaria infection prevalence were detected over both phases. Only a third of vectors were collected in hotspots in phase 1 (30 %) and phase 2 (33 %). Malaria prevalence hotspots accounted for only half of malaria infections detected in phase 1 (55 %) and phase 2 (47 %). Three quarters (76 % in phase 1 and 74 % in phase 2) of survey locations with detectable vector populations were outside of hotspots. Similarly, more than half of locations with higher infection prevalence (>10 %) occurred outside of hotspots (51 % in phase 1 and 54 % in phase 2). Vector proliferation hazard (exposure to *An. gambiae*) and malaria infection risk were only very loosely associated with each other (Odds ratio (OR) [95 % Confidence Interval (CI)] = 1.56 [0.89, 1.78], P = 0.52)).

Conclusion: Many small, scattered loci of local malaria transmission were haphazardly scattered across the city, so interventions targeting only currently identifiable spatially aggregated hotspots will have limited impact. Routine, spatially comprehensive, longitudinal entomological and parasitological surveillance systems, with sufficient sensitivity and spatial resolution to detect these scattered loci, are required to eliminate transmission from this typical African city. Intervention packages targeted to both loci and hotspots of transmission will need to suppress local vector proliferation, treat infected residents and provide vulnerable residents with supplementary protective measures against exposure.

*Correspondence: vmwakalinga@ihi.or.tz
[3] Environmental Health and Ecological Sciences Thematic Group, Ifakara Health Institute, Coordination Office, Kiko Avenue, Mikocheni, P.O. Box 78373, Dar es Salaam, United Republic of Tanzania
Full list of author information is available at the end of the article

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Keywords: Hotspots, Spatial clustering, Mapping, *Plasmodium falciparum*, Malaria, *Anopheles gambiae*, Mosquito

Background

In the city of Dar es Salaam, considerable progress has recently been made to ensure high coverage of standard interventions like rapid diagnostic tests (RDTs), artemisinin-based combination therapy (ACT), long-lasting insecticidal nets (LLINs) and other supplementary vector control measures, such as mosquito-proofed housing and regular application of microbial larvicides [1–5]. Nevertheless, stable residual malaria transmission persists (Msellemu et al. pers.comm. and [6]), so new or improved strategies for controlling malaria vectors [7–9] and parasites [8, 10] will be required to achieve elimination. However, even the most effective intervention measures can only be effective if they are delivered to locations where residual transmission persists [11]. Here the study describes how hotspots of spatially clustered locations with elevated malaria infection prevalence and vector densities were mapped across the city of Dar es Salaam, in an attempt to provide a basis for targeting supplementary interventions.

Methods

Study area

The study was conducted in the urban and peri-urban area of Dar es Salaam city. The city is Tanzania's commercial and economic capital located on the shores of the Indian Ocean (Fig. 1). Dar es Salaam has 4.4 million inhabitants [12] and is amongst the world's ten fastest growing cities [13] with an annual growth rate of 5.6 % [12]. However this growth is unplanned, resulting in about 70 % of residents living in informal settlements [14]. At the time of this study, Dar es Salaam had a mean human infection prevalence of approximately 10 %, arising from modest levels of transmission intensity, mediated by remarkably low vector densities, predominantly *Anopheles gambiae* sensu stricto [5, 15]. Administratively, the city comprises three municipalities namely Ilala, Kinondoni and Temeke and it is divided into 90 wards [12] (Fig. 1). The study area comprised 71 out of these 90 wards, covering 498.2 km^2 of the city with approximately 3.6 million residents. Of the study wards, 15 were in phase I and all 71 wards were in phase II. The initial 15 were central wards to which larviciding was originally implemented under the Urban Malaria Control Programme (UMCP) [16] and comprehensively scaled up by the preceding operational research programme in new 56 wards [17]. In total the study covered the whole of urban and peri-urban area of Dar es Salaam city (Fig. 1). Wards are further divided into smaller neighbourhood units called *mitaa* (a Kiswahili word for *street*, written in the singular form as *mtaa*) [18]. Each *mtaa* is subdivided into ten cell units (TCUs), comprising clusters of approximately 10–20 houses, although some TCUs contain a much larger number of houses [17].

With the exception of a break in activities while the programme was restructured between October and December 2010, *Bacillus thuringiensis* var. *israelensis* (*Bti*) was applied over the full course of the study, to the same 15 wards previously assessed during the operational research phase of the UMCP between 2004 and 2008, and this preventative service was scaled up to cover an additional 56 adjacent wards in January 2012 (Fig. 2). A coated granule formulation was used up to July 2011 (VectoBac®, Valent BioSciences Corporation), following which a pre-diluted aqueous suspension formulation (Bactivec®, Labiofam®) was used instead.

Data collection

This study is a secondary analysis of two distinct phases of parasitological and entomological survey data (Figs. 1, 2), the collection of which is described in detail elsewhere (Msellemu et al. pers. commun). Household cross sectional and longitudinal surveys were subsequently used to collect parasitological and entomological data respectively. While two different sampling frames were used for surveying adult mosquitoes and the infection prevalence, the latter was systematically overlaid upon the former in the first phase and the former was overlaid on the latter in the second phase of surveys because mosquito surveillance sites were reduced when fund for continuously monitoring mosquito vector densities ran out [19]. Infection with blood-stage *Plasmodium falciparum* parasites was tested for using RDTs (MAL-Pf®, ICT Diagnostics, Cape Town, South Africa).

The total number of households in each TCU within the mapped study area [17] was enumerated by census between January 2008 and May 2010. While awaiting completion of this enumeration of all the households in the study area, for selection of a population-weighted representative sample, a first phase of purposively-sampled household surveys were conducted. This first round of household parasitological surveys was carried out from March 2010 to September 2010; consisting of 291 housing compounds (median = 7 households), 156 of which were subjected to routine collection of adult mosquitoes (Msellemu et al. pers. commun), so that this novel system [19] for monitoring vector densities at high spatial resolution could be evaluated in terms of its epidemiological predictive power.

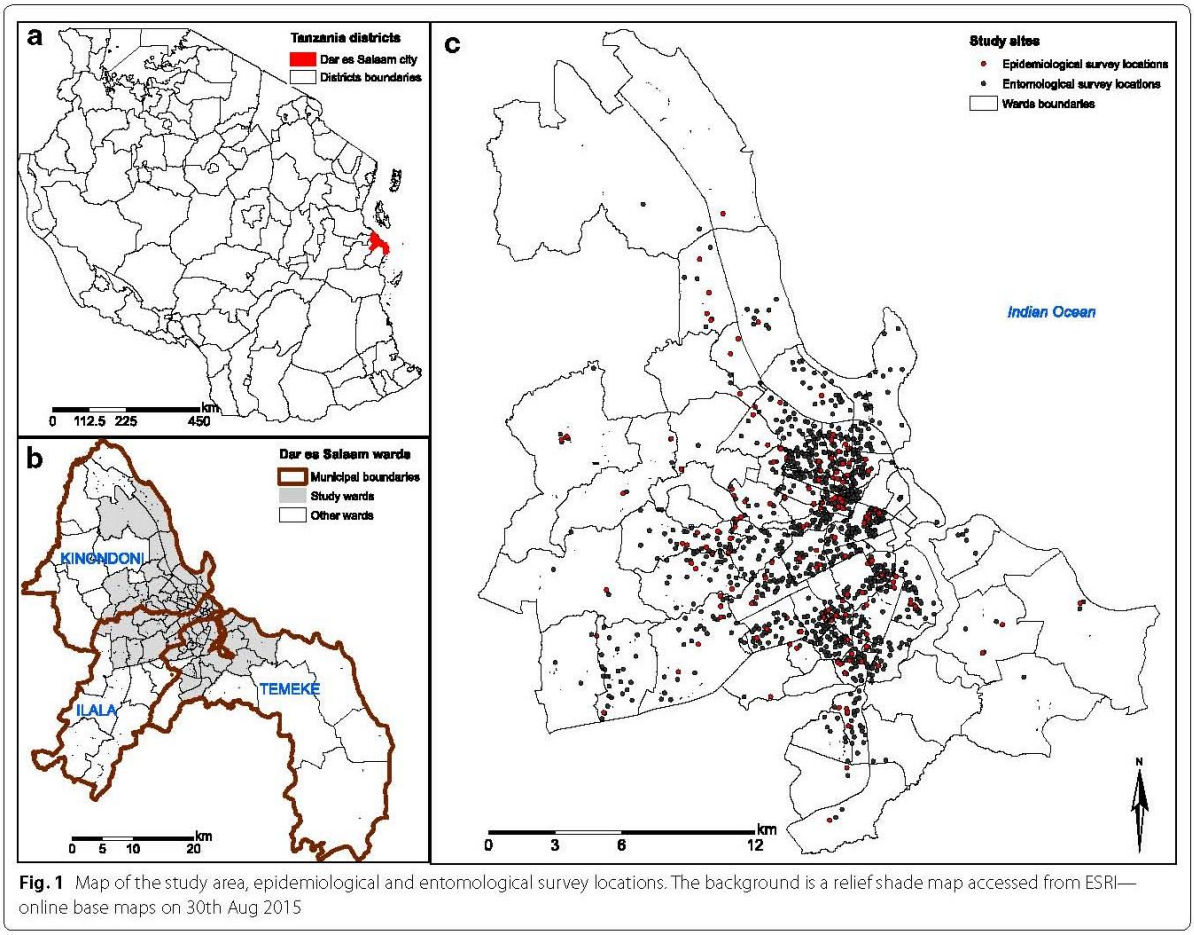


Fig. 1 Map of the study area, epidemiological and entomological survey locations. The background is a relief shade map accessed from ESRI—online base maps on 30th Aug 2015

Following completion of the household enumeration, a second phase of household surveys was begun, which sampled much smaller numbers of larger population clusters, selected randomly as index TCUs. The TCUs were weighted according to their population size and selected using a weighted sampling strategy (Msellemu et al. pers. commun). Between Oct 2010 and May 2012, a second phase of surveys was completed which encompassed a total of 86 clusters centred on index TCUs selected at random in proportion to their estimated population size (median = 392 households). Where the TCU had less than 20 consenting household heads, a neighbouring TCU was chosen at random from where the remaining number of households required to complete the sampling cluster were selected and recruited in exactly the same way. In this phase 30 of the 86 index TCUs were subjected to routine collection of adult mosquitoes. Selection of these co-surveyed areas relied upon willingness of the index TCU leaders to participate in the follow up study to monitor mosquito vector densities and also in TCUs where the environment were supportive for placement of ITT [20].

Anopheles mosquitoes were correspondingly collected in two different phases. The first phase lasted from March to October 2010 and consisted of 615 different sampling locations. These locations were set up within the previously studied 15 wards of the Dar es Salaam UMCP [17], which was designed to establish and evaluate systems for routine larvicide application at programmatic scales [2, 5, 16]. Following a break in funding, the second phase of entomological surveys was initiated in May 2011 and sustained through January 2013, with far greater scale-up to span a total of 1398 locations across the entire study area. The collections of adult mosquitoes were routinely conducted at each location on an approximately monthly basis, using Ifakara Tent Traps (ITT) [20] applied through a community-based system as described in detail elsewhere [19].

Throughout the study period, only modest levels of physiological resistance to pyrethroids, and behavioural

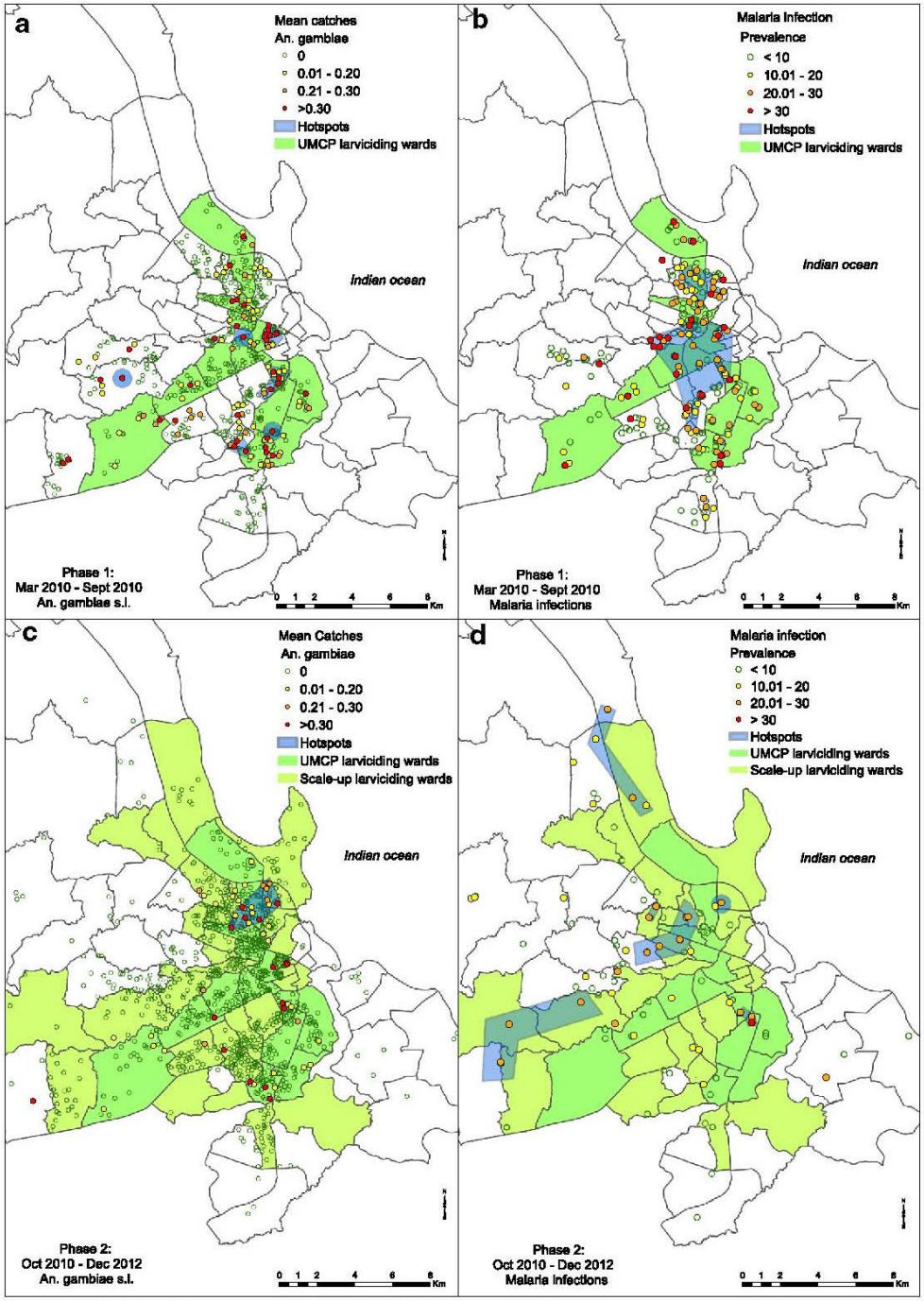


Fig. 2 Densities of *Anopheles gambiae* vector mosquitoes and malaria infection prevalence amongst humans

resistance or resilience [15] to indoor vector control measures by biting at dawn or dusk, were observed for the *An. gambiae* complex (Chaki et al. pers.comm.). Laboratory analysis of morphologically-identified specimens of *An. gambiae* sensu lato, by polymerase chain reaction [21], confirmed that this complex was

predominantly composed of the nominate sibling species *An. gambiae s.s.* [86 % (328/382)], with the small remainder being *Anopheles arabiensis* [10 % (40/382)]. *Anopheles gambiae s.s.* is the most anthropophagic and efficient sibling species from this complex, and very few *Anopheles funestus* [3 % (4/382)] or other *Anopheles* [1 % (10/382)] were caught. Vector density was therefore expressed in terms of total numbers of *An. gambiae* complex specimens caught per trap per night per TCU for subsequent analyses, and considered representative of this dominant, nominate sibling species.

The spatial references for both mosquitoes and cross-sectional sampling locations were obtained using hand-held global positioning systems (GPS) at an accuracy of 5 m. These were the basis for calculating the centroids of the sampling clusters. The TCU boundaries were mapped using a participatory mapping approach [17, 18].

Statistical analysis

Statistical analyses and data processing were performed using STATA (version 10; Statacorp). ArcGIS software (version 10; ESRI) was used to create spatial adjacency matrices, produce maps and perform exploratory spatial data analyses. FleXScan (version 3.1.2), an open source software [22] was used for the detection of spatial clusters (hotspots) in malaria infection prevalence and mosquito vector densities.

The global Moran's I statistics (MI) [23] were employed to test for any prevailing spatial autocorrelations in mosquito vector densities and malaria infection prevalence. Spatial autocorrelation occurs when there is clustering (+ve Z-score) or dispersion (−ve Z-score) and this is significant at $p \leq 0.05$ [23]. A p value > 0.05 suggests a homogeneous spatial pattern (random).

Local spatial clustering (hotspots) in mosquito densities and malaria infection prevalence were detected using the flexible spatial scan statistic (FleXScan) developed by Tango and Takahashi [24]. Flexible scan statistics create both circular and irregular shaped clusters. Since Dar es Salaam is a low transmission area, and these typical settings tend to restrict high transmission to patchier spatial scales, it was preferred to use flexible scan clustering method to enable detection of actual noncircular clusters even at highly focalized spatial scales [25]. This method identifies clusters based on a spatial weight matrix in which the detected cluster is allowed to be flexible in shape while at the same time confined within relatively small neighbourhoods of each sampling unit [25]. In developing the matrix file, spatial relationships were conceptualized based on Delaunay Triangulation, with Euclidian distance. Similar to Kulldorff's spatial scan statistics [26], the method uses a circular moving and systematically scanning window, in which not only the whole area inside the window can be considered as a potential cluster, but also spatially connected areas inside the window, which makes it possible to detect irregular-shaped clusters [24]. The analysis parameters were set to purely spatial analysis, scanning for clusters with high rates. Hotspots were defined as spatially aggregated TCUs with significantly higher than average levels of malaria infection prevalence or *An. gambiae* mosquito densities [11]. The median values of malaria infection prevalence i.e. 12.05 % for phase 1 and 8.49 % for phase 2 were used as cut-off values in stratifying the prevalence data at TCU level, to allow analysis based on a binary logistic variable, assuming a binomial distribution for this outcome, with prevalence above the median in each phase coded as 1 and below the median coded as 0. The likelihood of clusters in mosquito densities was calculated assuming a Poisson distribution. The numerator was aggregated counts of adult female *An. gambiae* mosquitoes per TCU and the denominator was expected population of *An. gambiae* mosquitoes per TCU. Clusters of malaria infection prevalence were detected using a binomial statistical model. Statistical significance for the identification of both primary and secondary clusters was set at $p < 0.05$, which was explored by means of Monte Carlo replication of data sets under the null hypothesis with at least 9999 replications to ensure adequate power for defining those clusters [27, 28]. The relative risk (RR) which is the standardized risk ratio of observed mean catches of *An. gambiae* or prevalent infections over the expected mean or prevalent infections ("expected number of cases within the cluster when the null hypothesis is true, that is, when the risk is the same inside and outside the cluster") was also presented (Table 2).

Ethical considerations

Only participants giving informed consent were included in the study, including the mosquito catchers and the house owners where the catches took place, as well as the participants in the epidemiological cross-sectional parasite surveys. Participants found to be infected with malaria parasites during the surveys were treated with artemether-lumefantrine (Coartem®; Novartis Pharma AG, Basel, Switzerland) following national treatment policies and guidelines. Ethical approval for all procedures implanted in this study was obtained from the Institutional Review Board of the Ifakara Health Institute (Approval A.50), the Medical Research Coordination Committee of the Tanzanian National Institute of Medical Research (Approval NIMR/HQ/R.8a/Vol.IX/801), the Research Ethics Committee of the Liverpool School of Tropical Medicine (09.60) and the Human Research Ethics Committee (HSEC) at University of the Witwatersrand (M120835).

Results

A total of 12,170 person nights (function of number of traps per night) of community-based ITT capture were conducted from March 2010 to January 2013. A total of 382 female *An. gambiae* were caught with an overall average catch per trap night of 0.024 (in phases I (0.064) and II (0.012). Out of 11,187 individuals who were tested for malaria infections; 1237 (11.1 %) were positive malaria cases and 9950 (88.9 %) were negative cases. The overall mean malaria prevalence was (11 %); in phase I the mean prevalence was 12.7 % (381/2754) and II was 10.8 % (854/8433).

Spatial autocorrelation

Spatial dependences were observed in all outcome variables (Table 1). The noted positive spatial autocorrelation in both measured outcomes indicated a tendency towards clustering, meaning that spatial samples of *An. gambiae* mosquito densities or malaria prevalence that were nearby to each other in space were more similar than would be expected by random chance (Table 1).

Spatial clustering in *Anopheles gambiae* mosquitoes

In the first phase of the survey, six spatially aggregated clusters of elevated *An. gambiae* density were found in the central, western and southern parts of the city (Fig. 2a). These clusters were small in size and highly focalized (median = 5 survey locations, range = 1–23), with only three out of the six containing more than one survey location. Of the detected clusters, only one cluster consisting of a single location occurred outside of the 15 wards covered by larviciding (Fig. 2a), confirming that targeted selection of these wards for the initial operational research phase of the UMCP [5, 17] was appropriately planned. The clusters of relatively high *An. gambiae* density detected in this phase consisted of less than a tenth of all survey locations, but accounted for almost one third of all *An. gambiae* caught (Table 2). Nevertheless, the remaining two thirds of all *An. gambiae* were caught outside these clusters (Table 2), and three quarters of the locations where any *An. gambiae* were caught (76 %; 95/125) were haphazardly scattered outside of these clusters, across a further small minority (9 %; 57/615) of all sampling units (Fig. 2a).

After one year of continued larviciding and extension of the survey sampling frames, all six of the *An. gambiae* hotspots detected in phase 1 could no longer be detected (Fig. 2c), consistent with epidemiological analyses indicating larviciding succeeded in suppressing populations of these hazardous malaria vectors [3]. Despite this generally encouraging picture of success for suppression of *An. gambiae*, one new, much larger cluster emerged in phase 2 in the north-eastern parts of the city (Fig. 2c) within some of the 15 wards with long-established larvicide delivery systems. As in phase 1, the one large cluster observed in phase 2 accounted for only one third of all *An. gambiae* collected (Table 2). In this second phase, the majority (73.7 %; 42/57) of scattered survey-locations where any *An. gambiae* were caught occurred outside of detected hotspots of spatially-aggregated clusters of elevated vector density.

Spatial clusters of human malaria infection prevalence

In phase 1, two spatially aggregated clusters of elevated malaria prevalence were detected (Fig. 2b). The primary cluster was a large one, located at the south of the city centre on either side of Msimbazi river valley. The only secondary cluster occurred immediately to the north of the primary cluster, in the eastern wards of Hanna Nassif, Mwananyamala and Kinondoni (Figs. 1, 2b). These clusters encompassed approximately two fifths of all survey locations and slightly more than half of all detected cases of malaria infection (Fig. 2b; Table 2). Nevertheless, the remaining majority (60 %) of locations with elevated (>10 %) prevalence, and almost half (45 %) of all detected malaria infections) occurred outside of these clusters haphazardly across disparate parts of the city (Fig. 2b; Table 2). These consisted of 50.8 % (67/132) of survey locations with higher prevalence. More than half (56.8 %, 37/65) of the survey locations in the clusters of higher malaria prevalence detected in phase 1, occurred within wards with active larviciding.

Although there was a substantial drop of malaria prevalence from the outset of phase 2, consistent with the

Table 1 Spatial autocorrelation/dependence of mosquito densities and malaria infection prevalence in Dar es Salaam city based on global Moran's I

Outcome variable	Phase 1: March 2010–September 2010			Phase 2: October 2010 – January 2013		
	Moran's I coefficient	p	Mean distance between points (m)	Moran's I coefficient	p	Mean distance between points (m)
Female *An. gambiae*	0.15	0.002	174	0.11	0.005	210
Malaria infection prevalence	0.17	0.020	208	0.34	0.011	799

$p < 0.05$ indicates tendency towards clustering

Table 2 Spatial clusters (hotspots) of *An. gambiae* and human malaria infection prevalence in Dar es Salaam city: a flexible scan statistic was used to detect the clusters using FleXScan software Version 3.1.2 which is freely available on https://sites.google.com/site/flexscansoftware/download_e

		Phase 1: March–September 2010						Phase 2: October 2010–January 2013					
Outcome variable	Hotspot clusters	Proportion of all mosquitoes or detected infections [%(n/N)]	Proportion of all survey locations in clusters [%(n/N)]	Proportion of survey locations under lar-viciding [%(n/N)]	Expected mosquitoes or prevalent infections	RR	p	Proportion of all mosquitoes or detected infections [%(n/N)]	Proportion of all survey locations in clusters [%(n/N)]	Proportion of survey locations under lar-viciding in [%(n/N)]	Expected mosquitoes or prevalent infections	RR	p
Mean catches per trap night of female *An. gambiae*	Primary cluster	13.6 (52/382)	3.7 (23/615)	34.8 (8/23)	12.89	4.58	<0.01	32.9 (23/70)	4.8 (67/1398)	67.2 (45/67)	6.10	5.22	<0.01
	Secondary cluster 1	6 (23/382)	3.6 (22/615)	68.2 (15/22)	2.32	10.54	<0.01						
	Secondary cluster 2	3.9 (15/382)	1.5 (9/615)	33.3 (3/9)	1.27	12.33	<0.01						
	Secondary cluster 3	2.4 (9/382)	0.2 (1/615)	100 (1/1)	1.06	8.72	0.01						
	Secondary cluster 4	2.1 (8/382)	0.2 (1/615)	100(1/1)	0.85	9.67	0.02						
	Secondary cluster 5	1.6 (6/382)	0.2 (1/615)	0	0.56	10.82	0.05						
Total		29.6% (1 13/382)	9.3 (57/615)	49.1 (28/57)				32.9 (23/70)	4.8 (67/1398)	67.2 (45/67)			
Human malaria infection prevalence	Primary cluster	39.4 (148/376)	29.8 (78/261)	46.2 (36/78)	124.31	1.82	<0.01	13.4 (114/852)	5.8 (5/86)	0.6 (3/5)	53.98	2.28	<0.01
	Secondary cluster 1	15.7 (59/376)	10.0 (26/261)	50 (13/26)	18.73	2.40	<0.01	5.9 (50/852	3.5 (3/86)	100 (3/3)	21.15	2.45	<0.01
	Secondary cluster 2							7.9 (67/852)	3.5 (3/86)	0	35.04	1.99	<0.01
	Secondary cluster 3							7.3 (62/852)	4.7 (4/86)	0	33.33	1.93	<0.01
	Secondary cluster 4							9.9 (84/852)	2.3 (2/86)	0	46.22	1.91	<0.01
	Secondary cluster 5							3.2 (27/852)	1.2 (1/86)	0	10.57	2.60	<0.01
Total		55.1 (207/376)	39.8 (104/261	47.1 (49/104)				47.4 (404/852)	20.9 (18/86)	33.3 (6/18)			

Hotspots of *An. gambiae* were identified using Poisson statistical model while those of infection prevalence were detected using binomial statistical model. The significance of the cluster (p value) was calculated based on MonteCarlo replications set at 9999. *RR* relative risk which refers to the standardized risk ratio of observed mean catches of mosquitoes or prevalent infections (indicated by 'n' in a thirdcolumn) over the expected mean of mosquito densities or prevalent infections

results of detailed epidemiological analyses (Msellemu et al. pers. commun), more clusters (six) of malaria prevalence were detected (Fig. 2d). The primary cluster did not change from its previous location, but was dramatically reduced in size compared to phase 1. The remaining five clusters were in small (<1 km across) or consisted of long narrow linear pockets, distributed across peripheral parts of the city that had not previously been surveyed. In this second phase, these clusters of elevated malaria prevalence included only one fifth of all survey locations but contained almost half of all detected cases of malaria infections (Table 2). However, the remaining majority of detected infections nevertheless occurred outside of these clusters (Table 2), mostly [54.3 % (19/35)] in small, haphazardly scattered single locations with relatively high malaria prevalence (>10 %).

Association between vector density and human infection prevalence

Although the data frames for entomological and epidemiological surveys used in this study were not entirely comparable, it is nevertheless remarkable just how dissimilar the clustering patterns are for human malaria infection prevalence and densities of the main vector in both survey phases (Fig. 2). Despite the major differences in spatial and temporal resolution of the entomological and parasitological data, it was nevertheless possible to examine their mutual association in survey locations where both types of surveys were conducted. Overall population-wide prevalence at these locations was not associated with local vector density (Odds Ratio (OR) [95 % Confidence interval (CI)] = 1.56 [0.89, 1.78], P = 0.52)). Indeed, in many locations with elevated prevalence (>10 %), no *An. gambiae* were caught despite having been surveyed at least 6 times with tent traps (17.7 % (20/113) in phase 1 and 13.2 % (10/76) in phase 2). Conversely, only a minority of co-surveyed locations (26.8 % (11/42)) in phase 1 and 37.5 % (3/8) in phase 2) where *An. gambiae* were detected had human infection prevalence exceeding 10 %.

Discussion

The results presented here suggest it may not be possible to eliminate malaria transmission in Dar es Salaam, if interventions are only targeted to spatially clustered hotspots that could be detected with current methods for cross-sectional household surveys and longitudinal entomological surveillance. Even though two very different sampling frames were used in the two phases (Fig. 2), geographic cluster analysis consistently excluded over two thirds of all vectors caught and almost half of all malaria infections detected (Table 2). Of course, by definition, these spatial aggregations of elevated transmission account for even lower fractions of all surveyed locations (Table 2), so they do represent useful initial priority areas for geographically targeting new or improved interventions. However, these detected clusters of vector density and parasitaemia accounted for insufficient levels of aggregation to satisfy the "80–20 rule" [29] that is classically used to justify targeting of interventions to high-risk groups. So while targeting only the clusters of elevated vector density or human infection prevalence could tackle substantial portions of malaria transmission in Dar es Salaam, to achieve the ambitious goal of eliminating malaria transmission [30], or even the vector itself [31], would also require targeting of all the additional small, scattered locations where local transmission persists.

The haphazard distribution of this very sparse vector population is fully consistent with the known opportunistic oviposition habits of *An. gambiae* generally [32, 33] and in Dar es Salaam specifically [34–36]. This species can complete development from egg to adult in less than a week in almost any water body which lasts long enough, is exposed to the sun and is not heavily contaminated with organic waste [36, 37]. In order to eliminate transmission hazard, larval source management, or other supplementary vector control measures [7–9], would therefore need to not only target the obvious large clusters of high *An. gambiae* density, but also these smaller, haphazardly-distributed pockets of vector proliferation.

The scattered and sporadic distribution of malaria transmission hazard and risk in this modestly endemic setting is also consistent with previous reports from elsewhere in Africa [6, 38, 39]. Elimination of malaria from such contexts will therefore require continuous, longitudinal surveillance of both entomological and epidemiological indicators at fine geographic scales, to give dynamic, high-resolution maps of all the small, sometimes transient, hotspots of persistent transmission, so new or improved interventions can be delivered in a targeted and timely manner [6, 40]. The need for very fast response times to react to the unpredictable occurrence of unstable hot spots of largely symptomatic malaria [6] is perhaps best illustrated by the recent work from elsewhere on the east African coast, showing that targeted responses must be implemented within a month of occurrence to capture these cases in a meaningful way [38].

Remote sensing to map environmental determinants of vector proliferation hazard has achieved considerable success at local scales [41–45] but often lacks sufficient spatial resolution to detect small habitats of the type commonly used by species like *An. gambiae* [32, 33]. Locally, in this specific context, quality-assured community-based systems for using Ifakara Tent Traps have been developed for more directly monitoring and

mapping transmission hazard, in terms of adult vector densities [19]. Consequently, the entomological indicators monitored here were surveyed at higher spatial (mean distance of 174 m in phase 1 and 210 m in phase 2 between survey locations) and temporal (monthly) resolution than was the epidemiological indicator. While quality-assured, community-based mosquito-trapping schemes at sentinel housing clusters centred on health facilities have been evaluated in rural Zambia [46], this study in urban Tanzania remains the only example in which such comprehensive, high-resolution coverage of an entire region has been achieved, so the general applicability of this approach will require further assessment in a greater diversity of settings.

The active cross-sectional parasitological surveys used here to assess epidemiological trends in Dar es Salaam only provided temporal snapshots of malaria dynamics, at far too coarse a geographical resolution to guide routine malaria control operations because they were distributed across a population exceeding three million people and a surface area of almost 500 km^2, but yielded results that are nevertheless consistent with those of other studies. On the coast of Kenya, similar annual cross-sectional surveys of much smaller populations within three small rural communities allowed mapping of stable hot spots of transmission that persisted from year to year, while active longitudinal cohort surveys to detect febrile malaria enabled mapping of sporadic, unstable transmission hot spots that occur unpredictably in different locations from year to year [34]. Furthermore, a variety of other studies using intensively collected cross-sectional [47], incidence cohort [39] or health facility [38, 44, 48, 49] data within small study areas have all illustrated how hot spots ubiquitously occur at scales far smaller than 1 km.

The inadequate spatial resolution of these active cross-sectional surveys when deployed on such large, programmatically-relevant scales is particularly clearly illustrated by the results of a recently piloted passive surveillance system for mapping of malaria cases in Dar es Salaam, by tracing the home residence locations of patients reporting to health facilities with acute malaria, which demonstrated that hot spots of malaria risk in Dar es Salaam can be less than 100 m across and associations of risk with topographic wetness index can occur at similar scales (Mlacha et al. unpublished). The surprising location of the small cluster of high diagnostic positivity identified in the ward of Buguruni illustrates how mapping clusters by tracing patient's residence from facilities data could be an effective system for detecting enigmatic, haphazardly-scattered locations of hotspots of transmission (Mlacha et al. unpublished), like the ones shown to occur all across the city by the study presented in this manuscript. Similar approaches to risk mapping using passively collected health facility data have also been successfully applied in a variety of other resource-limited contexts [38, 43–45, 48–50], so this overall strategy may offer an affordable and broadly applicable means to map malaria transmission, that yields particularly high geographic resolution in this urban context where transmission is very focal and grass-roots local government systems provide very fine-scale geographic reference points that community members can readily relate to (Mlacha et al. unpublished). Beyond scaleability and affordability, the other major advantage of facility-based mapping of malaria cases is the ability to rapidly detect sporadic, unpredictably distributed flare-ups of malaria transmission in sufficient time ($\leq$1 month) to enable effective targeting of responsive anti-parasite interventions [38], such as focal mass drug administration or mass screening and treatment [8, 10].

As observed elsewhere [51], clusters of malaria infection prevalence only partially coincided with those of *An. gambiae* in Dar es Salaam (Fig. 2). Indeed, population-wide malaria prevalence and *An. gambiae* densities in any given location were only loosely associated to each other, in spite of malaria primarily being locally transmitted in the city, rather than imported (Msellemu et al. pers. commun). The lack of an obvious overall relationship between spatial distribution of malaria and the level of hazard presented by local vector densities may, therefore, be largely explained by differences in city's population resilience levels, such as housing conditions, human behaviour and utilization of interventions [4, 52, 53]. Indeed more detailed epidemiological analyses of these same data confirm that high malaria risk appears to require both hazard and vulnerability: prevalence does increase dramatically with increasing local vector density among the small minority of households living in houses without protective window screening, but not among more resilient households protected by complete window screening [4]. It is, therefore, likely that intervention packages targeted to both stable and unstable hot spots of malaria transmission will need to not only reduce or eliminate the hazard represented by local vector proliferation, presumably with supplementary application of new or improved vector population abatement measures, they will also need to actively treat all local residents who are already infected with malaria [8, 10] as well as improve the resilience of the most vulnerable residents by providing them with protective measures such as bed nets [54], window screening [55] or spatial repellents [56, 57].

Study limitations

The sampling frames for mosquito densities and human malaria infection prevalence were incomparable due to differences in geographic and temporal resolution.

Similarly, the differences in sampling frames across the two phases made it impossible to compare and track temporal/spatial trends within same outcome variables. Comparison was only possible in a few sampling locations which were co-surveyed.

Conclusions

Small scattered locations of elevated malaria transmission and densities of vector mosquitoes were haphazardly scattered across the city, so interventions targeted only to hotspots identified by geographic cluster approaches with conventional entomological and epidemiological survey methods will probably have limited impact. Routine, spatially comprehensive, longitudinal entomological, parasitological surveillance systems, with sufficient sensitivity and high spatial and temporal resolution to detect those scattered locations with elevated infections and mosquito densities, will be required to eliminate transmission from this typical contemporary city of sub-Saharan Africa. Given the loose association observed between vector proliferation hazard and malaria infection risk, intervention packages targeted to hot spots of malaria transmission will need to not only suppress local vector proliferation and treat residents who are already infected, but also provide the most vulnerable population members with supplementary protective measures against exposure.

Authors' contributions

VMM led the design and implementation of the study, including data analysis, preparing maps and drafting of the manuscript. YPM, JMP, ZDM, AJL and DFM implemented the adult mosquito and household parasitology surveys, as well as data collection and management of the data, including spatial information. SD, BKDS, NJG, MC and GFK supervised the design and implementation of the study, interpretation of results, and preparation of the manuscript. All authors read and approved the final manuscript.

Author details

[1] School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. [2] Department of Housing and Infrastructure Planning, School of Urban and Regional Planning, Ardhi University, P.O. Box 35176, Dar es Salaam, United Republic of Tanzania. [3] Environmental Health and Ecological Sciences Thematic Group, Ifakara Health Institute, Coordination Office, Kiko Avenue, Mikocheni, P.O. Box 78373, Dar es Salaam, United Republic of Tanzania. [4] Discipline of Public Health Medicine, School of Nursing and Public Health, University of KwaZulu-Natal, Durban, South Africa. [5] Wits Research Institute for Malaria, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. [6] Vector Biology Department, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, UK. [7] Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, P.O. Box, 4002, Basel, Switzerland. [8] University of Basel, 4001 Basel, Switzerland.

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Competing interests

The authors declare that they have no competing interests.

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The epidemiology of residual *Plasmodium falciparum* malaria transmission and infection burden in an African city with high coverage of multiple vector control measures

Daniel Msellemu[1,2], Hagai I. Namango[1,3], Victoria M. Mwakalinga[1,4], Alex J. Ntamatungiro[1,2], Yeromin Mlacha[1,5], Zacharia J. Mtema[1], Samson Kiware[1,6], Neil F. Lobo[7], Silas Majambere[1,5], Stefan Dongus[1,5,8,9], Christopher J. Drakeley[2], Nicodem J. Govella[1,5], Prosper P. Chaki[1,5] and Gerry F. Killeen[1,5*]

Abstract

Background: In the Tanzanian city of Dar es Salaam, high coverage of long-lasting insecticidal nets (LLINs), larvicide application (LA) and mosquito-proofed housing, was complemented with improved access to artemisinin-based combination therapy and rapid diagnostic tests by the end of 2012.

Methods: Three rounds of city-wide, cluster-sampled cross-sectional surveys of malaria parasite infection status, spanning 2010 to 2012, were complemented by two series of high-resolution, longitudinal surveys of vector density.

Results: Larvicide application using a granule formulation of *Bacillus thuringiensis* var. *israelensis* (*Bti*) had no effect upon either vector density (P = 0.820) or infection prevalence (P = 0.325) when managed by a private-sector contractor. Infection prevalence rebounded back to 13.8 % in 2010, compared with <2 % at the end of a previous *Bti* LA evaluation in 2008. Following transition to management by the Ministry of Health and Social Welfare (MoHSW), LA consistently reduced vector densities, first using the same *Bti* granule in early 2011 [odds ratio (OR) (95 % confidence interval (CI)) = 0.31 (0.14, 0.71), P = 0.0053] and then a pre-diluted aqueous suspension formulation from mid 2011 onwards [OR (95 % CI) = 0.15 (0.07, 0.30), P ≪ 0.000001]. While LA by MoHSW with the granule formulation was associated with reduced infection prevalence [OR (95 % CI) = 0.26 (0.12, 0.56), P = 0.00040], subsequent liquid suspension use, following a mass distribution to achieve universal coverage of LLINs that reduced vector density [OR (95 % CI) = 0.72 (0.51, 1.01), P = 0.057] and prevalence [OR (95 % CI) = 0.80 (0.69, 0.91), P = 0.0013], was not associated with further prevalence reduction (P = 0.836). Sleeping inside houses with complete window screens only reduced infection risk [OR (95 % CI) = 0.71 (0.62, 0.82), P = 0.0000036] if the evenings and mornings were also spent indoors. Furthermore, infection risk was only associated with local vector density [OR (95 % CI) = 6.99 (1.12, 43.7) at one vector mosquito per trap per night, P = 0.037] among the minority (14 %) of households lacking screening. Despite attenuation of malaria transmission and immunity, 88 % of infected residents experienced no recent fever, only 0.4 % of these afebrile cases had been treated for malaria, and prevalence remained high (9.9 %) at the end of the study.

Conclusions: While existing vector control interventions have dramatically attenuated malaria transmission in Dar es Salaam, further scale-up and additional measures to protect against mosquito bites outdoors are desirable. Accelerated elimination of chronic human infections persisting at high prevalence will require active, population-wide campaigns with curative drugs.

*Correspondence: gkilleen@ihi.or.tz
[1] Environmental Health and Ecological Sciences Thematic Group, Ifakara Health Institute, Dar es Salaam, United Republic of Tanzania
Full list of author information is available at the end of the article

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Keywords: Malaria, *Plasmodium*, Mosquito, *Anopheles*, Vector control, Larval source management, Housing, Window screening, Chronic infection, Long-lasting insecticidal net

Background

Cities represent perhaps the best opportunities to eliminate local malaria transmission for a number of reasons [1–3]. First, dense aggregation of humans in urban areas reduces malaria transmission intensity, by simply diluting the biting burden created by local vector populations across larger numbers of people [4, 5]. Second, while a certain amount of human activity can increase the availability of aquatic habitat for vectors, the planning, construction and drainage processes associated with urban development can dramatically reduce it [6]. Third, cities often have far better infrastructure, health services, access to goods, institutional capacity and governance than rural areas, so some supplementary interventions, such as intensive larval source management (LSM), may be more feasible and effective than in rural areas [1–3, 7, 8].

Dar es Salaam in the United Republic of Tanzania is a typical African coastal city with ideal climatic conditions for malaria transmission, where *Plasmodium falciparum* is transmitted both indoors and outdoors [9, 10] by some of the most efficient vectors in the world, specifically *Anopheles gambiae*, *Anopheles arabiensis* and *Anopheles funestus* [11]. While Dar es Salaam historically experienced intense transmission and high infection prevalence, an operational research programme to develop and evaluate new municipal systems for larvicide application (LA) [12, 13] coincided with spontaneous uptake of window screening [14] to prevent mosquito entry, resulting in an overall decline of infection prevalence from 21 % in 2004 to only 2 % by 2008 [15].

Since then, considerable progress has recently been made in Dar es Salaam to not only ensure high coverage of standard interventions like rapid diagnostic tests (RDTs), artemisinin-based combination therapy (ACT) and long-lasting insecticidal nets (LLINs), but also supplementary vector control measures, specifically mosquito-proofed housing and regular LA with microbial active ingredients [9, 13–16]. This observational study in Dar es Salaam evaluates the influence of all these interventions upon malaria vector density and infection burden, and assesses opportunities for further progress towards elimination of malaria transmission from the city.

Methods

Study area

Dar es Salaam is the biggest and most economically important city in the United Republic of Tanzania, situated on the shores of the Indian Ocean (Fig. 1). The city has 4.36 million inhabitants [17] and is among the world's ten fastest growing cities [18], with an annual growth rate of 5.6 % [17]. However this growth is unguided, resulting in about 70 % of its inhabitants living in informal settlements [19]. Challenges resulting from unguided growth are huge and have exposed the city to floods, scarcity of piped water, overcrowding, poor sanitation, poor waste management, inadequate housing, unplanned settlement, and insecurity of residence tenure [20], all of which increase malaria transmission hazard while also increasing the vulnerability of residents to transmission exposure [21, 22].

Administratively, the city comprises three municipalities namely Ilala, Kinondoni and Temeke, which are collectively divided into 90 wards [17] (Fig. 1). The wards are further divided into smaller neighbourhood units called mitaa (a *Kiswahili* word for street, written in the singular form as *mtaa*) [23]. Each *mtaa* is subdivided into ten-cell units (TCUs), comprising clusters of approximately 10–20 houses, although some TCUs may contain more than 100 houses [23]. TCUs were the main units of sampling and analysis in this study, and also represent the geographic units that were mapped and allocated to individual community-based staff for implementation of LA [12, 23, 24]. The study area consists of the 71 urban and semi-urban wards (Fig. 1) which have been mapped in detail down to the level of TCU boundaries [23, 24], encompassing an overall population of 3.6 million living in >12,000 TCUs with >543,000 enumerated households.

Dar es Salaam has a well-documented history of successful health sector reform and malaria control programmes, with a particularly strong record of successful vector control operations [25–36]. Important decentralization, management and financing reforms of the health system in Dar es Salaam in the 1990s [26] not only improved the clinical services provided by the Ministry of Health and Social Welfare (MoHSW) [37], they also subsequently provided a suitable administrative platform for vertical but decentralized and community-based implementation of preventative public health measures, including vector control [12, 13, 38].

Intervention scenario

The way in which the overall intervention scenario in Dar es Salaam evolved over the course of the study is narrated below, summarized graphically in the context of the long-term intervention history of the city in Fig. 2a, and illustrated in detail in Fig. 3a.

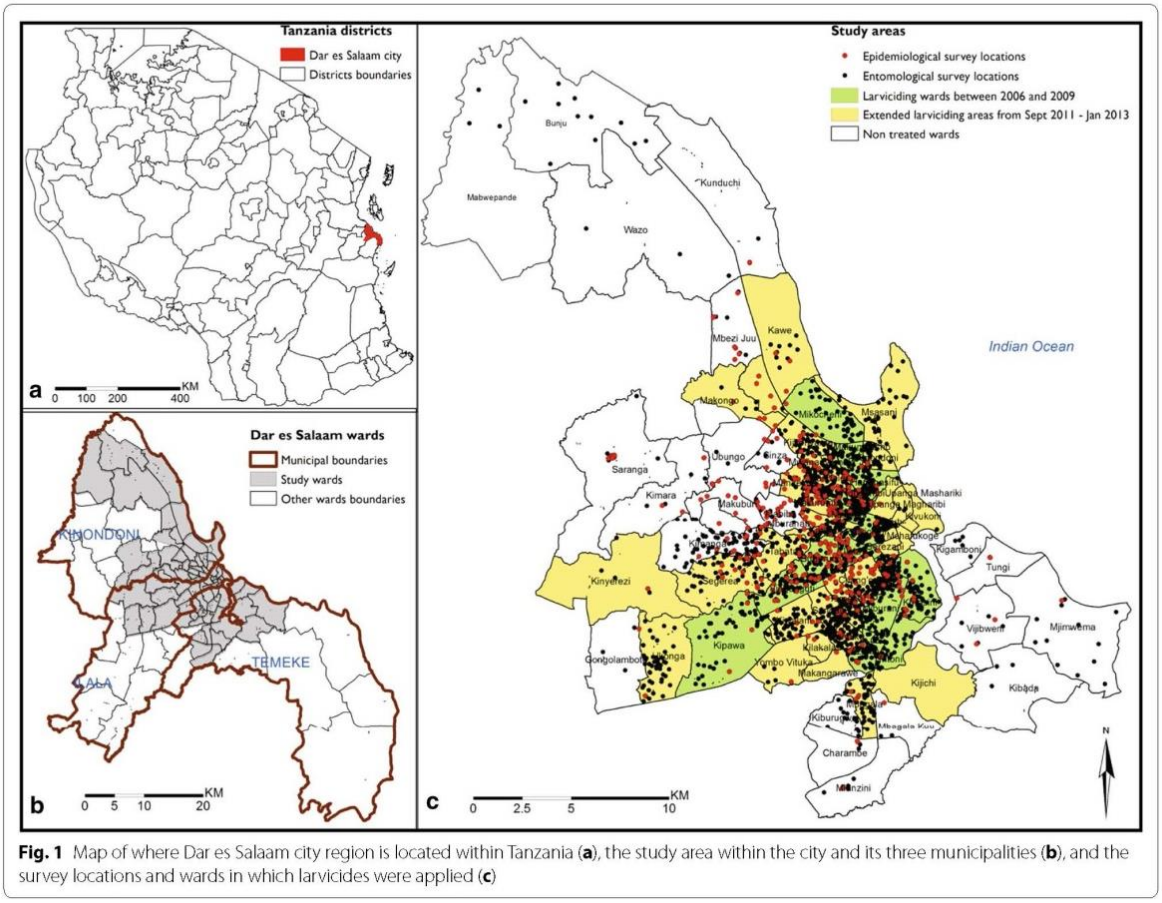


Fig. 1 Map of where Dar es Salaam city region is located within Tanzania (**a**), the study area within the city and its three municipalities (**b**), and the survey locations and wards in which larvicides were applied (**c**)

Drugs

At the outset of the study, subsidies for ACT in Tanzania were restricted to young children and pregnant women, so uptake remained poor across the country generally [39], and in Dar es Salaam specifically [40]. It is therefore unsurprizing that most residents predominantly relied upon private sector health facilities and drug outlets to access anti-malarials [39, 40]. The subsidy of ACT at source, to improve availability through such private sector outlets, was introduced nationally at the start of 2011 and rapidly achieved improved levels of availability and affordability, even in remote rural areas [41–43]. Nevertheless, at least a third of all malaria therapies used in all surveyed rural areas remained non-ACT [41, 43, 44].

Diagnostics

While microscopic diagnosis of malaria has been available at many health facilities across Dar es Salaam for decades, routine standards of practice were very poor, with gross levels of overdiagnosis consistently observed across all levels of facilities [45, 46]. Country-wide scale-up of rapid diagnostic tests (RDT) for malaria began in 2010, following a successful pilot in Dar es Salaam [46–48], but has so far only been evaluated in rural [49] or semi-urban areas [50].

Larval source management

Impressive historical successes with larval source management programmes, both before and after independence [27–36], were recently succeeded by an integrated operational research programme, which demonstrated the effectiveness and affordability of both environmental management [51, 52] and routine LA [15, 40, 53], as implemented, monitored and evaluated through contemporary, community-based strategies [12, 13, 23, 24, 54–57]. In addition to pilot-scale evaluations of environmental management spanning 2006 and 2007 [51, 52], new systems for implementing, monitoring and managing LA using microbial insecticides were developed and established in three

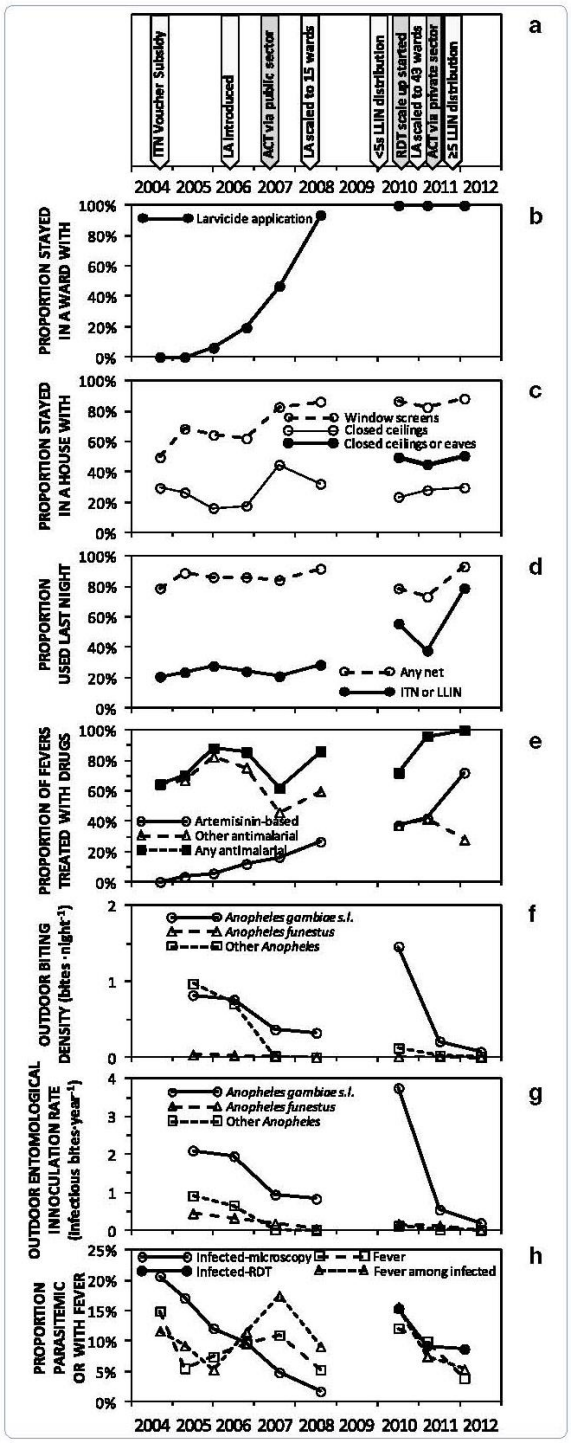


Fig. 2 Long-term trends in coverage with malaria control interventions, entomological malaria transmission hazard, and prevalence of fever and malaria infection. To allow direct comparison of results from this study from 2010 to 2012, with the previous study from 2004 to 2008 [15, 40], only data from the original 15 city centre wards common to both studies (Fig. 1) were included and summarized by survey round. **a** Schematic summary of specific intervention introductions; **b** Stayed in a ward with larvicide application (LA) last night; **c** Stayed in a house with mosquito-proofed windows, ceilings or eaves; **d** Used a bed net or long-lasting insecticidal nets (LLIN) the previous night; **e** Treated with an artemisinin-based therapy, including artemisinin-based combination therapy (ACT), or with any other anti-malarial, if had a fever in the previous 2 weeks; **f** Outdoor rates of human exposure to biting malaria vectors; **g** Outdoor rates of human exposure to infectious bites by malaria vectors; **h** Prevalence of reported fever and parasitologically-confirmed malaria infection

urban wards by May 2006, and then steadily scaled up to encompass 15 urban wards, 55 km^2 and 610,000 residents by early 2008 [12, 13, 15, 16, 23, 24, 54, 55].

Following completion of this operational research phase of the Dar es Salaam Urban Malaria Control Programme, the MoHSW of mainland Tanzania decided in 2009 to absorb LA activities into its National Malaria Control Programme (NMCP), but this institutionalization process was not completed until the end of 2010 [13]. In the interim, between January 2009 and October 2010, these LA activities were implemented in the same 15 wards covered in the original operational research phase of the programme (Fig. 1), temporarily under the direct management of a private sector contractor (Research Triangle International) during its last year of external funding support [58]. Once institutionalization of the programme management into the MoHSW had been completed at the end of 2010, LA was re-initiated in these same 15 wards in January 2011 and sustained until July of that year when stocks of *Bti* were exhausted. Up to this point, the larvicide product used was a WHOPES-recommended *Bacillus thuringiensis* var. *israelensis* (*Bti*) product (VectoBac®, Valent BioSciences Corporation), predominantly in the form of a coated corn cob granule formulation, but also occasionally water dispersible granules. From August 2011 onwards, aqueous suspension formulations of an alternative, non-WHOPES-recommended *Bti* product (Bactivec®, LABIOFAM®) was used. LA with this products was then scaled up to 28 additional neighbouring wards and sustained into 2015.

Mosquito-proofing houses

As improved, more appropriate and affordable construction materials became available on the open market in

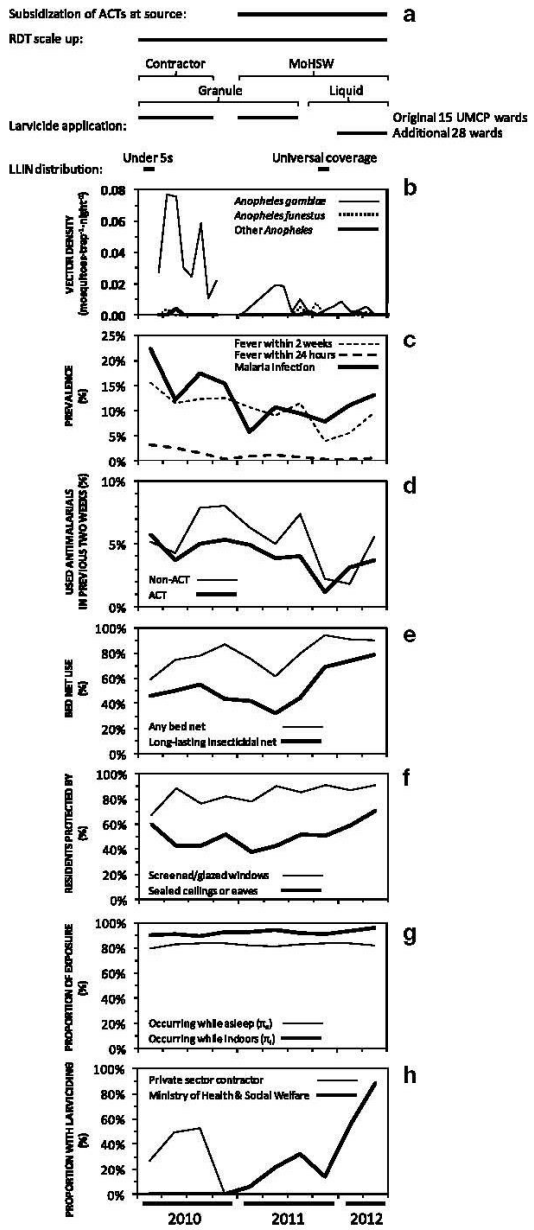


Fig. 3 Short-term trends in coverage with malaria control interventions across the city of Dar es Salaam over the course of this study, summarized by quarterly mean. **a** Schematic summary of specific intervention introductions; **b** Vector densities; **c** Prevalence of *Plasmodium falciparum* infection and recollection of fever; **d** Anti-malarial drug use; **e** Bed net use the previous night; **f** Stayed in a mosquito-proofed house; **g** Proportion of potential human exposure to biting vectors expected to occur while asleep or indoors in the absence of protective bed nets or mosquito-proofed housing; **h** Stayed in a ward with larvicide application (LA) last night

Dar es Salaam, protection of houses against mosquito entry with window screening, and with closed ceilings or eaves, steadily increased between 2004 and 2008, despite the absence of any programme to subsidize or promote these measures [14, 40]. Residents cited protection against mosquitoes as their primary motivation for investing in these housing improvements [14] and spent more time indoors in the evenings if both measures were in place [9]. Increasing uptake of these measures was associated with a steady decline in population-wide malaria prevalence and interacted synergistically with roll out of LA [15].

Long-lasting insecticidal nets

Insecticide-treated nets (ITNs) and then LLINs were the standard first-priority vector control measure in Tanzania throughout this study. The Tanzanian National Voucher Scheme was then initiated in 2004, to subsidize purchase of ITNs through a discount voucher provided to pregnant women seeking ante-natal care and mothers of young children when they are vaccinated [59]. However, progress with scale-up of LLINs to full universal coverage targets lagged behind that for LSM and house screening in Dar es Salaam. The city has been consistently classified as having relatively low levels of transmission and, therefore, correspondingly given the lowest priority in national "catch up" programmes for free net distribution. Dar es Salaam was the last region of Tanzania to be reached by the mass distribution to children under the age of 5 in early 2010 [60], and by the subsequent campaign to achieve universal coverage of remaining sleeping spaces in late 2011 [61].

Data collection procedures

Cross-sectional household surveys of malaria infection prevalence and sero-prevalence

The total number of households in each TCU within the mapped study area [24] was enumerated by census between January 2008 and May 2010. While awaiting completion of this enumeration of 543209 households in the city, a first phase of purposively-sampled household surveys were conducted. This first survey phase consisted of a single survey round of 264 housing compounds, 156 of which were also subjected to longitudinal, community-based surveys of vector density on a monthly basis between March and September 2010, so that this novel system for monitoring vector densities at high levels of spatial resolution could be evaluated in terms of its epidemiological predictive power [56]. Following completion of the household listing, a second phase of household surveys were conducted, beginning with a second survey round between October 2010 and September 2011 that sampled much smaller numbers of larger population clusters, selected randomly as index TCUs in

proportion to their estimated population size. A total of 68 index TCUs were randomly selected with probabilities weighted according to the number of household recorded for each by the household enumeration surveys. In each index TCU, households were listed afresh and 20 were randomly selected for cross-sectional surveys. Where the TCU had less than 20 consenting household heads, a neighbouring TCU was chosen at random, from where the remaining number of households required were selected and recruited in the same way. The second phase was then extended with a third round of cross-sectional surveys, carried out from October 2011 to May 2012, which repeated the second round of surveys in 28 of the originally sampled clusters and 17 new ones in cases where the TCU leaders of the clusters sampled in round 2 indicated unwillingness to participate in the follow up surveys.

All consenting and assenting household members of all ages, except for children of 3 months or less, were surveyed with a standardized questionnaire and RDT for *P. falciparum* Histidine Rich Protein 2 (HRP-2) antigenaemia in peripheral finger-prick blood samples, as previously described in detail [56, 62]. Individuals found to be infected were treated with artemether–lumefantine according to national guidelines of the MoHSW. Those with a negative RDT result who exhibited symptoms of illness were referred to the nearest public-sector health facility for examination, diagnosis and, where appropriate, treatment of the most likely cause(s) of disease. RDT cassettes were then stored at −20°C and subsamples of 1134 and 345 of the strips within them were eluted and tested for sero-reactivity to *P. falciparum* apical membrane antigen (AMA) [63] and the presence of parasite DNA by polymerase chain reaction (PCR) [64], respectively, as previously described.

Entomological surveys of mosquito densities and behaviour

The community-based system for using Ifakara tent traps (ITTs) [65] to continuously monitor vector densities that was initially developed and sustained until October 2010, when funding ran out, has been described in detail [56]. This system was reinitiated, inclusive of quality assurance surveys with both HLC and ITT by a carefully supervised team of specialist technicians, in May 2011 when additional funding was secured. This surveillance platform was then steadily scaled up by the end of 2011, to encompass monthly vector density measurements at 1062 locations across the entire study area, including 79 of the 85 population clusters for the second and third rounds of cross-sectional household surveys. These scaled-up mosquito surveys, spanning the entire city, were sustained until January 2013. In addition to these longitudinal surveys of vector population dynamics, a sequence of cross-sectional human landing catch surveys were conducted as components of a variety of studies of various mosquito traps and malaria prevention measures [9, 10, 66–69], so that the feeding behaviours of local vector populations were regularly characterized throughout the study period. All *Anopheles* captured were tested for the presence of *P. falciparum* circumsporozoite protein by enzyme-linked immunosorbent assay [70], including confirmation by re-assay after heating homogenates of apparently positive samples [71]. All specimens from the *An. gambiae* complex were also tested for species identity by PCR [72].

Statistical analysis

All statistical analyses were conducted with IBM® SPSS® and Microsoft® Excel® to prepare and conduct descriptive analysis of the data, as well as R software for fitting generalized linear mixed models (GLMMs).

Apart from descriptive summaries with tables and frequency distributions, all analyses of *P. falciparum* malaria infection prevalence were accomplished by fitting generalized GLMMs with a logit link function and binomial distribution for this binary dependent outcome, and including date and household nested within sample cluster as independent variables with random effects, using the *lme4* package. For all independent variables collected as continuous numbers and categorical variables with more than two possible values, initial exploratory analysis of their effect on malaria prevalence were conducted to establish how best to stratify or combine values for inclusion in more complex models with multiple variables. This same exploration and simplification approach was also applied to complex interactions between two or more variables, such as window screens, eaves, ceilings and LLINs. Surveyed human subjects were only considered to have possibly experienced potential benefits of LA if this intervention had been implemented in that ward for at least a month before the individual was interviewed and tested.

Given the clear evidence of outdoor transmission as a potential risk factor for malaria infection in Dar es Salaam [9, 10], the role of each surveyed individual's reported behaviours was evaluated by calculating and stratifying individual estimates [73] for the proportion of exposure to bites by malaria vectors that would occur indoors (π_i) or during sleeping hours (π_s) in the absence of any personal protection interventions like bed nets or mosquito-proofed housing [74–76]. Estimates for these two indicators of potential for exposure while outdoors (π_i) and awake (π_s), were calculated for each individual based on their specific responses to questions about their behaviour in that particular survey [73]. This was accomplished with the simple binary approach

to classifying each individual as being indoors or asleep, which was previously described for entire populations based on their median responses [74–76], using a customized Excel® spreadsheet (Additional file 1). The estimates used for the analyses presented here were made based on mean observed indoor and outdoor biting densities of *An. gambiae s.l.* for each hour of the night during intensive HLC surveys in 2006 [9, 10], before these cross-sectional household surveys commenced in 2010. However, all these analyses were also attempted with species-specific measurements based on PCR-identified *An. gambiae* sensu stricto or *An. arabiensis* alone captured in the same 2006 experiments [9, 10], or with equivalent HLC data from similarly intensive mosquito trap evaluations conducted in 2010, but none of these improved the goodness-of-fit statistic for relevant analytical models and had less precise estimates because of lower numbers of mosquitoes caught after vector populations had been suppressed by programmatic roll out of LA.

The impacts of LA upon densities of common mosquito taxa in the city were estimated using the *lme4* package by fitting GLMMs with negative binomial distributions to the counts of mosquitoes caught by each catcher on each night at a given location with an ITT as the dependent variable. LA for at least 2 weeks before the night of survey was included as a fixed effect, while TCU nested within ward was treated as random effects.

Longitudinal surveys of vector density were not active throughout all rounds of the cross-sectional household surveys of parasites amongst humans between 2010 and 2012: A break in funding support for this platform occurred between November 2010 and April 2011. Results from the first set of vector surveys that exactly matched to the locations and duration of the first round of cross-sectional parasite surveys were aggregated to generate mean trap catch estimates for each of the 156 co-surveyed TCUs to which these values were linked. Similarly, the subsequent entomological surveys that straddled the second and third round of cross sectional surveys, which used a different sampling frame, were aggregated to generate mean trap catches that were linked to the epidemiological data from the same 79 TCUs in one or both rounds of parasite surveys.

Ethics, consent and permissions

The study received ethical clearance from the Medical Research Coordination Committee of the Tanzanian National Institute of Medical Research (Reference numbers NIMR/HQ/R.8a/Vol.IX/279 and 324). Informed consent was obtained from all the participants, including the mosquito catchers and the house owners where the sampling took place, as well as the participants in the household surveys. All the volunteers recruited for conducting HLC were provided with prophylactic treatment with atovaquone–proguanil (Malarone®) free-of-charge, which they were obliged to take once a day to prevent malaria infection. In order to deal with the possibility of poor compliance or drug failure, participants in mosquitoes-trapping surveys who developed any symptoms such as fever, chills, headache or nausea, were tested for malaria parasites. They would have been offered free treatment if found to be infected, but this eventuality never occurred during the study. All participants in the household surveys who were found to be infected with malaria were offered supervised treatment with artemether–lumefantrine (Coartem®; Novartis Pharma AG, Basel, Switzerland), prescribed by a clinical officer and provided by the community health nurse, following national treatment policies and guidelines, as soon as the RDT test was complete. However, if the participant refused this offer of treatment, they were referred to a nearby health facility and given all required transport and other logistical assistance to attend. Women of child-bearing age who were found to be infected with malaria were offered treatment with artemether–lumefantrine unless they were known or suspected to be pregnant and in their first trimester, in which case they were instead treated with oral quinine as per national guidelines.

Results

Area-wide trends in malaria transmission and human infection prevalence

During the first phase of cross-sectional household surveys, at the outset of this study in 2010, mean malaria prevalence across the city appeared far higher (13.8 %) than in 2008 (1.7 %), at the end of an operational research programme during which LA was comprehensively scaled up to 15 wards in the city centre [12, 15, 40]. Restricting analysis, to the 15 central wards which were common to both studies, confirmed this return to high levels of malaria transmission hazard (Fig. 2f, g) and infection prevalence (Fig. 2h). This rise in malaria prevalence occurred despite continued financial support for LA across all 15 of these wards (Fig. 2b), sustained high coverage of mosquito-proofed housing (Fig. 2c), and LLIN usage almost doubling following free mass distribution to under five children [60] in early 2010 (Fig. 2d), and slightly increased proportions of fevers being treated with ACT (Fig. 2e).

This resurgence of malaria prevalence, following transfer of LA management to a private contractor in 2009 and 2010, is consistent with an observed rebound in *An. gambiae* densities (Fig. 2f, g), which prevalence trends generally tracked reasonably consistently over the long term (Fig. 2h). It is also consistent with the lack of any

obvious association between LA and either vector density (Table 1) or infection prevalence (Table 2) in 2010. While the estimate of 3.7 infectious bites·person^{-1} year^{-1} for the EIR mediated by *An. gambiae* in 2010 is undoubtedly biased upwards, because these surveys were restricted to a few months of the year with peak vector densities, this is nevertheless much higher than estimates for 2008 after LA had been scaled up (0.8 infectious bites·person^{-1} year^{-1}), and even than before LA was introduced in 2005 (2.1 infectious bites·person^{-1} year^{-1}) (Chaki et al., Unpublished).

Perhaps even more surprising is the observation that infection prevalence of approximately 10 % persisted throughout the study (Fig. 3c), despite sustained coverage of LA in 2010 and 2011, followed by scale up in 2012 (Fig. 3h), rapid upscale of LLINs from the end of 2011 onwards (Fig. 3e), and continuing progress with uptake of window screening (Fig. 3f), resulting in a dramatic crash in vector population density (Fig. 3b). By the third and final round of surveys, 93 % of participants slept under a net of some kind and 72 % under an LLIN specifically, 80 % slept in houses with mosquito-proofed windows and 57 % in houses with sealed ceilings or eaves, while 41 % lived in wards with ongoing LA (Additional file 2; Fig. 3e, f, h respectively). Despite all this additional intervention pressure upon host seeking adults by mosquito proofed houses and bed nets, the distribution of biting activity of *An. gambiae s.l.* across different times of the night remained approximately consistent with those observed previously, except perhaps for a slight shift to later hours of the night, between midnight and dawn (Fig. 4c). Human behaviour also remained stable throughout the study, with consistently high means for individual-level estimates for the proportions of potential exposure which would otherwise occur indoors (π_i) or while asleep (π_s) in the absence of any of these interventions (Fig. 3g).

Throughout the study period, only modest levels of physiological resistance to pyrethroids (Fig. 4a), and behavioural resistance or resilience [77] to indoor vector control measures by biting at dawn or dusk (Fig. 4c), were observed for the *An. gambiae s.l.* complex. Over the course of this study, composition of the *An. gambiae* complex was consistently predominated by the nominate sibling species *An. gambiae s.s.*, with the small remainder being *An. arabiensis* (Fig. 4b). *Anopheles gambiae s.s.* is the most anthropophagic and efficient sibling species from this complex [78], and very few *An. funestus* or other *Anopheles* were caught (Fig. 3b). Vector densities were therefore expressed in terms of mean numbers of *An. gambiae* complex specimens caught per trap per night for subsequent analyses, and considered representative of this dominant, nominate sibling species. While the mean sporozoite prevalence among *An. gambiae* specimens captured over this period (1.3 %, 2/150) was approximately comparable with those observed between 2004 and 2008, these data are far too sparse to determine whether reduced infection rates were also achieved by LLIN scale-up. Approximate estimates of entomologic inoculation rate (EIR) were, therefore, based upon the parsimonious assumption that this sporozoite prevalence estimate was constant throughout the study.

Anopheles gambiae densities had declined considerably by 2011, after the MoHSW took over management of LA, using the same granular *Bti* product as the private sector contractor responsible in 2010, resulting in an estimated EIR of 0.5 infectious bites·person^{-1} year^{-1} in the 15 previously-surveyed wards with which historical comparisons may be made (Fig. 2g). *Anopheles gambiae* densities

Table 1 Factors affecting numbers of *Anopheles gambiae* malaria vectors caught in Ifakara tent traps over 12,170 trap nights of capture in 1562 locations distributed across Dar es Salaam, Tanzania

Variable	Proportion (n)	Odds ratio [95 % CI]	P
Live in one of the original 15 Urban Malaria Control Programme (UMCP) study wards			
New study ward	51.0 % (6211)	1.00 [NA]	NA
Old UMCP study ward	49.0 % (5959)	3.36 [2.14, 5.29]	0.033
Living in a ward with or without active Bti larvicide application			
No larviciding	38.3 % (4664)	1.00 [NA]	NA
Granule application managed by contractor[a]	19.9 % (2416)	0.83 [0.16, 4.2]	0.820
Granule application managed by Ministry of Health & Social Welfare (MoHSW)	5.9 % (717)	0.31 [0.14, 0.71]	0.0053
Pre-diluted liquid application managed by MoHSW	35.8 % (4373)	0.15 [0.07, 0.30]	0.000000079
Population-wide LLIN use[b]			
Increase in coverage by final round	From 51.0 to 71.2 %	0.72 [0.51,1.01]	0.057

NA not applicable

[a] Excluded from the final model by merging with reference group because non-significant, but presented here for illustrative purposes

[b] Association with community-level mean LLIN scale-up, captured by fitting city-wide mean reported LLIN use the previous night as a continuous covariate, so the relative rate presented is that estimated based on community-wide usage in the last round of surveys (71.2 %) versus the first (51.0 %)

Table 2 Minimal logistic generalized linear mixed model describing risk factors for malaria among 9172 RDT-tested occupants of 2822 households in Dar es Salaam, Tanzania, surveyed between March 2010 and May 2012, for whom valid values of all significant variables were recorded

Variable	Proportion (n)	Odds ratio [95 % CI]	P
Live in one of the original 15 Urban Malaria Control Programme (UMCP) study wards			
New study ward	68.8 (7693)	1.00 [NA]	NA
Old UMCP study ward	31.2 (3494)	1.30 [1.02, 1.65]	0.033
Education of head of household			
Any	96.8 % (8882)	1.00 [NA]	NA
None	3.2 % (290)	1.90 [1.34, 2.71]	0.00035
Sex			
Female	63.9 % (5864)	1.00 [NA]	NA
Male	36.1 % (3308)	1.16 [1.03, 1.33]	0.020
Window screening[a] and the proportion of potential vector biting exposure occurring indoors (π_i)[b]			
Unscreened or screened but lowest π_i tercile	34.1 % (3132)	1 [NA]	NA
Screened and middle or highest π_i tercile	65.9 % (6040)	0.71 [0.62, 0.82]	0.0000036
Living in a ward with or without active larvicide application			
No larviciding	69.2 % (7744)	1.00 [NA]	NA
Granule application managed by contractor[c]	11.9 % (1329)	1.29 [0.78, 2.13]	0.325
Granule application managed by Ministry of Health & Social Welfare (MoHSW)	4.9 % (551)	0.26 [0.12, 0.56]	0.00040
Pre-diluted liquid application managed by MoHSW[c]	14.0 % (1563)	0.96 [0.67,1.37]	0.836
Individual use of a bed net the previous night			
Didn't use any bed net	19.4 % (1773)	[NA]	NA
Used an untreated bed net	29.8 % (2736)	1.29 [1.03, 1.60]	0.023
Used a long-lasting insecticidal net (LLIN)	50.8 % (4663)	1.42 [1.16, 1.74]	0.00063
Population-wide LLIN use[d]			
Increase in coverage by final round	From 51.0 to 71.2 %	0.80 [0.69, 0.91]	0.0013
Recent travel history over last month			
Had not slept away from home	79.8 % (7322)	1.00 [NA]	NA
Slept away from home at least once	20.2 % (1850)	0.69 [0.54, 0.88]	0.0024
Anopheles gambiae density[e] among households lacking window screening[a] only			
One mosquito caught per trap per night	Continuum	6.99 [1.12, 43.7]	0.037
Age group[c]			
Under 5 years	16.7 (1873)	1.00 [NA]	NA
5–14 years	18.4 (2062)	1.06 [0.86, 1.32]	0.542
15–24 years	22.6 (2526)	1.16 [0.95, 1.44]	0.143
25–34 years	18.2 (2040)	0.97 [0.77, 1.21]	0.776
35 years and above	24.0 (2686)	1.01 [0.82, 1.24]	0.947

NA Not applicable

[a] Based on exploratory analysis as described in the main text, with glass, completely screened with no holes and completely screened with holes classified as adequately-screened and protective, whereas unscreened, torn or only partially screened were all classified as inadequately screened

[b] See Fig. 8 for a description of the behavioural characteristics of the three terciles of this index of the proportion of human exposure to mosquitoes which occurs indoors and can be prevented with indoor vector control measures [74, 75, 106–109]

[c] Excluded from the final model because non-significant, but presented here for illustrative purposes

[d] Association with community-level mean LLIN scale-up, captured by fitting city-wide mean reported LLIN use the previous night as a continuous covariate, so the odds ratio presented is that estimated based on community-wide usage in the last round of1 surveys (71.2 %) versus the first (51.0 %)

[e] Presented here for illustrative purposes but excluded from the final mode, because reducing vector density is an intermediate outcome of both bed net use and larvicide application, so inclusion confounds evaluation of these vector control measures. Incorporated into the model as a square root-transformed continuous variable so the odds ratio presented represents that estimated for any area with an *Anopheles gambiae* density of one mosquito per tent trap per night compared with a location where none were detected by tent trapping. To get this threshold in context, the highest density of *An. gambiae* recorded was only slightly lower than this (Fig. 6)

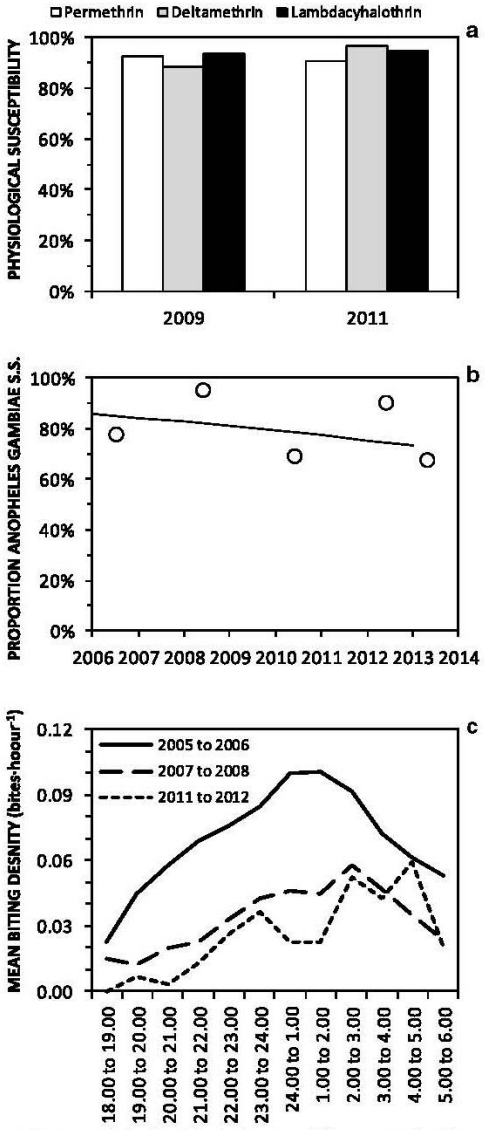


Fig. 4 Time trends in physiological susceptibility to pyrethroids (**a**), sibling species composition (**b**), and biting activity distribution (**c**) of *Anopheles gambiae* sensu lato in Dar es Salaam. Physiological susceptibility estimates (**a**) were obtained from published surveys [110]. Sibling species composition data (**b**) were obtained from PCR analysis of mosquitoes caught through both the routine surveillance collections described here and a range of published [9, 10, 66, 68] and unpublished experimental studies of trapping methods conducted at intense sampling in foci of high vector density. Biting activity distribution data (**c**) were obtained from outdoor HLC data obtained through either routine surveillance from 2005 to 2008, or through quality assurance surveys of routine CB mosquito trapping with Ifakara tent traps between 2011 and 2012

continued to decline, after transition to use of the liquid product from August 2011 onwards was then followed by scale-up of LA from 15 to 43 wards in January 2012, as well as mass distribution and correspondingly increased use of LLINs at the end of 2011 (Fig. 3d, e). This combination of interventions resulted in an estimated EIR of only 0.2 infectious bites·person^{-1} year^{-1} in 2012, in the 15 previously-surveyed wards with which historical comparisons may be made (Fig. 2g).

Increasing usage of LLINs (Fig. 3e), following a mass distribution campaign to "catch up" on universal coverage targets in late 2011, was associated with modestly reduced vector density (Table 1). Analysis of the cross sectional survey data of infection prevalence amongst humans confirms that, while no personal protection could be demonstrated for use of either untreated or treated nets (indeed both were counter-intuitively associated with increased malaria risk; Table 2), increasing city-wide LLIN use (Fig. 3e) was also associated with correspondingly modest community-level reductions of malaria prevalence (Table 2).

LA had no apparent impact upon vector density (Table 1; Fig. 5a) or human infection prevalence (Table 2; Fig. 5b) while directly managed by a private-sector contractor using the granular *Bti* formulation. However, following transition to MoHSW management at the start of 2011, it was consistently associated with dramatically reduced local vector densities, regardless of whether the granule or liquid product was used (Table 1), with no difference in apparent effect between the two formulations ($P = 0.208$). The obvious effects of MoHSW-managed application of the granular *Bti* product upon vector density in the first half of 2011 (Table 1; Figs. 3b, 5c) were matched by corresponding reductions of human infection prevalence (Table 2; Figs. 3c, 5d). However, after MoHSW switched to the liquid product in the second half of 2011, similarly impressive reductions of vector density (Table 1; Figs. 3b, 5e), were no longer associated with corresponding epidemiological impact upon infection prevalence, which remained static into 2012 (Table 2; Figs. 3c, 5f).

While the methods used to measure both human infection prevalence and vector density differed from those used by the preceding studies [15, 16], with which they are compared in Fig. 2f, g and h, careful examination of quality-assurance indicators for these new survey tools do not suggest any reason to doubt the authenticity of the apparent resurgence of malaria in 2010 and sustained high prevalence in 2011 and 2012. Out of the small subsample of 345 participants whose RDT test strip was also tested for the presence of *P. falciparum* DNA by PCR,

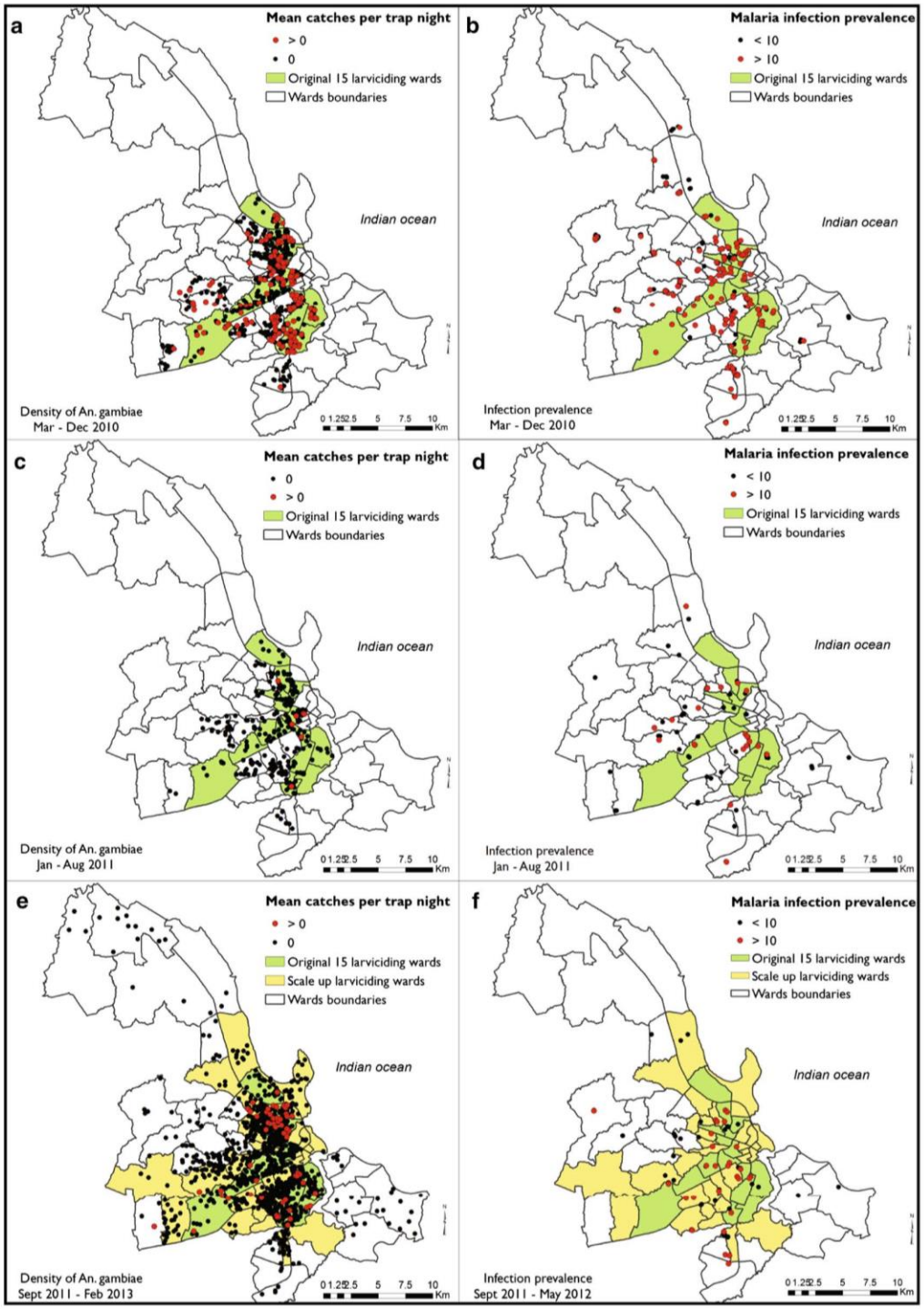


Fig. 5 The geographic distribution of surveyed locations with detectable populations of *Anopheles gambiae* vectors (**a**, **c**, **e**) and > 10 % *Plasmodium falciparum* infection prevalence (**b**, **d**, **f**) over the periods from March to December 2010 when application of a granular formulation of *Bacillus thuriniensis* var. *israelensis* (*Bti*) in the wards highlighted in *green* was managed by a private sector contractor (**a**, **b**), from January to August 2011 when the same granular formulation was applied under management of the Ministry of Health and Social Welfare (MoHSW) in the same wards highlighted in *green* (**c**, **d**), and from September 2011 onwards when a pre-diluted liquid formulation of *Bti* was applied under MoHSW management in the wards highlighted in *green* and *yellow* (**e**, **f**)

infection was confirmed in more than two-thirds (68.5 %; 37/54) of those found to be antigen-positive by RDT. Similarly, entomological surveys through community-based application of tent traps correlated well with the quality-assurance HLC surveys, were at least as sensitive in terms of absolute numbers of mosquitoes caught, and are correlated with local malaria infection prevalence [56], albeit only in fully-exposed houses lacking protective window screens (Fig. 6c, d; Table 2).

Household and individual risk factors for malaria infection

Across all three survey rounds from 2010 to 2012, malaria risk was higher among males and individuals whose household head lacked any education (Table 2). In stark contrast to the previous studies, before most of these interventions had been fully scaled up, no strong variation in RDT-detected prevalence across age groups was obvious (Fig. 7; Table 2).

Despite this apparent loss of immunity (Fig. 7; Table 2), substantive malaria prevalence persisted, simply because the vast majority of infected participants (88 % (1090/1237) had not experienced fever recently, and only 0.37 % (4/1090) of these chronic carriers had been treated for malaria. By the end of the study (Fig. 3c; Additional file 2), the final round of surveys reveals improved rates of treatment of fevers (144 cases) with anti-malarial drugs (91 %; 131 cases), but that use of ACT specifically remained mediocre (42 %; 62 cases). Recent, routine treatment, with neither an ACT (P = 0.984) nor any other anti-malarial drug (P = 0.862), had any detectable effect upon risk of RDT-detected malaria antigenaemia, presumably because drug treatment is an outcome of malaria infection, rather than vice versa, and the antigenaemia which these RDTs detect can last 2 weeks after termination of infection [79].

As observed previously in this setting [15], having stayed elsewhere over the previous month was associated with reduced malaria infection probability (Table 2). Re-analysis of the legacy data from previous studies [15] not only confirmed this observation, but also allowed disaggregation of those who slept elsewhere in Dar es Salaam from those who had slept outside of the city. No difference in risk between travel within and outside the city was apparent (P = 0.331), with a similar trend towards reduced risk in the former [OR (CI) = 0.88 (0.77, 1.02), P = 0.082] and the latter [OR (CI) = 0.77 (0.58, 1.02), P = 0.071], relative to those who had not slept elsewhere. Travel history, therefore, seems unlikely to be a major contributor to ongoing exposure and persistent high prevalence at the end of the study, so most malaria cases were probably locally acquired within the city.

Even more surprisingly, using a bed net was counter-intuitively associated with increased, rather than decreased, malaria risk (Table 2). Of course an equally valid question is whether bed net use behaviour is stimulated by experience of malaria infection, rather than vice versa. Fortunately, RDT eluates from a subsample of 1134 subjects were tested serologically for evidence of a history of previous exposure to malaria AMA antigen. In this subset of subjects, use of a bed net the previous night was positively associated with AMA-reactive serum [OR (95 % CI) = 1.67 (1.04, 2.69), P = 0.034] but not with infection at the time of the survey (P = 0.681), indicating that past experience of malaria infection probably motivates bed net use, rather than immediately active but presumably chronic infection at the time of the survey. Reassuringly, however, increased community-wide LLIN use was associated with substantial reductions of malaria vector density (Table 1) and infection prevalence amongst residents (Table 2).

In contrast to previous studies [15], window screening that was complete but had holes appeared to provide similar levels of protection to complete screening without holes [OR (95 % CI) = 0.74 (0.57, 0.97), P = 0.028 versus OR = 0.89 (0.69, 1.13), P = 0.339, respectively, and P = 0.096 when compared with each other], so these were combined into a single category in the final fitted model (Table 2). Stratified analysis revealed that local vector density was only predictive of increased malaria risk [OR 95 % CI = 22.5 (2.7, 186.2), P = 0.0039] among the minority of participants (14 %; 1308 RDT-tested occupants from 347 households) staying in houses lacking window screening (Fig. 6c, d). No effect of local vector density was observed (P = 0.428) among the majority of participants (86 %; 8036 RDT-tested occupants of 2492 households) staying in houses with window screening (Fig. 6e, f). The final model using data from all households therefore only considers vector density conditional upon lack of window screens (Table 2).

The estimated proportion of exposure to *An. gambiae* bites that would occur while asleep in the absence of a bed net or window screening (π_s) had no apparent influence upon infection probability among all residents (P = 0.456), and among those living in houses with (P = 0.468) or without (P = 0.576) window screening. However, high values for the estimated proportion of exposure to *An. gambiae s.l.* bites that would occur indoors in the absence of a bed net or window screening (π_i) was protective against malaria risk, but only for the majority of participants who lived in well-screened houses (P = 0.00832), and not those living in unscreened houses (P = 0.792). More careful examination revealed no apparent difference in malaria risk between the upper and middle terciles of this behavioural metric of maximum potential for indoor protection among participants with window screening [OR (95 % CI) = 0.71 (0.59, 0.86),

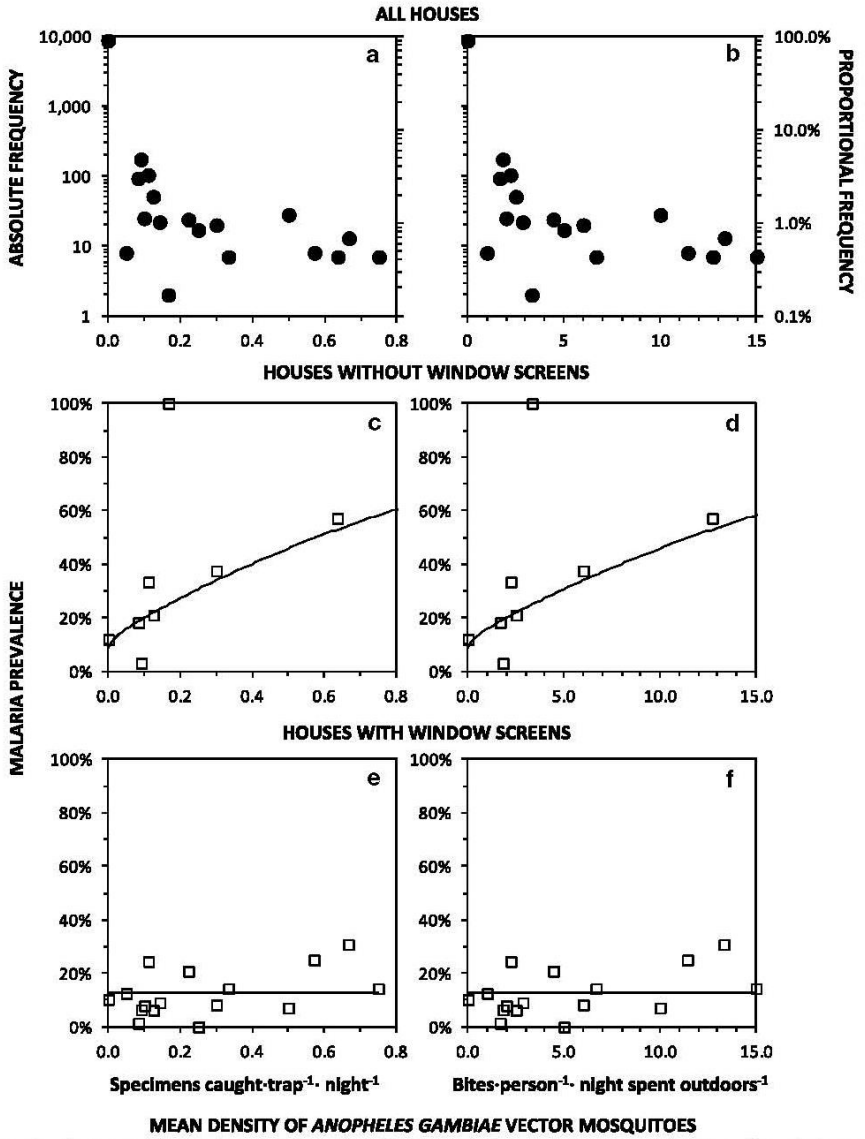


Fig. 6 The frequency distribution and dependence of *Plasmodium falciparum* malaria prevalence upon densities of *Anopheles gambiae* sensu lato in Dar es Salaam. The number and proportion (**a**, **b**) of RDT-tested human subjects, as well as the proportion of those which were diagnosed as infected with malaria in houses with (**e**, **f**) and without (**c**, **d**) window screening, are plotted against vector density, as measured by community based surveillance with Ifakara tent traps (**a**, **c**, **e**) and converted into the estimated equivalent outdoor human landing catch (**b**, **d**, **f**). Continuous lines represent the best fit of models relating malaria infection prevalence to vector density in houses with (**c**, **d**) and without (**e**, **f**) window screens

P = 0.000304 and 0.72 (0.57, 0.89), P = 0.00327] for highest and middle terciles versus the lowest, respectively, and P = 0.970 for the contrast between the middle and high strata), or between the lowest tercile living well-screened houses versus those living in unscreened houses (P = 0.611). The final model using data from all households therefore captures the interaction between window screens and human behaviour in terms of one high risk category and one low risk category: Lack of complete window screening or well-screened windows but lowest π_i tercile versus well-screened windows and middle or upper π_i tercile (Table 2).

Of all the contributing human behaviour variables used to estimate the proportion of exposure to *An. gambiae*

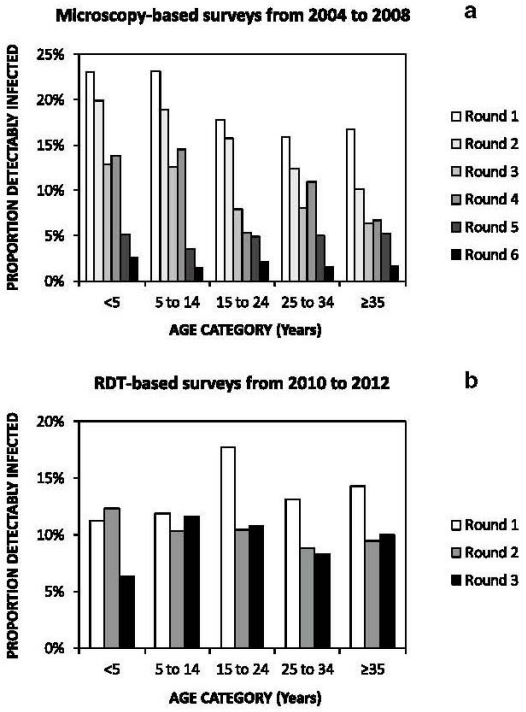


Fig. 7 Age-prevalence profiles for *Plasmodium falciparum* malaria infection observed by microscopy in previous cross-sectional surveys from 2004 to 2008 [15] (**a**) and by rapid diagnostic test in surveys during these subsequent surveys between 2010 and 2012 (**b**)

s.l. bites that would occur indoors in the absence of a bed net or window screening (π_i), none were predictive of malaria risk in their own right. Neither the time at which residents went indoors (P = 0.413) and then went to bed in the evening (P = 0.583), or got out of bed (P = 0.198) and then left the house in the morning (P = 0.121) had any obvious influence upon malaria infection risk. However, examining the distribution of values reported for all these variables reveals remarkably subtle differences between these epidemiologically-relevant behavioural strata: Few participants stayed outdoors beyond 23.00 h or left the house before 05.00 h (Fig. 8), so it seems that even a few extra hours of outdoor exposure in the evenings or mornings result in comparable malaria risk to spending all night in a house with no window screens.

Discussion

The greatest strength and weakness of this study is its purely observational nature, because no effort was made to experimentally control routine, programmatic delivery of any malaria control measure. Observational studies are inevitably prone to biases [80], so this study only provides evidence of *plausibility* rather than *probability* [81]. However, observational studies also have the advantage of being highly relevant to policy and practice if they are conducted by an independent evaluation team and the interventions themselves are delivered under representative conditions of routine programmatic practice [81]. All these surveys of malaria prevalence and mosquito densities were conducted by an independently-funded research team at the Ifakara Health Institute, completely independently of the UMCP staff based at either the municipal councils of Dar es Salaam or at the NMCP of the MoHSW [13]. So, unlike the impact evaluations conducted in the operational research phase of the UMCP between 2004 and 2008 [12, 15, 40], during which the research team was actively involved in planning, delivering and monitoring the LA intervention, this study can be described as a fully representative assessment of programmatic effectiveness [81] of all the interventions implemented in Dar es Salaam over this period.

The most important African malaria vectors are historically notorious for primarily feeding on humans while they are asleep indoors [75], so outdoor exposure may be of minor epidemiological importance in African settings where predominantly indoor transmission persists [73]. Nevertheless, several recent studies from across the continent with only entomological outcomes have suggested cause for concern [82–84] and this study demonstrates unambiguously that outdoor exposure is not only epidemiologically significant in this typical African city, but also varies according to individual human behaviour patterns (Table 2; Fig. 8).

The observation that even spending one or two extra hours outside of well-screened houses, by going indoors just after 22.00 h and 23.00 h rather than before 22.00 h, or by leaving the house just before 06.00 h rather than afterwards, increases malaria risk to a level equivalent to living in a house without window screening is surprising. It is not obvious why most of the increment risk of malaria infection associated with outdoor exposure appears to occur within such a narrow temporal window, but the brevity and predictability of this exposure window does suggest that time-targeted behavioural and/or protective interventions may be quite feasible. Topical repellents [85], vapour-phase insecticides [69, 86, 87], or insecticidal clothing [88–90] may, therefore, have important applications to prevent residual malaria transmission occurring outside of mosquito-proofed houses and sleeping spaces in Dar es Salaam, and many other settings across the tropics.

The surprising observed positive association of personal net use with malaria risk (Table 2) appears to be at least partially explained by human behavioural responses to experience of malaria episodes (Msellemu et al.,

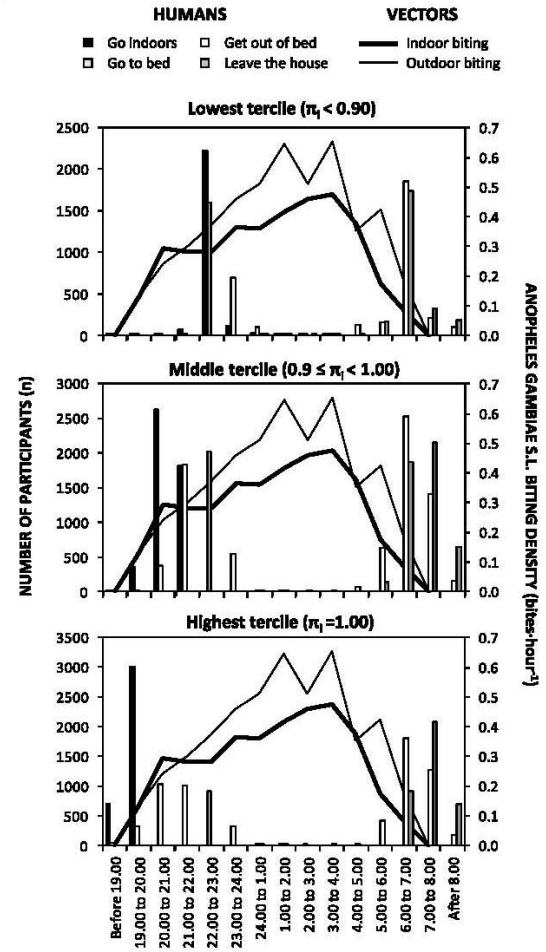


Fig. 8 Times at which individuals interviewed during cross-sectional household surveys in Dar es Salaam reported having gone indoors for the evening, gone to bed for the evening, gotten out of bed in the morning and left the house in the morning, the previous night, stratified by derived individual estimates for the proportion of exposure to *An. gambiae* bites that would occur indoors in the absence of a bed net or window screening (π_i). For comparison with the biting activity profile of the most important malaria vector in the city, these frequencies of human behaviours are plotted alongside the human biting rates measured by human landing catch (HLC) in selected areas of relatively high vector density in 2006 [9, 10] that were used to calculate these individual estimates for π_i

Unpublished). Furthermore, the clear reductions of vector density (Table 1) and human infection risk (Table 2) associated with improved community-wide uptake of LLINs in the last year of the study strongly suggests that individual-level protective effects do occur but have probably been masked by this reverse causality.

The lack of any obvious entomological (Table 1; Fig. 5a) or epidemiological impact of LA (Table 2; Fig. 5b) when managed temporarily by a private-sector contractor is striking, particularly when contrasted with the apparent reductions of vector density associated with LA under MoHSW management throughout the remainder of the study (Table 1; Fig. 5c), as well as the reductions of infection prevalence in the first half of 2011 (Table 2; Fig. 5d). It is not clear from our data why implementation by the private-sector contractor was so ineffective, and no records of process or coverage indicators could be obtained to examine why this might have been the case. However, this observational evidence of apparently successful implementation of LA under the management of MoHSW is especially encouraging and timely, now that the Government of Tanzania has made a long-term commitment to scale up LA across all major urban centres of the country. However, given the disappointing results while LA was temporarily managed by a private contractor, and inconsistency of the epidemiological and entomological results after MoHSW switched from the granular product to the liquid product in the second half of 2015 (Tables 1, 2; Fig. 5e, f), it is essential that an equally strategic approach is taken to operational research for developing increasingly effective implementation, monitoring and evaluation systems for routine LA.

Nevertheless, the lack of any obvious epidemiological impact of LA with the liquid formulation, and the persistence of remarkably high levels of human infection prevalence from mid 2011 onwards (Table 2; Fig. 5f), despite very clear impact upon entomological transmission metrics (Table 1; Fig. 5e), merits careful consideration. While it is possible that the apparent entomological impacts arose spuriously from the biases inevitably associated with any observational study [80], this seems unlikely based on the consistency with the results for first half of 2011 with the granule formulation. Given just how sparse the vector population became over this period, how low the EIR estimates became, and the lack of evidence for suppression of infection detection by acquired immunity, a more likely explanation is probably the persistence of chronic infections [91] among residents. Indeed the EIR estimates presented, including that of only 0.2 infectious bites·person^{-1} year^{-1} in 2012, were calculated for someone sleeping outdoors all year round, without adjusting for the fact that most residents slept inside mosquito-proofed houses and/or bed nets (Table 2). The actual mean EIR experienced by the average resident was therefore most probably well below the threshold of 0.1 infectious bites·person^{-1} year^{-1}, at which malaria transmission may become unstable and prone to elimination [92–94].

In the absence of longitudinal cohort survey data and associated molecular analyses to identify new, recently acquired infections, it is not possible to conclude

definitively that the persisting high levels of parasitaemia observed at the end of the study really are predominantly comprised of chronic infections [95, 96]. Furthermore, such surprisingly high prevalence may also at least partially reflect the fact that once immunity wanes in a population (Table 2; Fig. 7), infection prevalence becomes chaotically dynamic and very difficult to interpret over such short time scales [97]. Nevertheless, the vast majority of infected residents in Dar es Salaam did not report having experienced fever recently, and almost none of these apparently afebrile cases were treated for malaria, even though transmission (Figs. 2, 3) and immunity (Fig. 7) have both clearly waned in recent years. Although further declines in immunity might increase the proportion of malaria infections that cause sufficiently acute clinical symptoms to motivate higher utilization rates of testing and treatment services offered passively at health facilities [98], eliminating human-to-mosquito transmission will probably require more pro-active approaches [91, 99]. Untreated *P. falciparum* infections typically last months or years, during which time they are infectious to mosquitoes [99], so infection prevalence can take several years to respond to changes in transmission intensity [100–104]. Given that such persistent sub-acute infections can also be more accurately described as *chronic* than truly *asymptomatic*, because they cause considerable long-term morbidity and mortality [91], population-wide campaigns to treat chronic, sub-acute infections will probably be required to rapidly and decisively bring an end to local transmission in the city.

Conclusions

Dar es Salaam is a typical African city in many respects, but is also clearly unusually advanced in terms of delivering integrated malaria control programmatically, using several layers of preventative and therapeutic interventions, to the majority of the population through diverse delivery mechanisms. While this programmatically-sustained integrated malaria control programme has clearly achieved dramatic reductions in malaria burden, the persistence of endemic transmission by remarkably sparse populations of efficient vectors, much of which occurs outdoors [9, 10], is equally notable. While additional measures to protect against outdoor transmission exposure [69, 85–90] are clearly desirable, perhaps the most immediate opportunity for progress towards malaria elimination is further scale-up of LA and mosquito-proofed housing, ceilings and closed eaves in particular. However, accelerated elimination of malaria from this urban setting will also probably require active, population-wide mass screen-and-treat or mass drug administration campaigns to cure chronic human infections [91, 99], which can otherwise persist for many years [100–104].

Additional files

Additional file 1. Excel® spreadsheet template for calculating individual-level estimates for the proportion of exposure of bites by *Anopheles gambiae* sensu lato that would occur indoors or while asleep in the absence of any protective interventions such as window screens or bed nets. This example is populated with a sample of questionnaire data describing the times residents reported having gone indoors for the evening, gone to sleep for the night, woke up in the morning and left the house in the morning, as well as published patterns of vector biting activity as measured by human landing catch in parts of Dar es Salaam with vector densities that were high enough to measure [9, 10].

Additional file 2. Excel® spreadsheet summaries of sampled households and participants.

Abbreviations

ACT: artemisinin-based combination therapy; AMA: apical membrane antigen; *Bti*: *Bacillus thuringiensis* var. *Iisraelensis*; CI: confidence interval; DNA: deoxyribonucleic acid; GLMM: generalized linear mixed model; EIR: entomological inoculation rate; HLC: human landing catch; HRP: histidine-rich protein; ITN: insecticide-treated net; ITT: Ifakara tent trap; LA: larvicide application; LLIN: long-lasting insecticidal net; MoHSW: Ministry of Health and Social Welfare; NMCP: National Malaria Control Programme; OR: odds ratio; PCR: polymerase chain reaction; RDT: rapid diagnostic test; RR: relative rate; TCU: ten cell unit; UMCP: Urban Malaria Control Programme.

Authors' contributions

Conceived and designed the study: DM, NFL, CJD, NJG, PPC & GK. Implemented the study: DM, HIN, VM, AN, YM, ZJM, SSK, NFL, SM, SD, NJG, PPC and GK. Conducted or contributed to the analysis: DM, HIN, VM, AN, SM, SD, CJD, NJG, PPC and GK. Drafted or edited the manuscript: DM, HIN, VM, AN, YM, ZJM, SSK, NFL, SM, SD, CJD, NJG, PPC and GK. All authors read and approved the final manuscript.

Author details

[1] Environmental Health and Ecological Sciences Thematic Group, Ifakara Health Institute, Dar es Salaam, United Republic of Tanzania. [2] Department of Immunology and Infection, London School of Hygiene and Tropical Medicine, London, UK. [3] School of Biological Sciences, University of Nairobi, Nairobi, Kenya. [4] School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. [5] Department of Vector Biology, Liverpool School of Tropical Medicine, Liverpool, UK. [6] Department of Mathematics, Statistics and Computer Science, Marquette University, Milwaukee, WI, USA. [7] Eck Institute for Global Health, Notre Dame University, Notre Dame, IN, USA. [8] Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland. [9] University of Basel, Basel, Switzerland.

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Competing interests

The authors declared that they have no competing interests.

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Annexure Ic: Original paper III

Upgrading of informal settlements and house screening provide effective urban planning interventions against malaria transmission hazard and risk to complement bed net and microbial larviciding in Dar es Salaam Tanzania

Victoria M. Mwakalinga[1, 3*], Marco Burra[1], Benn Sartorius[4], Maureen Coetzee[5], Stefan Dongus[2, 6, 7, 8] and Gerry F. Killeen[2, 8]

[1] Ardhi University, School of Spatial Planning and Social Sciences, Department of Urban and Regional Planning, P.O. Box 35176, Dar es Salaam, Tanzania

[2] Ifakara Health Institute, Environmental Health and Ecological Sciences Thematic Group, Kiko Avenue, Mikocheni, P.O. Box 78373, Dar es Salaam, Tanzania

[3] School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[4] Discipline of Public Health Medicine, School of Nursing and Public Health, University of KwaZulu-Natal, Durban, South Africa

[5]Wits Research Institute for Malaria, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[6] Swiss Tropical and Public Health Institute, Department of Epidemiology and Public Health, Socinstrasse 57, P.O. Box, 4002 Basel, Switzerland

[7] University of Basel, Petersplatz 1, 4003 Basel, Switzerland

[8] Liverpool School of Tropical Medicine, Pembroke Place, Vector Biology Department, Liverpool L3 5QA, United Kingdom

*Corresponding Author: (vmwakalinga@cartafrica.org; Tel +255-689-672874)

Abstract

Large efforts for malaria control in Dar es Salaam are effectively directed to promoting bednet use and scale-up of larviciding activities while other important community and multi-sectoral complementary measures are neglected. This study aims to provide the relative contribution of households and sectoral factors of malaria transmission in Dar es Salaam and use them to generate a prediction map of hotspots for malaria transmission hazard and risk. Densities of mosquito vectors was collected using longitudinal surveys while malaria positivity was collected from cluster-sampled cross sectional surveys. Household information was collected through questionnaires. Distances from households to nearest infrastructures were calculated using proximity spatial analysis. The maps for landuses and surveyed/non-surveyed plots were used to collect supplementary information for each household. A GPS was used to collect spatial data. Boosted Regression Trees (BRT) model with a Bernoulli family was used in the analysis. The results for malaria hazard and risk models showed a cross-validated performance score (Area Under the Receiver Operator Characteristic Curve, ROC AUC) of 0.88 and 0.89 for hazard and risk models respectively. Of the 20 predictors in the hazard model, 13 were the most important factors for exposure to malaria hazard. While, of the 17 predictors of malaria risk only 9 were most influential for malaria risk transmission. Factors with higher influence in the hazard model were associated with environmental quality such as residing in upgraded settlements (11.2%) and distance to rivers (9.3%) while those related to risk were related to social economic status i.e. security of tenure (32.5%) and housing quality (11.2%). The correspondent partial dependence plots for the predictors in both models showed expected relationship with malaria hazard and risk s except that of bednet use which contradicted the existing understanding by showing that hotspots of malaria infection were among households using bednets. The BRT predictive hotspots maps for each model are presented. The findings may be useful in improving surveillance and interventions for urban malaria control and also for guiding design of integrated approach for malaria control.

Background

Despite the advanced interventions in place, malaria remains a major public health problem and a leading cause of morbidity and mortality globally (WHO., 2013). In 2010, 82.7 million disability-adjusted life years (DALYs) were due to malaria globally (Murray et al., 2012a). In recent years, malaria has been successively reduced in many endemic countries as a result of the availability of more key frontline interventions such as Insecticide Treated Nets (ITNs), Indoor Residual Spraying (IRS), larvae management, rapid diagnostic tests and artemisinin-based combination therapy (ACT) (WHO., 2013). These achievements have triggered many endemic countries to re-focus their control goals to target elimination. This ambitious goal can only be achieved if the existing control measures are complemented with collective intervention efforts from health, community and other development sectors such as infrastructures.

Tanzania like many other countries in Sub-Saharan Africa has put best intervention strategies in place (Kramer et al., 2014). One is through distribution of free bednets to all households with under-five children all over the country (Schellenberg et al., 2001). In parallel, the government provides discount vouchers for pregnant women at their first antenatal visit to buy nets at subsidized prices (Hanson et al., 2008). These initiatives have substantially reduced malaria among these vulnerable groups across the country (Mboera et al., 2013). Despite the reduction, malaria still persists as a huge burden in many parts of the country and accounts for nearly one third of the country's disease and mortality burden (President's Malaria Initiative, 2012, Mayala et al., 2014).

In Dar es Salaam, the annual malaria prevalence has decreased to about 11.1% (Msellemu, et al *in-preparation*) and the entomological inoculation rate (EIR) of one infectious mosquito bite per person per year (Chaki et al., 2012a). This prevalence is highly localized spatially such that 95% of it is confined to only a small (23%) area of the city (Mwakalinga et al, 2016). In this

epidemiological setup, control measures aiming to target these few spatial units are most effective (Bousema et al., 2012b) than blanket coverage of intervention. Apart from relying on identification of high risk areas (hotspots), successful targeted interventions also depend upon appropriate determination of the factors driving persistence of malaria infection hotspots. Meanwhile much efforts of the National Malaria Control Program (NMCP) are focused on promoting, subsidizing and distributing bed nets, IRS and larvicides across large part of the city but fewer efforts are put on enhancing community uptake of interventions such as house screening which have recently shown huge influence on the persistence of malaria infections in the city (Ogoma et al., 2009a). As it is well documented that ITNs and IRS alone are not enough to eliminate malaria even in low transmission settings such as Dar es Salaam, further research is required to reveal complementary interventions that will help to control both indoor and outdoor transmission and guide control programs such as NMCP to make further progress in suppressing malaria transmission. Unfortunately, most recent interventions by the NMCP are explicitly designed based on health sector while the factors which are also important for malaria transmission are not sectoral bound. In Dar es Salaam it is even much complex because of recently ongoing demographic and spatial transformations and urban restructuring. This study therefore uses Boosted Regression Trees to reveal contribution of community and multi-sectoral complexities which are associated with spatial variations of malaria infection hotspots in Dar es Salaam city and use them to generate a spatial prediction map of malaria hotspots in the city.

Materials and Methods

Study area

The study was conducted in Dar es Salaam, a coastal city in the South-Eastern shores of Indian Ocean in Tanzania. Dar es Salaam is a fast growing and the most important economic and political city in the country (World Bank, 2006). The city has a total of 1400km^2 and 4.6 million inhabitants with an annual growth of 5.6% (National Bureau of Statistics., 2013). Its climatic

condition is hot and humid, with two rain seasons per year. The long rains are observed in the months of March, April and May while short rains are in October, November and December (National Bureau of Statistics, 2003). Malaria transmission in Dar es Salaam is low but stable across the age groups (Msellemu et al, 2016).

Administratively, Dar es Salaam operates under the Local Government hierarchical set up i.e. city, municipality, ward, neighborhood and Ten Cell Unit (TCU). The city has three municipalities namely Ilala, Kinondoni and Temeke which are subdivided into 90 wards and 504 neighborhoods (National Bureau of Statistics., 2013). Each ward has a minimum of 2 to a maximum of 15 neighborhoods. The neighborhoods are further subdivided into TCUs, comprising clusters of approximately 10 to a maximum of 100 houses (Dongus et al., 2011a). This study was conducted in all municipalities including 51 wards, 102 neighborhoods and 150 TCUs, with a total surface of 378.9km^2.

Variables

The outcome variables of this study include 1) hotspots of malaria transmission hazard and 2) hotspots of malaria transmission risk at household level. These variables were binary (hotspot and non-hotspot). The explanatory variables were 37 including households, community and multi-sectoral factors (Mutero et al., 2014) as shown in Table 1.

Data collection

Data for mosquito vectors (which was a measure of transmission hazard) were routinely collected using longitudinal surveys in 2015 locations distributed across the city. Malaria infections were collected from cluster-sampled cross sectional surveys conducted across the entire city in three different rounds of the Malaria Transmission Consortium (MTC) project (Msellemu et al, 2016). The first round took place from March until December 2010. The second started in May and ended in July 2011 and the third round began in September up to

December 2012. During the surveys, a total of 11,187 individuals were screened for malaria parasites using the Rapid Diagnostic Tests (RDTs). A detailed structured malaria indicator survey (MIS) questionnaire was used to collect individuals and household information. The information collected include (i) *demographic structure* (sex, age), (ii) *socio economic status* (number of householders, education level of household head, wall type, roof type, ceiling type, type of window screening and floor materials), (iii) *housing/physical protections* (eaves condition, ceiling quality, condition of window air brick gap), (iv) *household's utilization of health sectors interventions* (bed net use, spray in 12 months, use of insecticide sprays, use of repellents and net soaked/dipped, treatment seeking behavior, if they had fever in the past two weeks and use of any drugs in the last two weeks) and (v) *human behavior* (time went indoors last night, time went to bed last night, time got out of bed and time went out that morning) (Table 1).

Spatial data

Coordinates for all houses in the study area were taken using a hand-held Global Positioning System (GPS) device at an accuracy of 5m; and later mapped using Universal Transverse Mercator (UTM) WGS 84, Zone 37 Southern Hemisphere on ArcGIS software. It was important to do all spatial analyses at household level to allow finer spatial scale detection of the effect of each factor on human malaria infections which could probably explain the observed fine-scale spatial clustering of malaria in Dar es Salaam, where extreme variations were observed between TCUs within same neighborhoods (Mwakalinga et al., 2014).

Multi sectoral data collected involved infrastructures mainly health facilities, roads, drainage, education facilities, water supply and solid waste collection services. In urban planning sector this study involved data on types of landuse (agriculture areas, industrial areas, swampy areas, protected/hazard areas, residential areas, commercial-residential areas, garages, informal sectors, markets and office areas), settlement typology (here it refers to whether the household was in a planned or unplanned settlement). From lands and surveying sectors information on

plots where the household was living whether surveyed or not, had a security of tenure or not were collected.

The sectoral data used here were accessed from different sources. All infrastructure data (was for 2012) except solid waste collection services and sanitation type which were accessed from the National Bureau of Statistics (NBS). The landuse map for 2012 (was accessed from the National Landuse Planning Commission), surveyed/non-surveyed plots/security of tenure, informal/formal settlements (all accessed from the Ministry of Lands, Housing and Human Settlements Developments (MLHSD). Data on sanitation types and waste collection services were collected through a household survey conducted in January to March 2014).

The criteria to determine distances whether the household was near of far from infrastructures/landuses was based on urban planning principles (urban neighborhoods and compact city design rules) which have been used for centuries in guiding physical development of cities (UN-Habitat, 2014, MLHSD, 2007, Collison, 1954). These principles provide spatial ranges (catchments) suitable for appropriate services/utilities provision in urban areas. Proximity analysis on ArcGIS software was done to determine households which were within or beyond these catchment areas in terms of landuses and infrastructures. For health facilities, this range varies according to hierarchy (type of facility). For a dispensary, the catchment is 0 – 500m, health centre is 501m to 1000m and for hospital is >1000m. For early diagnostic and treatment of malaria parasites and implementation of health sectors interventions such as distribution of discounted bed nets to pregnant women; dispensaries and health centers are important levels to be within catchment areas (walking distances). Households which were within 500m of any health facility were considered to be near and those beyond 500m were considered to be far. Similar spatial analysis was done in other services such as water, drainage and roads. By principle, these services should be accessible within a walking distance which is 500m. Other sectoral factors and their spatial ranges used in this study are shown in Table 1.

However, for the purpose of this study the spatial ranges were categorized into three i.e. 0-100m, 101m to 500m, and >500m in order to provide clear outlook of the data at different distances.

Data analysis

Univariate analysis was conducted to scrutinize factors associated with malaria transmission hazard and risk. Polychoric correlation analysis was further employed to check for collinearity among variables. Only variables with a Polychoric Correlation Coefficient (ρ) of <0.7 were retained for BRT modelling. The association between households and multi-sectoral factors and malaria hazard/risk hotspots was identified using Boosted Regression Trees (BRT), a machine learning algorithm developed by (Friedman et al., 2000a). BRT was preferred in this study because of its capability in dealing with complex relationships including nonlinearities, interactions and adaptation of predictor variables of any type including numeric, binary, categorical and spatial (Elith et al., 2008a, Cheong et al., 2014b).

R software version 3.0.2 was used to fit the BRT model with package "*dismo*" version 0.8-17 (Cheong et al., 2014b) and package "*gbm*" version 2.1 (Ridgeway, 2013b). The BRT provides the relative importance of each explanatory variable in the model based on the number of times a variable is selected for splitting, weighted by the squared improvement and averaged over all trees (Friedman and Meulman, 2003). The relative importance of each variable is then scaled to the sum adds to 100 as percentages and a variable with highest percentage has a stronger effect on the outcome (Elith et al., 2008a). Only variables above the randomness threshold i.e. 100%/Total number of explanatory variables will be presented. Partial dependence plots will be used to visualize and interpret the effect of most influential predictors on the hotspots of malaria infections.

The steps forward function (Elith et al., 2008a) an alternative to Ridgeway cross-validation function (Ridgeway, 2013b) with bagging factor of 0.5 (Friedman, 2001a) meaning that the first regression tree is fitted to the dependent variable while randomly selecting 50% of the training data (Cheong et al., 2014b) was used. A slower learning rate (*lr*) usually suggested (and also opted for this study) for a better model building process (Elith et al., 2008a). The number of splits levels of each tree i.e. tree complexity (*tc*), determines the degree to which predictors may interact with each other in relation to the response. More levels of interactions are explained with a higher *tc* (Cheong et al., 2014b). The maximum number of trees was not set to allow identification of the optimal number of trees (*nt*) (Elith et al., 2008a). In this study, BRT was fitted with a "bernoulli" family because the outcome variables were binary as explained above. Three different combination of *lr* (0.0002, 0.001 and 0.05) and four *tc* (3, 5, 7 and 10) parameters were tested. The model with the highest cross-validated Receiver Operating Characteristic Area Under the Curve (ROC AUC) score was selected (Hastie et al., 2009).

The spatial BRT prediction was done using package "*raster*" version 2.2-30 and package "*rgdal*" version 0.8-16 (Elith et al., 2008a) and final maps prepared in ArcGIS. Spatial prediction was done to identify the probability of malaria hotspots occurrence in the study area. The inputs for the spatial model were the most influential predictors only i.e. those above randomness thresholds which was 5.0% for hazard model and 5.8% for risk model.

Results

Results of univariate model are shown in Table 2. The Polychoric correlation coefficient indicated that 8 out of 37 (remaining 29) variables were correlated ($\rho>0.7$) and hence omitted for univariate and also BRT modelling to avoid multicollinearity problems (Table 2). Only factors with significant association with malaria transmission hazard or risk were retained for further modelling. For hazard model, only 9 variables did not have significant association with

hazard hotspots and hence omitted for BRT modelling, meaning only 20 variables were retained. While in a risk model only 17 variables were retained for BRT after univariate analysis.

- **Boosted Regression Trees**

The selected BRT models were fitted using a lr of 0.0002, tc of 5 and a total of 8500 decision trees. The ROC AUC scores were 0.88 and 0.89 for hazard and risk models respectively. Both models had a mean total deviance of 0.85 and a mean residual deviance of 0.63. The estimated cross-validation deviance was 0.67 with a standard error of 0.005 for hazard model and 0.69 with a standard error of 0.006 for risk model. The correlation with the training data was 0.59 and the cross-validation correlation was 0.51 in both models.

Relative importance of predictors

Out of 20 predictor variables for transmission hazard only 13 had a substantial relative importance which was above the randomness threshold of 5% (100%/20) (Table 3). While for malaria risk, only 9 variables out of 17 had a substantial relative importance which was above the randomness threshold of 5.9% (100%/17) (Table 4). In these two models, that of malaria risk was highly skewed in terms of relative importance because only three top variables had carried more than half (50%) of the relative importance. And it is interesting to note that all these variables are indicators of social economic status of the household. However, relative importance of from hazard model was relatively normally distributed because although the ones with higher influence belong to environmental quality. The correspondent partial dependence plots for each of the predictors with relative importance above the threshold size are presented in Figure 4 for malaria hazard and 5 for risk.

Risk of malaria transmission was higher in certain locations with detectable *An. gambiae s.l.* than those without any *An. gambiae s.l.* caught over the study period. However, these vectors

were only predictive [RR (95% CI) = 22.5 (20.7, 186.2), P = 0.004] of malaria risk in only a small portion (14%) of city dwellers residing in houses lacking window screening[8] (See Figs. 6c & d and Table 2 in Annex 1b) and those in unscreened houses whose human behaviour indicators (πi[9]) belong to the lowest tercile of indoor transmission exposure (See Fig. 8 and Table 2 in Annex 1b). The distribution of biting activity of *An. gambiae s.l.* across different times of the night remained consistent with those observed previously (Fillinger et al., 2008, Geissbuhler et al., 2007), except perhaps for a slight shift to later hours of the night, between mid-night and dawn (See Fig. 4c).

Increased community-wide coverage of LLINs significantly reduced both malaria infection hazard (Table 3) and risk (Table 4). The effect of individual use of treated bed nets was also associated with decreased (as indicated by a negative step function in 1c Fig. 4j) densities of *An. gambiae s.l.* In stark contrast, results (Table 4 and Fig. 5f) models show positive association of malaria infections and individual use of bed nets rather than vice versa. More interestingly, this variable was among the most influential indicators of malaria risk (Table 3). This counter-intuitive association was however rationalized through focus group discussions and revealed that bed net usage behaviour was elicited by past experience of malaria infections rather than immediately active cases but presumably chronic infection at the time of the survey (Msellemu et al, unpublished). This observation was further confirmed by a serological test on >1000 serum samples which provided evidence of a history of previous exposure to malaria (detected via AMA antigen), suggesting that use of a bed net the previous night was positively associated with AMA-reactive serum [OR (95% CI) = 1.67 (1.04, 2.69), P = 0.034] but not with infection at the time of the survey [OR (95% CI) = 1.01 (0.81, 1.26), P = 0.901].

[8]Based on exploratory analysis as described in the main text, with glass, completely screened with no holes and completely screened with holes classified as adequately-screened and protective, whereas unscreened, torn or only partially screened were all classified as inadequately screened

[9]*Πi* is a measure of human behaviour which is calculated based on the time spent indoors and outdoors during mosquito peak hours (Msellemu et al, 2016).

Larviciding did not have any detectable effect on either hazard [OR (95% CI) = 0.89 (0.72, 1.09), P=0.247] or risk [OR (95% CI) = 0.68 (0.38, 1.21), P=0.187] of malaria transmission when its activities were managed and financed by an external contractor (RTI) (See Annex 1b for detailed analysis). Its effect was intensely noticed in 2011 when the GoT, through the NMCP, took over all the management and financial responsibilities of larvicide application using a granular *Bti* product similar to what RTI used in 2010. During this period, malaria hazard was reduced by 69% and risk by 74%. Further reduction of malaria hazard (85% reduction) was observed in 2012, when the government started using a pre-diluted liquid suspension product of *Bti*. However, malaria risk did not reduce any further following continuation with the liquid *Bti* product (see Table 3, Figs. 3c & 5f). Further results of BRT models indicate that, residing in wards under larviciding had collective effects on reducing hazard (See Fig. 4d) as well as risk (See Fig. 5i) of malaria transmission. For *An. gambiae*, larviciding was among the four most important predictors of malaria hazard in the city.

History of travel within (sleeping elsewhere within the city) and outside (sleeping elsewhere outside the city) Dar es Salaam did not show any apparent difference in risk of malaria transmission (Msellemu et al, 2016). Further results of BRT models indicated no difference in hazard [OR (95% CI) = 1.08 (0.95, 1.22), P = 0.242] or infection risk [OR (95% CI) = 1.18 (0.91, 1.51), P = 0.208] between households residing within 500m radius of train/bus/taxi/lorry terminals and those living elsewhere, outside these catchments in the city. Travel history, therefore, seems unlikely to be a major contributor to ongoing exposure and persistent high and chronic prevalence in this study area, so most malaria cases were probably locally acquired within the city.

Of all the contributing human behaviour variables used to estimate the proportion of exposure to *An. gambiae s.l.* bites that would occur indoors in the absence of a bed net or window screening (πi), none were predictive of malaria risk in their own right (Msellemu et al, 2016).

Neither the time at which residents went indoors [OR (95% CI) = 0.37 (0.11, 1.18), P = 0.413] and then went to bed in the evening [OR (95% CI) = 0.46 (0.15, 1.39), P = 0.583), or got out of bed [OR (95% CI) = 1.78 (0.87, 3.67), P = 0.198) and then left the house in the morning [OR (95% CI) = 1.05 (0.49, 2.25), P = 0.121] had any obvious association with malaria infection risk. However, examining the distribution of values reported for all these variables reveals remarkably subtle differences between these epidemiologically-relevant behavioural strata. Few participants stayed outdoors beyond 23.00 h or left the house before 05.00 h (Msellemu et al, 2016) had more malaria similar to those sleeping in unscreened houses. So, it seems that even a few extra hours of outdoor exposure in the evenings or mornings resulted in comparable malaria risk to spending all night in a house with no window screens.

House screening (Msellemu et al., 2016) reduced risk of malaria transmission [OR (95% CI) = 0.74 (0.57, 0.97), P = 0.028 for partial window screening and OR (95% CI) = 22.5 (2.7, 186.2), P = 0.0039, for complete window screening). No effect of local vector density was observed [OR (95 % CI) = 0.79 (0.53, 1.16), P = 0.428] among the majority of participants (86%) staying in houses with window screens (Msellemu et al, 2016). Together with window screening, simple features such as closed eaves[10] and/or ceilings were also associated with reduced malaria risk [OR (95% CI) = 0.36 (0.14-0.89), P = 0.028] because these features limit the entry of mosquito vectors in the house. Notably, house screening only reduced risk of infections [OR (95% CI) = 0.71 (0.62, 0.82), P = <0.001]; and Fig. 5d) if the evenings and mornings were spent indoors (among individuals belonging to highest and middle tercile of human behaviour). Both hazard and risk were significantly lower among individuals whose houses were built with higher quality building materials (See Tables 3 & 4; and Figs. 4d & 5b). Better-quality housing appeared to be amongst the most influential factors underlying the variations on malaria hazard (see Table 3) and infections risk (see Table 4) probably because higher quality building is an

[10]the gap between the top of the wall and the over-hanging roof

indication of higher social economic status (SES) and people with higher SES are able to purchase protection measures against mosquito bites and treatment of malaria infections.

Unexpectedly, having a right of occupancy (security of tenure) was a leading protective factor against risk (See Table 5.3) and the third against hazard (See Table 3) of malaria transmission in Dar es Salaam. Security of tenure had a very strong negative association with both malaria hazard (See Fig. 4c) and risk (See Fig. 5a). More remarkably, 93% of perfectly screened houses (windows, airbrick gaps and roof) and 96% of houses built with high quality building materials had title deeds. This implies that security of tenure motivated residents to build standard houses which in other ways lessens human contact with mosquito vectors and hence reduced risk of malaria transmission.

Informal settlements licensing programme (under the Ministry of Lands through MKURABITA) did not show any detectable effect on both hazard [OR (95% CI) = 0.82 (0.18, 3.64), P = 0.794] and risk [OR (95% CI) = 0.76 (0.28, 2.05), P = 0.583] of malaria transmission. This observation was similar to informal wards which were not covered by any urban planning program. Dramatic reduction of malaria transmission hazard and risk (See Tables 3 & 4; and Figs. 4a & i; 5c & h) was noted in the wards which were under housing and infrastructure upgrading (under CIUP financed by the GoT/World Bank) as well as informal settlements regularization programmes (under supervision of local governments but financed by local communities themselves). In both cases the two programmes were among the most influential factors for malaria hazard (Table 3) and risk (Table 4). This is presumably because apart from legalizing the plots/houses by offering long term (33, 66 and 99 years) title deeds, the programmes involved systematic spatial organization and surveying of all settlements under the project areas. The CIUP for instance, went further to financing and constructing roads, drainage networks, sanitation, sewerage and garbage collection facilities. The settlement plans under these programmes designated and allocated plots for all other urban amenities such as

health facilities. Although these projects were intended for upgrading of informal settlements, their impact went further to reduction of breeding habitats within the project areas through constructed drains. They also contributed to improved accessibility to effective diagnostic and treatment services through bringing social services including health closer to individuals, among other elements of the programmes to empower the urban poor.

iv) Thresholds and catchments of urban infrastructure and services

Surprisingly, living at shorter distance (within 500m) from major roads and drainage (Fig. 2a) was positively associated with malaria hazard (Table 3) and risk (Table 4). Closer proximity to roads have been reported elsewhere (Kazembe, 2007) to enhance access to diagnostic and treatment facilities. Both of these factors were among the most influential determinants of hazard (Table 3) and only distance to roads for transmission risk (Table 4). Nevertheless, shorter distances to these roads and drainage had no detectable effects [OR (95% CI) = 2.17 (0.49, 9.61), P = 0.309] for hazard and for risk [OR (95% CI) = 1.75 (0.67, 4.59), P = 0.254] among the households who were living in upgraded settlements and those with security of tenure. In addition to roads and drainage, hazard and risk of malaria transmission was also high among households residing within shorter distances (up to 500m) from main water pipes (See Fig. 2a) and waste collection/dump sites (Table 3 & 4) particularly in informal settlements. Access to informal structure however is a reflection of lower SES which influence affordability to protection and treatment measures. Living within 500m radius from any health facility (dispensary, hospital, health centre and medical shops) reduced malaria risk but did not have any detectable effect [OR (95% CI) = 0.43 (0.02, 10.95), P= 0.613] on hazard of transmission.

Similar to findings from elsewhere (Klinkenberg et al., 2003, Klinkenberg et al., 2008, Leon, 2008), diversity of urban land use types is strongly associated with the presence of multiple distinct aquatic larval habitat types of *An. gambiae*, diverse proliferation of adult mosquitoes and malaria infections at different spatial scales. In Dar es Salaam, foci (Carter et al., 2000) of

malaria transmission occurred within a 500m radius from agricultural, open spaces, commercial and industrial uses (See Fig. 2). This finding suggests that households residing within these catchments experienced higher hazard and risk of malaria transmission (Table 3 & 4) than those living elsewhere in the city, unless the resilience of these households is high enough to reduce risk of exposure. Moreover, densities of *An. gambiae* correlated with shorter distances to garages, markets and areas designated for petty trading (Table 3) while malaria risk was lower in households living closer to institutional land uses (Table 4).

- **Spatial predictions**

This theme highlights the importance of local population resilience when mapping risk of malaria transmission. Inclusion of RSI in the CAR models improved performance in hazard prediction ($R^2 = 0.88$) when only topography was included and improved by a further 3% ($R^2 = 0.91$) when RSI was accounted for (See Table 5). Correspondingly, very high performance of the CAR risk model was found when hazard and resilience were included as predictors together with topography (R^2 was only 0.55 when topography alone was used and it improved by a further 31%, $R^2 = 0.86$, when RSI and hazard were added). More interestingly, in the risk model RSI accounted for more than half of the contribution of model performance, while topography and hazard accounted for less than a third of the contribution (See Table 5).

Discussions

This study has managed to explain different relationships between households/sectoral factors and hotspots of malaria transmission hazard and risk in Dar es Salaam. It has also demonstrated the spatial pattern of malaria hotspots based on the identified most influential factors for malaria transmission in the city and also the inclusion of resilience and topography in the prediction.

Other than frontline and widely used interventions for malaria control worldwide, this study finds that the most important factors for malaria infections in Dar es Salaam are the ones which are programmatically given little or no attention by government control programs such as National Malaria Control Program (NMCP) and Urban Malaria Control Program (UMCP). These include window screening a simple and direct community intervention with a huge impact in malaria control. The effectiveness of window screening in providing powerful complementary strategy towards malaria elimination has been well documented (Ogoma et al., 2009a, Kirby MJ et al., 2009). Although many houses seems to be screened already in Dar es Salaam, the intervention remains important to sensitive appropriate screening that aims to provide protection against mosquito entry in the houses (Ogoma et al., 2009a). However, the effect of house screening was much high when interacted with human behaviour. Showing that poor houses did not provide protection to residents who were indoors at night and early morning and good housing was less effective in protecting individuals spending much time outdoors during mosquito peak hours. Subsidies are directed to bednets (which was the fourth among the most important factors) but not to building material which could enable residents even those with lower socio economic status to afford them and manage to build decent and well screened houses.

Contra intuitively, living near major roads (up to 100m) increased exposure to malaria infections. The current knowledge indicates that living at shorter distance to roads likely increase chances to access health services for timely diagnostic and treatment and therefore can contribute to reduction of overall malaria infections. The possible explanation in Dar es Salaam might be due to ongoing large roads construction projects (almost all major roads (in different phases) started to be reconstructed in 2009 to date) which are accompanied by digging and leaving out uncovered holes for long time which in turn during rains these holes become potential breeding habitats for mosquitoes. Although most of these areas fall within UMCP wards, there are no interventions such as killing mosquito larvae in place to target road

construction areas. This might be due to the fact that the breeding habitats in road construction sites are new breeding areas that the current control programs never identified them when the programs were starting. Hence through this study the UMCP for instance may use these results to include road construction sites as potential places for larvicing. Another explanation would be lack of security of tenure to the residents living near the roads because of ongoing city's restructuring and demolition of houses which are mostly built on illegal areas (Right of Way i.e. 15m to 120m depending on the road hierarchy) to leave spaces for roads. These residents tend not to invest in improving their houses e.g. through screening because they count it as a loss expenditure since they expect to be evacuated any time. The issue of drainage although they tend to be built next to the roads did not come as among most influential factors although most of them are were seen destructed, blocked or not functioning well because they keep polluted water which are not suitable for mosquitoes transmitting malaria.

Bednet use indicated high malaria infections. This is a contradicting relationship as it is well known that bednet use reduces malaria. However, this finding strengthens the results from a recently study in Dar es Salaam (Msellemu et al, 2014, in preparation) which used a different approach but found a similar association. The interpretation could be that net use is triggered by repeated episodes of malaria infections; hence more net use in the households provides an indication of more experience of malaria (Msellemu et al, 2014, in preparation). A further study can be done to explore this association and determine if hotspots of malaria infections can be mapped based on distribution of bednet uses.

All in all, the most influential factors for malaria infections in Dar es Salaam emerged from sectors other than health. Health sector interventions such as bednet use and larviciding had less relative influence compared to those from housing and infrastructures sectors. Despite their importance, they were given less attention.

Limitations

Data on infrastructure were not collected parallel to malaria surveys. However for consistency, we managed to get the maps for infrastructure and landuse for the same year the surveys were conducted. It was challenging to get data which were not in the maps retrospectively because it took long time for some households to recall back the situation during the time malaria survey was conducted. However, apart from this challenge, the study managed to provide most influential factors and to predict hotspots of malaria. Adding on that, it would be important to know if the pools of water within road construction consisted larvae for malaria parasite during the time of survey in order to confirm the observed association between malaria and distance to roads.

Conclusion: Subsidizing and promoting net use remains an important intervention strategy for malaria control, but its success towards elimination relies upon community uptake interventions such as adapting protective human behaviour and house screening. Multi-sectoral interventions such larvae management in ongoing city restricting projects such as road construction, settlements upgrading, water supply and drainage improvement should not be ignored. Hence it is needed to redesign the ongoing intervention for malaria control in Dar es Salaam, to include complementary measures such as subsidizing building materials to enhance adequate access to suitable screening materials to contribute towards achieving malaria elimination goal in Dar es Salaam.

Competing interests

All authors declare that they have no competing interest.

Authors' contributions (still under construction)

VMM contributed to the design of the study, data collection and analysis and drafted the manuscript.

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Table 1: Description of resilience indicators as used in this study

S/N	Information recorded	Description
A: Household epidemiological surveys		
i.	geographical identification of the area	Coordinates of the compounds
ii.	house structure with an emphasis on features that prevent mosquito entry	Eaves, ceiling and window air brick gap (this presence, included condition and quality of materials used)
iii.	information about education, occupation and knowledge about malaria of the head of the household	
iv.	assets, expenditures and income sources	
v.	anti-malarial measures in use, including specific drugs used in the previous two weeks, and	
vi.	individual, demographic, behavioural and health related information like sleeping behaviour, travelling habits and treatment-seeking behaviour	Age, sex and education of the head of the households, PIi, PIs, sleeping outside, staying in the house last night, having fever last two weeks, having used drugs after getting fever, use of ACTs, seeking health advice when fall sick,
B: Physical infrastructure, social amenities, landuses and livelihoods		
vii.	roads	household access to road networks, coded 1 for less access (> 500m to access and collector roads and >1000m for regional roads) and 2 for higher access (< 500m to access and < 1000m for regional and other higher roads)
viii.	storm drain	availability of storm drainage system within catchments area (500m), coded 1 = NO and 2 = YES
ix.	Bus stops	access of daladala bus stops within urban catchments area (500m), coded 1 = NO and 2 = YES
x.	Health facilities	access to government health facilites within urban threshold size (dispensary <500m, health centre within 1000m and hospital at least 5km); coded to 1= no access, 2=access to dispensary 3=access to dispensary and health centre and 4=access to all up to re
xi.	education	access to primary and secondary schools within urban catchment size (500m for PS and 1km to SS), coded 1 = no access to both 2=access to either one 3= access to both
xii.	water	access to piped water supply within threshold size (400m); coded 1 = not within 2 within cathment
xiii.	Sanitation	type of sanitation used by household, coded 1= no toilets and pit latrines 2=WC and 3=central sewer
xiv.	Waste collection	method of solid waste disposal, coded 0 = onsite dumping, nearby open spaces/valleys/drains, 1 = nearby collection points/cart pullers and 3 = waste collection trucks
xv.	Markets	availability of any market within walking distance (500m), 1 = NO and 2 = YES
xvi.	industrial	availability of any industry within catchment areas (manufacturing 1km, processing, furniture or light within 500m), coded 1=NO and 2=YES
xvii.	commercial	availability of any commercial area within walking distance (500m); coded 1=NO and 2=YES
xviii.	offices	distance to any nearyby offices (governmental or private) within walking distance (500m); coded 1=NO and 2=YES
xix.	Building use	Household's building uses; 1 = pure residential 2= mixed uses
xx.	Urban Agriculture	distance to nearby crop cultivation areas or horticulture; coded 1 = < 500 of either one or both 2>500 of both
xxi.	Open Spaces	distance to nearby open spaces; coded 1 = <500m and 2=>500m
xxii.	Typology	type of settlements, coded 0=unplanned settlement 1= planned settlements
xxiii.	Security of land tenure	legal plot ownership; coded 0 = no any legal ownership documents 1= have licence of ownership and 2 = have a title deed/letter of offer
xxiv.	Larviciding	areas under larviciding, coded 0 = NOT 1 =YES
xxv.	Livelihoods	availability of designated (formal) areas for income generating activities within walking distance; coded 1=NO and 1=YES
xxvi.	Hazardous	distance from designated hazard/protected areas (hazard lands (buffer zone 60m), swamps (60) and rivers(20)); 0 = located within one of hazard areas (<60m) 1= located nearby one of hazard areas (60m - 500m) 3=Intermediate distance (501 - 100m) 4=Non haza
xxvii.	Rounds	Survey rounds (1=Mar to Aug 2010 sample frame 1, 2=Oct 2010 to Sept 2011 sample frame 2, Oct 2011 to May 2012 on sample frame 2)
xxviii.	Index TCU	TCU number for the index TCU used to define the cluster rather than the TCU number of where this individual lives

Table 2: Summary of results from Polychoric factor analysis of local resilience

S/N	Resilience group variable	Variables	Factor 1	Factor 2	Factor 3	Uniqueness	Validity and reliability
1.	Socio Economic Status (SES)	Education of head of household	0.6837	×		0.5292	Eigenvalue: Factor1= 1.7806 Factor2= 1.2206 Cumulative: 0.5002 KMO test: 0.5813* Alpha: 0.3580
		Walling materials	0.7264	×		0.4672	
		Roofing materials	0.3935	-0.6394		0.4440	
		Ceiling materials	×	-0.8113		0.2783	
		Window screening materials	0.6172	×		0.6163	
		Floor materials	0.4315	0.3872		0.6639	
2.	Housing protection	Eaves condition	0.8622			0.2566	Eigenvalue: Factor1= 2.1219 Cumulative: 0.7073 KMO test: 0.6623* Alpha: 0.6223*
		Ceiling quality	0.8913			0.2055	
		Condition of window airbrick gap	0.7642			0.4160	
3.	Utilization of health sector's interventions	Use of any kind of insecticide	×	0.6944		0.5153	Eigenvalue: Factor1= 2.39744 Factor2= 1.01461 Cum: 0.6824 KMO test: 0.6578* Alpha: 0.5920*
		Seek health advice	×	0.7321		0.4639	
		Have bed net	0.8234	×		0.3206	
		Use bed net	0.9453	×		0.1060	
		Soak bed net	0.9047			0.1816	
4.	Social resilience (human behaviour)	PIi	×	0.8987		0.1630	Eigenvalue: Factor1= 2.57245 Factor2= 1.34272 Cum: 0.7830 KMO test: 0.6466* Alpha: 0.7499**
		PIs	0.7693	0.3676		0.2730	
		PIi window screening	×	0.9017		0.1831	
		PIs any net use	0.8331	×		0.3048	
		PIs LLINs use	0.9061	×		0.1609	
5.	Urban system (infrastructure)	roads	0.8700	×	×	0.2344	Eigenvalue: Factor1= 2.59374 Factor2= 1.23039 Factor3= 1.14672 Cum: 0.6214 KMO test: 0.5869* Alpha: 0.4681
		storm drains	0.7033		×	0.4240	
		Bus stops	×	0.8566	×	0.2263	
		Healthfaci~s	×	×	0.8074	0.3431	
		education	×	0.7524	0.3121	0.2891	
		water	0.7711	×	×	0.2687	
		Sanitation	-0.3484	×	0.4130	0.7058	
		Wastecollection	0.4084	×	0 .5432	0.5377	
6.	Urban system (Landuses)	Markets	0.5434	×	0.4293	0.4847	Eigenvalue: Factor1= 2.42822 Factor2= 1.47647 Factor3= 1.11955 Cum: 0.7177 KMO test: 0.2970 Alpha: 0.4208
		Industrial	0.5816	0.7046	×	0.1510	
		Commercial	0.8453	×	×	0.2761	
		Offices	0.8594	×	×	0.2475	
		Urban agriculture	×	0.9434	×	0.1084	
		Open spaces/recreational	×	-0.5309	-0.5852	0.3635	
		Residential	×	×	0.8020	0.3446	
7.	Institutional capacity (urban governance)	Typology	×	0.8543		0.2656	Eigenvalue: Factor1= 2.05490 Factor2= 1.36417 Cum: 0.8548 KMO test: 0.4660 Alpha: 0.2717
		Larviciding scale up	-0.9848	×		0.0229	
		Livelihood creation areas	×	0.8511		0.2701	
		Hazard land management	0.9881	×		0.0223	

Note x represents loadings <.3

Table 3: Relative influence of factors associated with hotspots of malaria transmission hazards in Dar es Salaam from a boosted regression tree model

Variable	Relative rate [95 % CI]	P	Relative importance (%)	Interpretation (variable indication)
Indicators of human and city resilience/vulnerability				
Residing in upgraded settlements (CIUP)	0.528 [0.421, 0.662]	< 0.001	11.2	Resilience, community†
Distance to rivers	2.287 [2.2673.634]	< 0.001	9.3	Hazard, household
Security of tenure (right of occupancy)	0.522 [0.397, 0.685]	< 0.001	8.6	Resilience, household†
Residing in larviciding wards	0.318 [0.157, 0.644]	0.001	8.4	Resilience, community†
Housing quality (highest quantiles)	0.188 [.129, 0.273]	< 0.001	7.6	Resilience, household†
Distance to main roads	0.329 [0.202, 0.536]	< 0.001	7.3	Resilience, household†
Distance to protected/hazard areas	3.258 [2.558, 4.148]	< 0.001	7.2	Hazard, household
Distance to water pipes	4.234 [3.364, 5.329]	< 0.001	6.9	Hazard, household
Residing in regularized informal settlements	0.709 [0.563, 0.894]	0.004	6.7	Resilience, community†
Bed net uses	0.714 [0.586, 0.870]	0.001	6.1	Resilience, household†
Distance to agricultural area	4.101 [2.701, 6.227]	< 0.001	5.2	Hazard, household
Distance to waste collection/dump sites	4.721 [3.856, 5.779]	< 0.001	5.1	Hazard, household
Distance to storm water drains	3.841 [2.571, 5.740]	< 0.001	5.0	Hazard, household
Distance to garages	1.628 [1.204, 2.205]	0.002	2.1	Hazard, household
House screening (highest quantiles)	0.659 [0.510, 0.852]	0.001	1.3	Resilience, household†
Distance to markets	1.735 [1.182, 2.548]	0.005	0.8	Hazard, household
Distance to open spaces	1.606 [1.228, 2.101]	0.001	0.6	Hazard, household
Distance to commercial areas	3.004 [2.228, 4.0510	0.007	0.4	Hazard, household
Distance to industrial areas*	1.297 [1.022, 1.645]	0.032	0.1	Hazard, household
Designated areas for informal sector activities	3.493 [2.176, 5.610]	< 0.001	0.1	Hazard, household
Natural landscapes				
Slope	2.076 [1.2-3.7]	0.013	60.1	Hazard, household
Topographic wetness index	7.111 [6.2-8.2]	0.010	27.2	Hazard, household
Topographic ruggedness index	2.051 [1.7-2.5	< 0.001	22.0	Hazard, household
Profile curvature	9.9 [8.3-11.5]	< 0.001	15.3	Hazard, household

Note: The parameters and relative influence of indicators of human and city resilience were estimated using multivariable Boosted Regression Trees (with Poisson function). For natural landscape predictors, multivariable Poisson - CAR was used to estimate the parameters. Resilience Status Index (RSI) for malaria hazard was thereafter computed for further analysis using factor analysis based on variables marked with †) and adjusted for multiple testing of variables using Bonferroni correlation.

Table 4: Relative influence of factors associated with hotspots of malaria transmission risk in Dar es Salaam from a boosted regression tree model

Variable	Odds ratio [95 % CI]	P	Relative importance (%)	Interpretation (variable indication, effect level)
Indicators of human and city resilience/vulnerability				
Security of tenure (right of occupancy)	0.247 [0.105, 0.581]	0.001	32.5	Resilience, household†
Housing quality (highest quantiles)	0.068 [0.010, 0.467]	0.006	11.2	Resilience, household†
Residing in upgraded settlements (CIUP)	0.175 [0.073, 0.419]	< 0.001	8.1	Resilience, community†
House screening (highest quantiles)	0.436 [0.228, 0.831]	0.012	6.6	Resilience, household†
Distance to main roads	5.242 [1.471, 18.678]	0.011	6.3	Vulnerability, household
Bed net uses	3.360 [1.316, 8.576]	0.011	6.1	Resilience, household†
Human behaviour (highest/middle tercile)	0.329 [0.132, 0.819]	0.017	6.0	Resilience, household†
Residing in regularized informal settlements	0.086 [0.015, 0.475]	0.005	5.9	Resilience, community†
Residing in larviciding wards	0.352 [0.136, 0.915]	0.032	5.9	Resilience, community†
Distance to water pipes	2.162 [1.017, 4.598]	0.042	3.5	Vulnerability, household
Distance to agricultural area	3.916[1.714, 8.945]	0.001	1.8	Vulnerability, household
Distance to protected/hazard areas	3.026 [1.541, 5.940]	0.001	1.4	Vulnerability, household
Distance to rivers	2.256 [1.081, 4.705]	0.030	1.4	Vulnerability, household
Distance to health facilities	0.135 [0.019, 0.936]	0.043	1.3	Resilience, household†
Distance to storm water drains	0.818 [0.674, 0.995]	0.044	1.1	Resilience, household†
Distance to waste collection/dump sites	2.576 [1.454, 4.562]	0.001	0.5	Vulnerability, household
Distance to institutional areas*	0.323 [0.123, 0.848]	0.022	0.4	Resilience, household†
Natural landscapes				
Elevation	0.98 [0.97-0.99]	0.008	60.4	Vulnerability, household
Planform curvature	1.66 [1.64-1.67][b]	0.002	26.2	Vulnerability, household

Note: The parameters and relative influence of indicators of human and city resilience were estimated using multivariable Boosted Regression trees (with Bernoulli function). For natural landscape predictors, multivariable Binomial - CAR was used to estimate the parameters. Resilience Status Index (RSI) for malaria risk was thereafter computed for subsequent analyses using factor analysis based on variables marked with †) and adjusted for multiple testing of variables using Bonferroni correlation.

Figure 1: Households under the study: indicating malaria infection hotspots and non-hotspots per household

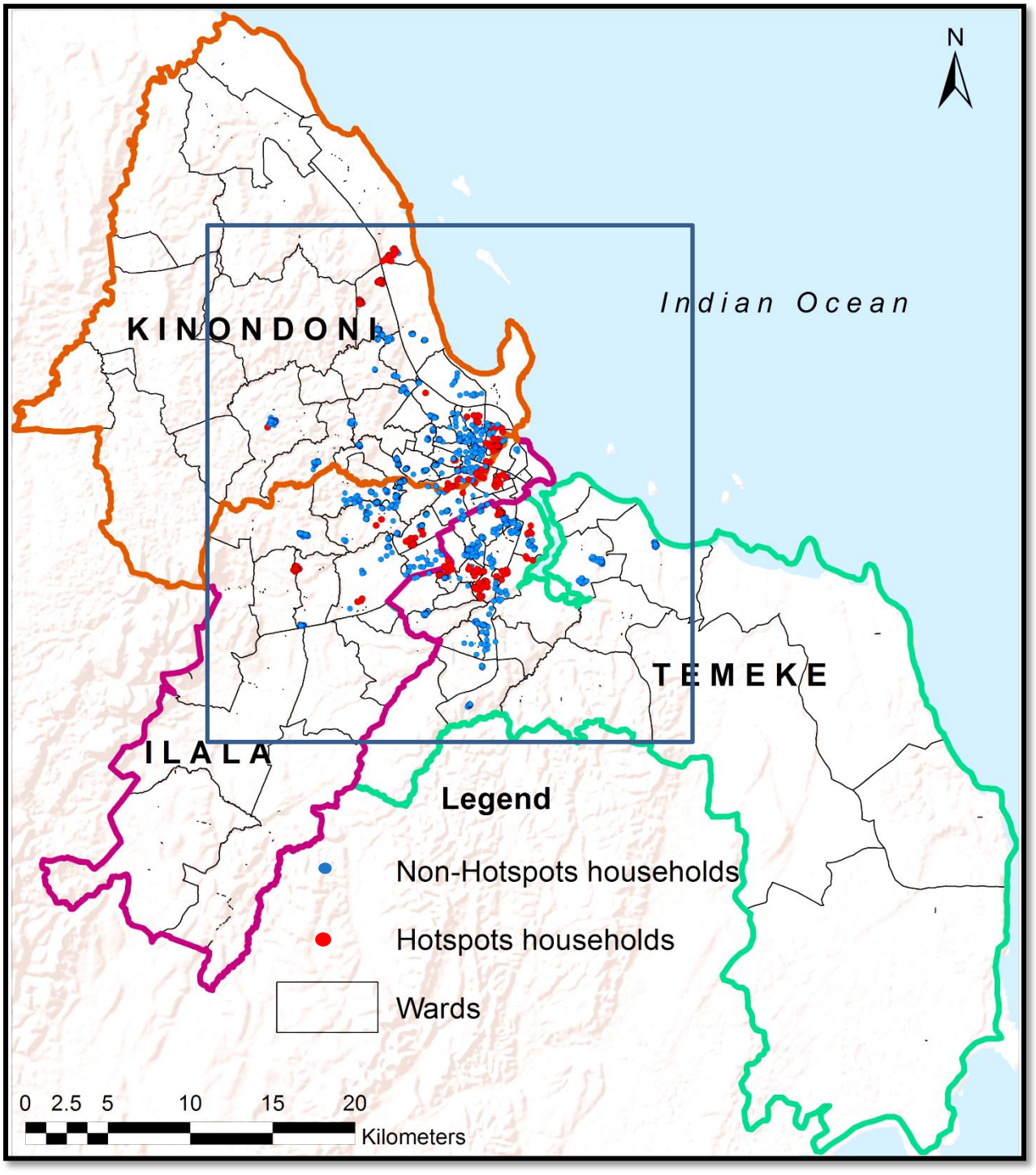


Figure 2: Landuse map in Dar es Salaam: Used to derive landuse and sectoral information for the study

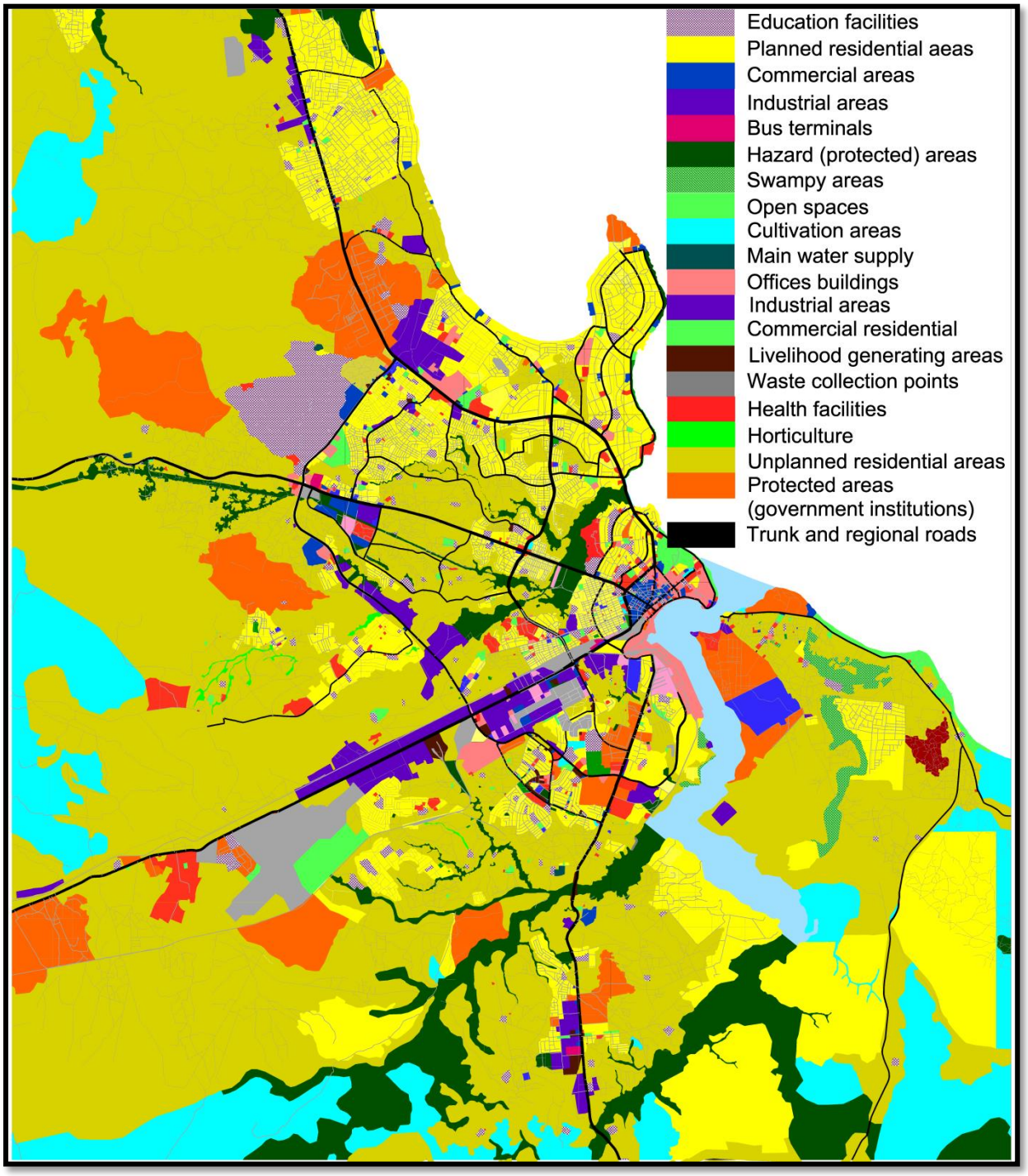


Figure 3: Infrastructure and land tenure predictors of malaria hotspots

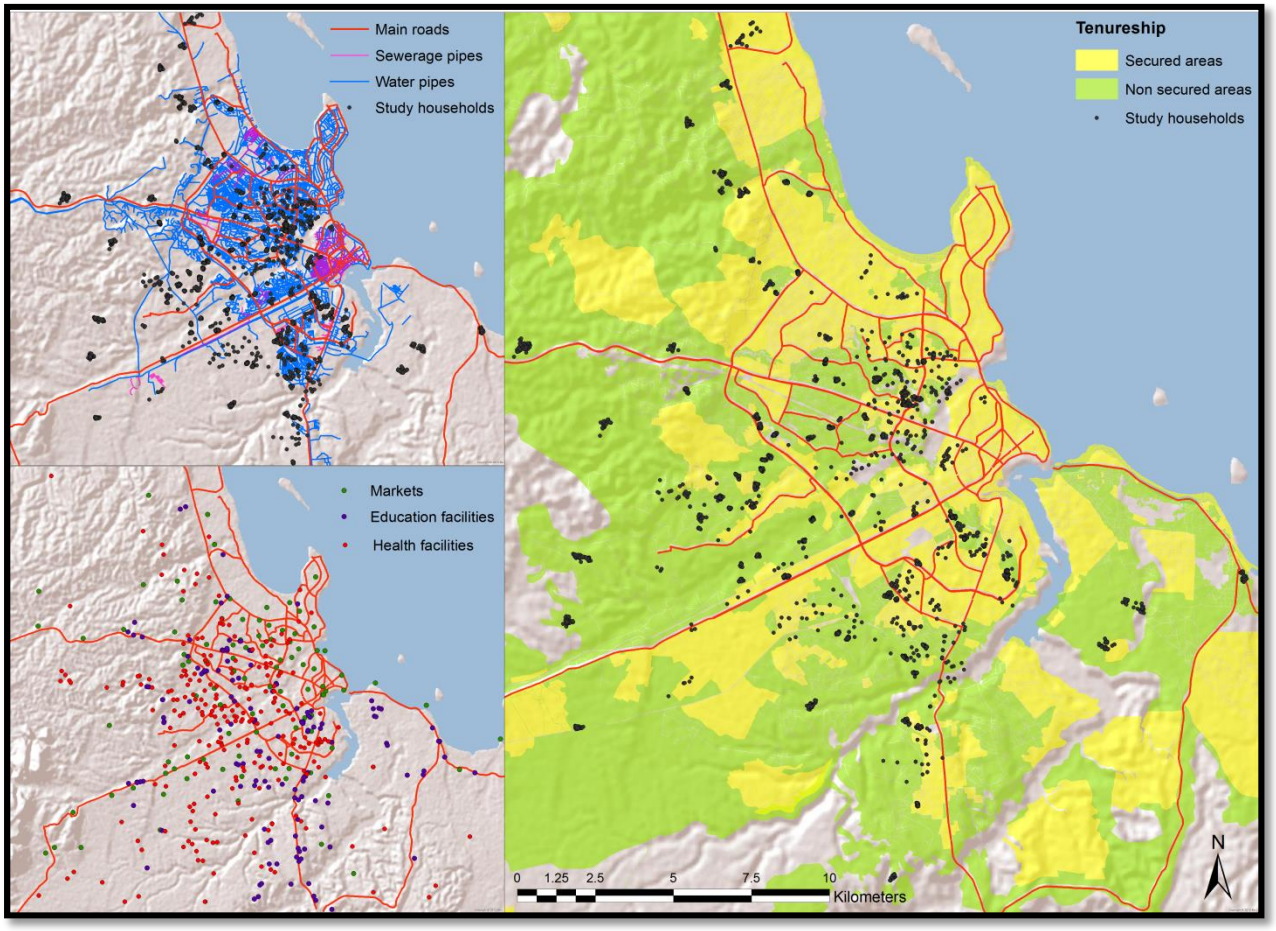


Figure 4: Boosted regression tree model functions: Indicating most influential factors of malaria transmission hazards in Dar es Salaam ranked according to their relative influence

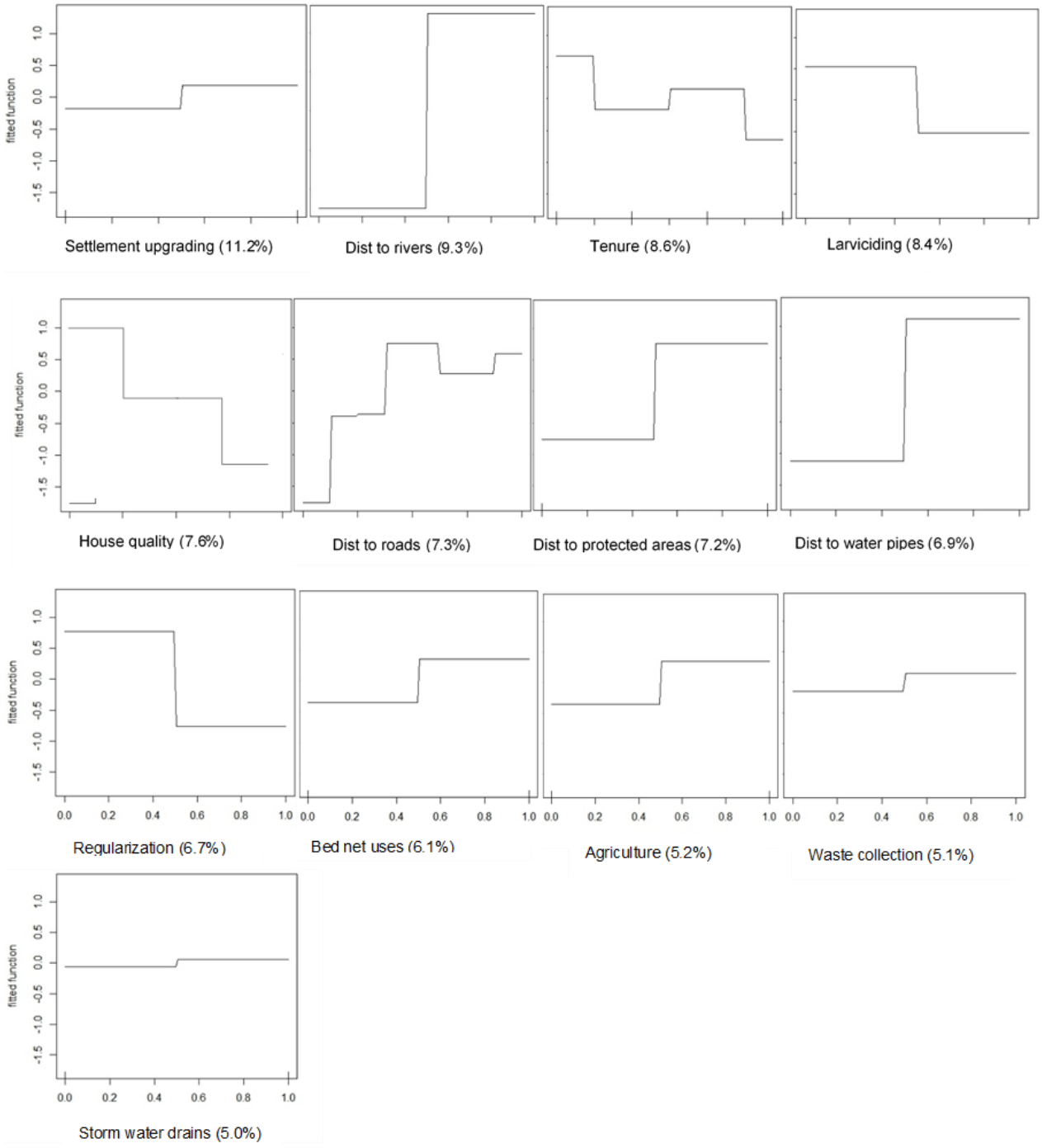
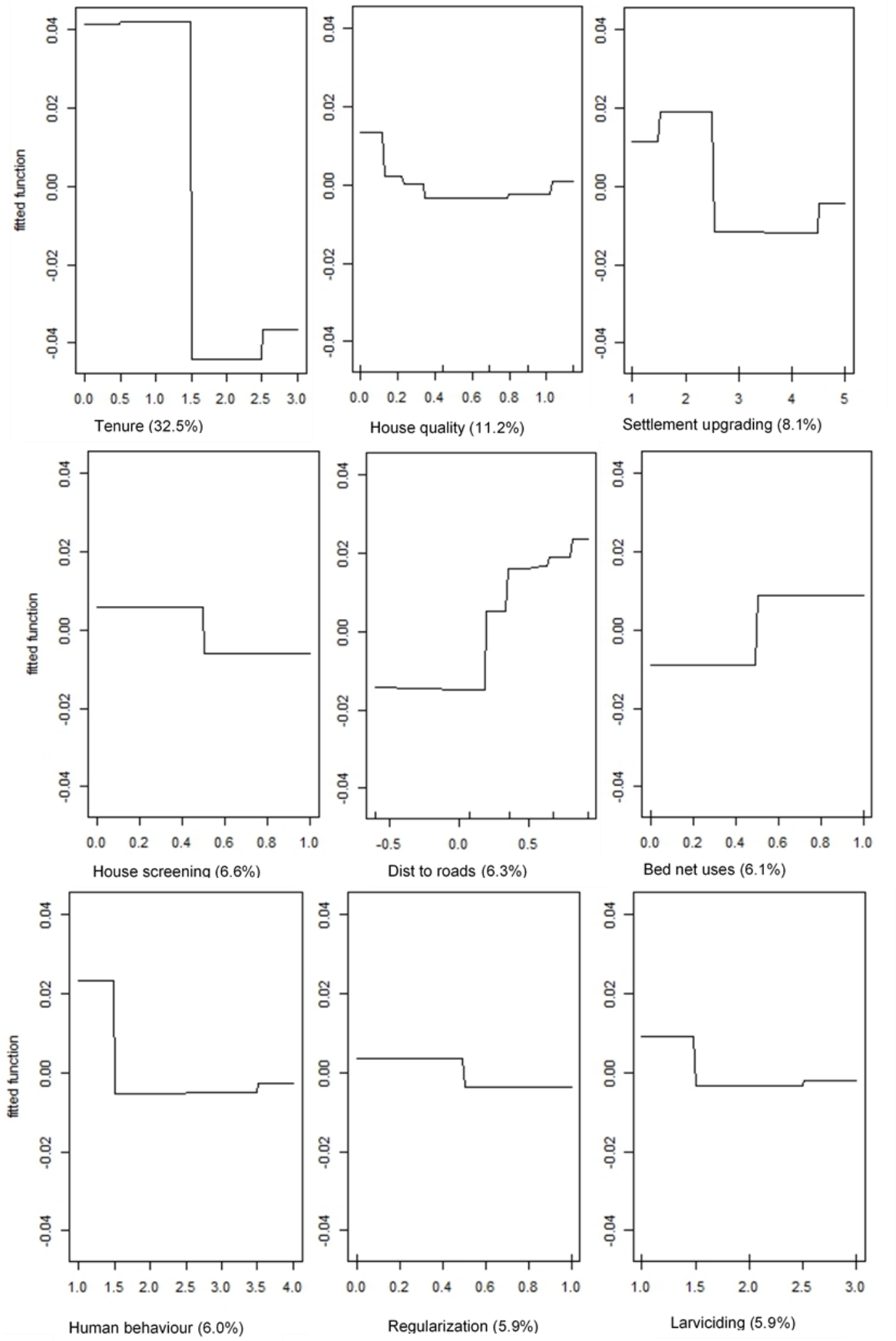


Figure 5: Boosted regression tree model functions: Indicating nine most influential factors of hotspots of malaria risk in Dar es Salaam ranked according to their relative influence



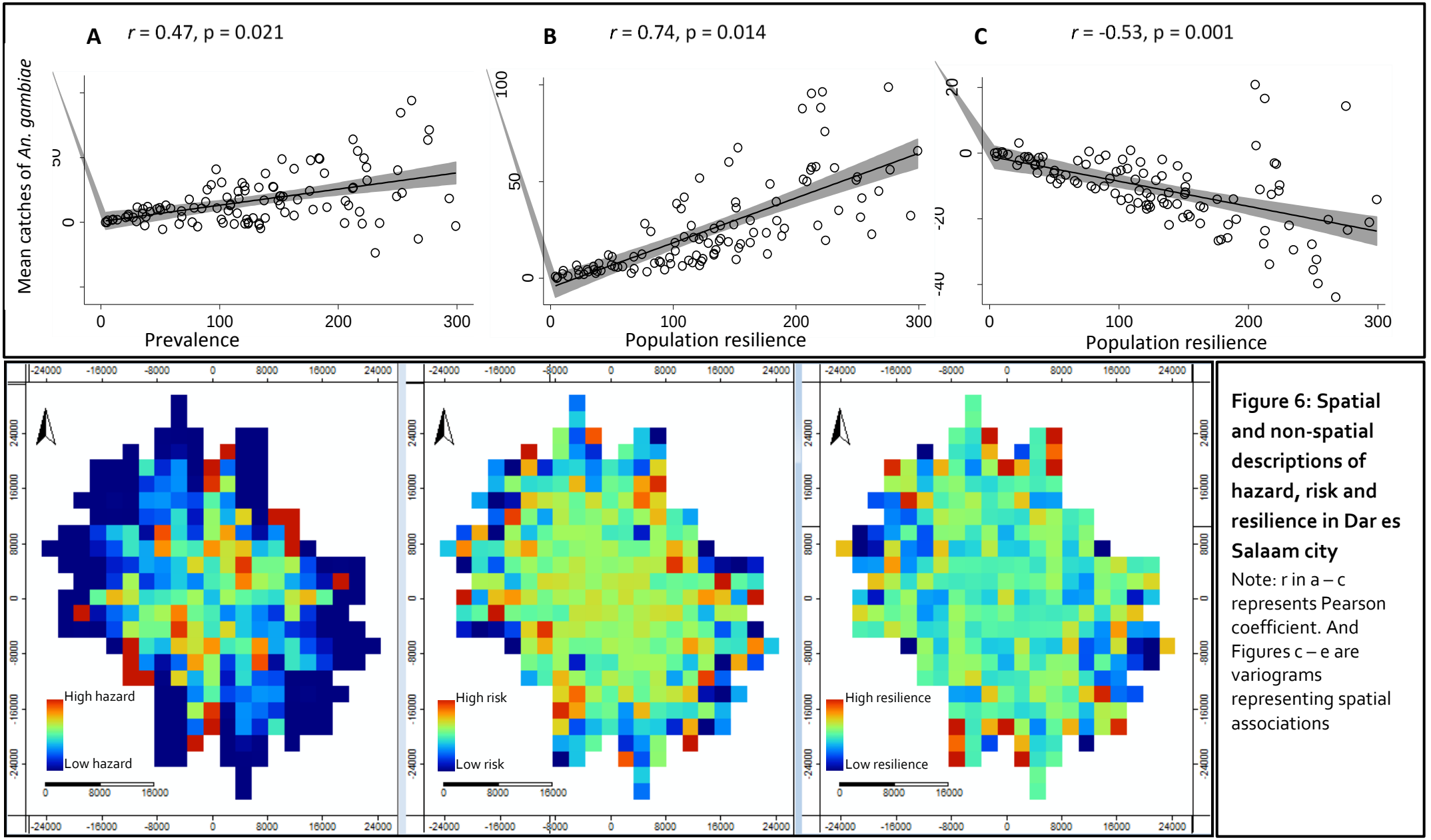
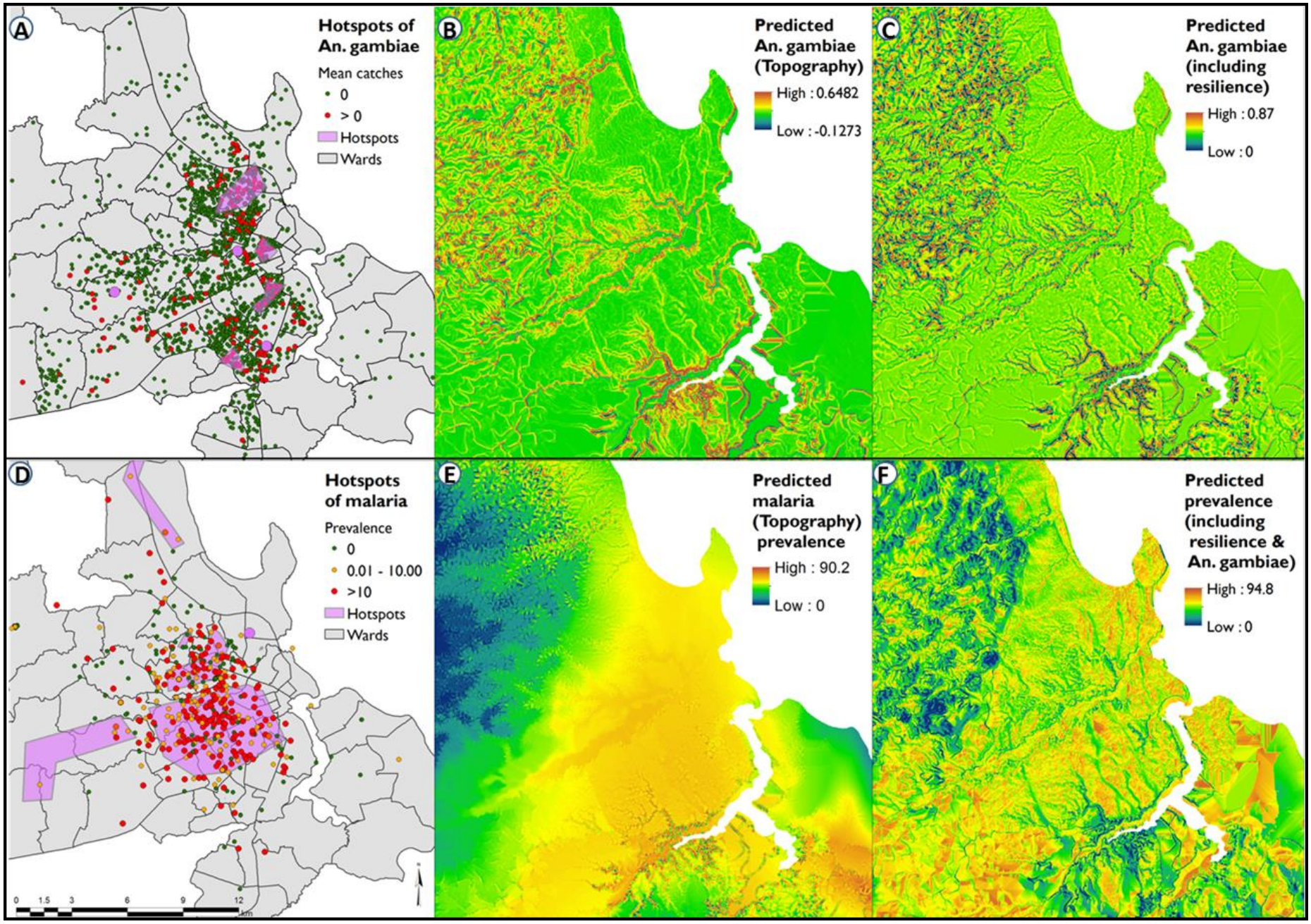


Figure 6: Spatial and non-spatial descriptions of hazard, risk and resilience in Dar es Salaam city

Note: r in a – c represents Pearson coefficient. And Figures c – e are variograms representing spatial associations

Figure 7: Mapping of location with high hazard and risk using different spatial resolution of predictors to determine areas for selective spatial targeted interventions: Panel **a** was mapped based on entomological surveys (slightly high resolution), **d** based on epidemiological surveys (low resolution), **b** & **e** based on topography (high resolution), **c** based on topography controlling for resilience and **f** based on topography controlling for hazard and resilience.



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ROYAL SOCIETY
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Topographic mapping of the interfaces between human and aquatic mosquito habitats to enable barrier-targeting of interventions against malaria vectors

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Complete List of Authors:	Mwakalinga, Victoria; Ardhi University School of Urban and Regional Planning, Housing and Infrastructure Planning Sartorius, Benn; University of KwaZulu-Natal, Discipline of Public Health Medicine, School of Nursing and Public Health Limwagu, Alex; Ifakara Health Institute, Department of environmental health and ecological sciences Mlacha, Yeromin; Ifakara Health Institute, Department of environmental health and ecological sciences Msellemu, Daniel; Ifakara Health Institute, Depatment of environmental health and ecological science Chaki, Prosper; Ifakara Health Institute, Department of environmental health and ecological sciences Govella, Nicoderm; Ifakara Health Institute, Department of environmental health and ecological sciences Coetzee, Maureen; University of the Witwatersrand Dongus, Stefan; Schweizerisches Tropen- und Public Health-Institut, Department of Epidemiology and Public Health, Socinstrasse Killeen, Gerry; Ifakara Health Institute, Biomedical and Environmental Thematic Group
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Keywords:	Plasmodium falciparum, Anopheles gambiae, Geophysic al topography, Malaria, Spatial modelling, Barrier - targeted interventions
Subject Category:	Earth science

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Victoria Mathew Mwakalinga,
Ardhi University,
PO Box 35176, Dar es Salaam.
Tel: +255 22 2774714 ...
Fax: +255 22 277 1714
Mob: +255 689 672874...
Email: vmwakalinga@cartafrica.org

Chief editor,
Journal of Royal Society Open Science,

Dear Prof./Dr./Ms./Sir

It is with excitement that on behalf of my colleagues, I resubmit to you a revised version of manuscript ID RSOS-161055 for the Journal of *Royal Society Open Science* entitled "**Topographic mapping of the interfaces between human and aquatic mosquito habitats to enable barrier-targeting of interventions against malaria vectors**". Thank you for giving us the opportunity to revise and resubmit this manuscript. In keeping with my last communication with you, I am resubmitting this revision before the agreed upon deadline, 28th October, 2017. I appreciate the time and detail provided by each reviewer and by you. We have made every effort to fully address all of the comments and have incorporated all suggested changes into the manuscript to the best of our ability. The manuscript has unquestionably benefited from these constructive revision suggestions. We look forward to working with you and the reviewers to move this manuscript closer to publication in the *Journal of Royal Society Open Science*.

We have responded specifically to each suggestion below, beginning with your own. To make the changes easier to identify where necessary in the manuscript, we have highlighted all the adjustments in yellow.

Finally, I thank you for using your valuable time to review our manuscript. The responses to reviewers are on the following pages.

Regards,

Mathew

Victoria Mathew Mwakalinga
Lecturer, Ardhi University, United Republic of Tanzania

Response to reviewers

Reviewer: 1

Major review:

The paper represents a breakthrough into a new and potentially exciting area for malaria control. This is somewhat preliminary, which is fine, but the authors should talk more about how their study might apply to, and be validated in, other localities (smaller cities, other countries).

Response:

The approach presented could be readily applied and assessed in other African settings, as a means to identify heterogeneity in malaria risk patterns and detect zones for spatially selective targeted interventions. Specifically, it may be used to predict the distribution of malaria transmission across the landscapes where dense human populations surround aquatic habitats such as rivers, swamps and flooding zones, or *vice versa* in some flood-prone rural settings. In urban Africa, these zones tend to be illegally occupied informal settlements [70], inhabited mostly by the poor whose human resilience against malaria risk is very low [71, 72]. In order to tap the full potential of this approach to mapping areas for selectively targeted interventions against adult mosquitoes, the resolution of geophysical indicators needs to be high enough to accurately capture transmission at fine spatial scales that hazard and risk really occur at [17, 73]. For this reason, the approach is really only suitable for use by locally-managed, decentralized mosquito control programmes that can practically target appropriate interventions at very fine geographic scales, rather than for cruder prioritization of interventions across larger provincial or national scales [20, 74, 75]. Beyond evaluating in a wider diversity of settings where sufficient entomological and epidemiological data are available that have been mapped at high resolution, this approach also needs to be field-validated in by empirically evaluating the actual, rather than predicted, impacts vector control activities directed by these targeting criteria.

The role of the exploratory analysis (2.3.1) is never made clear. The authors state in 2.3.1 that they removed variables with high inflation factors, but in 2.3.2 they seem to have put them back (they later take them out again). None of the authors' citations support their use of the "rule of 10" for VIFs – [36] in fact cautions against it. Could this whole step be skipped?

Response:

We have agreed to skip the whole step, as we have now opted to use a ridge regression, as suggested by the reviewer, which handles multicollinearity better than the standard ordinary least squares method. However, we retain Table 2 which justifies that some covariates have serious multicollinearity issue such as altitude above channel network which is perfect collinear with elevation (VIF > 50 while the cut off is 10).

The sub title in section 2.3.1 has been changed from *"Exploratory spatial regression analysis"* to ***"Spatial Autocorrelation testing"*** as it is important to indicate that spatial autocorrelation was considered to justify the choice of the Conditional Autoregressive model which handles spatial effects for this specific case in predicting malaria hazard or risk at finer spatial scales.

The text under 2.3.1 have been deleted, and has been completely revised as follows "**Assessment of spatial autocorrelation was performed in the preceding study [17], using Moran's *I* (MI) statistic in ArcGIS v10. Briefly, the assessment revealed that both *Anopheles* mosquitoes (MI = 0.15) and malaria infection prevalence (MI = 0.17) were spatially autocorrected, showing tendency towards clustering."**

Stepwise fitting is always a problematic approach (there is never a guarantee that you won't miss a much better model than the one you settle on). The authors do not make any attempt to justify this choice (it may be that it's the only practical one in the context of their spatial fits)? I don't have experience with MCAR models, but in general the approach I would prefer for this sort of question would be ridge regression (lasso regression is closely related, and would be fine, but I don't like it as much for making predictions).

Response:

Thank you for this critical comment. We have reviewed our statistical analyses. We have dropped the stepwise regression approach, instead we have used a ridge regression for covariate selection. Since certain of the covariates used in this study are highly collinear, a ridge regression is more suitable as it handles this problem while improving the precision of the model fitting. The final covariates selected through ridge regression were incorporated in the Conditional Autoregressive

(CAR) model used to spatially predict areas with high malaria hazard and risk at high resolution that can be used to guide geographically-selected targeted interventions. Since the outcome variables are spatially auto correlated, CAR models are more practical in the context of their spatial fits because they accounts for these spatial effects.

The subtitle in section 2.3.2 *"Spatial modelling"* has been renamed to read ***"Spatial modelling and predictions"*** and moved to 2.3.3. In 2.3.2 a new subtitle reading ***"Geophysical covariate selection"*** has been introduced. The text in this newly added section 2.3.2 is as follows:

"2.3.2. Geophysical variable selection

A Non Parametric Bayesian (NPB) Ridge regression [33], using marginal maximum likelihood (MML) estimation [34], was used to select potential covariates to retain in the final model, which was used to predict malaria hazard and risk in Dar es Salaam city. Ridge regression was fitted using a Bayesian software called 'BayesRegression' Version 11June2016 [35]. The software is an open source and can be downloaded from ***http://georgek.people.uic.edu/BayesSoftware.html*****.**

The outcome variables were mean catches of adult female *Anopheles gambiae* per trap person night and human malaria infection prevalence. All geophysical covariates were included in the ridge regressions. These covariates were highly correlated as indicated by Variance Inflation Factor (VIF) in Table 2, where many variables have VIF > 10 indicating presence of high multi-collinearity [36]. Ridge regression is one of the better approaches to handle multicollinearity because it shrinks the coefficient estimates of irrelevant covariates towards zero, thus useful for nonlinear regressions [33]. In short, the ridge regression method adds a penalty parameter λ into the model to adjust for the collinearity between covariates. As parameter λ increases, the coefficient values shrink towards 0 [37]. The relationship between parameter λ and coefficients have been shown by the trace plots (ridge trace) for mosquitoes and infection prevalence models are shown in Figures 1A and 1B respectively. Standardized

coefficient estimates can be conveniently viewed from Love plots in Figures 2A for mosquitoes densities and 2B for infection prevalence."

The results of ridge regression model are presented in Figure 1 and 2 (ridge trace and Love plots); which were established from the 95% Bayesian Credibility Intervals for the posterior means.

In section 2.3.3, new texts highlighted in yellow were added. And those highlighted in green were deleted from the manuscript.

2.3.3. Spatial modelling and prediction

Only variables with 95% Bayesian credible intervals that did not cross zero were considered significant and hence retained for the next step of the modeling and spatial prediction. Two distinct Multivariate Conditional autoregressive models (MCAR), adjusted for larvicide application regimes, were fitted to elucidate the spatial interactions that arise between geophysical topography, densities of *An. gambiae* and malaria infection prevalence and map their spatial predictions. The CAR model accounts for spatial effects and in essence the mean or probability values estimated at any given location are conditional on the levels in the neighboring areas. Unstructured area specific random effect was included in the model to account for noise. The model for densities of *An. gambiae* was fitted using a Poisson-lognormal MCAR model [38] and malaria infection prevalence was fitted using a Binomial logit MCAR [39]. The auto regression parameters and confidence intervals for each model were obtained using Markov chain Monte Carlo (MCMC) methods [39, 40]. Coefficients for *An. gambiae* model and infection prevalence logit model were exponentiated to present relative rates (RR) and odds ratios (OR) respectively. ~~Back-wise elimination technique was used in the fitting process, starting with a large model with all geophysical topographical covariates as described in Table 1 for each outcome; except AAC because when included the models failed to solve due to its perfect collinearity with elevation, AACHN and TPI (Table 2). The succeeding~~

~~model was then re-fitted after removing one variable with the highest *p value* observed in the preceding model. This process was repeated until when a reduced model with all significant covariates was attained.~~ Transect of all significant geophysical topographic variables as well as predicted entomology/parasitology in different parts of the city were prepared to aid interpretation of the results. The CAR spatial modelling were all performed using CrimeStat IV® (for obtaining auto regression parameters) [41] and SAGA GIS® (for mapping the final model results), both open source GIS software. Transects values were extracted using SAGA GIS® and graphs prepared using Microsoft Excel.

The acronyms TCU and ITT are never defined. The former omission causes actual confusion.

Response:

TCU and ITT have been defined in the manuscript, and can be found in the second paragraph of section 2.2. The text now reads ….. weighted averages (based on TCUs **a short form of Ten Cell Units which represent the lowest level of administrative boundaries in Tanzania usually constituting at least 10 houses to a maximum of 100 houses)** for discrete geophysical topographic variables were computed to obtain values of each geophysical topographic predictor for each of the study locations. …….A handheld Global Positioning System (GPS) receiver at an accuracy of 5m was used to provide spatial references of specific locations for **Ifakara Tent Traps** (ITTs) as well as households in the cross sectional surveys.

Table 3 needs better explanation, and should probably use different units. At the least, the units need to be explained: profile curvature has a "relative rate" that is 10,000× higher than that of GoT liquid, but their model contributions are essentially the same. Neither "relative importance" nor "proportion of variance" are clearly explained, and it is surprising that they don't fall in the same order (e.g., GoT liquid explains more variance, but has less "importance" than TWI).

Response:

Thank you for this valuable comment that made us think carefully regarding the choice of the model we initially used in the analysis. Please see response above regarding removal of the stepwise regression approach in favor of a more superior modelling alternative. A ridge regression (for variable selection) and MCAR (spatial prediction) approved to provide a much more robust model

with better overall fit to the data. Our updated model results are presented in **Figure 1 and 2** for the ridge regression and **Table 3** for MCAR models.

The figure resolution is very low. I guess this is something about the journal and not the authors. But why should the pro-bono reviewer have to deal with low-quality figures? Nonetheless, it seems to me that much better use could be made of the color maps by basing them on quantiles rather than on values. With quantiles, you should see lots of each color in each map, revealing more features. Many of the current color maps are dominated by one or two colors. This should certainly be done for predictors, where the primary interest is the signal they provide to explain the response variables. There are tradeoffs in doing it for the response variables -- the authors might want to show the relatively low resolution in prevalence graphically.

The authors should also give thought to their color choices. Although I have low-resolution versions, I feel the color choices in Figure 1 are clearer than in Figure 3. My favorite color maps go from red (cold) through yellow to white (hot); this is the best way to make the quantities look quantitative.

Response:

The colors used in the figures (particularly the final model results in Figure 5, which was initially named Figure 3) have been changed. However, we still use values to present the results on the maps due to the fact that the predictors particularly those predicting the interfaces between where humans live and where mosquitoes oviposit have very fine scale in such a way that quantiles lose their quantitative look. What we did to keep the effects of these kind of predictors in the models was to change the color intensities which to our knowledge it has helped to improve the presentation of our results.

The authors should give a little more detail about their spatial analyses, and state that they are providing code (or else explain why not).

Response:

We have given details about our spatial analyses in sections 2.3.1 and 2.3.2. The software used in the analysis (BayesRegression version 11June2016 and CrimeStat version IV) are both menu driven software packages, hence we may not provide the code for this specific analysis. However, we fitted the ridge regression model in R using MASS package version 7.3-47, for comparison of the results. The code can be shared upon request.

The authors should explain which of the data needed to reproduce their results are and are not being made available.

Response:

All data needed to reproduce the results of this research have been made available as supplementary files.

Minor review

Authors should avoid over-generalizing about mosquitoes (e.g., p2L10 should say anopheles mosquitoes)

Response:

The manuscript text have been reviewed to add Anopheles.

The abbreviation AMSL could be skipped

Response:

The abbreviation AMSL have been removed from the manuscript

What is "temporal management"?

Response:

"Temporal management" has been changed to read "**short-term management**"

The language could be edited more carefully for run-ons, correct hyphenation, etc. Some particular examples:

* p4L29 However is confusing. "Currently" seems better.

Response:

Thank you for your observation. The sentence was changed in the manuscript to begin with **"Currently,** three quarters of all malaria vector mosquitoes ……"

* p5L8. The whole preamble to this sentence is unnecessary. It should start with "Urban".

Response:

The preamble "**However, because it is a city**," has been deleted from the manuscript. The sentence starts with "Urban Dar es Salaam has historically experienced relatively modest, but nevertheless stable and persistent, malaria transmission ……"

* p13L3 "focally and disproportionately" should be "disproportionately"

Response:

The words **"focally and"** have been removed, and the sentence reads as "This is therefore where residents are **disproportionately** exposed to adult ……"

* Don't hyphenate after "ly" or when hyphenated phrase is not a modifier.

Response:

Hyphenation was removed from topographically-identifiable to read "…. **topographically identifiable** geophysical …" in page 2 and topographically-mapped changed to **topographically mapped** in page 13.

* Do hyphenate to help readers with parsing, e.g., "indicators of local water-accumulation potential"

Response:

Hyphenation has been added to all parsing words in the manuscript such as "local **water-accumulation** potential …." in page 2.

The definition of planform curvature refers incorrectly (typo) to profile curvature

Response:

Thank you for bringing this to our attention. We have interchanged the variables (plan curvature down in row 8 and profile curvature up in row 7) in table 1 to reflect the correct definition of each.

p7L48 ArGIS is a typo.

Response:

Thanks we have edited this to read **ArcGIS v10**

p9L20. Meaning of "it" is unclear.

Response:

"it" has been changed to **the intensity** in the sentence to read "at which **the intensity** may be de-stabilized"

Reviewer: 2

Although mentioned in the manuscript, the authors have not clearly stated how they dealt with the issue of spatial autocorrelation. This should be clear to reader without looking for it in between the lines.

Response:

The issue of spatial autocorrelation have been analyzed and published in *Mwakalinga VM, Sartorius BKD, Mlacha YP, Msellemu DF, Limwagu AJ, Mageni ZD, et al. 2016 Spatially aggregated clusters and scattered smaller loci of elevated malaria vector density and human infection prevalence in urban Dar es Salaam, Tanzania. Malar J.* ***15****, 9 (doi: 10.1186/s12936-016-1186-9*). A short paragraph on auto correlation has been added in section 2.3.1

To deal with for spatial autocorrelation in this study, a Conditional Autoregressive (CAR) model was employed because it accounts for spatial effects using a contiguous neighbor structured random effect. This is described in the manuscript text as "**The CAR model accounts for spatial effects as it was important to deal with the issue of spatial autocorrelation in our outcome variables.**"

Also there are several abbreviations that could be reduced in the manuscript.

Response:

Thanks for the comment. Abbreviations, such as AMSL, AAC, PL and PC, have been omitted from the manuscript text.

Reviewer: 3

Comments to the Author(s)

Page 6 line 37. Basillus thuringiensis should be correctly spelt as Bacillus thuriengiensis

Response:

This has been corrected "…..of ***Bacillus thuriengiensis*** var. *israelensis* (*Bti*)…"

On the same page 6: The information that Research Triangle Information of the private consultant implementing larviciding in Dar es Salaam is INCORRECT. The firm that did the larviciding was knowns as RESEARCH TRIANGLE INTERNATIONAL

Response:

Thank you for this important observation. The typo Information is now changed to international in the manuscript text to read "….. contractor (Research Triangle **International**) ….."

Conclusion: The conclusion does not answer the objectives but rather making references to other studies. The authors should make conclusion based on their current study.

Response:

The first sentence of the conclusion answers the objective of this research because it indicates how geophysical variables have predicted areas of higher densities of *An gambie* and malaria infections. The references were made to support the applicability of different options of targeted interventions recommended in Dar es Salaam city.

Topographic mapping of the interfaces between human and aquatic mosquito habitats to enable barrier-targeting of interventions against malaria vectors

Victoria M. Mwakalinga[1,2,3*], Benn K.D. Sartorius[4], Alex J. Limwagu[2], Yeromin P. Mlacha[2], Daniel F. Msellemu[2], Prosper P. Chaki[2], Nicodem J. Govella[2], Maureen Coetzee[5], Stefan Dongus[2,6,7,8] and Gerry F. Killeen[2,8]

[1] Ardhi University, School of Urban and Regional Planning, Department of Housing and Infrastructure Planning, P.O. Box 35176, Dar es Salaam, Tanzania

[2] Ifakara Health Institute, Department of Environmental Health and Ecological Sciences, Kiko Avenue, Mikocheni, P.O. Box 78373, Dar es Salaam, Tanzania

[3] School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[4] Discipline of Public Health Medicine, School of Nursing and Public Health, University of KwaZulu-Natal, Durban, South Africa

[5]Wits Research Institute for Malaria, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[6] Swiss Tropical and Public Health Institute, Department of Epidemiology and Public Health, Socinstrasse 57, P.O. Box, 4002 Basel, Switzerland

[7] University of Basel, Petersplatz 1, 4003 Basel, Switzerland

[8] Liverpool School of Tropical Medicine, Pembroke Place, Vector Biology Department, Liverpool L3 5QA, United Kingdom

* Author for correspondence: Victoria Mwakalinga, e-mail: vmwakalinga@cartafrica.org

Abstract

Geophysical topographic metrics of local water-accumulation potential are freely available and have long been known as high resolution predictors of where aquatic habitats for immature *Anopheles* mosquitoes are most abundant, resulting in elevated densities of adult malaria vectors and human infection burden. Using existing entomological and epidemiological survey data, here we illustrate how topography can also be used to map out the interfaces between wet, unoccupied valleys and dry, densely populated uplands, where malaria vector densities and infection risk are focally exacerbated. These topographically identifiable geophysical boundaries experience disproportionately high vector densities and malaria transmission risk because this is where *Anopheles* mosquitoes first encounter humans when they search for blood after emerging or ovipositing in the valleys. Geophysical topographic indicators accounted for 67% of variance for vector density but only 43% for infection prevalence, so they could enable very selective targeting of interventions against the former but not the latter (targeting ratios of 5.7 *versus* 1.5 to 1, respectively). So in addition to being useful for targeting larval source management to wet valleys, geophysical topographic indicators may also be used to selectively target adult *Anopheles* mosquitoes with insecticidal residual sprays, fencing, vapour emanators or space sprays to barrier areas along their fringes.

Keywords: Geophysical topography, Spatial modelling, *Plasmodium falciparum*, Malaria, *Anopheles gambiae*, Barrier - targeted interventions

1. Introduction

Recent attempts to demonstrate the value of targeting malaria transmission *hotspots* with elevated vector densities and human infection burden, yielded disappointing results in a rural setting with dispersed settlement patterns and variable but ubiquitous transmission [1]. However, it has been suggested that this geographically selective approach might be more effective in settings with more aggregated populations because this will result in less dispersal of *Anopheles* mosquitoes and dispersion of malaria transmission across the landscape [1]. Taking this rationale further, the urban contexts of towns and cities may perhaps offer the most ideal settings for geographic targeting of supplementary interventions: Dense human populations surrounding aquatic larval habitats allows *Anopheles* mosquitoes to feed nearby and then return to oviposit, thus limiting their dispersal and the diffusion of malaria transmission across the landscape [2-4]. Also, urban settings have lower transmission intensity than rural areas, because high population density dilutes out vector biting burden [5, 6] and urban planning can reduce it even further [2, 7, 8]. Transmission in urban settings may therefore be more vulnerable to control with effective interventions generally and targeted interventions specifically. Furthermore, infrastructure, institutional capacity and governance systems are often better developed than in rural areas, and greater numbers of people can be protected per unit of surface area covered, so several intervention strategies may be viable in towns and cities that would otherwise be considered infeasible [2, 8-11]. However, one of the greatest challenges to selective geographic targeting of malaria is the very fine scales that heterogeneity occurs at [12-16]. Hotspots can occur at scales of less than 100 meters, and even at the level of single households [1, 13, 14], so mapping these out at sufficiently high resolution may not be realistically feasible across large programmatic scales with existing entomological and epidemiological survey techniques [1, 14, 17].

Geophysical topographic indicators of local water-accumulation potential have long been recognized as high-resolution (as fine as 10 to 20 m) predictors of locations with abundant aquatic larval habitats for mosquitoes, and therefore high densities of adult vectors and human malaria infection burden [18-25]. Geophysical topographic predictors of local wetness could therefore be useful for identifying even very small geographic hotspots of malaria transmission. Specifically, topographic predictors of local wetness could enable spatial targeting of supplementary interventions at the very fine spatial resolutions that are probably required to achieve improvements in impact or efficiency, relative to blanket coverage [1, 14, 17].

Dar es Salaam in Tanzania is a typical African coastal city, where local government programmes for larval source management have been highly effective [26] and sustainably institutionalized [27]. At the time of this study, three quarters of all malaria vector mosquitoes and half of all human infections occur in small, scattered, haphazardly distributed loci, outside of spatially aggregated hotspots that could be detected with existing field survey techniques [17]. This study was therefore undertaken to assess a comprehensive range of geophysical topographic indicators as high-resolution predictors of malaria transmission, with which to map out areas for targeting larval source management interventions. However, in addition to the expected hydrological indicators of where larval habitat occurred, novel geophysical topographic indicators for barrier targeting of supplementary vector control interventions against adult *Anopheles* mosquitoes were also identified.

2. Methods

2.1. Study area

The study was conducted in urban and peri-urban areas of Dar es Salaam, covering a total of 498 km^2, encompassing an overall population of 3.6 million people [26]. The city is situated along the shores of Indian Ocean in Tanzania, having a hot (mean daily temperature of 26°C) and humid climate (two rain seasons), which provide ideal conditions for *An. gambiae* proliferation and malaria transmission [28]. Urban Dar es Salaam has historically experienced relatively modest, but nevertheless stable and persistent, malaria transmission intensity, with an entomologic inoculation rate just above one infectious bite per person per year [26, 28].

The geophysical topography of Dar es Salaam is divided into three distinct zones [29]; *the upland zones* (>100m above mean sea level) consisting of hilly areas, with plains dissected by many well-drained streams in the West and Northern sides of the city; *the middle plateau* (62-100m) which is characterized by gently, undulating plateaus with isolated hills, rock outcrops, dissected by many streams in the central parts of the city; *and the lowlands* (0-62m), consisting of uniform relief with gentle slopes invariably less than 3%, except along the immediate margins of the three big river valley systems, the Msimbazi river in the central, the Keko drain and the Mzinga river in the southern parts of the city. This zone consists of the coastal belt extending from northern to southern parts of the city [29].

The study encompassed of 71 of the 90 (79%) wards in the city, of which 15 are the same original wards first covered with larvicide application by the Dar es Salaam Urban Malaria Control Programme (UMCP) during its operational research phase that ended in 2009 [28]. Following transition to fully programmatic funding and management [26, 27], blanket coverage

with microbial larvicides had just been re-introduced to these same 15 wards at the outset of this study in March 2010, before comprehensive scale up to cover 56 wards by January 2012 [30]. Between March and October 2010, a coated granule larvicide formulation (VectoBac®, Valent BioSciences Corporation) of *Bacillus thuriengiensis* var. *israelensis* (*Bti*) was applied under short-term management of a private sector contractor (Research Triangle International), before the Government of Tanzania (GoT) through Ministry of Health and Social Welfare (MoHSW) took over direct management of all larviciding activities in January 2011. The MoSHW re-initiated larvicide application in February 2011 using the same granule *Bti* product as used by external contractor until end of July 2011, before moving to a pre-diluted aqueous suspension formulation (Bactivec®, Labiofam®) of *Bti* from September 2011 through to end of this study [26].

2.2. Data collection and collation

This study uses secondary data collected from two distinct phases of entomological and epidemiological surveys which have been described in detail elsewhere [26]. Briefly, malaria infection prevalence was recorded using two distinct phases of rolling, cross-sectional, cluster-sampled household surveys with rapid diagnostic tests for *Plasmodium falciparum* malaria from March 2010 to July 2012, while a community-based trapping scheme to conduct longitudinal surveys of mosquito densities at high spatial resolution was scaled up across the study area over the same period, with a brief interruption over the last quarter of 2010 and the first of 2011.

Additionally, a comprehensive range of geophysical topographical indicators of hydrology (Table 1) were derived from a 20x20m grid of the study area. This was done with SAGA GIS, a free, open-source software package (www.saga-gis.org) [31], based on a digital elevation model

of Dar es Salaam with 20m resolution, which was freely obtained from the Faculty of Geo-Information Science and Earth Observation University of Twente. The weighted averages (based on Ten Cell Units (TCUs), which represent the lowest level administrative unit in Tanzania, usually constituting at least 10 to a maximum of 100 houses) for discrete geophysical topographic variables were computed to obtain values of each geophysical topographic predictor for each of the study locations. The extracted values of geophysical topography were linked with those of mosquito vector densities and infection prevalence in each location using TCU centroids, which were calculated with ArcGIS v10 software (ESRI Corporation, Redlands, CA). The subsequent analyses were done at TCU level. The boundaries of sampling clusters for both mosquitoes and cross-sectional sampling clusters were obtained through participatory mapping approach as described elsewhere [30, 32]. A handheld Global Positioning System (GPS) receiver with an accuracy of 5m was used to provide spatial references of specific locations for Ifakara Tent Traps (ITTs) used to catch mosquitoes, as well as households included in cross sectional surveys. These were the basis for calculating the centroids of the sampling clusters.

2.3. Data analysis

2.3.1. Spatial Autocorrelation testing

Assessment of spatial autocorrelation was performed in the preceding study [17], using Moran's *I* (MI) statistic in ArcGIS v10. Briefly, the assessment revealed that both *Anopheles* mosquitoes (MI = 0.15) and malaria infection prevalence (MI = 0.17) were spatially auto correlated, showing tendency towards clustering.

2.3.2. Geophysical variable selection

A non-Parametric Bayesian (NPB) Ridge regression [33] using marginal maximum likelihood (MML) estimation [34] was used to select potential covariates to retain in the final model, which was used to predict malaria hazard and risk all across Dar es Salaam city. Ridge regression was fitted using a Bayesian Software called 'BayesRegression' Version 11 (June2016) [35]. The software is an open source and can be downloaded from *http://georgek.people.uic.edu/BayesSoftware.html*. The outcome variables were mean catches of adult female *Anopheles gambiae* per trap person night and human malaria infection prevalence. All geophysical covariates were included in the ridge regressions. These covariates were highly correlated as indicated by Variance Inflation Factor (VIF) in Table 2, where many variables have VIF > 10 indicating presence of high multi-collinearity [36]. Ridge regression is one of the better approaches to handle multicollinearity because it shrinks the coefficient estimates of irrelevant covariates towards zero, thus useful for nonlinear regressions [33]. In short, the ridge regression method adds a penalty (shrinkage) parameter λ into the model to adjust for the collinearity between covariates. As this parameter increases, the coefficient values shrink towards zero [37]. The relationship between shrinkage parameter and posterior mean of the coefficients have been shown by the trace plots (ridge trace) in Figures 1A and 1B for *An. gambiae* and infection prevalence models respectively. Standardized coefficient (95% Bayesian Credibility Intervals for the posterior mean) estimates can be conveniently viewed from love plots in Figures 2A for densities of *An. gambiae* and 2B for malaria infections prevalence.

2.3.3. Spatial modelling and prediction

Only variables with 95% Bayesian credible intervals that did not cross zero were considered significant and hence retained for the next step of the modeling and spatial prediction. Two distinct conditional autoregressive models (CAR) adjusted for larvicide application regimes were fitted using a contiguous neighbor structured random effect, to elucidate the spatial interactions that arise between geophysical topography, densities of *An. gambiae* and malaria infection prevalence and map their spatial predictions. The CAR model accounts for spatial effects and in essence the mean or probability values estimated at any given location are conditional on the levels in the neighboring areas. The model for densities of *An. gambiae* was fitted using a Poisson-lognormal CAR model. [38] and malaria infection prevalence was fitted using binomial logit CAR [39]. The auto regression parameters and confidence intervals for each model were obtained using Markov chain Monte Carlo (MCMC) methods [39, 40]. Coefficients for *An. gambiae* model and infection prevalence logit model were exponentiated to present relative rates (RR) and odds ratios (OR) respectively. Transects of all significant geophysical topographic variables as well as predicted entomology/parasitology outcome in different parts of the city were prepared to aid interpretation of the results. The CAR spatial modelling were all performed using CrimeStat IV® (for obtaining auto regression parameters) [41] and SAGA GIS® (for mapping the final model results), both open source GIS software packages. Transects values were extracted using SAGA GIS® and graphs prepared using Microsoft Excel.

3. Results

3.1 Selected geophysical predictors of malaria hazard and risk

Ridge trace plots in Figure 1 shows the number of significant variables retained for spatial prediction and mapping of *An. gambiae* densities and malaria infections prevalence. In Figure

1A, posterior means (standardized coefficients) of six variables describing significant associations with densities of *An. gambiae* are shown. Of the variables, half showed negative associations with densities of *An. gambiae* while the remaining half indicated positive associations. Introduction of a shrinkage penalty into the *An. gambiae* model, in this case a value of 428.3, allowed all coefficients for non-significant covariates to shrink closer to zero (Figure 1A). However, the ridge regression model explained only a 0.34 proportion of the variance in densities of *An. gambiae.* Similarly, the ridge trace in Figure 1B shows five significant variables to be retained for modelling and predicting malaria infection prevalence in Dar es Salaam. The posterior mean of three variables show negative association while the remaining two had positive relationship with infection prevalence. Seven variables were irrelevant and therefore shrunk towards zero (Figure 1B). In this model, the ridge shrinkage penalty was 263.2 and the explained proportion of variance was 0.39. Notably, in the ridge trace, variables which are far from zero are more important that those which are closer to zero.

Position of Figure 1

Position of Figure 2

In Figures 2A and B, the ridge Love plots show variable names and their posterior association with both *An. gambiae* mosquito densities and malaria infection prevalence, respectively. Names of the six covariates identified in Figure 1A, are GoT granular (Application of the granular *Bti* formulation by the Government of Tanzania), GoT liquid (Application of the liquid *Bti* formulation by the Government of Tanzania), topographic wetness index, planform curvature,

topographic roughness index and slope. GoT granule and GoT liquid had the expected negative association with vector density (Figure 2A), indicating lower densities of mosquitoes in areas where larvicide was applied. Also, the expected positive association was observed between malaria vector densities and planform curvature, confirming that locations with concave planform curvature (Figure 3C), where water is more likely to accumulate, had higher mosquito densities. Of the variables in table 3 for which intuitively expected associations were observed, GoT liquid was the most important, followed by GoT granule and then planform curvature. Figure 2A also shows variables that are positively associated with densities of *An. gambiae.* These are topographic wetness index, slope and topographic roughness index. Slope was the most important, followed by topographic roughness and lastly topographic wetness index (Figure 2A). However, slope and topographic roughness are counter-intuitive variables, as they show higher densities of *An. gambiae* in landscapes that should be well drained and therefore unlikely to provide aquatic habitats for mosquito breeding. Likewise, the five significant covariates for malaria infection prevalence identified in Figure 1B are GoT granular, elevation, topographic wetness index, profile curvature and topographic roughness index. GoT granule, topographic wetness index, topographic roughness index and elevation were intuitively associated with malaria infection as they indicate lower prevalence in areas with larviciding, or higher prevalence in wetter areas, poorly drained areas, and lowlands, respectively. Unexpectedly, Figure 2B shows positive association between prevalence and profile curvature, which is an indication of well-drained, drier locations (Figure 3G).

Position of Figure 3

Position of Figure 4

3.2 Geophysical predictors of malaria hazard and risk at fine spatial scales

Results of the CAR models are presented in Table 3. Consistent with results from ridge regression and also with previous analyses [26], application of larviciding with granular *Bti*, after but not before the MoHSW took over management of all delivery activities from an external contractor, resulted in reduction of both densities of adult *An. gambiae* and human malaria infection prevalence (Table 3). Densities of *An. gambiae* continued to decline after the MoHSW introduced liquid larvicide formulation, and malaria entomological inoculation rate dropped below the threshold of 0.1 infectious bites per person per year [26] below which transmission may be de-stabilized [42-44]. However, this had little effect upon malaria infection prevalence (Table 3), presumably due to long-term persistence of untreated, chronic malaria infections at high prevalence [26] which can take years to slowly dissipate [45-48]. The impacts of larviciding upon vector densities estimated with these models that allow for spatial autocorrelation (Table 3) were considerably greater than those previously estimated with non-spatially-explicit regression models, presumably because the latter treated each surveyed location as geographically independent and did not allow for the effects of *Anopheles* mosquitoes flying into larvicide-treated areas from untreated areas nearby.

Consistent with previous reports [18-21, 23, 25, 49-51], spatial variations of malaria vector density and human infection prevalence were associated with local geophysical topographic predictors of aquatic habitat suitability in an intuitively obvious manner (Table 3). Higher densities of *An. gambiae* were found in locations with concave planform curvature (Figure 3C)

occurring at the bottoms of steep slope, while elevated malaria infection was associated with high topographic wetness index, or with lower elevations (Table 3), both of which clearly map out the bottoms of valleys and other depressions across Dar es Salaam (Figure 3E and A, respectively).

However, some associations of malaria vector density and infection prevalence with additional geophysical topographic indicators were observed that were initially surprising and counter-intuitive. High densities of *An. gambiae* and elevated malaria infection prevalence were associated with indicators of good natural drainage, at the boundaries between dry and wet areas (Table 3), which would normally be considered least likely to provide suitable aquatic larval habitats for *Anopheles* mosquitoes [18, 24, 25, 52-56]. Specifically, higher densities of adult *An. gambiae* mosquitoes were caught in locations with steep slopes (Figure 3B), or with high topographic roughness index (TRI: Figure 3F), which is essentially equivalent (Table 2) to slope (Figure 3B). Similarly, higher malaria infection prevalence amongst humans was surprisingly associated with convex profile curvature (Figure 3G) occurring at the tops of steep slopes. The panels in Figure 3 are grouped into vertical pairs so that topographically similar indicators of hydrology and ecosystem geography can be compared and contrasted: While the two left-hand panels (**A** and **E**) clearly map out valleys and depressions with high local water-accumulation and wetness, the next two panels to the right of these (**B** and **F**) clearly delineate the well-drained slopes leading from the bottoms of those wet valleys to the higher, drier areas above them where most of the residents of Dar es Salaam actually live. Moving right again, to panels **C** and **G**, it can be seen that these two geophysical topographic indicators map out the tops of those slopes at the edges of valleys.

To illustrate how these three different sets of geophysical topographic indicators of elevated malaria hazard and risk are closely associated with each other, and often vary across their full range of values within distances of <100m, a detailed geophysical topographic, entomological and epidemiological profile of the transect illustrated in Figure 3D is presented in Figure 4. Figure 4 illustrates how steep slopes, high topographic roughness index, high (convex) profile curvature, and high (convex) planform curvature are found at the edges of valleys with low elevation and high topographic wetness index. The most obvious biological explanation for this observation is that these interfaces between lowlands and uplands are where most host-seeking adult *Anopheles* mosquitoes first encounter and attack humans, when they disperse in search of blood after emerging or ovipositing.

Accounting for spatial autocorrelation in the CAR improved the model fit by 52% and 13% for *An. gambiae* and malaria infections, respectively. This compares the adjusted R^2 from 34% in ridge regression to 86% in CAR for *An. gambiae* densities, and 39% in ridge regression to 58% in CAR for malaria infection model fits. Models combining geophysical topographic predictors with larvicide intervention status accounted for very high proportions of variance in *An. gambiae* densities but far less so for malaria infection prevalence. Only three geophysical topographic predictors of *An. gambiae* accounted for more than half (67%) of the variance in malaria vector density transmission hazard, with most of the remainder (19%) accounted for by larvicide application status (Table 3). In contrast, the geophysical topographic indicators of malaria prevalence account for only 43% of variance in this indicator of infection burden (Table 3). Indeed, the map of the vector densities predicted by the fitted model presented in Table 3 (Figure 5A) has far greater contrast than that for predicted malaria infection prevalence (Figure 5B).

Vector densities are predicted to be very focal indeed, specifically localized so clearly along the edges of valleys that the cartographic expression of this model fit (Figure 5A) is essentially identical to maps of geophysical topographic variables capturing steep slopes (Figure 3B and F) or convex curvatures at the tops of those steep slopes (Figure 3C and G). In contrast, malaria infection prevalence amongst humans is far more homogenously distributed across the city, with what little contrast there is in the maps of predicted risk (Figure 5B) defining the flood-prone valley bottoms where very few people actually live.

Position of Figure 5

Position of Figure 6

Correspondingly, geophysical topographic indicators provide a far more selective basis for geographically targeting the vectors of malaria (Figure 6A) than human infections (Figure 6B) in Dar es Salaam. Figure 6A illustrates just how selective targeting of adult vector control to these geophysical topographically mapped boundaries could be: Geographic targeting in order of model-predicted vector density would account for 85% of all the *An. gambiae* caught if only the 15% of survey locations with the highest predicted hazard were included. In contrast, Figure 6B reveals that only 60% of detected malaria infections would be captured by targeting a full 40% of survey locations with highest predicted infection prevalence risk. Expressing these proportions of locations and mosquitoes or malaria infections covered relative to each other gives estimated targeting ratios of 5.7 and 1.5 to 1, respectively (Figure 6).

4. Discussion

The results of this study illustrate, for the first time, that while conventional geophysical topographic predictors of wetness, such as concave planform curvature, topographic wetness index and low elevation may be valuable for spatial targeting of larval source management, indicators of dryness on steep slopes, and at the tops of those steep slopes, also have unforeseen utility for targeting adult malaria vector mosquitoes. These steep, dry slopes occur at the periphery of human settlements, immediately adjacent to wet, low-lying areas with abundant aquatic habitat. This is therefore where residents are disproportionately exposed to adult *Anopheles* mosquitoes dispersing from nearby aquatic habitats after emerging or ovipositing [2-4, 8, 57].

The observed predictive value of geophysical topographic indicators of wetness for elevated densities of *An. gambiae* and malaria infection prevalence, predominantly in the main river valleys, drainage lines and local depressions of the city landscape [32] is fully consistent with previous studies in Kenya [18, 55, 58, 59] and Tanzania [19, 60, 61]. However, the observation that local geophysical topography not only predicts the distribution of aquatic habitats, but also the peripheries of human settlements that surround them, is novel and was not foreseen at the outset of the study. These narrow boundaries between dry human habitat and wet mosquito habitat are where malaria vectors first encounter and attack human hosts when they seek blood after emerging or ovipositing. They could therefore be exploited to define target zones for *barrier* interventions to kill adult mosquitoes, such as the residual surface spraying [62] methods this term was originally applied to [63], or alternatives such as insecticide netting barriers [64], vapour-phase insecticide emanators [65], or nocturnal space spraying [66]. Barrier targeting of

adult vector control at high spatial resolution (Figure 6A) would not only directly protect the local residents, but also shield the rest of the population in upland areas further away from these wet valleys [62, 67], thus maximizing communal benefit to all residents through mass suppression of vector populations.

Similar geophysical topographic indicators of abundant vector larval habitat, and the steep banks of the valleys where they usually occur, were also predictive of human infection prevalence but had far less predictive power. The weaker predictive value may well be explained by variations in human resilience factors, such window screening, bed net use and time spent indoors [26], all of which could attenuate the dependence of infection risk on exposure hazard. For example, human infection prevalence is known to be highly dependent upon local vector density among household lacking window screens but essentially unaffected by it in well-screened houses [26]. Furthermore, many of the human infections detected in these surveys appear to have been long-standing chronic infections [26], that might not necessarily be directly related to ongoing transmission exposure. Also, what little contrast can be seen in maps of model-predicted malaria infection risk depicts the wet valley bottoms (Figure 6B) where very few people actually live (Figures 3H and 4B). Such geophysical topographic indicators of likely infection burden are therefore far less useful for targeting interventions to increase human resilience against exposure hazard, such as bednets, mosquito-proofed housing or repellents, as well as testing and treatment or mass administration curative drugs to tackle chronic morbidity burden [68] and clear the infectious reservoir [69], than they are for targeting vector population suppression interventions against adult vectors.

The approach presented could be readily applied and assessed in other African settings, as a means to identify heterogeneity in malaria risk patterns and detect zones for spatially selective targeted interventions. Specifically, it may be used to predict the distribution of malaria transmission across the landscapes where dense human populations surround aquatic habitats such as rivers, swamps and flooding zones, or *vice versa* in some flood-prone rural settings. In urban Africa, these zones tend to be illegally occupied informal settlements [70], inhabited mostly by the poor whose human resilience against malaria risk is very low [71, 72]. In order to tap the full potential of this approach to mapping areas for selectively targeted interventions against adult mosquitoes, the resolution of geophysical indicators needs to be high enough to accurately capture transmission at fine spatial scales that hazard and risk really occur at [17, 73]. For this reason, the approach is really only suitable for use by locally-managed, decentralized mosquito control programmes that can practically target appropriate interventions at very fine geographic scales, rather than for cruder prioritization of interventions across larger provincial or national scales [20, 74, 75]. Beyond evaluating in a wider diversity of settings where sufficient entomological and epidemiological data are available that have been mapped at high resolution, this approach also needs to be field-validated in by empirically evaluating the actual, rather than predicted, impacts vector control activities directed by these targeting criteria..

Another limitation of this study is that these spatial models relied exclusively on geophysical topographical factors as the only geographic predictor variables. The formation of larval *An. gambiae* habitats and risk of malaria transmission also depend on many other geographically variable factors [76, 77], such as ground water levels, soil characteristics, weather, vegetation, human behavior, land use, drainage infrastructure and education, as well as health service access

and quality [78, 79]. It is therefore possible that better predictive models of malaria infection risk could be developed using richer sets of independent indicator variables.

5. Conclusion

Geophysical topographic indicators of local water-accumulation potential may not only be used to target aquatic habitats with larval source management, but also the peripheries of human settlements along the drier banks of these wet valleys, where adult *Anopheles* mosquitoes seeking blood first encounter and attack the residents. Vector control interventions against adult mosquitoes, such as residual surface spraying [62, 63], treated netting barriers [64], vapour-phase insecticides [65] or nocturnal space sprays [66] could be selectively and efficiently deployed to barrier zones using geophysical topographic predictors of steep slopes and the tops of those steep slopes.

Ethics

The permission to carry out this research was obtained from the Institutional Review Board of the Ifakara Health Institute (Approval A.50), the Medical Research Coordination Committee of the Tanzanian National Institute of Medical Research (Approval NIMR/HQ/R.8a/Vol.IX/801), the Research Ethics Committee of the Liverpool School of Tropical Medicine (09.60) and the Human Research Ethics Committee (HSEC) at University of the Witwatersrand (M120835). Only participants who provided informed consent were included in the study, including the mosquito catchers, the owners of houses where mosquito catches took place, and the participants in the epidemiological cross-sectional parasite surveys. Participants found to be infected with malaria parasites through the parasitological surveys were treated with artemether-lumefantrine

(Coartem®; Novartis Pharma AG, Basel, Switzerland) following national treatment policies and guidelines.

Data availability

Our data are available in Dryad: http://datadryad.org/review?doi=doi:10.5061/dryad.51012. For questions or additional information contact us via email (vmchuma@gmail.com).

Competing interests

The authors declare no competing interests.

Authors' contributions

VMM led the design and implementation of the study, including data analysis, preparing maps and drafting of the manuscript. AJL, YPM and DFM implemented the adult mosquito and household parasitology surveys, as well as data collection and management of the data, including spatial information. SD, BKDS, PPC, NJG, MC and GFK supervised the design and implementation of the study, interpretation of results, and preparation of the manuscript. All authors read, commented on and approved the final manuscript.

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Table 1: Definitions of geophysical topographical indicators that describe local hydrology in Dar es Salaam city

Variables	Descriptions
Altitude above channel network	This is the vertical distance to a channel base level. It is the difference between interpolated channel network base level and this base level from the original elevations [25, 80].
Aspect	This is the direction of maximum gradient and relates to the degree of solar exposure. The aspect determines the effect of solar heating, air temperature, and moisture (micro-climatic influence). The orientation that the hill slope faces, ranging from 0º to 360º (0º and 360º North, 90º East, 180º South, 270º West) Aspect is [22].
Channel network	This is a naturally created drain, may either be dry (valley) or conveying water (river). It defines the extent/coverage of rivers and other local drainages/valleys [25, 80].
Elevation	The vertical distance of a point or level on or affixed to the surface of the Earth, measured from mean sea level. Elevation was derived from Digital Elevation Model. Primarily influences water movement throughout a landscape as well as within drainage channels.
Hills shading	This shows local areas with shadows thrown upon raised landscapes [81]. The higher shading values the lighter and warmer the surface (more exposed to sun rays) and the lower the hill shading values the darker and cooler the surface it becomes.
Profile curvature	Is the curvature in a horizontal plane and it is perpendicular to the direction of the maximum slope. A positive value indicates the surface is sidewardly convex at that cell. A negative plan indicates the surface is sidewardly concave at that cell. A value of zero indicates the surface is linear. Profile curvature relates to the convergence and divergence of flow across a surface [82, 83].
Planform curvature	Profile curvature is the curvature intersecting with the plane defined by the Z axis and maximum gradient direction. Positive values describe convex profile curvature, negative values concave profile. A negative value indicates that the surface is upwardly convex at that cell, and a positive value indicates that the surface is upwardly concave; a value of zero indicates that the surface is linear. The Profile Curvature affects the flow velocity of water draining the surface and influences erosion and deposition. In locations with convex (negative) [83].
Slope	Is a measure of the angle of descent or ascent for each pixel (calculated as the rate of change in altitude). The angle of incline on a hillside is called slope, and the lower the slope value, the flatter the terrain; the higher the slope value, the steeper the terrain. Slope has a strong influence on overland and subsurface flow velocity, drainage and accumulation of water [84].
Topographic Convergence Index (TCI)	TCI is the direction of water flow between adjacent cells based on the aspects of neighboring cells. It determines whether water flow from neighboring cells diverges (positive values ≤100 indicating dry areas) or converges (negative values ≥ −100 indicating saturated areas) [25, 80].
Topographic Position Index (TPI)	The difference between the elevation at a cell and the average elevation in a neighborhood surrounding that cell. TPI is used to measure geophysical topographic slope positions and to automate landform classifications where by negative values indicate valleys, while positive values signify ridges [85].
Topographic Ruggedness Index (TRI)	A measure of terrain roughness, may be the standard deviation of slope, standard deviation of elevation, slope convexity, variability of plan convexity, or some other measure of geophysical topographic texture [85]. In this study, TRI corresponds to average elevation

	change between any point on a digital elevation model grid (one grid is 20x20metres) and its surrounding area [86].
Topographic Wetness Index (TWI)	This is the estimate of predicted water-accumulation (provides an index of potential moisture availability), it was calculated as the ration of contributing upslope drainage area and local slope as developed by Tarboton [87]. The TWI ranges from less than 0 to infinity [88]. High values (TWI >20) are found for converging terrain and valleys, while low values (TWI <20) are typical of steep and diverging terrains [89, 90]. TWI is proxy to depth of groundwater, soil pH, vegetation species richness and soil organic matter [91-93].

Table 2: Summary of multicollinearity assessment among predictors of mosquito vector densities and malaria infection prevalence based on their Variance Inflation Factors (VIFs)

Predictors	VIF	Covariates
Altitude above channel network	86.41	Elevation (58.67)
Aspect	**1.01**	-
Elevation	**1.25**	CHN (58.67)
Planform curvature	**2.67**	PRC (4.29), TPI (4.29), TRI (0.86), Slope (0.43), TWI (0.43)
Profile curvature	**2.95**	Slope (6.15), TRI (8.15), TWI (5.15), PLC (4.29)
Slope	**8.21**	TRI (8.57), TWI (6. 57), TPI (8.28), PRC (6.15), PLC (0.43)
Topographic Convergence Index	**1.48**	-
Topographic Position Index	**4.83**	PRC (8.57), Slope (8.58), TRI (8.58), TWI (8.15), PLC (4.29)
Topographic Ruggedness Index	**7.02**	Slope (8.57), TWI (5.13), TPI (8.28), PRC (6.15), PLC (0.86)
Topographic Wetness Index	**3.02**	Slope (6.57), TRI (5.13), PRC (5.15), TPI (8.15), PLC (0.43)
RTI granule	**1.51**	-
GoT granule	**1.21**	-
GoT liquid	**1.61**	-

RTI granule: Larviciding with granular formulation of *Bacillus thuriniensis var. israelensis* (*Bti*), managed by an external contractor, the Research Triangle Initiative (RTI), between March and October 2010
GoT granule: Larviciding with granular formulation of *Bacillus thuriniensis var. israelensis* (*Bti*), managed by the Government of Tanzania, between January and July 2011
GoT liquid: Larviciding managed by the Government of Tanzania using a pre-diluted liquid formulation of *Bti*, from August 2011 onward

Note: VIF >10 is multicollinearity

Table 3: Association between mosquito vector densities/malaria infection prevalence and geophysical topographic indicators of local wetness, the interface between human settlements and aquatic habitat and effective interventions

8	Predictor	Relative rate[a] or Odds Ratio[b] [95% CI]	Proportion of Variance	Relative importance	*p*	Interpretation
Mean catches of adult female *Anopheles gambiae* per trap person night[a]	GoT granule	0.31 [0.14-0.69]	0.06	7.0	0.008	Effective intervention
	GoT liquid	0.089 [0.087-0.092]	0.13	15.1	<0.001	Effective intervention
	Slope	1.78 [1.75-1.82]	0.26	30.2	0.004	Wet-dry boundary
	Topographic roughness index	1.11 [1.04-1.18]	0.12	14.0	0.005	Wet-dry boundary
	Planform curvature	0.80 [0.78-0.82]	0.29	33.7	0.001	Local wetness
	Adjusted R^2	0.83				
	Targeting ratio	85/15 (5.7:1)				
Human malaria infection prevalence[b]	GoT granule	0.85 [0.83-0.88][b]	0.15	25.9	<0.001	Effective intervention
	Topographic wetness index	1.79 [1.52-2.10][b]	0.12	20.7	0.011	Local wetness
	Elevation	0.74 [0.70-0.79][b]	0.10	17.2	0.006	Local wetness
	Profile curvature	3.70 [2.46-5.55][b]	0.21	36.2	<0.001	Wet-dry boundary
	Adjusted R^2	0.58				
	Targeting ratio	60/40 (1.5:1)				

TWI: Topographic Wetness Index
TRI: Topographic Roughness Index
GoT granule: Larviciding with granular formulation of *Bacillus thuriniensis var. israelensis* (*Bti*), managed by the Government of Tanzania, between January and July 2011
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[a] For the Poisson log-normal-distributed mean mosquito catch outcome variable.
[b] For the binomial-distributed human infection prevalance outcome variable.
[c] The proportion of variance is computed in two groups separately. The groups are interventions and geophysical indicators. For example in *An. gambiae* model, interventions contributed a total of 19% (R^2 = 0.19) in the overall model. Of these 13% is shared by GoT liquid and only 0.06% is contributed by GoT granule. Similarly, for geophysical indicators, which all together contributed a total of 67% to the model, of which planform curvature had the highest portion which is 29% and the smallest was contributed by TWI which has 12%. Similar approach applies to the relative importance.
[d] Relative importance is the weighted average of the proportion of variance times 100%

Figure 1: Ridge trace plot showing penalized coefficients in An. gambiae and malaria infections models

Figure 2: Ridge love plots showing distribution of significant covariates and their standardized coefficients

Figure 3: Spatial distributions and patterns of geophysical topographic predictors which significantly predicted mosquito vector densities and malaria infection prevalence

Figure 4: Profile of the transect illustrating the cross cutting relationship between geophysical topography and human population density as well as entomological and epidemiological indicators

Figure 5: Predicted spatial distribution of location with highest mosquito vectors densities and malaria infection prevalence

Figure 6: Spatial targeting efficiency of the locations with the highest predicted densities of *An. gambiae* and human infection prevalence

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[d] Relative importance is the weighted average of the proportion of variance times 100%

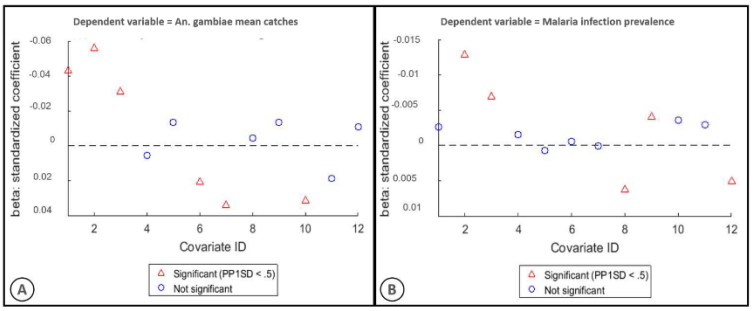


Figure 1: Ridge trace plot showing penalized coefficients in An. gambiae and malaria infections models

338x190mm (150 x 150 DPI)

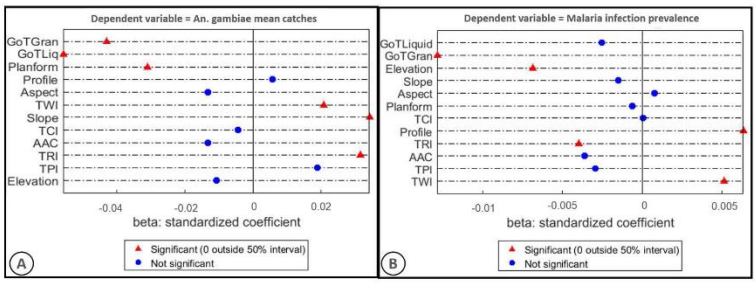


Figure 2: Ridge love plots showing distribution of significant covariates and their standardized coefficients

338x190mm (149 x 149 DPI)

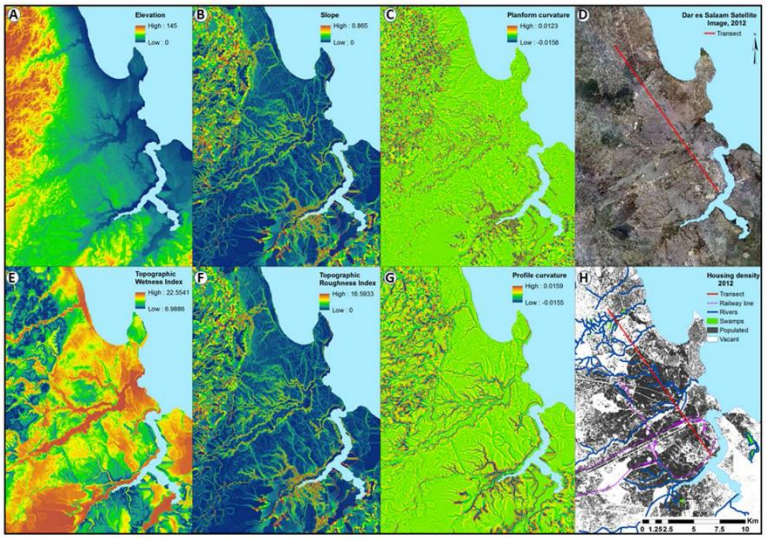


Figure 3: Spatial distributions and patterns of geophysical topographic predictors which significantly predicted mosquito vector densities and malaria infection prevalence

254x190mm (96 x 96 DPI)

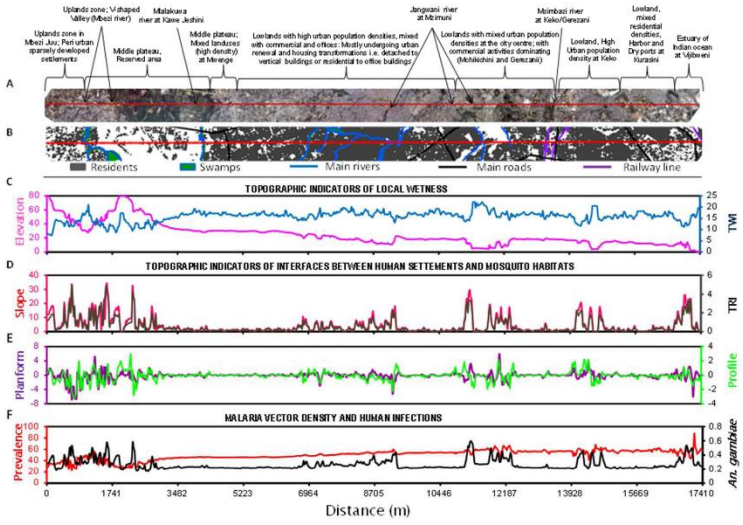


Figure 4: Profile of the transect illustrating the cross cutting relationship between geophysical topography and human population density as well as entomological and epidemiological indicators

254x190mm (96 x 96 DPI)

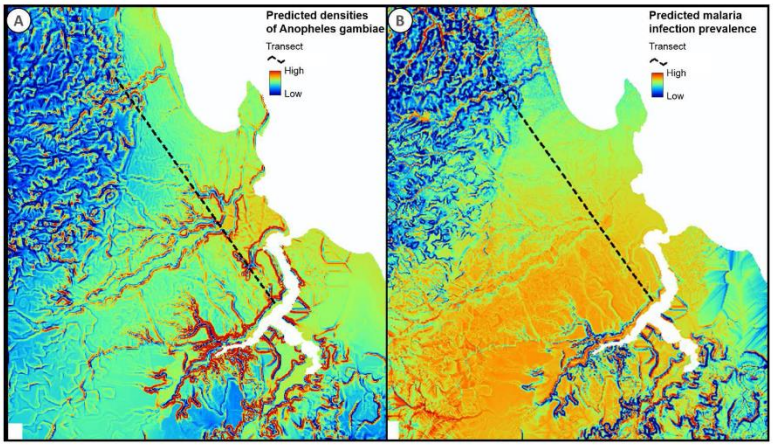
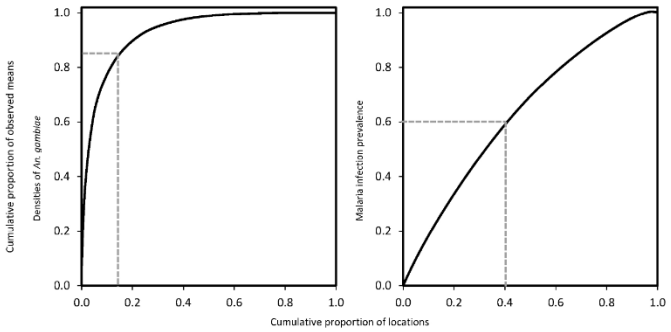


Figure 5: Predicted spatial distribution of location with highest mosquito vectors densities and malaria infection prevalence

334x190mm (150 x 150 DPI)



338x190mm (200 x 200 DPI)

Annexure II: Ethical clearance certificate from Wits

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Ms Victoria M Chuma

CLEARANCE CERTIFICATE	**M120835**
PROJECT	Integrated Spatial Information Tools Can Enable Targeted Urban Planning Interventions to Control Malaria and Lymphatic Filariasis in Dar es Salaam
INVESTIGATORS	Ms Victoria M Chuma.
DEPARTMENT	School of Public Health
DATE CONSIDERED	31/08/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 26/11/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof Maureen Coetzee

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Annexure III: Ethical clearance from Tanzania

THE UNITED REPUBLIC OF
TANZANIA

National Institute for Medical Research
P.O. Box 9653
Dar es Salaam
Tel: 255 22 2121400/390
Fax: 255 22 2121380/2121360
E-mail: headquarters@nimr.or.tz

NIMR/HQ/R.8c/Vol. I /163

Ministry of Health and Social Welfare
P.O. Box 9083
Dar es Salaam
Tel: 255 22 2120262-7
Fax: 255 22 2110986

27th May 2011

Dr Gerry F Killeen
Ifakara Health Institute
P O Box 78373,
Dar es Salaam

CLEARANCE CERTIFICATE FOR CONDUCTING MEDICAL RESEARCH IN TANZANIA

This letter is to confirm that your application for an amendment 01 on the research entitled: Monitoring and Evaluation tools to allow sustained elimination of malaria transmission, (Killeen G F *et al*), whose local Investigator is Dr. Silas Majambere, Ifakara Health Institute, NIMR/HQ/R.8a/Vol. IX/801, dated 21st April 2009, has been granted ethics clearance to be conducted in Tanzania.

The Local Investigator Dr Silas Majambere, must ensure that the approval is for:
Amendment 01:

1. To replace school based cohort design with community cohort design of equivalent sample size.
2. To conduct limited human landing catches in order to complete the process of developing, refining and evaluating this technology for quantifying the proportion of human exposure which occurs.

Approval of the study protocol is up to 20th April 2012.

Name: Dr Mwelecele N Malecela

Signature

CHAIRPERSON
MEDICAL RESEARCH
COORDNATING COMMITTEE

Name: Dr Deo Mtasiwa

Signature

CHIEF MEDICAL OFFICER
MINISTRY OF HEALTH
AND SOCIAL WELFARE

RMO
DMO

Annexure IV: Ethical clearance from Liverpool School of Tropical Medicine (LSTM)

Dr Gerry Killeen
Liverpool School of Tropical Medicine
Pembroke Place
Liverpool
L3 5QA

LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Pembroke Place,
Liverpool, L3 5QA, UK
Tel: +44 (0)151 705 3100
Fax: +44 (0)151 705 3370
www.liv.ac.uk/lstm

Wednesday, 23 February 2011

Dear Dr Gerry Killeen

Re: Research Protocol (09.60) Monitoring and Evaluation tools to allow sustained elimination of malaria transmission

Thank you for your email dated 18 February 2011 clarifying your amendments to the Committee.

These changes have been noted and accepted.

Yours sincerely

Yours sincerely

Prof David Lalloo
Chair, Research Ethics Committee

cc:

Annexure V: Data access letter

IFAKARA HEALTH INSTITUTE
research | training | services

Human Research Ethics Committee (HREC)
Wits University
1 Jan Smuts Avenue
Braamfontein 2000
Johannesburg, South Africa

6th August 2012

Re: Data access permission from IHI

Dear Members of the Wits Ethics Committee

On behalf of the Ifakara Health Institute (IHI), I am writing to formally indicate our awareness of the study titled "integrated spatial information tools can enable targeted urban planning intervetion to control malaria and lymphatic filariasis in Dar es Salaam" proposed by Ms. Victoria Mwakalinga, an employee of the Ifakara health Institute and a Phd student at the University of the Witwatersrand.
We are aware that Ms. Mwakalinga intends to use the data collected by Malaria Transmission Consortium (MTC) and avecnet projects at our institution.

As one of Principal Investigators of these projects, I authorize Ms Mwakalinga to use the data under the conditions that she keeps the data confidential among herself and her supervisors; and she commits to use the data only for her study as indicated in her PhD protocol and not otherwise.

Should you have any questions or concerns, please feel free to contact me.

Sincerely,

Gerry Killeen

Gerry Killeen, PhD
Thematic Group Leader, Environmental Sciences, Ifakara Health Institute, Tanzania
Reader, Vector Group Liverpool School of Tropical Medicine, UK

MONITORING AND EVALUATION TOOLS TO ALLOW SUSTAINED ELIMINATION OF MALARIA TRANSMISSION

Amendment Appendix 1:

Malaria Indicator Survey (MIS) questionnaire for Community cohort survey monthly follow ups

Version 1.0

Form Information

Form Serial Number (IC1): **[Copy from Informed Consent agreement of Household Head]**	
Date (DT):	
Interviewer Name:	
Interviewer signature:	
Supervisor Name:	
Supervisor signature:	
Ten-cell unit leader name:	

Study Information:

Site (SE):	101 (Dar es Salaam, United Republic of Tanzania)

Part I-Household Information-Fill out once for each house

1. Enumeration area (EA; concatenated numeric codes for Municipality-Ward-Neighbourhood)

Geographic area unit:	Municipality	Ward	Neighbourhood/Street
Digits:	1	2	2
Code:			

2. House location and identity within the sampling frame

Housing unit:	Ten-cell unit cluster (CR)	Compound or Plot (CP)	Household (HH)
Digits:	3	3	3
Code:			

3. Registered House Number_____

4. Name of Head of Household_____

Part II-Household Listing-Fill out questionnaire for each person who stayed in house previous night.

1. Name of person_____
2. Informed Consent form number (IC1) of (NAME:_____
3. Assign an Individual Identity (II) number within the household: [ ]
4. Is (NAME) male or female?
    a. MALE
    b. FEMALE
5. Does (NAME) usually live here?
    a. YES
    b. NO
6. Did (NAME) stay here last night?
    a. YES
    b. NO (Go direct to question 11)
7. To the nearest hour, what time last night did (NAME) go indoors for the evening? [ ]
8. To the nearest hour, what time last night did (NAME) go to bed? [ ]
9. To the nearest hour, what time this morning did (NAME) get out of bed? [ ]
10. To the nearest hour, what time this morning did (NAME) first go outdoors? [ ]
11. In the past month, has (NAME) slept somewhere outside of this house?
    a. YES
    b. NO
    c. NOT SURE
12. Has (NAME) been ill with a fever at any time in the last 2 weeks?
    a. YES
    b. NO
    c. NOT SURE
13. Did you seek advice or treatment for the fever from any source?
    a. YES
    b. NO
14. Where did you seek advice or treatment? (Check all that apply)
    a. GOVT. HOSPITAL [ ]
    b. GOVT. HEALTH CENTER [ ]
    c. GOVT. HEALTH POST [ ]
    d. MOBILE CLINIC [ ]
    e. FIELD WORKER [ ]
    f. OTHER PUBLIC [ ]
    g. PVT. HOSPITAL/CLINIC [ ]
    h. PHARMACY [ ]
    i. PRIVATE DOCTOR [ ]
    j. MOBILE CLINIC [ ]

k. PROJECT COMMUNITY HEALTH NURSE [ ]
l. OTHER PVT. MEDICAL)_____ [ ]
m. SHOP [ ]
n. TRAD. PRACTITIONER [ ]
o. OTHER)_____ [ ]

15. Has (NAME) had a fever in the last 24 hours?
    a. YES
    b. NO
    c. DON'T KNOW

16. Has (NAME) taken any drugs in the last 2 weeks? (Check all that apply)
    a. SP/FANSIDAR [ ]
    b. CHLOROQUINE [ ]
    c. AMODIAQUINE [ ]
    d. QUININE [ ]
    e. COARTEM [ ]
    f. OTHER ANTIMALARIAL (SPECIFY)_____ [ ]
    g. ASPIRIN [ ]
    h. ACETAMINOPHEN/PARACETAMOL [ ]
    i. IBUPROFEN [ ]
    j. OTHER (SPECIFY)_____ [ ]
    k. DON'T KNOW [ ]

17. Is this person present for a malaria/anemia test?
    a. YES (Fill out results in Section IV)
    b. NO

18. Are there any other persons who live in this house that we have not listed?
    a. YES (Go back to QUESTION 1 and fill out this form for that person)
    b. NO

19. Are there any other persons such as small children or infants that we have not listed?
    a. YES (Go back to QUESTION 1 and fill out this form for that person)
    b. NO

20. In addition, are there any other people who may not be members of your family, such as domestic servants, lodgers or friends who usually live here?
    a. YES (Go back to QUESTION 1 and fill out this form for that person)
    b. NO

Part III-Malaria infection status and risk factors for each participant

1. Assigned individual identifier number (II) of child within the household: [ ]
2. Serial number from Informed Consent agreement for this individual (IC1):_____
3. Did (NAME) stay here last night?
    a. YES
    b. NO
4. To the nearest hour, what time last night did (NAME) go indoors for the evening? [ ]
5. To the nearest hour, what time last night did (NAME) go to bed? [ ]
6. To the nearest hour, what time this morning did (NAME) get out of bed? [ ]
7. To the nearest hour, what time this morning did (NAME) first go outdoors? [ ]
8. In the past month, has (NAME) slept somewhere outside of this house?
    a. YES
    b. NO
    c. NOT SURE
9. Did (NAME) sleep under a net last night?
    a. YES
    b. NO (Go to question 17)
    c. NOT SURE
10. How long ago was the net obtained?
    Months: [ ] Years: [ ] Don't know: [ ]
11. What is the brand of net used:
    a. PermaNet
    b. Olyset
    c. SupaNet
    d. Safinet
    e. Mbu net
12. Since you got the mosquito net, was it ever soaked or dipped in a liquid to repel mosquitoes or bugs?
    a. YES
    b. NO (Go to question #7)
    c. NOT SURE (Go to question #7)
13. How long ago was the net last soaked or dipped? (If less than 1 month, enter '00')

    Months: [ ] Years: [ ]

Part IV-Malaria/Anemia-Record the RDT result for each participant

14. Assigned number of individual within the household (II): [ ]

15. Serial number from Informed Consent agreement for this individual (IC1):_____

16. RDT Result
    a. Positive
    b. Negative

17. Blood smear taken?
    a. YES
    b. NO

18. Dried blood spot sample on filter paper taken?

    a. YES
    b. NO

19. Are there any other persons who live in this house that we have not tested?
    a. YES (Go back to QUESTION 1 and fill out this form for that person)
    b. NO

Annexure VII: A plagiarism report from "*Turnitin*" software

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