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Tusting, L (2016) Agriculture, development and malaria in rural Uganda. PhD thesis, London School of Hygiene & Tropical Medicine. DOI: <https://doi.org/10.17037/PUBS.02572615>

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Agriculture, development and malaria in rural Uganda

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Thesis submitted in accordance with the requirements
for the degree of
Doctor of Philosophy of the University of London

August 2015



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**Funded by the Leverhulme Centre for Integrative Research
in Agriculture and Health**

I, Lucy Sara Tusting, confirm that the work presented in this thesis is my own.

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Lucy Sara Tusting

30th July 2015

Abstract

While malaria remains a major global public health problem, total annual incidence fell by 30% during 2000–2013, largely due to the scale-up of long-lasting insecticide-treated nets and indoor residual spraying. In the future, sustainable methods of control and elimination are needed to maintain this progress. Since malaria is associated with poverty, malaria control and economic development can be mutually supportive. This thesis tests specific hypotheses relating to the causal pathways between poverty and malaria, to identify potential routes to controlling malaria alongside development.

Two systematic reviews found that in sub-Saharan Africa: (1) parasite prevalence and clinical malaria incidence are on average halved in the wealthiest children, compared to the poorest within a community and (2) parasite prevalence and clinical malaria incidence are on average halved in residents of modern housing, compared to traditional housing. In-depth interviews and cross-sectional surveys collected socioeconomic information for all children aged six months to 10 years living in 100 households, who were followed for 36 months in Nagongera, an agrarian and highly endemic setting in rural Uganda. Analyses of the relationships between socioeconomic position (SEP), potential determinants of SEP and malaria found that: (3) relative success in smallholder agriculture was associated with higher SEP, (4) human biting rate (HBR) and parasite prevalence were approximately halved in children of highest SEP, compared to the poorest, (5) wealth indices, income and education were more sensitive indicators of socioeconomic inequalities in malaria risk than occupation, (6) HBR and parasite prevalence were halved in modern housing, compared to traditional housing and (7) house quality may partly explain the association between SEP and malaria.

Together, these studies indicate that housing improvements and agricultural development interventions to reduce poverty merit further investigation as 'intersectoral' interventions against malaria.

Foreword

This thesis was funded as an interdisciplinary PhD by the Leverhulme Centre for Integrative Research in Agriculture and Health (LCIRAH). LCIRAH leads research on agriculture and health with a focus on international development goals and is hosted within the London International Development Centre.

Acknowledgements

First and foremost, I am indebted to my supervisors Professor Steve Lindsay, Dr Jo Lines and Dr Deborah Johnston for their generous support, guidance and interest in the pursuit of these studies. I would like to express my special appreciation and thanks to Steve, who has been a tremendous mentor and provided tireless insight and support. I also offer my great thanks to Christian Bottomley for his extensive advice.

I would like to thank the Leverhulme Centre for Integrative Research on Agriculture and Health (LCIRAH), who funded my position at the London School of Hygiene & Tropical Medicine, and all those involved, particularly Jeff Waage, Richard Smith, Ibi Wallbank and Alice Vahanian.

I am extremely grateful to Grant Dorsey for his support of my work in Uganda, as well as Sarah Staedke, Chris Drakeley, Moses Kanya, Emmanuel Arinaitwe, John Rek, Humphrey Wanzira, Lilian Taaka, Tom Adutia, Soita Jamba and Moses Oburu of the PRISM study; the Infectious Diseases Research Collaboration; the families and communities who kindly participated in our study and Nicholas Strelczuk of the Courtyard Partnership. I thank the Betts family for their kindness in Kampala.

I thank my co-authors on papers included in my thesis, not already mentioned: Jorge Cano, Roly Gosling, Matthew Ippolito, Immo Kleinshmidt, Henry Lucas, John Thompson and Barbara Willey; my upgrading panel Delia Boccia, Simon Brooker, Kate Hampshire and Jeroen Ensink; Helen White, James Logan, Ron Behrens and Joanna Schellenberg; and colleagues and friends within the Department of Disease Control, LCIRAH, Malaria Centre and Public Health Entomology Group.

Finally, I thank my family, especially my parents Sara and Nick, my godmother Jane and of course Angus, for their incredible support along the way.

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Acronyms

ACT	Artemisinin combination therapy
AIM	Action and Investment to Defeat Malaria
CI	Confidence intervals
COREQ	Consolidated Criteria for Reporting Qualitative Studies
DALY	Disability-adjusted life year
DDT	Dichlorodiphenyltrichloroethane
DHS	Demographic and Health Survey
EIR	Entomological inoculation rate
EPOC	Effective Practice and Organisation of Care
GDP	Gross domestic product
GFATM	Global Fund for AIDS, Tuberculosis and Malaria
GNI	Gross national income
GPRIM	Global Plan for Insecticide Resistance Management
GRADE	Grading Quality of Evidence and the Strength of Recommendations
GTS	Global Technical Strategy for Malaria
HBR	Human biting rate
IDI	In-depth interview
IPTi	Intermittent preventive treatment in infants
IPTp	Intermittent preventive treatment in pregnancy
IRR	Incidence rate ratio
IRS	Indoor residual spraying
ITN	Insecticide-treated net
IV	Instrumental variable
IVM	Integrated vector management
kdr	Knock-down resistance
LLIN	Long-lasting insecticide-treated net
MIS	Malaria Indicator Survey
NAADS	Uganda National Agriculture Advisory Service
OR	Odds ratio
PCA	Principal component analysis
PDR	People's Democratic Republic
PPY	Per person year at risk
PRISM	Programme for Resistance, Immunology, Surveillance and Modelling of Malaria
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RR	Rate ratio
RBM	Roll Back Malaria Partnership
RCT	Randomised controlled trial
RDT	Rapid diagnostic test
SDG	Sustainable Development Goal
SEP	Socioeconomic position
SES	Socioeconomic status
SSA	Sub-Saharan Africa
UNDP	United Nations Development Programme
WASH	Water, sanitation and hygiene
WHA	World Health Assembly
WHO	World Health Organization
YLD	Years lived with disability

Introduction

As attention shifts to the Sustainable Development Goals (SDGs), malaria control is at a pivotal juncture. While the disease remains a major global public health problem, with an estimated 198 million cases and 584,000 deaths in 2013, the past 15 years have seen a widespread decline in transmission and an approximately 30% fall in annual global incidence [1]. Reductions have been achieved mainly with long-lasting insecticide-treated nets (LLINs) and indoor residual spraying (IRS) at an annual cost of around US\$ 2 billion [1]. However, future progress may be slowed by insecticide resistance in mosquitoes [2]. Furthermore, as countries approach elimination, sustainable interventions are needed once LLINs and IRS are withdrawn. Since malaria is associated with poverty and the environment, coordination with non-health sectors, including water and sanitation, urban planning and housing, can support long-term intervention. Reflecting this, in 2013 the Roll Back Malaria (RBM) and United Nations Development Programme *Multisectoral Action Framework for Malaria* proposed practical steps to target the social and environmental determinants of malaria [3]. Launched earlier in 2015, the World Health Organization's new *Global Technical Strategy for Malaria 2016-2030* [4] and the complementary *RBM Action and Investment to Defeat Malaria* [5] both acknowledge that malaria control and sustainable development are linked.

Yet while it may seem obvious that malaria control can be accelerated by development, we lack specific knowledge of where to intervene [3]. This evidence gap partly stems from a limited understanding of the underlying causal pathway between poverty and malaria. Also, while the determinants of poverty in rural Africa have been well studied outside epidemiology, there has been little attempt to link these basic determinants through to malaria. This thesis aims to improve our understanding of the household-level association between malaria and poverty, to guide future research into reducing malaria through development. First, a conceptual framework is proposed (Figure 0.1 and Chapter 2) to outline the causal pathways hypothesized to link socioeconomic position (SEP) and malaria. The remaining chapters test specific hypotheses generated by this conceptual framework using primary data collected in Nagongera, rural Uganda and secondary data from systematic reviews of the literature. The hypotheses tested are that:

1. Agricultural success is a key determinant of household SEP in Nagongera, since agriculture is the main source of livelihood in that setting.
2. Low SEP is associated with higher malaria risk, regardless of the direction of causality.
3. The association between SEP and malaria is mediated by: (1) treatment-seeking behaviour, (2) housing quality and (3) food security amongst other factors.
4. Poor housing is associated with higher malaria risk after controlling for SEP, through its effect on mosquito house entry.

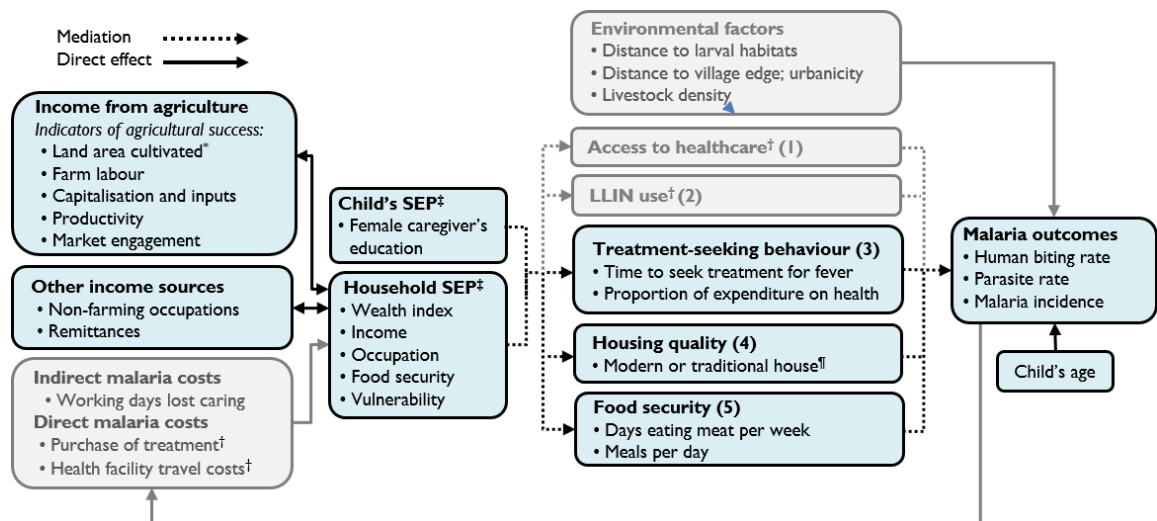


Figure 0.1. Conceptual framework for the relationship between relative agricultural success, socioeconomic position (SEP) and malaria in Nagongera, Uganda.

A full explanation for this conceptual framework is given in Chapter 2. In sub-Saharan Africa, the odds of malaria infection are on average halved in children with the highest SEP within a community, compared to children with the lowest SEP [6]. Household SEP may be approximated using metrics such as a wealth index, income or occupation and personal SEP approximated using the education level of female caregivers.‡ Wealthier children are hypothesised to have a lower risk of malaria due, among other factors, to: (1) greater disposable income, that makes prophylaxis, treatment and transport to clinics more affordable and therefore improves access to health care [7], (2) greater ownership and use of LLINs [8-11], stemming from greater affordability of LLINs and better education [7, 12, 13], (3) improved healthcare-seeking behaviour among caregivers [14, 15] (though the evidence is inconsistent [16, 17]), (4) better housing, which lowers the risk of exposure to malaria vectors indoors [18, 19] and (5) greater food security, which reduces undernutrition and protein-energy malnutrition and possibly susceptibility to malaria infection and progression to severe disease [20-23] (though the evidence is inconsistent [24, 25]). Modern houses¶ were defined as those with cement, wood or metal walls; and tiled or metal roof; and closed eaves. All other houses were classified as traditional. Access to healthcare† and LLIN use† were not hypothesised to be associated with SEP in this study population, since LLINs and all healthcare were provided free of charge. Other household-level risk factors for malaria include distance to larval habitats [26], distance to village periphery [27], urbanicity [28] and the density of livestock nearby [29], which were outside the scope of this study. In turn, malaria imposes costs that can cause poverty, but this feedback loop was not analysed in this study [30, 31]. Heterogeneity in SEP is hypothesised to be driven largely by relative success in smallholder agriculture, since agriculture is the primary livelihood source in Nagongera. There are many other determinants of SEP that are well-studied outside the health sphere [32-34], but we include here only non-agricultural income and access to remittances. This conceptual framework is not an exhaustive representation of all malaria risk factors, confounders, mediators and causal associations, but includes only those analysed in this study. The conceptual framework adds greater complexity to those by de Castro [31] and Somi [30], which primarily demonstrate bi-directionality, while this study is chiefly interested in dissecting the strands of the poverty-to-malaria direction.

Aims and Objectives

Goal:

- To improve our understanding of the relationship between poverty and malaria in sub-Saharan Africa (SSA), to identify potential routes to advancing malaria control through socioeconomic development.

Aims:

1. To develop a conceptual framework outlining the causal pathways hypothesized to link socioeconomic position (SEP) and malaria.
2. To test quantitatively specific hypotheses generated by the conceptual framework, using primary data collected in Nagongera, rural Uganda and secondary data from systematic reviews of the literature.

Objectives:

1. To review existing literature on socioeconomic development and malaria (**Chapter 1**).
2. To develop a conceptual framework outlining the causal pathways hypothesized to link SEP and malaria and to use this to formulate the study hypotheses and guide data collection, analysis and interpretation (**Chapter 2**).
3. To evaluate the association between SEP and malaria in SSA, through a systematic review and meta-analysis (**Chapter 3**).
4. To assess the importance of house quality on the causal pathway between SEP and malaria risk, through:
 - a. A systematic review and meta-analysis (**Chapter 4**).
 - b. An analysis of the association between house construction and malaria risk at three sites in Uganda (**Chapter 5**).
5. To investigate the relationships between SEP, potential determinants of SEP and malaria in Nagongera, Uganda, through:
 - a. In-depth interviews to understand heterogeneity in SEP (**Chapter 7**).
 - b. Household and women's surveys to collect socioeconomic data, to:
 - i. Compare methods of measuring socioeconomic inequalities in relation to malaria risk (**Chapter 6**).
 - ii. Explore potential determinants of SEP, with specific focus on smallholder agriculture, and analyse the causal mediation pathway between SEP and malaria (**Chapter 8**).

Thesis overview

Chapter 1 reviews the existing literature on the relationship between socioeconomic development and malaria. **Chapter 2** outlines a conceptual framework of the causal pathways hypothesised to link socioeconomic position (SEP) and malaria. The remaining chapters investigate specific hypotheses generated by the conceptual framework using two data sources: (1) reviews of the literature and (2) a field study encompassing in-depth interviews and cross-sectional surveys in Nagongera, rural Uganda, nested within the Programme for Resistance, Immunology, Surveillance and Modelling of malaria (PRISM) cohort study.

Chapter 3 assesses the association between SEP and malaria through a systematic review and meta-analysis. **Chapters 4** and **5** assess the importance of housing on the causal pathway between SEP and malaria through a systematic review and meta-analysis (Chapter 4) and through analysis of data from the PRISM study in Uganda (Chapter 5).

Chapters 6 and **7** evaluate data indicators for the final analysis in **Chapter 8**. Specifically, Chapter 6 explores indicators of relative success in smallholder agriculture in Nagongera, Uganda while Chapter 7 compares four indicators for estimating socioeconomic inequalities in malaria in the same site. Chapter 8 investigates the relationships between SEP, potential determinants of SEP and malaria in Nagongera.

Finally, **Chapter 9** discusses the main findings, study limitations and future directions.

Contributions

Chapters 1 and 3 use material from Tusting *et al.*, 2013 (*Lancet* 382: 963-972). Steve Lindsay and Richard Smith conceived the study. Lucy Tusting, Steve Lindsay, Richard Smith, Henry Lucas and John Thompson developed the study design and the outline of the report. Lucy Tusting searched the literature, did the meta-analysis and prepared the first draft of the report. Barbara Willey provided advice on the systematic review and meta-analysis. Hmooda Kafy contributed the case study from Sudan. **Chapter 2** was written by Lucy Tusting.

Chapter 4 was published as Tusting *et al.*, 2015 (*Malaria Journal* 14: 209). Steve Lindsay, Roly Gosling, Grant Dorsey and Immo Kleinschmidt conceived the study. All authors developed the study design. Lucy Tusting and Matthew Ippolito searched the literature. Lucy Tusting extracted and analysed the data and prepared the manuscript. Immo Kleinschmidt analysed the entomology data. Barbara Willey advised on the systematic review and meta-analysis.

Chapters 5 to 8 describe work conducted within an ongoing cohort study (PRISM), coordinated by the Infectious Diseases Research Collaboration, Kampala; University of California, San Francisco and London School of Hygiene & Tropical Medicine.

Chapter 5 was published as Wanzirah *et al.*, 2015 (*PLoS ONE*, 10 (1): e0117396). Grant Dorsey, Steve Lindsay, Emmanuel Arinaitwe, Sarah Staedke and Moses Kamya conceived and designed the experiments. Lucy Tusting, Humphrey Wanzirah, Kilama Maxwell, John Rek, Agaba Katureebe and Sarah Staedke collected the data. Lucy Tusting, Christian Bottomley, Grant Dorsey and Steve Lindsay analysed the data. Lucy Tusting, Christian Bottomley, Grant Dorsey and Steve Lindsay prepared the manuscript.

Chapters 6 and 8 were prepared as two pending publications. Lucy Tusting conceived and designed the study with guidance from Grant Dorsey, Steve Lindsay, Jo Lines and Deborah Johnston. Sarah Staedke, Emmanuel Arinaitwe, Humphrey Wanzirah, John Rek, Kilama Maxwell and Agaba Katureebe collected the clinical data for the main PRISM study. Lucy Tusting, John Rek, Lilian Taaka and Emmanuel Arinaitwe collected the additional socioeconomic data for the nested study. Lucy Tusting and Christian Bottomley analysed the data. Jorge Cano conducted the spatial analysis. Lucy Tusting, Christian Bottomley and Jorge Cano prepared the manuscripts with input from the other authors.

Chapter 7 describes unpublished pilot work. Lucy Tusting conceived and designed the study with guidance from Grant Dorsey, Steve Lindsay, Jo Lines and Deborah Johnston. Lucy Tusting, Humphrey Wanzirah, John Rek and Lilian Taaka collected the data. Lilian Taaka produced the transcripts and translations. Lucy Tusting analysed the data and wrote the chapter.

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Licensed content issue number	9896
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Chapter 1. Introduction

Adapted from: Tusting LS, Willey B, Lucas H, Thompson J, Kafy HT, Smith R, Lindsay SW. Socioeconomic development as an intervention against malaria: a systematic review and meta-analysis. *Lancet* 2013; **382**: 963-972.

1.1. The epidemiology and control of malaria

1.1.1. The global burden of malaria today

Malaria remains a major global public health problem, with 3.3 billion people at risk in 2013 [1]. The disease produces severe acute and chronic health and cognitive problems which affect morbidity and mortality; there were an estimated 198 million cases and 584,000 deaths in 2013 [1, 35]. Though malaria was historically endemic in much of the world, transmission today is restricted to tropical and sub-tropical regions of Africa, Asia and South America. The greatest burden of disease lies in sub-Saharan Africa (SSA), where 80% of cases occur (Figure 1.1) [1]. In total, 97 countries had ongoing malaria transmission in 2014 of which 19 were classified as being in the 'pre-elimination' or 'elimination' phase and seven in the 'prevention of reintroduction' phase. 80% of cases are estimated to occur in 18 countries alone, with Nigeria and the Democratic Republic of the Congo together accounting for over 34% of malaria cases globally [36, 37].

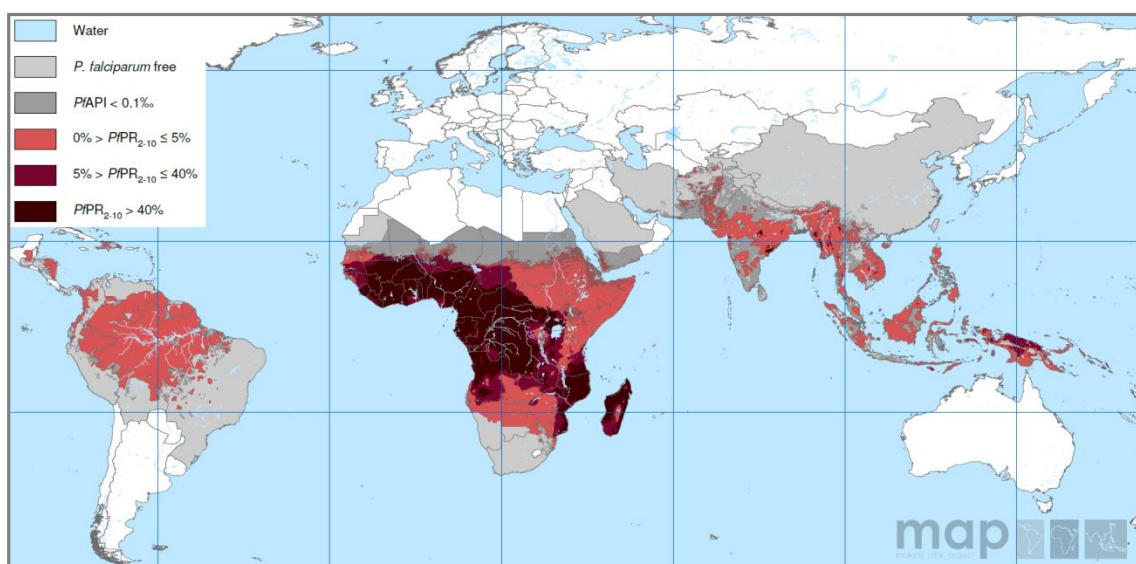


Figure 1.1. Spatial distribution of *Plasmodium falciparum* malaria in 2010, stratified by endemicity [38].

1.1.2. Malaria control 1897-2015

After Ross demonstrated the transmission of malaria by mosquitoes in 1897 [39], early malaria control focused on reducing larval sources through environmental management [40, 41].

Following the development of dichlorodiphenyltrichloroethane (DDT) as a public health insecticide in the early 1940s, indoor residual spraying (IRS) with DDT became the primary method of malaria control [42]. The use of DDT was encouraged by the adaption of the Ross model of malaria transmission by Macdonald, which showed that transmission was highly sensitive to adult mosquito mortality rates [43]. Macdonald's influential analysis reinforced the prevailing notion that DDT was a sufficient tool for malaria elimination [44, 45], providing impetus for the Global Malaria Eradication Campaign, launched by WHO in 1955 [42]. Following the widespread emergence of DDT resistance in the 1960s, the eradication campaign was abandoned in 1969, leading to a period of neglect that was associated with a resurgence in incidence in some countries, such as Sri Lanka [46].

Over the past two decades malaria has received renewed international attention. In the late 1980s insecticide-treated nets (ITNs) were shown to halve the incidence of malaria in children [47], providing an additional method for controlling the disease. The primary strategies today recommended for malaria control are vector control using long lasting insecticide-treated nets (LLINs) and IRS; intermittent preventive treatment for high-risk groups including pregnant women (IPTp), infants (IPTi) and, in areas of high seasonal transmission, children ≤ 5 years; and confirmed parasitological diagnosis together with prompt and effective chemotherapy with an artemisinin combination therapy (ACT) [4]. After the formation of the Roll Back Malaria (RBM) Partnership in 1998, the inclusion of malaria in the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) in 2001 and with added momentum from donor organisations including the Bill & Melinda Gates Foundation, advocacy and funding for malaria control dramatically improved, with international disbursements increasing at an annual rate of 22% between 2005 and 2013, reaching US\$ 2.2 billion in 2013 [1]. Domestic funding has also increased at an average annual rate of 4% since 2005 to an estimated US\$ 527 million in 2013 [1].

Funding increases have precipitated extensive LLIN distribution campaigns and IRS operations alongside efforts to improve case management. Subsequently, the proportion of people at risk of malaria in SSA with access to an ITN has risen from 3% in 2004 to 49% in 2013 [1], and the proportion of people at risk protected by IRS increased from 5% in 2005 to 11% in 2011, although IRS coverage fell to 7% in 2013. Due in part to these efforts, malaria is now declining in numerous endemic countries including many in SSA [48-53], a number of which are now working towards elimination [54]. Globally, average parasite prevalence in children aged 2–10 years declined from 26% in 2000 to 14% in 2013 and malaria incidence decreased by 30% in the same period [35]. Malaria control interventions have averted an estimated 803 million

clinical cases since 2000. Of cases averted, ITNs contributed 70%. The World Health Assembly (WHA) and RBM target was to reduce malaria incidence by 75% by 2015 from 2000 rates. Fifty five countries are on track to achieve this, although these 55 countries account for only 4% of total estimated malaria cases [1].

1.1.3. Malaria control post-2015

The new WHO *Global Technical Strategy for Malaria 2016-3030* (GTS) has set targets to reduce malaria case incidence by 90% globally and to eliminate malaria in 35 endemic countries by 2030 and specifies the interventions needed to achieve these targets [4]. In order to implement these interventions, a wide range of supporting and enabling activities will be needed at national and international levels, and these are outlined in the RBM document *Action and Investment to Defeat Malaria* (AIM) [5]. Challenges to achieving the proposed targets include the need to sustain funding (US\$ 102 billion is needed to finance the GTS until 2030, with approximately 50% needed for vector control, excluding research and development) and to manage insecticide resistance, artemisinin resistance and residual malaria transmission:

Sustaining funding

An important future challenge will be to maintain the high levels of funding needed to implement the GTS. Even at its 2011 peak, funding fell far short of the total US\$ 5.1 billion required annually for full coverage of interventions worldwide. Thus despite impressive increases in coverage, shortfalls remain. For example, in 2013 an estimated 278 million of 840 million people at risk in SSA lived in households with no ITNs [1]. It is sobering to reflect that the Global Malaria Eradication Campaign in the 1950s and 1960s, together with many national malaria control programmes, have floundered due to insufficient financial backing [55, 46]. Today the need to sustain funding remains imperative [56], but the potential benefits are great. While the total implementation costs of the GTS are estimated at US\$ 102 billion, achieving the proposed targets could save more than 10 million lives and generate over US\$4 trillion of additional economic output [1].

Insecticide resistance

The emergence of mosquitoes resistant to pyrethroids (the only insecticide currently available for impregnating bednets) and organochlorines, organophosphates and carbamates (the three additional insecticide classes currently available for IRS) in SSA represents a threat to the future effectiveness of LLINs and IRS [2]. By 2014, pyrethroid resistance had been detected in

78% countries in SSA reporting insecticide resistance data [1]. While a systematic review found insufficient evidence overall to determine the impact of resistance on malaria transmission [57], studies in Benin [58], Burkina Faso [59], Kenya [60] and Liberia [61] indicate that insecticide resistance can compromise the effectiveness of vector control. New active ingredients are in the pipeline and their introduction to the market is of high priority [62]. The Global Plan for Insecticide Resistance Management was released by WHO in 2011 to guide efforts to contain the emergence and spread of further resistance [63], but implementation to date has been slow [64].

Artemisinin resistance

First detected in Cambodia in 2008 [65], artemisinin-resistant *Plasmodium falciparum* is today established in east Myanmar, south Vietnam, west Cambodia and Thailand, and is emerging in southern Laos People's Democratic Republic (PDR) and Cambodia [66]. Should resistance become globally established, an estimated 116,000 additional annual deaths may occur, with extra medical costs for the retreatment of clinical failures and management of severe malaria potentially exceeding US\$ 32 million per year [67]. New antimalarial drugs will not be available for a number of years. Radical measures, including the elimination of *P. falciparum* in the Greater Mekong subregion [68], are needed to prevent resistant parasites spreading to the Indian continent and subsequently to Africa [66].

Residual transmission

Residual malaria transmission is that which persists despite universal coverage with effective LLINs and/or IRS, due to specific behavioural characteristics of malaria vectors including natural or insecticide-induced avoidance of treated surfaces within houses, outdoor biting, feeding upon animals or resting outdoors [69]. While most exposure to infectious bites occurs indoors at night [70], early evening and morning biting is prevalent in many settings [69]. It is plausible that the use of insecticides indoors may be selecting for outdoor-biting mosquitoes [71]. Since residual transmission fundamentally limits the power of LLINs and IRS, methods to mitigate against this are needed, particularly in elimination settings [72]. Specifically, new interventions that enhance adult vector control indoors, kill or repel adult mosquitoes when they bite humans or animals outdoors or feed on sugar may be useful, in addition to larval source management [69].

In light of these challenges, long-term approaches to malaria may need to move beyond traditional health interventions [73]. Historically, medical approaches to malaria may have

faltered since they ‘fail to accept the fundamental human ecology of malaria’ [73]. Today, major research and control programmes still focus on medical and technical strategies. Yet while LLINs, IRS and IPT are highly efficacious [47, 74, 75], the emergence of insecticide and artemisinin resistance highlights the limits of a purely clinical approach. The recent *Multisectoral Action Framework for Malaria* from RBM and the United Nations Development Programme (UNDP) advocates tackling the social and environmental determinants of malaria [3]. This builds upon the concept of integrated vector management (IVM), which encourages interventions outside the health sector for vector-borne disease [76]. More recently launched, WHO’s GTS and RBM’s complementary AIM both acknowledge that malaria control and sustainable development can be mutually supportive. This shift in thinking is pertinent in the context of the new Sustainable Development Goals (SGDs) which acknowledge that ill health remains a significant cause and a consequence of poverty [77].

1.2. The relationship between socioeconomic development and malaria

Socioeconomic development has been closely associated with malaria throughout history [6]: while malaria can impede development through its costs and effect on productivity, the disease itself can be a product of poverty and the environmental changes linked to development. While there are other ‘diseases of poverty’, such as tuberculosis [78], development is especially important for malaria because its mosquito vectors are highly sensitive to their environment.

1.2.1. Effect of malaria on socioeconomic development

Malaria has a profound impact on socioeconomic development. Indeed, it has been stated that ‘where malaria prospers most, human societies have prospered least’ [79]. The macro-level association between malaria and development is shown in the relationship between an index of income and education and the cumulative probability of malaria deaths in 43 African countries in children aged ≤ 5 years ($R^2=0.331$, $p<0.001$) and all age groups ($R^2=0.256$, $p=0.001$) in 2010 (Figure 1.2). While this association does not prove causality in either direction, the economic costs of malaria are significant.

Household-level costs

At the household level, the direct cost of prophylaxis, travel to clinics and treatment can be considerable [80-82]. These costs are often proportionally greater for those in lower socioeconomic groups as observed in Nigeria [83] and Tanzania [30]. Added to the direct medical costs of malaria are substantial indirect costs since severe acute malaria episodes and chronic illness associated with anaemia and neurological disabilities reduce productivity,

increase absenteeism, create unfavourable dependency ratios, lower fertility and cause premature mortality, which together reduce income [84]. In 2010, malaria was estimated to cause 4.1 million years lived with disability (YLDs) globally [85]. Malaria and neglected tropical diseases accounted for 11.4% of total YLDs in SSA.

Macro-level costs

Malaria incurs macroeconomic costs that stem from its effect on tourism, trade and foreign investment [79, 86]. For example, non-endemic countries require systems to detect and treat imported cases. Malaria chemoprophylaxis is expensive and a deterrent to visiting and working in malaria-endemic countries [87]. Additionally malaria discourages trade and foreign investment. For instance, in 1998 the metals and mining company Billiton invested US\$ 1.4 billion to build an aluminium smelter in Mozambique and recorded over 7,000 cases of malaria among its employees in the first two years [79].

Effect on human development

Malaria in pregnancy can cause premature birth, low birth weight and anaemia [88, 89]. Low birth weight is a risk factor for poor behavioural, cognitive and neuro-sensory development in addition to substandard school performance [90]. Subsequent malaria infection during childhood can also impair educational attainment [91, 90] by producing deficits in memory, attention, visuo-spatial skills, executive functions and language [92]. Two randomised trials in Sri Lanka found that repeat attacks of malaria influenced school performance [93] and that chloroquine chemoprophylaxis given weekly could improve school examination results [94]. A cluster-randomised controlled trial (RCT) in Kenya demonstrated that IPT given to schoolchildren significantly increased scores in tests of sustained attention [95]. A more recent RCT in Kenya found no effect of intermittent screening and treatment on educational outcomes [96], but there was also no effect of the intervention on prevalence of anaemia or parasite prevalence in that setting.

Total economic cost

Five types of evidence have been used to approximate the overall cost of malaria [97]. First, the impact of malaria on economic growth has been estimated. Overall, malaria-endemic countries have lower national incomes [98] and slower economic growth rates [79]. During 1965-1990, the economies of countries with intensive malaria were estimated to grow 1.3% less per person per year than countries without, and a 10% reduction in malaria was found to be associated with 0.3% higher growth [98]. In 2010, the total annual cost of malaria was

estimated to be US\$12 billion in lost gross domestic product (GDP) [99]. Second, the effects of malaria on human capital development have been analysed [97]. For example, in Paraguay, it was estimated that a 10% decrease in malaria incidence was associated with 0.1 more school years completed and a 1-2% greater probability of being literate [100]. Third, studies have estimated the overall cost of prevention and treatment. For example, the total annual costs of treatment in 2009 were estimated to be US\$ 38.9 million in Ghana, US\$ 131.9 million in Tanzania and US\$ 109.0 million in Kenya [101]. Fourth, the cost-effectiveness of malaria interventions has been calculated. In 2010 the cost effectiveness ratio per disability-adjusted life year (DALY) averted was US\$ 27 for ITNs, US\$ 143 for IRS and US\$ 24 for IPT [102]. Fifth, the economic returns of malaria control have been estimated. In 2004 it was concluded that US\$ 13 billion for malaria prevention and treatment would deliver benefits of more than US\$ 400 billion [103]. More recently, a cost-benefit analysis estimated the total net value of malaria control and elimination during 2013-2035 to be US \$208.6 billion in 2013 prices [97].

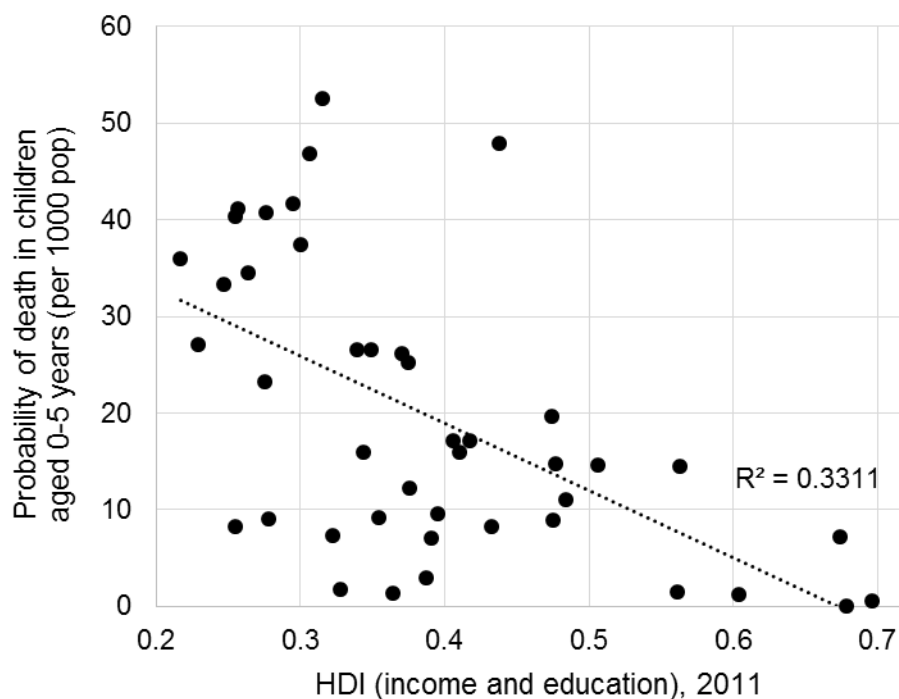


Figure 1.2. Malaria burden in relation to a human development index (HDI) of income and education in 43 countries in sub-Saharan Africa.

Data for cumulative probability of malaria death (per 1000 population) in children aged ≤ 5 years in 2010 were taken from Murray *et al.* [104]. The human development index of income and education in 2011 was available from the UNDP website, where it was derived from three variables: 2011 gross national income (GNI) per capita in purchasing power parity (PPP) terms (constant international 2005 US\$); expected years of schooling as of 2011 (of children); mean years of schooling as of 2011 (of adults) (for methods see Appendix 1).⁶ All countries in sub-Saharan Africa with data for both variables were included in the figure and analysis (n=43).

1.2.2. Effect of socioeconomic development on malaria

Not only is malaria an impediment to socioeconomic development, but the disease and its mosquito vectors are themselves sensitive to changes in the social environment [105, 7]. Two aspects of development can impact on malaria. First, increased household wealth can lower individual risk. Second, environmental changes such as urbanisation, agricultural development, deforestation and water development projects can alter local malaria transmission ecology.

Socioeconomic development is thought to have been important in the decline of malaria in Europe and the USA, alongside advances in treatment, health systems and environmental management [106, 107]. Malaria receded in central and southern England after the 1850s with improved living conditions and increased use of quinine [108]. In Finland [109] and Sweden [110], malaria is thought to have declined after the 18th century alongside social changes. After Ross deduced the mode of malaria transmission in 1897, more specific interventions became possible including habitat modification (the permanent elimination of breeding sites, for example by installing and maintaining drains), habitat manipulation (temporarily producing unfavourable conditions for the vector, for example by fluctuating water levels in reservoirs) and modifications to human habitation or behaviour that reduced human-vector contact, such as mosquito-proofing houses [111]. Consequently, most of Europe and North America is today characterized by 'anophelism without malaria' which is testament to the effectiveness of these control efforts, together with a reduced innate receptivity to malaria transmission stemming from advances in nutrition, health care and development [112]. Similarly, urbanisation and development can have an impact in SSA. In Zanzibar, parasite prevalence declined from 60% pre-World War Two to 35-40% by the mid-1990s and this was thought to be due to urbanisation and development among other factors [113]. Today, as malaria recedes in much of SSA, modelling the impact of ITNs, IRS and IPT on malaria during 2000-2015 does not entirely account for the observed recession [35].

1.2.2.1. Increases in socioeconomic position (SEP)

Socioeconomic position (SEP), the suite of social and economic factors that determine the position held by individuals and groups within a society, is a long-established risk factor for malaria. An early review by Worrall and colleagues found mixed evidence for the relationship between SEP and malaria incidence, but the review's outcomes included self-reported malaria which is unreliable [105]. More recently, a systematic review and meta-analysis concluded that the odds of malaria infection and clinical malaria were doubled in the poorest children within a community, compared to the least poor children [6] (Chapter 3). The pathways linking SEP and

malaria are poorly understood, but hypothesised mechanisms for a protective effect of wealth include differential access to health care, uptake of LLINs and other preventive measures, treatment-seeking behaviour, housing quality and nutrition, among other factors (Chapter 2):

Access to healthcare, malaria intervention coverage and treatment-seeking behaviour

Greater disposable income can render prophylaxis, treatment and transport to clinics more affordable, improving access to health care [7]. Ownership and use of LLINs is often higher in wealthier homes, as observed in Tanzania [8, 9] and Malawi [10, 11]. This is partly due to greater affordability of LLINs but also due to better levels of education [12]. Although the evidence is not consistent in all settings [16, 17], heterogeneity in educational status can also lead to a marked divergence in healthcare-seeking behaviour, with individuals of higher SEP using formal government or private health facilities while the poor rely primarily on unqualified providers or self-treat with medicines purchased from shops or drug sellers [14, 15].

Housing

Greater wealth may improve house construction, lowering the risk of exposure to malaria vectors. Closed eaves reduce house entry by *Anopheles gambiae*, the major African malaria vector, [114] while full house screening and screened ceilings can reduce the prevalence of anaemia in children [115]. Other potentially beneficial features include tiled or metal roofs instead of thatch, and cement walls instead of mud [19, 116]. House screening was the first intervention trialled against malaria and better housing helped to eliminate malaria in the USA and Europe [117]. Today, studies indicate that modern, well-built housing can be protective in SSA [18, 19].

Food security and nutrition

There remains a lack of consensus on the effect of nutrition on malaria, complicated by the observation that routine iron and folic acid supplementation was found to increase the risk of severe illness and death from malaria in a high transmission setting [24]. Furthermore, intervention studies in Burkina Faso [118] and Tanzania [25] found no effect of zinc supplementation on malaria morbidity in children. However, these trials targeted micronutrient deficiencies, while there is evidence that undernutrition is associated with greater susceptibility to malaria infection and progression to severe disease [20-22] and that protein-energy malnutrition may be associated with greater malaria morbidity and mortality [23]. IPTp may also be less effective if a patient is undernourished, as observed in Ghana [119].

1.2.2.2. Reverse causality?

Of course, the observed association between SEP and malaria is not evidence of causality and malaria imposes costs that can induce poverty within a household (Chapter 2.1). The evidence for dual causation between malaria and SEP at the household level has been examined by two studies in Tanzania. First, Somi and colleagues analysed data from 52 villages in three high transmission districts in Tanzania [30]. Household SEP was measured using an asset-based wealth index and instrumental variable probit regression was used to assess the association between malaria parasitaemia and SEP. Causality was found in both directions: each malaria infection resulted in a reduction of 0.32 units in the wealth index and a one unit increase in the wealth increase resulted in a 4% decrease in infection prevalence. More recently, Castro and colleagues applied the same statistical methods to a larger survey (the 2007-2008 Tanzania Demographic and Health Survey (DHS)) and found that children testing positive for malaria infection had a wealth index that was 1.9 units lower than uninfected children, but malaria infection status was unrelated to household SEP [31]. In other words, there was no causality from SEP to malaria.

Overall, the interplay between malaria and poverty may constitute a vicious cycle for the poorest households, since they are not only more susceptible to the disease but also more vulnerable to its costs. Findings from Kenya indicate that wealthier households suffered smaller setbacks from malaria, from which they quickly recovered [120]. Costs of malaria treatment in both Kenya and Nigeria were found to be higher for poorer households as a proportion of non-food monthly income [30, 83].

1.2.2.3. Ecological changes linked to socioeconomic development

Socioeconomic development is not limited solely to increased wealth, but can also produce ecological changes that can affect malaria transmission [121, 111]. Here, the impact on malaria in SSA of four ecological products of development is reviewed: (1) agriculture and forestry, (2) water development projects, (3) urbanisation and (4) human migration.

Agriculture and forestry

Agriculture and forestry variously affect malaria transmission ecology in SSA. First, deforestation can reduce malaria transmission by removing the shaded breeding sites preferred by some vectors, while elsewhere it can increase transmission by providing the open sunlit breeding sites preferred by vectors such as *An. gambiae* [122]. Second, agricultural practices can alter transmission ecology. In urban areas, agriculture can introduce larval

habitats where otherwise there are few [123, 124]. Rice irrigation can increase the number of malaria vectors and subsequently malaria incidence in areas of unstable transmission [125], although irrigation is often associated with a reduction in incidence in areas of stable malaria, which may be due to the ‘paddies paradox’ of increased wealth in the local population (due to increased crop yields) and subtle changes in vector ecology [126] (Panel 1.1). Third, the large-scale application of insecticides to crops has been linked to the emergence of insecticide resistance in mosquitoes [127], as observed in the late 20th century in parts of Asia and Central America [128]. More recently, the use of insecticides in West Africa may have selected for pyrethroid resistance in *An. gambiae* [129-131]. The knock-down resistance (kdr) allele initially spread most widely in areas where pyrethroids are extensively used in farming, such as Benin and Burkina Faso [132, 127].

Water development projects

Over the past half century, an estimated 40,000 large dams and 800,000 small dams have been built worldwide and 13 million hectares of land are now under irrigation in SSA [133, 134]. Water development projects can provide aquatic habitats for malaria vectors. For example, the risk of malaria in children living near the Gilgel-Gibe hydroelectric dam and eight micro dams in Tigray, Ethiopia, was found to be greater than in children living further away [125], although a later study found no association between distance to the dam and malaria incidence [135]. At a continental level, any detrimental impact of water development projects is debatable, since a relatively small proportion of the population at risk of malaria lives near such schemes and the impact of water projects on malaria is location-specific [133].

Panel 1.1. Malaria and rice irrigation in SSA

Although the density of adult vectors is generally higher in irrigated areas, the association between malaria transmission and irrigation in SSA is not consistent. Generally, in areas of unstable transmission (where population immunity is low), irrigation increases malaria morbidity [136, 137]. Conversely, in areas of stable transmission (where population immunity is relatively high), irrigation does not always increase parasite prevalence, as observed in Burkina Faso [138], Senegal [126] and Côte d’Ivoire [139], and may even be associated with reduced prevalence, as observed in Tanzania [140], The Gambia [141] and Mali [142]. There are a number of possible explanations. Rice irrigation may be associated with increased wealth as observed in Cameroon [143], Burkina Faso [138], Côte d’Ivoire [139] and Tanzania [140] which possibly reduces vulnerability to malaria through improved nutrition, house construction, LLIN coverage and access to malaria chemotherapy [126]. However these dynamics are complex; the intensification of rice cultivation to two annual crops in Côte d’Ivoire may have increased the susceptibility of women and children to disease [144]. Irrigation may also change the abundance of different vectors [126] or alter the seasonal pattern of transmission [142].

Urbanisation

SSA is a 'continent in transition': over a quarter of the world's 100 fastest-growing cities are now in Africa and from 2010 to 2050 the number of urban dwellers is expected to increase from 400 million to 1.26 billion, with the overall urbanisation level reaching 50% by 2035 [145]. While urban dwellers remain vulnerable to malaria [146], urbanisation generally is associated with lower malaria transmission in SSA for four main reasons [147, 148]. First, larval habitats are fewer, since there is more concrete and tarmac and *An. gambiae* generally avoids highly polluted water. Thus, urbanisation has a greater impact on transmission where rainfall is low and seasonal [149]. Second, an increase in human population density relative to vectors reduces individual human exposure to infectious bites [150, 151]. Third, access to health facilities is typically greater in towns and cities [152]. Fourth, house quality may be better in urban areas, with closely fitting doors and windows for security and fewer overall entry points for mosquitoes [18].

Human movement and migration

Human movement can increase malaria transmission by introducing parasites into susceptible populations or introducing susceptible populations into high-risk areas, as observed in Venezuela [153], Colombia [154], Thailand [155] and Iran [156]. Large-scale movement complicates malaria elimination, as in Zanzibar where an influx of parasites is maintained by travel to mainland Tanzania [157, 158]. Additionally, air travel allows rapid carriage of a pathogen across the globe within hours [159], making difficult the containment of antimalarial resistance [160]. There has also been concern that air travel from Africa to climatically similar regions could transport malaria vectors [159], but a search of flights from Africa to London concluded that the risk of importation of malaria vectors is low [161].

1.3. Socioeconomic development as an intervention against malaria?

SSA is undergoing rapid economic growth, population expansion and urbanisation. GDP growth during 2000-2010 increased at double the rate of the 1980s and 1990s [162] and although 48% of Africans were still living on incomes below the international poverty line of US\$ 1.25 per day in 2010 [163], the middle class (arguably those living on US\$ 2-20 per day) is expected to grow from 355 million people in 2010 to 1.1 billion in 2060 (an increase of 34% to 42% of the total population) [162]. Can these social and economic changes contribute to sustainable malaria control, as they did historically in North America and Europe? Clearly, the impact of socioeconomic development will depend on baseline transmission; the high malaria burden in SSA is not merely a product of poverty, but also malaria's ecological requirements [164] and it is no coincidence that countries which have achieved malaria elimination are mainly

temperate, sub-tropical or islands [98]. Nonetheless, there is a growing body of evidence that development can have an impact today in SSA [6, 147].

What might 'development' interventions look like? And how might these compare with primary malaria interventions in terms of impact and cost-effectiveness? One example of a potential 'development' intervention against malaria is better housing [19]. A RCT of screened homes in The Gambia reduced the risk of anaemia in children by 50% [115]. At a cost of around US\$ 11 per person, full screening was similar to the cost of LLINs or IRS. In the same study, untreated screened ceiling reduced house entry by vectors by 50% using untreated screening and cost US\$ 8.69 assuming the netting was donated or US\$ 21.17 if not [115]. In Kenya, building ceilings from papyrus reeds and encouraging LLIN use reduced mosquito densities by 78-86% in houses. Ceiling construction was relatively inexpensive, at about US\$ 1 per person protected [165]. In Sri Lanka, the cost of improving poorly constructed houses to protect against malaria was found to be US\$ 850 per house [166]. The costs of house screening may compare favourably with primary malaria interventions. A recent review reported that the cost-effectiveness of LLINs ranged between US\$ 8-110 per DALY averted, IRS US\$ 135-150 per DALY averted and IPT US\$ 1-44 per DALY averted [102]. Clearly, more evidence of the impact of housing and other development interventions on malaria would be required to establish cost-effectiveness in a manner directly comparable with primary malaria interventions. Since development interventions are not primarily targeted at malaria, the health benefits they provide are additions to core focus, and the cost at present is not borne by health agencies. It is therefore difficult to accurately cost the portion of development that contributes to malaria control.

Despite the clear potential benefit from the health and development sectors working together (Panel 1.2), we do not know where investment in development would be of most benefit. The *Multisectoral Action Framework for Malaria* proposes specific interventions under broad themes including: agricultural practices and production systems, urban and peri-urban interventions, housing, land use, economic development projects, poverty and education, and nutrition, yet there is a paucity of evidence to support these recommendations [3]. Indeed, the Framework acknowledges that 'there is a need to better understand causality, including identifying those intersectoral interventions that have the greatest impact on malaria'. Further research is thus needed to explicate the causal pathway that leads from development to successful malaria control, and *vice versa*, in order to identify entry points for intervening through development.

Panel 1.2. Multisectoral malaria control in Khartoum, Sudan

Malaria control today in Khartoum demonstrates that the responsibility for malaria control can be successfully delegated beyond the Ministry of Health, as part of development and broader improvements to infrastructure. Malaria was the major cause of outpatient attendances, admissions and deaths in Khartoum in the 1980s and 1990s and this led to the launch of the Khartoum Malaria Free Initiative (MFI) in 2002 by the State and Federal Ministry of Health [167] which targets an approximate total population of 2,075,000 in urban areas, 3,200,000 in peri-urban areas and 650,000 in rural areas [168]. Since the start of the programme, total malaria deaths (confirmed and unconfirmed) have declined by almost 75% from 1,070 in 1999 to 274 in 2004 [167] and parasite prevalence has declined from 0.78% to 0.04% (1995-2008) [168].

Integral to the sustainability of the programme has been strong political support for the control programme at both State and Federal level [169] together with close coordination of the Ministries of Health, Education, Public Works & Agriculture. This delegation of responsibilities has also helped maintain the annual cost, which is covered largely by the government, at the relatively low level of US\$ 600,000 in total or around US\$ 0.10 per person protected per year [168]. The robust structure of the programme is particularly important given that funding is so difficult to maintain, new agricultural schemes and new construction sites continually create more breeding sites [168] and the health system has been weakened by two decades of conflict [169].

While the MFI has three main components (diagnosis & treatment, prevention and epidemic surveillance), its mainstay is the control of the population of the primary mosquito vector *Anopheles arabiensis*, which largely breeds in irrigation canals, pools created from broken water pipes, water basins and storage tanks [169]. To achieve this, the removal of water basins and storage tanks is enforceable by law and the Ministry of Health collaborates with the Public Works Department (PWD) to repair broken water pipes. The MFI is responsible for surveillance, reporting and transportation while the PWD provides engineers and equipment. Similarly, the regular drying of irrigated fields, which reduces vector breeding, is compulsory in both government and private irrigation schemes. This initiative is supported by the Farmers' Union and the Ministry of Agriculture. In 2011, 98.2% irrigation schemes were dried for at least 24 hours [168]. Leakages from irrigation canals are also repaired and vegetation around canals is cleared in conjunction with the Ministries of Irrigation and Agriculture [169]. In addition, the MFI itself employs 14 trained medical entomologists, 60 public health officers, 180 sanitary overseers, 360 assistant sanitary overseers and 1170 spraying men [168] who are responsible for routine larviciding and environmental management to reduce mosquito breeding.

Another factor contributing to the sustainability of the MFI is strong community support, generated through the distribution of information leaflets, regular radio broadcasts and television coverage, health education in schools in collaboration with the Ministry of Education, the organisation of an annual 'Khartoum State Malaria Day', public meetings and the establishment of malaria control committees and societies [169]. 405 schools and 287,000 pupils are involved in mosquito larval control activities [168]. IRS and LLIN distributions are not conducted in Khartoum, but LLINs are exempt from import tax in order to encourage private sector sales [169]. The MFI also seeks to strengthen case management through the improvement of microscopy, staff training and provision of antimalarial drugs through the 'revolving drugs fund'.

1.4. Summary

Malaria has been a major public health problem throughout history and long associated with socioeconomic development. Encouraged by advances in biomedical research, contemporary malaria control has largely focused on household-level risk factors for the disease and paid less attention to large-scale social, economic and environmental factors operating at the population level. Clearly, malaria-specific interventions have been very successful, are highly cost-effective in many cases and are undoubtedly a major reason for the decline in malaria recently observed in many endemic regions. However, this chapter illustrates that a broader approach to malaria control may be appropriate in future years, encompassing non-health sectors. Development interventions such as improved housing may have a substantial impact on malaria, while comparing favourably in economic terms.

Chapter 2. Conceptual framework

Abstract

Socioeconomic position (SEP) is closely associated with malaria. Here a conceptual framework is proposed to guide an investigation of the association between SEP, its determinants, and malaria in Nagongera, rural Uganda. The framework was developed by drawing on the literature reviewed in Chapter 1, but was not intended as an exhaustive representation of all malaria risk factors, confounders, mediators and causal associations. In summary, wealthier children are hypothesised to have a lower risk of malaria due to greater: (1) disposable income, (2) ownership and use of long-lasting insecticide-treated nets, (3) healthcare-seeking behaviour among caregivers, (4) housing quality and (5) food security, among other factors. A feedback loop from malaria risk to SEP reflects the costs of malaria which can induce poverty within households. Heterogeneity in SEP is hypothesised to be driven largely by relative success in smallholder agriculture, since agriculture is the primary livelihood source in Nagongera. Four study hypotheses were generated from the conceptual framework, that: (1) agricultural success is a key determinant of household SEP, since agriculture is the main source livelihood in Nagongera; (2) low SEP is associated with increased malaria risk, regardless of the direction of causality; (3) the association between SEP and malaria is mediated by (i) treatment-seeking behaviour, (ii) housing quality and (iii) food security amongst other factors; (4) poor housing is associated with increased malaria risk after controlling for SEP, through its effect on mosquito house entry.

2.1. Background

Socioeconomic position (SEP) is closely associated with malaria, yet Chapter 1 illustrates how the causal pathways between SEP and malaria have not been fully elucidated. This limits our understanding of where investment in development would be of most benefit to malaria control. The present chapter outlines a conceptual framework to guide an investigation of the association between SEP, its determinants, and malaria in Nagongera, a highly endemic setting in rural Uganda. Conceptual frameworks outline the main variables to be studied and the presumed relationship among them, enabling the evaluation of underlying causal mechanisms and guiding data collection, analysis and interpretation [170, 171]. Any conceptual framework represents a simplification of reality and is subject to initial bias (the knowledge of the individual) and also may create ongoing bias (giving prominence to certain factors and ignoring others). These limitations are discussed in the final discussion (Chapter 9). Based on the conceptual framework, hypotheses are generated and individually addressed in Chapters 3-8.

2.2. Study area

This PhD research was nested within the Programme for Resistance, Immunology, Surveillance and Modelling of Malaria (PRISM) cohort study. The PRISM study was carried out at three sites in Uganda: urban Walukuba sub-county, Jinja district; rural Kihhi sub-county, Kanungu district and rural Nagongera sub-county, Tororo district. This thesis analyses data collected between August 2011 and September 2014 (Figure 2.1). While Chapter 5 analyses data from all three study sites, additional data for Chapters 6-8 were collected only in Nagongera, the highest transmission setting (Section 2.3).

Nagongera (00°46'10.6"N, 34°01'34.1"E) is a rural setting with high year-round malaria transmission [172] despite high long-lasting insecticide-treated net (LLIN) coverage and good access to treatment with artemisinin combination therapies (ACTs) [172]. In 2011-2012 annual entomological inoculation rate (aEIR) was estimated to be 125 and parasite prevalence was estimated to be 29% [173, 174]. The primary malaria vector is *Anopheles gambiae* s.s., which accounts for 81.5% infectious bites and the secondary vector is *An. arabiensis*, which accounts for 18.5% infectious bites [174]. There are two rainy seasons (March to May; August to October). The total population of Tororo district is around 38,000, with children aged 1-10 years comprising 37% of the population [175]. Nagongera Health Centre is the main health facility. Most of the population is rural, the major ethnic groups being the Jopadhola, Iteso, Basamia, Bagwere and Banyoli. Rainfall is bimodal, with long rains from March to June and short rains from August to December. The area is characterised by low-lying agricultural land, with rocky hills and a sandy loam soil of medium to low fertility. Agriculture is the major

livelihood. Village houses generally have a mud-plastered stick framework with thatched roofs, or brick walls with tin roofs.

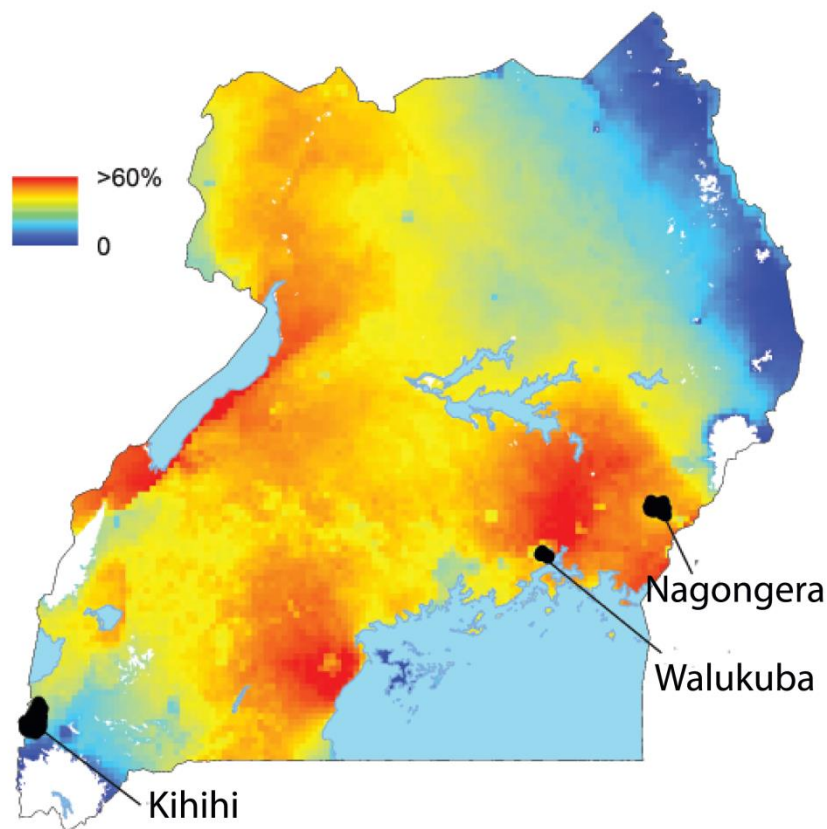


Figure 2.1. *Plasmodium falciparum* parasite rate (PfPR) and location of the three PRISM study sites in Uganda.

The colours represent PfPR in children aged 2–10 years from the Malaria Atlas Project 2010 dataset [38]. PRISM: Programme for Resistance, Immunology, Surveillance and Modelling of malaria.

2.3. Study design

2.3.1. PRISM study

Detailed descriptions of the PRISM study are published elsewhere [173, 174]. In brief, all children aged six months to 10 years and their primary caregivers were enrolled from 100 randomly selected households in each of Walukuba, Kihhi and Nagongera sub-counties in August-September 2011. Recruitment was dynamic, such that children reaching six months of age and meeting the eligibility criteria were enrolled and children reaching 11 years were withdrawn. Households with no remaining study participants were withdrawn and seven additional households were recruited in September 2013. Participants were followed for all their health care needs at the designated study clinic in Nagongera for 36 months, until

September 2014. At enrolment, study participants were given a LLIN (PermaNet®, Vestergaard Frandsen, Switzerland) and reported LLIN coverage (slept under LLIN the previous night) was 99.9% across all clinic visits. Outcomes measured were: (1) human biting rate (HBR), measured by one night of CDC light trap catches each month per house, (2) prevalence of parasitaemia measured routinely every three months and confirmed by microscopy and (3) incidence of all malaria episodes measured by passive case detection.

2.3.2. Nested study

The nested study was conducted between April and November 2013, with two components: (1) in-depth interviews (IDIs) in 25 of 100 study households in Nagongera and (2) a cross-sectional survey consisting of a household and women's survey in all 100 study households. These studies are described in brief below and fully in Chapters 6-8.

- i. *IDIs*: As formative research, IDIs were conducted after 18 months of follow-up in April-May 2013 with a designated adult respondent by a trained social scientist in the appropriate language (Japhadola, Kiswahili or English), if the respondent met the following eligibility criteria: (1) aged at least 18 years, (2) present in the sampled household the night before the interview and (3) agreed to provide informed written consent.
- ii. *Cross-sectional surveys*: Data on socioeconomic variables were collected through a household survey and women's survey conducted after 24 months of follow-up in September-October 2013. The household survey was administered as a structured interview by trained study staff to one designated adult respondent from each household, if they met four inclusion criteria: (1) usually resident, (2) present in the sampled household the night before the survey, (3) aged at least 18 years and (4) agreed to provide informed written consent. The women's survey was administered as a separate structured questionnaire after the second household survey to all adult women of childbearing age, resident in each study household, who met four inclusion criteria: (1) usual female resident, (2) present in the sampled household the night before the survey, (3) age 18-49 years, (4) agreed to provide informed written consent. Households were excluded if no adult respondent could be located on more than three occasions over two weeks.

2.4. Conceptual framework

2.4.1. Defining SEP

Central to the conceptual framework (Figure 0.1) is SEP, the suite of social and economic factors that determine the position held by individuals and groups within a society [176, 171]. SEP has become the preferred term for describing ranked socioeconomic measures in studies of health inequalities. It differs from socioeconomic status (SES), a measure commonly used in health research (and often erroneously instead of SEP [177]), in that SES is more narrow and pertains to an individual's status rather than material resources, while SEP captures both resources and prestige [178, 177]. Four indicators of SEP are included in the conceptual framework: (1) wealth index derived from assets, (2) occupation, (3) household income and (4) education. The relative sensitivity of these indicators is evaluated in Chapter 7.

2.4.2. Determinants of SEP

Competing macro-level theories of development exist for SSA. However, at the micro-level, development is generally accepted to involve a reduction in livelihood vulnerability, changes in livelihood activities and increased productivity and incomes (see footnote¹) [179]. Specifically, poverty reduction involves a move from low productivity activities (as in many rural, agricultural based livelihoods), to more specialised and productive activities. In rural areas, such activities are initially grounded in agriculture before shifting towards non-agricultural activities. Indeed, while agriculture makes varying contributions to African gross domestic product (GDP) at the macro-level, it remains the backbone of many rural economies and a significant main and secondary livelihood in both rural and urban areas [33]. This is true of Uganda, where the population is largely rural (84%) and the economy is agriculture-based, with the agricultural sector accounting for 66% of total employment in 2009 [180]. Overall, smallholder farming contributes around three-quarters of production [181].

However, in rural Uganda, as elsewhere, livelihood strategies also diversify away from crop and livestock production towards activities that generate additional income through the production of non-agricultural goods [182]. These factors must also be examined to understand the processes of accumulation, production and social reproduction that can explain socioeconomic differences between rural people. Where there is high natural resource

¹A livelihood is 'the activities, the assets, and the access that jointly determine the living gained by an individual or household'. Livelihood diversification is 'the process by which households construct a diverse portfolio of activities and social support capabilities for survival and in order to improve their standard of living.' Ellis, F., *Rural livelihood diversity in developing countries: evidence and policy implications*, in *Natural Resource Perspectives*. 1999, Overseas Development Institute: London.

potential, crop farming is typically important to poor people's livelihoods, providing opportunities for 'hanging in' (i.e. maintaining livelihood levels) and in the short term, to 'step up' (invest in assets to expand current activities, to increase production and income and improve livelihoods), or to accumulate resources to 'step out' (move into different activities with higher returns) [179, 32]. Where the local economy is dynamic, there is more scope to 'step up' and 'step out' through unskilled labour and petty trading [32].

The causes of poverty are well-studied outside epidemiology [181, 34, 179, 183-185] so it was beyond the scope of this thesis to elucidate how livelihood sources and other factors create or lessen poverty in Nagongera, nor to assess the potential of agricultural or other development interventions. Instead, the conceptual framework uses as a starting point the *outcomes* of the main livelihood strategies in Nagongera. Since smallholder agriculture is the main livelihood, it is hypothesised that key indicators of agricultural success (e.g. use of capital inputs) will be associated with SEP [34, 179, 183-185]. Oya [186] and Scoones [34] proposed the following indicator domains for agricultural success: (1) patterns of land use and ownership, (2) farm labour (e.g. the proportion of farm labour conducted by paid labour rather than family or unpaid labour), (3) type of farming and degree of capitalisation (e.g. use of synthetic fertiliser, ownership or use of capital equipment such as ox ploughs), (4) yields and productivity and (5) market engagement. Chapter 6 presents formative research to select those indicators of agricultural success most appropriate for Nagongera.

To account for diversification of some livelihoods outside farming, non-agricultural income including access to remittances is also included in the conceptual framework. Non-agricultural income is difficult to measure in low-income settings such as Nagongera since the complexity of occupational life creates ambiguity around 'occupation' [187] and income can also be unclear due to reliance on the informal economy, multiple household income sources, home production and seasonal or annual variation in income. Crude indicators of non-agricultural income include the primary occupation of the household head, the main source of income for the household, and access to remittances.

2.4.3. Effect of SEP on malaria

Based on the literature reviewed in Chapter 1, household SEP is hypothesised to affect the risk of malaria through five main pathways: (1) access to healthcare, (2) LLIN use, (3) treatment-seeking behaviour, (4) housing quality and (5) food security among other factors; although it is hypothesised that the pathways *via* access to healthcare and LLIN use are not applicable in the Nagongera study population, as explained below.

First, wealth can render prophylaxis, treatment and transport to clinics more affordable, improving access to health care [188-190, 8]. Access to healthcare can be approximated using the distance from and means of travel to the nearest health facility. Second, ownership and use of LLINs can be higher in wealthier homes [105, 7, 10, 191]. LLIN coverage can be measured using standard household survey questions as in Malaria Indicator Surveys [192], coupled with direct observation. Access to healthcare and LLIN use are shown in grey since the study population receives reimbursement of expenses for travel to the clinic and health care and LLINs free of charge. It is therefore hypothesised that access to healthcare and LLIN uptake do not vary with SEP in the study population. Third, there is often marked divergence in health expenditure and healthcare-seeking behaviour between socioeconomic groups [14, 15]. Health expenditure can be approximated using survey questions on the proportion of total cash expenditure on health care. Malaria understanding and treatment-seeking behaviour can be assessed using standard MIS questions [192]. Fourth, wealthier households may have better quality homes and house construction is an important determinant of malaria risk through its effect on house entry by vectors [193-196, 115, 114]. House features known to be risk factors for mosquito entry, including open eaves and rudimentary wall and roof materials may be evaluated through visual assessment of dwellings. Fifth, while there is not yet a consensus on the effect of nutrition on malaria, some evidence indicates that undernutrition may be a risk factor for infection and progression to severe disease [21]. Food security can be approximated using questions on the average number of meals per day in the past week and the number of days on which meat was consumed in the past week [197].

2.4.4. Effect of malaria on SEP

Not only are the poorest households more susceptible to malaria, but they are also more vulnerable to its costs, such that malaria can induce poverty within households [83]. This is reflected in the feedback loop from malaria risk to SEP via the direct costs of the disease. The conceptual framework also recognises that while agricultural success may be a determinant of SEP and malaria risk, a high malaria burden may reduce agricultural productivity through: (1) reductions in the work effort and (2) reduced investments in agriculture [198-202]; effects that are heightened wherever the main malaria transmission season coincides with the main farming season [203], as occurs in Nagongera. For smallholder farmers in particular, with narrow margins of survival, short periods of illness that coincide with or delay planting or harvesting can have catastrophic economic effects [204] which may be exacerbated by the need to purchase LLINs and antimalarials using meagre cash reserves [205] and absence of

social security systems [206, 202]. By incurring costs which deplete household cash reserves, malaria may also reduce local demand for produce.

2.4.5. Direct effect of agriculture on malaria

Agriculture, the main rural livelihood, may affect malaria risk directly, rather than indirectly through SEP. For example, time spent working in fields at night when transmission occurs may increase malaria risk [207] and mode of cultivation can affect transmission ecology, for example rice irrigation can produce larval habitats [136, 137]. Both time spent in fields and crop type are shown in grey in Figure 0.1 since these are beyond the scope of this study. Rice is cultivated by only a small proportion of Nagongera households and unlike in other settings, such as Tanzania, people do not spend time in their fields late at night.

2.5. Study hypotheses

Based on the conceptual framework, it is hypothesised that in Nagongera:

1. Agricultural success is a key determinant of household SEP, since agriculture is the main source livelihood in that setting.
2. Low SEP is associated with increased malaria risk, regardless of the direction of causality.
3. The association between SEP and malaria is mediated by (1) treatment-seeking behaviour, (2) housing quality and (3) food security amongst other factors.
4. Poor housing is associated with increased malaria risk after controlling for SEP, through its effect on mosquito house entry.

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Student	Lucy S. Tusting
Principal Supervisor	Jo Lines
Thesis Title	Agriculture, development and malaria in rural Uganda

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When was the work published?	2013		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I helped develop the study design. I searched the scientific literature, did the meta-analysis and prepared the first draft of the report.
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Student Signature: 

Date: 30.07.2015

Supervisor Signature: 

Date: 30.7.15

Chapter 3. Socioeconomic position and malaria: a systematic review and meta-analysis

Adapted from: Tusting LS, Willey B, Lucas H, Thompson J, Kafy HT, Smith R, Lindsay SW. Socioeconomic development as an intervention against malaria: a systematic review and meta-analysis. *Lancet* 2013; **382**: 963-972.

ABSTRACT

Background: Malaria incidence has fallen by 30% globally since 2000, driven partly by mass scale-up of interventions. However, future progress may be hampered by the development of drug and insecticide resistance. In the past, control was often achieved without malaria-specific interventions. Here, to understand the potential role of socioeconomic development in malaria control today, we critically evaluate the association between poverty and malaria.

Methods: A systematic review and meta-analysis was carried out to assess whether socioeconomic position (SEP) is associated with prevalence and incidence of malaria in children aged ≤ 15 years. Studies published in English from 1980 to 2011 that measured the association between SEP and parasitologically-confirmed malaria infection or clinical malaria in children were reviewed. Crude and adjusted effect estimates were combined using fixed- and random-effects meta-analysis, with subgroup analyses of different measures of SEP. We evaluated bias within studies using the Newcastle-Ottawa Scale and we evaluated bias across studies using funnel plots and Egger's linear regression.

Findings: Of 4,696 studies reviewed, 15 studies met the inclusion criteria and contained the necessary data to include in the quantitative analysis. In the meta-analysis of both crude and adjusted results, there was very strong evidence that the odds of malaria infection were higher in the poorest children, compared with the least poor children (crude results: odds ratio (OR) 1.66, 95% confidence intervals (CI) 1.35 to 2.05, $p < 0.001$, $I^2 = 68\%$; adjusted results: OR 2.06, 95% CI 1.42 to 2.97, $p < 0.001$, $I^2 = 63\%$), an effect consistent across subgroups.

Conclusion: The odds of malaria are on average doubled in the poorest children within a locality, compared to the wealthiest children. Whilst discontinuing existing malaria control efforts is not recommended, greater investment in interventions to support poverty reduction may prove to be effective against malaria in the long term.

3.1. Background

Although malaria is declining globally, morbidity and mortality remain high, with 584,000 estimated deaths in 2013 [1, 35]. Efforts to control malaria are almost always focused on reducing transmission with interventions that derive solely from the health sector and lend themselves to rapid and massive scale-up. Long-lasting insecticide-treated nets (LLINs) and indoor residual spraying (IRS) are both highly efficient methods of reducing transmission quickly and, combined with artemisinin combination therapies, are undoubtedly a major reason for the decline in malaria seen in sub-Saharan Africa (SSA) [49]. However, strong pressure on vector and parasite populations inevitably leads to the selection and spread of resistant strains of parasites and vectors. Resistance to artemisinins has emerged in malaria parasites in South-East Asia and may spread globally [66]. Resistance to all four classes of insecticide available for IRS (including pyrethroids, the only insecticide presently available for LLINs) is increasingly widespread in SSA [64].

Given that malaria control in many countries has been achieved historically without malaria-specific interventions, socioeconomic development could potentially provide an effective and sustainable means of control in endemic countries today. Here this hypothesis is explored with the first systematic review and meta-analysis of the evidence for the relationship between socioeconomic position (SEP) and malaria in children. The primary objective was to determine whether the risk of malaria infection or clinical malaria in children aged ≤ 15 years is associated with SEP. We followed recommendations made by the Meta-analysis of Observational Studies in Epidemiology [208] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) groups [209].

3.2. Methods

Search Strategy: We searched Medline, Web of Science, Embase, the Cochrane Database of Systematic Reviews, the Campbell Library, the Center for Reviews and Dissemination, Health Systems Evidence, and the Evidence for Policy and Practice Information and Co-ordinating Centre Evidence Library to identify studies published between 1st January 1980 and 12th July 2011. Synonym terms were selected by authors and used to develop the search strategy (Figure 3.1). Bibliographies of relevant retrieved studies were hand-searched for additional publications. The search was limited to the published literature. The search strategy was not limited by study design. We excluded reports not published in English or published before 1980, since we sought to examine the era with most applicability to the current status of malaria control.

1. malaria (MeSH term (Medical Subject Headings))
2. socioeconomic factors (MeSH term)
3. risk factors (MeSH term)
4. socio economic (key word)
5. socioeconomic (key word)
6. socio-economic (key word)
7. wealth (key word)
8. income (key word)
9. case-control studies (MeSH term)
10. survey (key word) or Data Collection (MeSH term)
11. poverty (key word)
12. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. 1 and 12
14. limit 13 to (English language and humans and year="1980 -Current")

Figure 3.1. Search strategy in Medline and Embase for a systematic review of socioeconomic position and malaria

Eligibility criteria: Studies were eligible for inclusion if they fulfilled the following criteria: the study population consisted of children aged ≤ 15 years, the association between SEP and malaria was assessed and the outcome of interest was prevalence of microscopically or rapid diagnostic test (RDT)-confirmed *P. falciparum* infection or clinical malaria (fever plus *P. falciparum* infection). Low SEP was indicated by (1) not owning defined household assets, (2) having relatively low household income, (3) a low score in an asset-based index of SEP, constructed by principal component or factor analysis or (4) parents having an unskilled rather than a skilled occupation. Cross-sectional, case-control and cohort studies were all included in the analysis. Studies with low response rates were included. Only studies pertaining to the local populations of countries classified as malaria-endemic [210] were included and studies with a population of migrants, displaced people or members of the military were excluded. Studies in which the outcome was severe malaria or congenital malaria or where most infections were not *P. falciparum* were excluded.

Data extraction: Titles and abstracts were initially screened and relevant full-text articles were reviewed by LST. A subset of 10% of the full-text articles screened (n=22) was also reviewed by SWL and any discrepancies resolved by RS. LST extracted study characteristics (study site, study design, sample size, participants, exposure, outcome, comparison, measure of effect), crude and adjusted effects with 95% confidence intervals (CIs) and factors adjusted for into a standard form (Appendix 3.1). Quality assessment and risk of bias assessment were undertaken as recommended (Appendix 3.2) [211].

Analysis: Studies that met the eligibility criteria described above and which presented crude or adjusted odds ratios (ORs) with 95% CIs, or which presented sufficient data for the calculation of crude ORs and 95% CIs, were included in a meta-analysis. The generic inverse variance

method was used to combine studies in the meta-analysis, giving weight to each study according to the inverse of the variance of the effect, in order to minimise uncertainty around the pooled effect estimates. Both outcomes (*P. falciparum* infection and clinical malaria) were combined in the analysis. The studies included in the meta-analysis were allocated to four subgroups, according to the measure of SEP used: (1) asset ownership, (2) household wealth, (3) wealth index or (4) parents' occupation. The meta-analysis was restricted to comparisons between the highest (least poor) and lowest (poorest) quintile groups, as earlier defined. Both sub-group and overall effects were calculated. Separate meta-analyses were conducted for crude and adjusted ORs. Missing data were not problematic since meta-regression of individual data was not carried out.

Initially a fixed effects meta-analysis was conducted. Where I^2 was large (>50%), indicating significant heterogeneity between studies, random-effects analysis was done. Random-effects analysis adjusts the standard errors of each study estimate of effect to include a measure of variation among the effects observed between studies. Forest plots were produced to visually assess the ORs and corresponding 95% CIs of each study. Funnel plots were used to assess publication bias across studies, showing study size as a function of effect size. Egger's linear regression method was used to test for funnel plot asymmetry (i.e. to quantify the bias captured by the funnel plot) [212]. Analyses were conducted in Stata11 and RevMan5.

3.3. Results

Our initial search yielded 6,106 potentially eligible records of which 4,696 remained after the removal of duplicates (Figure 3.2). 20 records met our inclusion criteria and of these, 15 contained the necessary data for inclusion in the quantitative analysis. Five records were excluded from the quantitative analysis as it was either not possible to calculate 95% CIs because Bayesian credible intervals were given (n=2) or because it was not possible to calculate ORs using the given data (n=3). Characteristics of included studies (study design, participants, exposure, comparison groups, outcome of interest and variables adjusted for) are described in Appendix 3.1. Despite considerable overlap between CIs for both crude and adjusted results, relatively high I^2 values from fixed-effects analysis indicated considerable heterogeneity between studies (crude results: $I^2=68%$, adjusted results: $I^2=63%$).

Sub-group analysis indicated that low SEP was associated with increased odds of malaria, regardless of the measure used for SEP, with the exception of one study using parents' occupation [213], and it was therefore judged appropriate to pool all results. In the meta-

analysis of both crude and adjusted results, there was very strong evidence that the odds of malaria infection were higher in the poorest children, compared with the least poor children (crude results: OR 1.66, 95% CI 1.35 to 2.05, $p < 0.001$, $I^2 = 68\%$; adjusted results: OR 2.06, 95% CI 1.42 to 2.97, $p < 0.001$, $I^2 = 63\%$; Figure 3.3, Figure 3.4). Visual assessment of funnel plots suggested that the studies were relatively symmetrically distributed about the combined effect size, suggesting a low degree of publication bias. Egger's test gave no evidence of funnel plot asymmetry in the crude results (bias coefficient 1.70, 95%CI -0.97-4.37, $p = 0.191$; Appendix 3.3). The test for funnel plot asymmetry was not possible for the adjusted effects since fewer than ten studies were included in the meta-analysis.

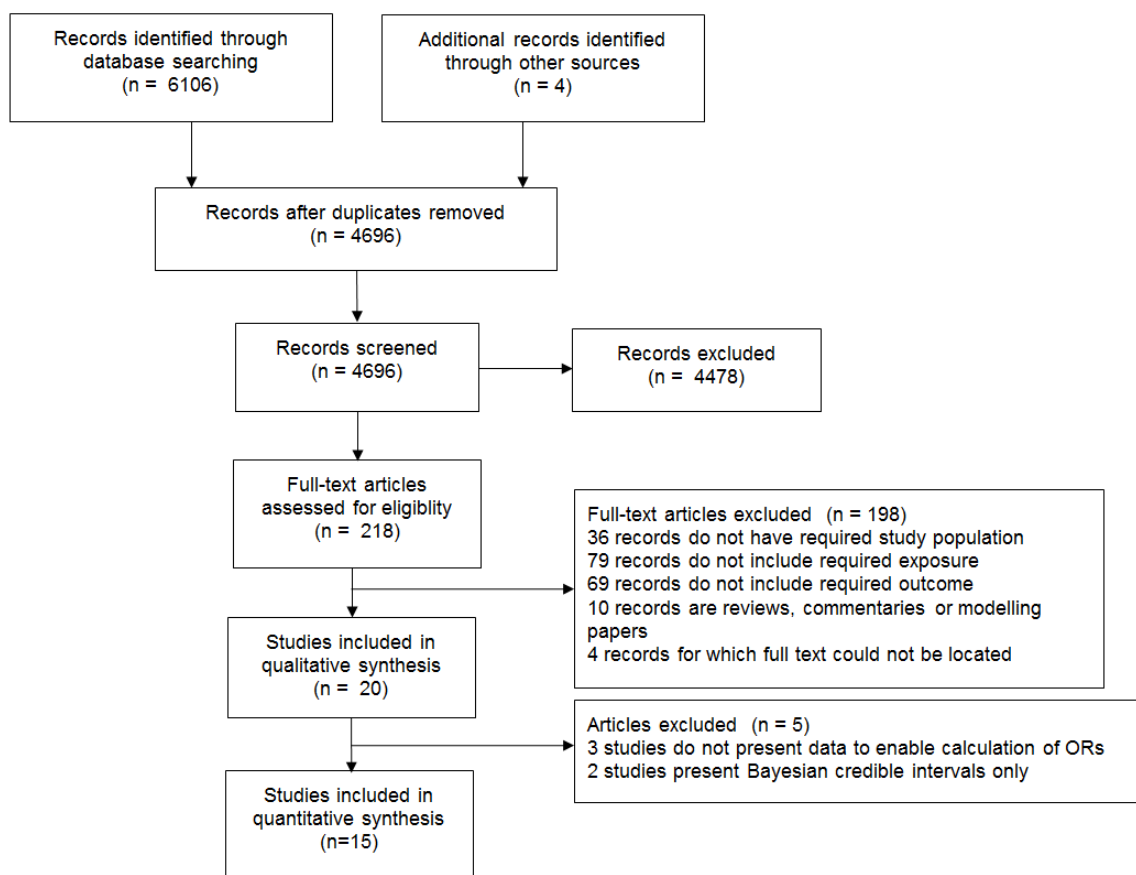


Figure 3.2. Study profile for a systematic review of socioeconomic position and malaria

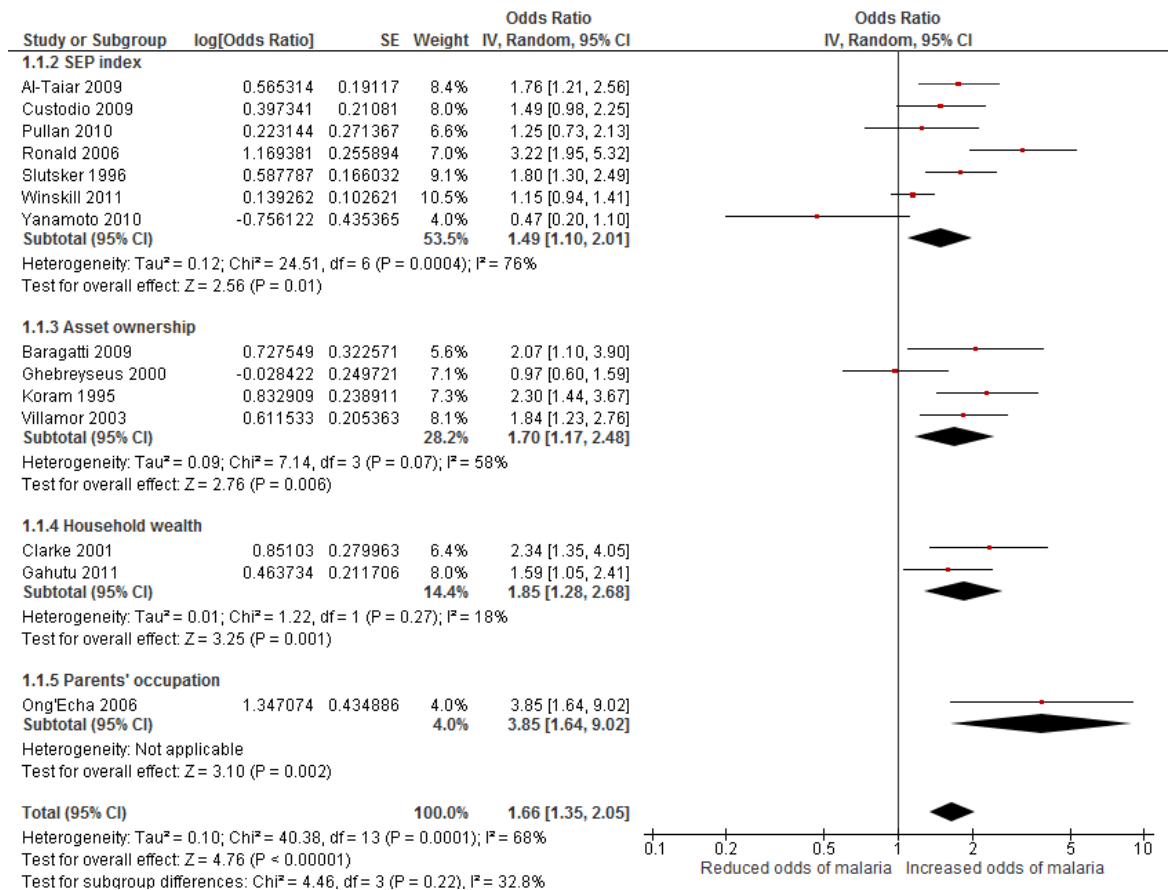


Figure 3.3. Random-effects meta-analysis of the association between low socioeconomic position and clinical malaria or parasitaemia in children aged ≤15 years (crude results).

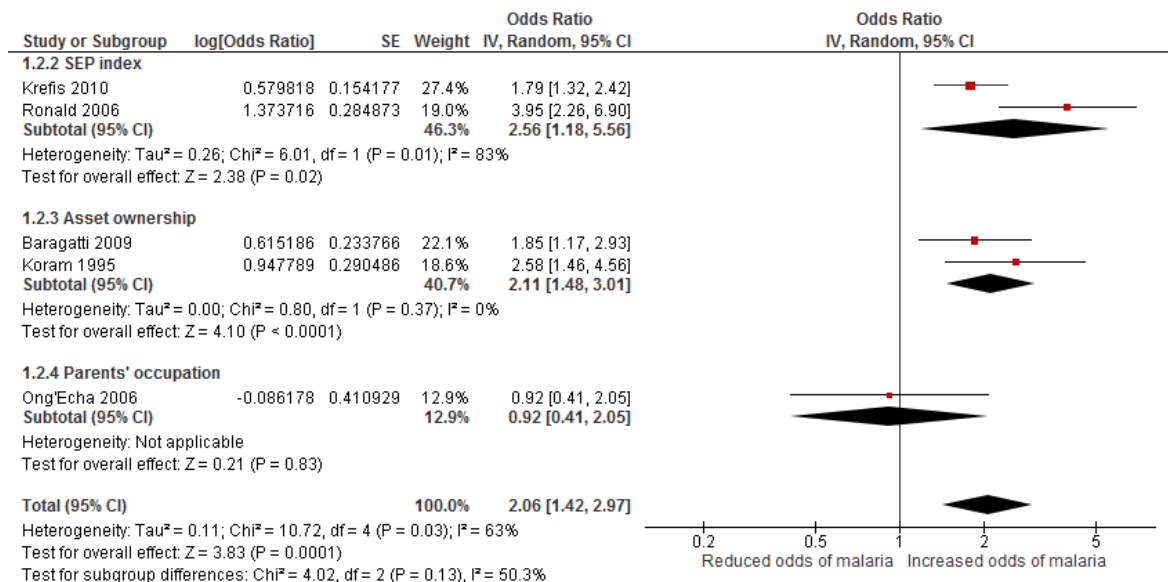


Figure 3.4. Random-effects meta-analysis of the association between low socioeconomic position and clinical malaria or parasitaemia in children aged ≤15 years (adjusted results).

3.4. Discussion

We present the first systematic review and meta-analysis of the association between poverty and malaria. Our findings indicate that low SEP is associated with approximately doubled odds of clinical malaria or parasitaemia in children, compared to those of highest SEP within communities in SSA. Since the analysis represents a comparison of the very poorest children with the least poor children within highly impoverished communities, the difference in the odds of malaria would likely be even greater if the studies were expanded to include children from wealthier homes. Our findings represent the strongest evidence to date that wealth can be protective against malaria. We build on a non-systematic review by Worrall and colleagues that found mixed evidence for the relationship between SEP and malaria incidence, but that included self-reported malaria as an outcome [105].

Wealth is likely to have a protective effect against malaria since it renders prophylaxis and treatment more affordable [8, 190, 189] and is positively associated with other factors known to be protective, including better educated parents (which improves prophylaxis and treatment for children), greater quality of housing (which reduces house entry by malaria mosquitoes), and improved nutritional status of children (which may increase their subsequent ability to cope with malaria infection [214]). However, these causal pathways remain poorly understood. Furthermore, the observed association between SEP and malaria does not provide evidence of the direction of causality, since the poorest households are not only more susceptible to the disease but are also more vulnerable to its costs, such that the disease itself can induce poverty. For example, low SEP and malaria parasitaemia were found to be associated in 52 villages in Tanzania, with causality in both directions [215]. A later analysis of a national Tanzania survey found that children with malaria parasitaemia had a wealth index that was 1.9 units lower than uninfected children, but malaria infection status was unrelated to household SEP [31]. In other words, there was no causality from SEP to malaria. In reality, the interplay between malaria and poverty is likely to constitute a vicious cycle for the poorest households, since they are not only more susceptible to the disease but also more vulnerable to its costs. Findings from Kenya [80] and Nigeria [83] indicate that the costs of malaria treatment (as a proportion of non-food monthly income) and subsequent financial setbacks are greater for poorer households. Costs also vary geographically; in Kenya and Papua New Guinea, the risk of clinical disease is greater in 'low' transmission districts, with subsequently higher income loss [216, 80].

Based on our findings, we advocate further research into the potential of poverty reduction to control malaria. Malaria elimination in many, what are now high-income, countries was achieved without malaria-specific interventions and began to decline in Europe and North America as a by-product of improved living conditions and greater wealth [106, 107]. It is possible that development can similarly have an impact in SSA today; in Zanzibar, parasite prevalence declined from 60% pre-World War Two to 35-40% by the mid-1990s and this was thought to be due to urbanisation and development among other factors [113]. Further research is needed to galvanize specialists in both health and development to work more closely together on malaria control.

Our study has a number of potential limitations. First, the meta-analysis included studies that measured risk factors across studies and although sub-group and random-effects analysis were conducted, these are unlikely to have fully accounted for heterogeneity in study design. Second, all studies included in the meta-analysis were observational, which derives from the nature of the study question (it is not ethical or practical to randomise SEP). While this weakens the overall strength of the evidence [217], consistency across studies and settings gives weight to the finding of increased odds of malaria in children of lower SEP. Third, we searched only studies in English, which may have led to the exclusion of many studies. In particular not synthesising the Spanish language literature may have largely excluded the South American experience, so that the findings of the meta-analysis are not generalizable to that region [217]. While Egger's test indicated no forest plot asymmetry, statistical tests for forest plot asymmetry tend to have low power [218]. Incomplete retrieval (four full-text studies could not be retrieved) may also have introduced bias. Fourth, our meta-analysis does not provide evidence of causality in either direction, nor did we account for the effect of other diseases and health outcomes that can coexist in malaria-endemic settings, or the effect of differences in treatment-seeking behaviour [217].

In conclusion, our study provides preliminary support for the argument that increased wealth and improved standards of living directly stemming from socioeconomic development could prove important in sustainable malaria control in SSA, as is thought to have been the case historically in Europe and North America.

Acknowledgements

The study was supported by the UK Department for International Development, the Malaria Centre at the London School of Hygiene and Tropical Medicine and SWL was supported by the

Research and Policy for Infectious Disease Dynamics (RAPIDD) Programme of the Science and Technology Directorate, Department of Homeland Security, and Fogarty International Center, National Institutes of Health. We are grateful to Frida Kasteng (LSHTM) for information on the costs of malaria and development interventions.

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Principal Supervisor	Jo Lines
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Student Signature: 

Date: 30.07.2015

Supervisor Signature: 

Date: 30.7.15

Chapter 4. The evidence for improving housing to reduce malaria: a systematic review and meta-analysis

Published as: Tusting LS, Ippolito MM, Willey B, Kleinschmidt I, Gosling R, Dorsey G, Lindsay SW. The evidence for improving housing to reduce malaria: a systematic review and meta-analysis. *Malar J* 2015; **14**: 209.

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ABSTRACT

Background: The global malaria burden has fallen since 2000, sometimes before large-scale vector control programmes were initiated. While long-lasting insecticide-treated nets and indoor residual spraying are highly effective interventions, this study tests the hypothesis that improved housing can reduce malaria risk by decreasing house entry by malaria mosquitoes.

Methods: A systematic review and meta-analysis was conducted to assess whether modern housing is associated with a lower risk of malaria than traditional housing, across all age groups and malaria-endemic settings. Six electronic databases were searched to identify intervention and observational studies published from 1 January, 1900 to 13 December, 2013, measuring the association between house design and malaria. The primary outcome measures were parasite prevalence and incidence of clinical malaria. Crude and adjusted effects were combined in fixed- and random-effects meta-analyses, with sub-group analyses for: overall house type (traditional *versus* modern housing); screening; main wall, roof and floor materials; eave type; ceilings and elevation.

Results: Of 15,526 studies screened, 90 were included in a qualitative synthesis and 53 reported epidemiological outcomes, included in a meta-analysis. Of these, 39 (74%) showed trends towards a lower risk of epidemiological outcomes associated with improved house features. Of studies assessing the relationship between modern housing and malaria infection (n=11) and clinical malaria (n=5), all were observational, with very low to low quality evidence. Residents of modern houses had 47% lower odds of malaria infection compared to traditional houses (adjusted odds ratio (OR) 0.53, 95% confidence intervals (CI) 0.42-0.67, p<0.001, five studies) and a 45-65% lower odds of clinical malaria (case-control studies: adjusted OR 0.35, 95% CI 0.20-0.62, p <0.001, one study; cohort studies: adjusted rate ratio 0.55, 95% CI 0.36-0.84, p=0.005, three studies). Evidence of a high risk of bias was found within studies.

Conclusions: Despite low quality evidence, the direction and consistency of effects indicate that housing is an important risk factor for malaria. Future research should evaluate the protective effect of specific house features and incremental housing improvements associated with socioeconomic development.

4.1. Background

Despite considerable advances in malaria control since 2000, with a 30% fall in incidence in all age groups worldwide, the disease remains a major global public health problem with an estimated 198 million cases in 2013 [1]. Reductions have been achieved mainly through extensive long-lasting insecticide-treated net (LLIN) distribution and indoor residual spraying (IRS) campaigns. However, the future success of these interventions may be undermined by the spread of insecticide-resistant mosquitoes [219], creating a need for supplementary interventions not reliant on current insecticides. Interestingly, in some locations malaria has declined before intervention scale-up, suggesting additional causes of the reduction [220, 50]. Since malaria is a disease of poverty and the environment, there is increasing interest in the potential contribution of socioeconomic development to malaria control [6], and in coordinating with sectors outside health, including agriculture, water and sanitation, education, city planning and housing, to meet long-term sustainable development goals [221].

Housing improvements, traditionally a key pillar of public health, remain underexploited in malaria control. Yet in sub-Saharan Africa (SSA), where up to 80-100% of malaria transmission occurs indoors at night, the home can be a place of high risk [70]. House screening was the first intervention tested in Italy after the link between malaria and mosquitoes was discovered [222]. Screening homes was subsequently shown to reduce malaria risk in India, South Africa and the USA [221] and better housing contributed to malaria elimination in the USA and Europe [117]. More recent studies indicate that well-built, modern housing can be protective in many tropical countries [18] and that simple features, including closed eaves (the gap between the top of the wall and the over-hanging roof), brick walls, tiled or metal roofs, or ceilings can reduce mosquito house entry [221]. In a randomised-controlled trial (RCT) in The Gambia, untreated door and window screens and closed eaves halved the prevalence of anaemia in children [115].

Ninety per cent of malaria deaths in five year-olds occur in Africa, the economy of which is rapidly growing, with a 6% annual increase in gross domestic product expected until 2025 [223]. Increased personal wealth is precipitating continent-wide housing improvements, such as the replacement of traditional thatch with metal and tiled roofs (Figure 4.1). The expanding population, expected to triple to 1.23 billion by 2050, also needs accommodating, with an estimated 144 million new houses required by 2030 in rural areas alone [224]. This economic and cultural transition presents an opportunity to document and influence incremental housing improvements that might protect against malaria and to build healthy homes.

Yet despite the historical precedent for improving housing to control malaria, few rigorously conducted studies exist. Furthermore, the evidence on housing and malaria has not been systematically characterized, with no specific evaluation of the size and consistency of the direction of effect, nor the quality of the evidence. The recent *Multisectoral Action Framework for Malaria* [3] emphasizes throughout the need for good housing, yet there is a paucity of evidence supporting this recommendation and uncertainty about how to select, scale-up and sustain interventions [221]. Here the potential for modern house construction to reduce malaria risk was evaluated. Specifically, the first systematic review and meta-analysis was conducted to assess whether ‘modern’ homes are associated with reduced exposure to infectious bites, malaria infection and clinical malaria in people of all ages in malaria-endemic regions, compared to ‘traditional’ homes. Since few intervention studies exist, observational study designs were also included. The study aimed first to characterize all published and unpublished data and second to assess the strength and quality of these data, in order to rigorously evaluate the evidence for the impact of housing improvements on malaria.

4.2. Methods

Recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis of Observational Studies in Epidemiology groups were followed [208, 209]. The study is registered with the International Prospective Register of Systematic Reviews [225]. The study aimed to compare modern with traditional homes in any malaria-endemic settings. In SSA, traditional homes were considered to have mud walls, thatched roofs and earth floors, except in areas of exceptionally high rainfall including Equatorial Guinea, where concrete or wood is the basic wall material [226]. Traditional homes were considered to have mud or stone walls, thatched, wood or mud roofs, and earth floors in North Africa [227], wood or bamboo walls, thatched roofs and earth or wooden floors in Southeast and South Asia [228], and adobe or mud and wood walls, thatched roofs and earth floors in South America [229]. Universally, traditional homes were considered to have open eaves, no ceiling and no screening.

Eligibility criteria: Studies were included with participants of any ages (excluding migrants, displaced people or military) and conducted in real (not experimental) houses, that compared modern with traditional house features and that measured any outcomes of interest. Both observational and intervention study designs were included: (1) case-control; (2) cohort; (3) cross-sectional studies; (4) RCTs; (5) controlled before-and-after studies, if arms were comparable at baseline and there was at least one unit per arm; (6) cross-over studies, if there

were at least one unit per arm; and, (7) interrupted time-series studies. Studies were excluded if arm follow-up periods differed.

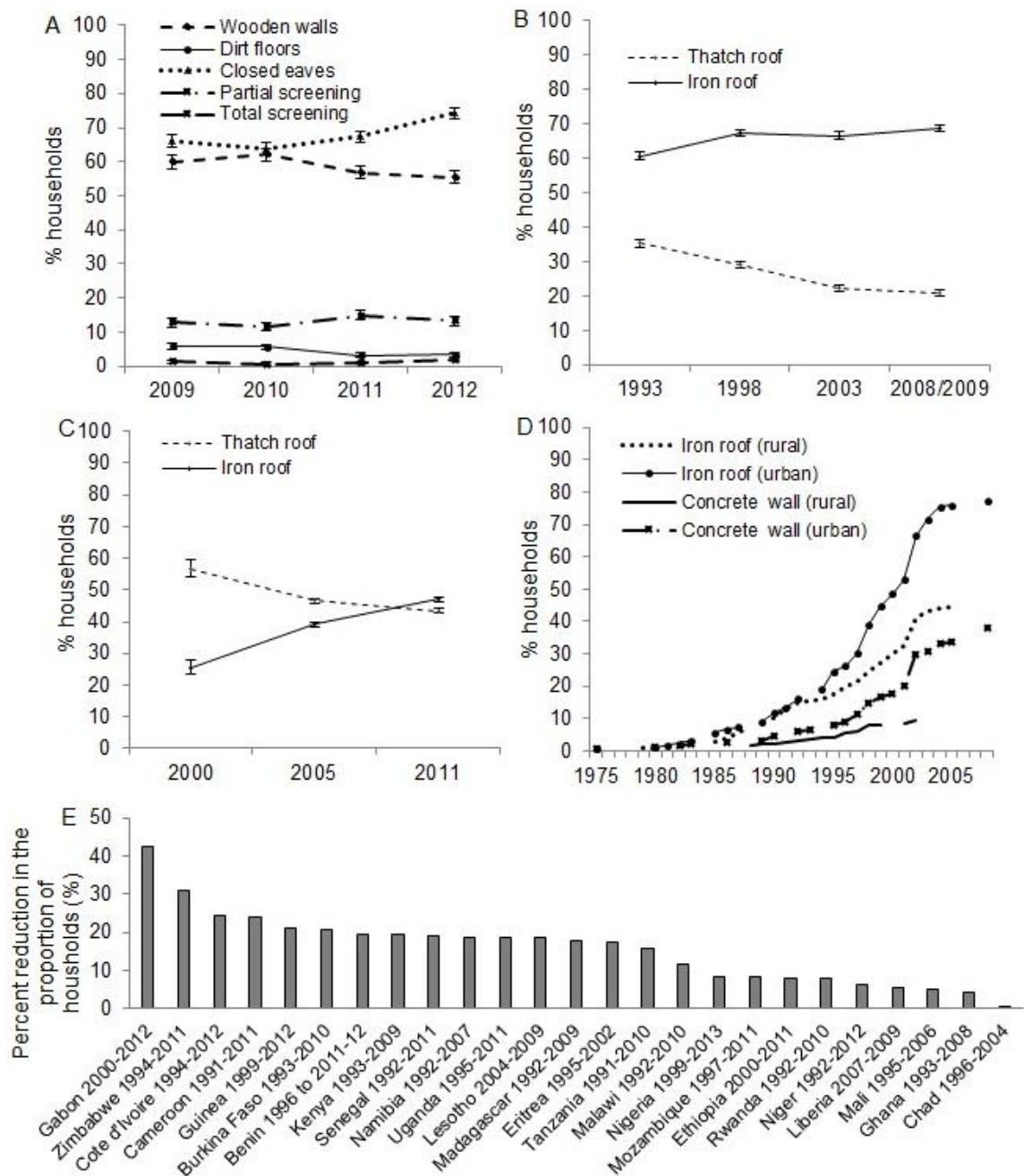


Figure 4.1. Changes in housing in sub-Saharan Africa, 1975-2012

Despite limited data, there is evidence that the quality of both urban and rural housing is improving in parts of SSA, including Bioko, Kenya, Ethiopia and Tanzania. **A.** Trends in housing in Bioko, Equatorial Guinea, 2009-2012 [226]. **B.** Proportion of homes with thatch and iron roofs in Kenya, 1993-2009 [230]. **C.** Proportion of homes with thatch and iron roofs in Ethiopia, 2000-2011 [231]. **D.** Estimated proportion of homes with concrete walls and iron roofs in Korogwe, Tanzania, 1975-2008 [232]. **E:** Percent reduction in the proportion of households with natural or rudimentary flooring in SSA (comparing earliest and latest available Demographic and Health Surveys (DHS); dates are shown for each country) [233].

Epidemiological outcomes in human subjects were: clinical malaria (fever with parasitaemia confirmed by microscopy or rapid diagnostic test (RDT), in any age group); malaria infection (confirmed by microscopy or RDT, in any age group); and, anaemia in children aged under 11 years. Entomological outcomes were: entomological inoculation rate (EIR, the estimated number of bites by infectious mosquitoes per person per time period, measured directly using human baits or indirectly using light traps or other methods); human biting rate (the number of mosquitoes per person per time period); and indoor density of adult vector mosquitoes (number of mosquitoes per house or person).

Search strategy and data extraction: PubMed, Embase, LILACS, the Meta-Register of Controlled Trials, Cochrane Infectious Diseases Group Specialized Register, and Cochrane Central Register of Controlled Trials were searched with no language restrictions, using specified search terms (Appendix 4.1) to identify studies published from 1 January, 1900 to 13 December, 2013. The following databases were searched: US Armed Forces Pest Management Board online database (1900-1947) and proceedings of the MIM Pan-African Malaria Conferences (2005 and 2013), American Society of Tropical Medicine and Hygiene (2004-2013) and Society for Vector Ecology (2010-2012). Reference lists of identified studies were searched. Authors were contacted for additional references. LST and MI independently screened titles and abstracts before screening the full text of relevant studies using a standard form. Disagreements were resolved by SWL.

Data extraction: Study characteristics (participants, sampling, exposures, comparisons, outcomes, study design, setting, sample size, follow-up period, vector(s), LLIN and IRS coverage, transmission intensity, and funding) were extracted by LST and a 10% sub-sample randomly selected for validation (MI). Study authors were contacted for missing data.

Risk of bias of and quality of evidence: Risk of bias for RCTs, controlled before-and-after studies, cross-over studies and interrupted time-series studies was assessed using the Effective Practice and Organisation of Care (EPOC) tool [234], and for case-control, cohort and cross-sectional studies using the Newcastle-Ottawa Scale [211]. Risk of bias across studies (publication bias) was assessed using funnel plots and Egger's test for funnel plot asymmetry [235]. Quality and strength of the evidence were evaluated for the main comparison (modern *versus* traditional homes) using the Grading Quality of Evidence and the Strength of Recommendations (GRADE) approach [236].

Data analysis: Analyses were structured first by house feature, second by outcome and third by study design. All eligible studies were included in a qualitative synthesis. Studies were also included in a quantitative analysis, comparing modern with traditional house features, if crude or adjusted odds ratios (ORs) or rate ratios (RRs) with 95% confidence intervals (CIs), or sufficient data to calculate crude effects, were reported. Specifically, epidemiological data were combined in meta-analysis and entomological data presented in tables. Analyses were done in Stata13 and RevMan5.

Epidemiological data: Study effects were combined in the meta-analysis using the generic inverse variance method, which assigns each effect a weight equal to the inverse of its variance. Pooled ORs or RRs were calculated using fixed-effects meta-analysis where significant heterogeneity was not detected and random effects meta-analysis where significant heterogeneity was found ($I^2 > 50\%$). Separate meta-analyses were done for crude and adjusted results.

Entomological data: Data and study characteristics were presented in tables. Where no effect measure was reported the crude effect was calculated as the ratio of the outcomes in the treatment and control groups. Ninety-five percent CIs were calculated by estimating the standard errors of the outcomes from their stated 95% CI. Where 95% CIs of outcomes were non-symmetrical, it was assumed that standard errors and CIs were calculated on log-transformed values.

4.3. Results

Search results: The search yielded 15,526 studies after removing duplicates (Figure 4.2). Ninety studies met the inclusion criteria, of which 18 were included in the qualitative synthesis only and 72 were included in the quantitative analysis (Appendix 4.2). Of these 72 studies, 53 reported epidemiological outcomes (included in the meta-analysis) and 25 reported entomological outcomes (presented in tables only).

Study characteristics: The six intervention studies dated from 2009 to 2013. All were conducted in rural SSA, using house screening as the intervention. One study, a cluster RCT in The Gambia, collected both epidemiological and entomological outcomes [115] and was included in the meta-analysis. Five studies collected entomological data only: three pilot RCTs in Ethiopia, Mozambique and Tanzania [237-239], one randomised cross-over trial in The Gambia [240], and one non-randomised cross-over trial in Tanzania [241]. The 84 observational studies, dating from 1935 to 2015, had cross-sectional (n=39), cohort (n=30),

and case-control (n=15) designs. These were conducted mainly in SSA (n=58) and Asia (n=13) and largely in rural settings (n=62) (Appendix 4.2). In the 53 observational studies included in the meta-analysis, comparisons included modern *versus* traditional housing (n=15); modern *versus* traditional wall (n=22), roof (n=18), and floor (n=4) materials and closed *versus* open eaves (n=11).

Risk of bias and quality of the evidence: High risk of bias was found across numerous domains of the EPOC risk of bias for intervention studies, particularly for allocation concealment, length of follow-up and blinding (Appendix 4.3). Risk of bias within individual case-control, cross-sectional and cohort studies was generally high (Appendix 4.3). Across studies, there was evidence of publication bias in the meta-analysis of house type and malaria infection (Appendix 4.4), with no evidence of funnel plot asymmetry (bias coefficient 0.52, 95% CI -1.61 to 2.65, p=0.60). There were insufficient studies to test for asymmetry in the meta-analysis of house type and clinical malaria. GRADE quality of the evidence for the main comparison, modern *versus* traditional housing, ranged from very low to low (Table 4.1).

Modern versus traditional housing: Residents of modern homes had lower odds of malaria infection than residents of traditional homes (crude OR 0.46, 95% CI 0.33-0.62, p <0.001, nine studies, low quality evidence; adjusted OR 0.53, 95% CI 0.42-0.67, p <0.001, five studies, very low quality evidence) (Figure 4.3, Table 4.2). Modern homes were associated with lower odds and incidence rate of clinical malaria (case-control and cross-sectional studies: crude OR 0.32, 95% CI 0.19-0.54, p <0.001, one study, very low quality evidence; adjusted OR 0.35, 95% CI 0.20-0.62, p <0.001, one study, very low quality evidence; cohort studies: crude RR 0.22, 95% CI 0.14-0.35, p <0.001, three studies, low quality evidence; adjusted RR 0.55, 95% CI 0.36-0.84, p=0.005, three studies, very low quality evidence) (Figure 4.4). In seven studies with entomological outcomes, modern housing was associated with no effect to a 66% reduction in density of adult anophelines (Appendix 4.5).

House screening: In one cRCT in The Gambia, full or ceiling screening reduced anaemia in children by 48% (adjusted OR 0.52, 95% CI 0.34-0.80, p=0.003), with no effect on malaria infection. Screening was not consistently associated with lower odds of anaemia in children or malaria infection in seven case-control, cross-sectional and cohort studies, but was associated with a lower incidence of clinical malaria in three cohort studies (Table 4.2).

Modern versus traditional wall, roof and floor materials: Modern wall materials were associated with an approximately quarter reduction in the odds of malaria infection, although results were inconsistent for incidence of clinical malaria. Modern roof materials were not consistently associated with reduced odds of infection, but were associated with up to a two thirds reduction in the incidence of clinical malaria. There was inconsistent evidence that modern floor materials gave protection against any epidemiological outcome (Table 4.2).

Eaves, ceilings and house elevation: Closed eaves were associated with a quarter reduction in the odds of malaria infection and a quarter to a half reduction in clinical malaria in five case-control and cross-sectional studies and two cohort studies. The presence (*versus* absence) of a ceiling was associated with a third reduction in the odds of clinical malaria. In one cross-sectional study, house elevation was not associated with the odds of malaria infection (Table 4.2).

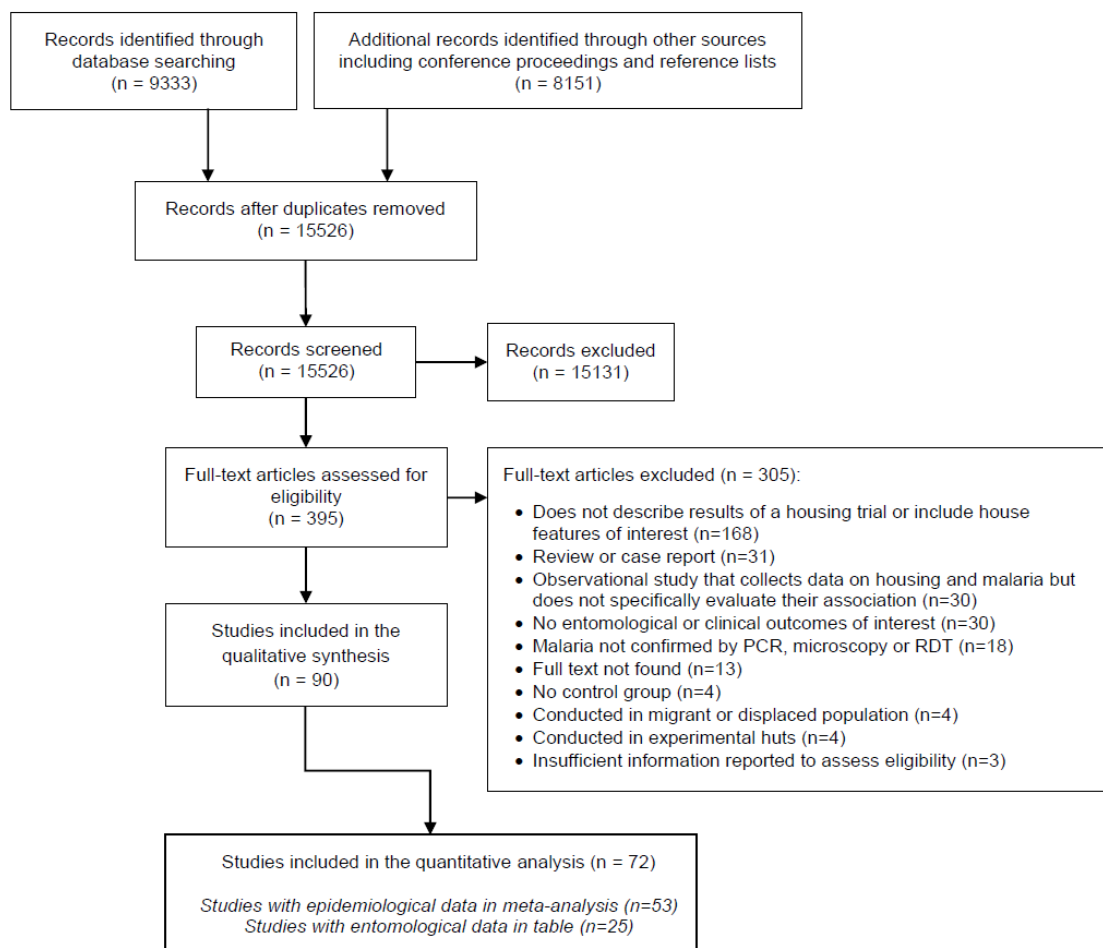


Figure 4.2. Study flow for a systematic review of housing and malaria

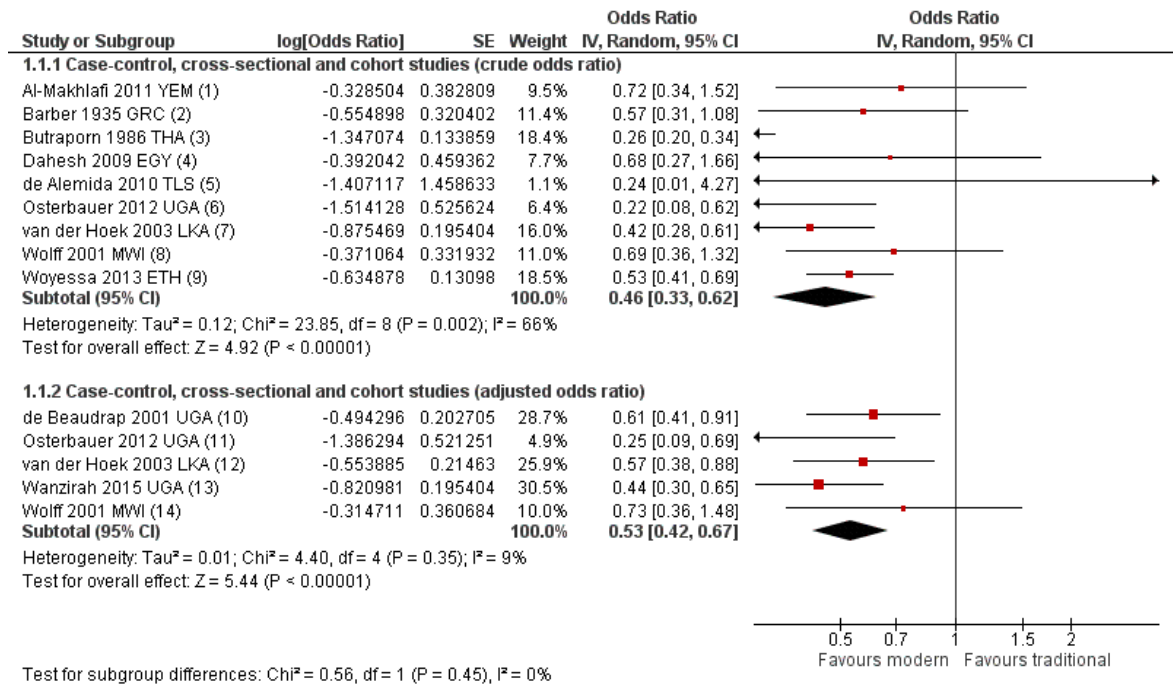


Figure 4.3. Meta-analysis of the association between modern housing and malaria infection
Pooled effects from random-effects meta-analyses for crude (1.1.1) and adjusted (1.1.2) results are shown. Studies are divided into sub-groups by study design. Error bars show 95% CIs; df=degrees of freedom. 1. Al-Makhlafi 2011 YEM: Good vs poor house quality; 2. Barber 1935 GRC: Modern (tiled roof, ceiling) vs traditional (thatched roof, reed or no ceiling); 3. Butraporn 1935 THA: Permanent vs semi-permanent or temporary; 4. Dahesh 2009 EGY: Painted brick walls and cement ceilings vs mud walls and wood or mud ceilings; 5. de Alemida 2010 TLS: Complete vs incomplete house; 6. Osterbauer 2012 UGA: Modern (iron roof, burnt brick or cement walls and cement floor) vs traditional; 7. van der Hoek 2003 LKA: Modern (brick walls and permanent roof material) vs traditional (mud walls or thatched roof); 8. Wolff 2001 MWI: Modern vs traditional; 9. Woyessa 2013 ETH: Good vs dilapidated house, 10. de Beaudrap 2001 UGA: Brick walls and iron roof vs mud walls and thatched roof (OR adjusted for age, weight, socioeconomic status, education, altitude, ITNs), 11. Osterbauer 2012 UGA: Modern (iron roof, burnt brick or cement walls and cement floor) vs traditional (OR adjusted for age, HIV-exposure, enrolment period, gender, mother's age, prophylaxis); 12. van der Hoek 2003 LKA: Modern (brick walls and permanent roof material) vs traditional (mud walls or thatched roof) (OR adjusted for age, gender, distance to stream, distance to cattle shed, coil use, ITNs, IRS); 13. Wanzirah 2015 UGA: Modern (cement, wood or metal wall; tiled or metal roof and closed eaves) vs traditional (OR adjusted for age, gender, study site, household wealth); 14. Wolff 2001 MWI: Modern vs traditional (OR adjusted for water source, occupation, education, malaria knowledge, waste disposal method).

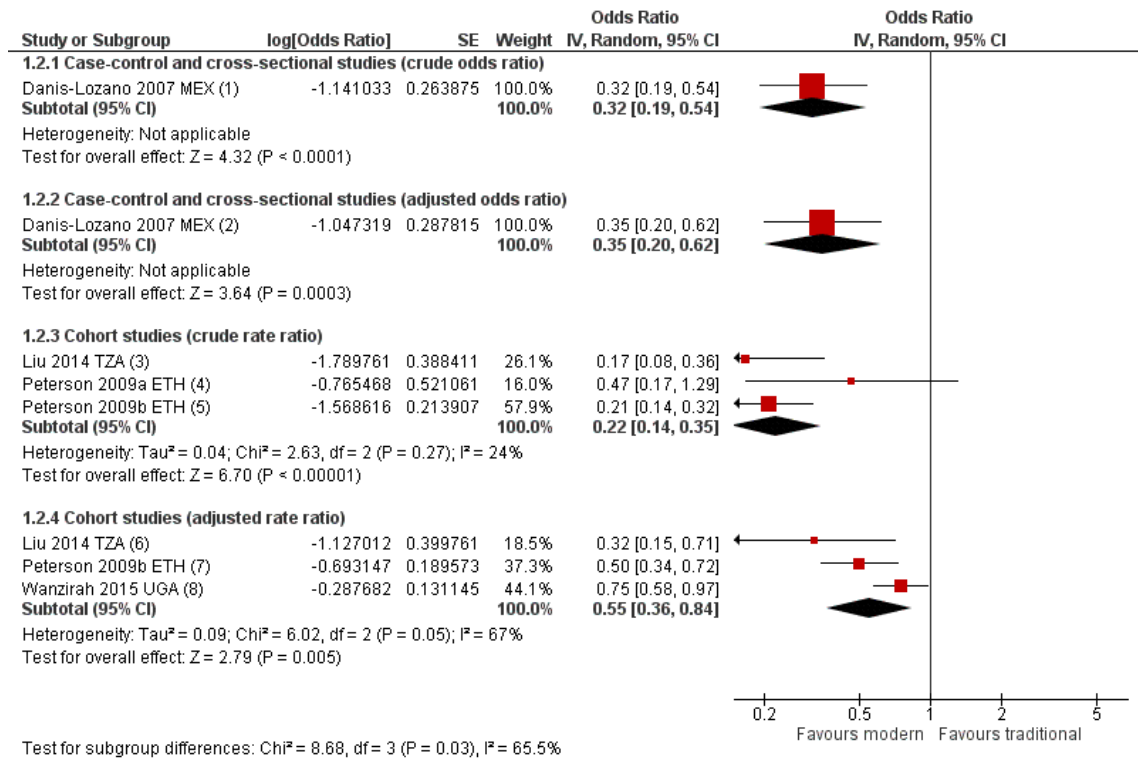


Figure 4.4. Meta-analysis of the association between modern housing and clinical malaria
Pooled effects from random-effects meta-analyses for crude (1.2.1; 1.2.3) and adjusted (1.2.2; 1.2.4) results are shown. Studies are divided into sub-groups by study design. Error bars show 95% CIs; df=degrees of freedom. 1. Danis-Lozano 2007 MEX: House constructed with non-perishable vs perishable materials; 2. Danis-Lozano 2007 MEX: House constructed with non-perishable vs perishable materials (OR adjusted for occupation, village); 3. Liu 2014 TZA: Highest quintile of housing index compared to lowest quintile (based on roof, wall and floor material and presence of ceiling, eaves, screening); 4. Peterson 2009a ETH: Medium or good vs poor house construction; 5. Peterson 2009b ETH: Good vs poor house construction; 6. Liu 2014 TZA: Highest quintile of housing index compared to lowest quintile (based on roof, wall and floor material and presence of ceiling, eaves, screening) (RR adjusted for age, mother's education, wealth index, prophylaxis, socioeconomic status, urban site, intermittent preventive treatment in infants (IPTi) trial arm); 7. Peterson 2009b ETH: Good vs poor house construction (RR adjusted for ITNs, vegetation, temperature, rainfall, larval densities); 8. Wanzirah 2015 UGA: Modern (cement, wood or metal wall; tiled or metal roof and closed eaves) vs traditional (RR adjusted for age, gender, study site, household wealth).

Table 4.1. GRADE quality of evidence for the association between modern housing and clinical malaria outcomes

Outcomes	Summary of findings		Quality of the evidence					Overall quality of the evidence (GRADE)
	Relative effect (95% CI)	No. participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
Malaria infection Case-control, cross-sectional and cohort studies (crude OR)	OR 0.46 (0.33-0.62)	22,700 (9 studies)	Serious ¹	No serious inconsistency ²	No serious indirectness ³	No serious imprecision ⁴	Undetected ⁵	⊕⊕⊕⊖ LOW ^{1,2,3,4,5,6,7} due to risk of bias, large effect
Malaria infection Case-control, cross-sectional and cohort studies (adjusted OR)	OR 0.53 (0.42-0.67)	3,949 (5 studies)	Serious ¹	No serious inconsistency ⁸	No serious indirectness ⁹	No serious imprecision ⁴	Undetected ⁵	⊕⊕⊕⊖ VERY LOW ^{1,4,5,7,8,9,10} due to risk of bias
Clinical malaria Case-control and cross-sectional studies (crude OR)	OR 0.32 (0.19-0.54)	357 (1 study)	Serious ¹	No serious inconsistency ¹¹	Serious ¹²	No serious imprecision ⁴	Undetected ¹³	⊕⊕⊕⊖ VERY LOW ^{1,4,6,7,11,12,13} due to risk of bias, indirectness, large effect
Clinical malaria Case-control and cross-sectional studies (adjusted OR)	OR 0.35 (0.20-0.62)	357 (1 study)	Serious ¹	No serious inconsistency ¹¹	Serious ¹²	No serious imprecision ⁴	Undetected ¹³	⊕⊕⊕⊖ VERY LOW ^{1,4,6,7,11,12,13} due to risk of bias, indirectness, large effect
Clinical malaria Cohort studies (crude RR)	RR 0.22 (0.14-0.35)	1,653 (3 studies)	Serious ¹	No serious inconsistency ¹⁴	Serious ¹⁵	No serious imprecision ⁴	Undetected ¹³	⊕⊕⊕⊖ LOW ^{1,4,7,13,14,15,16} due to risk of bias, indirectness, large effect
Clinical malaria Cohort studies (adjusted RR)	RR 0.55 (0.36-0.84)	2,237 (3 studies)	Serious ¹	No serious inconsistency ¹⁷	Serious ¹⁵	No serious imprecision ⁴	Undetected ¹³	⊕⊕⊕⊖ VERY LOW ^{1,4,13,15,17,18} due to risk of bias, indirectness

Patient or population: People of all ages living in malaria-endemic regions.

Settings: East Timor, Egypt, Ethiopia, Greece, Malawi, Mexico, Sri Lanka, Tanzania, Thailand, Uganda and Yemen.

Intervention: modern (*versus* traditional) housing.

GRADE Working Group grades of evidence: **High quality:** Further research is very unlikely to change confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** The estimate is very uncertain.

Table 4.1 (Continued)

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- ¹ Downgraded by 1 for serious risk of bias: All studies were non-randomised and observational.
- ² No serious inconsistency: All nine studies observed a protective effect of modern housing, compared to traditional housing. The smallest effect was a 28% reduction in the odds of malaria infection.
- ³ No serious indirectness: These nine studies were conducted in a variety of sites, both urban and rural, in settings across sub-Saharan Africa (SSA), Asia and Europe. The findings are generalisable elsewhere.
- ⁴ No serious imprecision: The overall effect was statistically significant and clinically important.
- ⁵ Publication bias not detected: Egger's test for bias in crude results found no evidence funnel plot asymmetry (bias coefficient 0.52, 95% CI -1.61 – 2.65, $p=0.60$).
- ⁶ Upgraded by 1 for large effect: Odds ratio (OR) lies within the range 0 to 0.5.
- ⁷ No evidence that residual confounding would reduce the demonstrated effect: no significant difference between crude and adjusted effects.
- ⁸ No serious inconsistency: All five studies observed a protective effect of modern housing, compared to traditional housing. The smallest effect was a 27% reduction in the odds of malaria infection.
- ⁹ No serious indirectness: These five studies were conducted in a variety of sites, both urban and rural, in SSA and Asia. The findings are generalisable elsewhere.
- ¹⁰ No large effect: OR does not fall into the range 0 to 0.5.
- ¹¹ No serious inconsistency: only one study.
- ¹² Downgraded by 1 for indirectness: only one study was included, which was conducted in rural Mexico and the findings may not be generalisable elsewhere.
- ¹³ Publication bias not detected: insufficient studies to construct funnel plots.
- ¹⁴ No serious inconsistency: all three studies observed a protective effect of modern housing, compared to traditional housing. The smallest effect was a 53% reduction in incidence of clinical malaria.
- ¹⁵ Downgraded by 1 for serious indirectness: all studies were conducted in rural SSA. The results may not be generalisable to other settings.
- ¹⁶ Upgraded by 2 for very large effect: Rate ratio (RR) and 95% confidence intervals lie within the range 0 to 0.5.
- ¹⁷ No serious inconsistency: all three studies observed a protective effect of modern housing, compared to traditional housing. The smallest effect was a 25% reduction in the incidence of clinical malaria.
- ¹⁸ No large effect: RR does not fall into the range 0 to 0.5.
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Table 4.2. Summary of findings of meta-analyses of the association between specific house features and malaria

Comparison	Outcome	Study design	Total studies	Effect estimate (95% CI)
1 Modern versus traditional housing	1.1 Malaria infection	1.1.1 Case-control, cross-sectional and cohort studies (crude OR)	9	0.46 [0.33, 0.62]
		1.1.2 Case-control, cross-sectional and cohort studies (adjusted OR)	5	0.53 [0.42, 0.67]
	1.2 Clinical malaria	1.2.1 Case-control and cross-sectional studies (crude OR)	1	0.32 [0.19, 0.54]
		1.2.2 Case-control and cross-sectional studies (adjusted OR)	1	0.35 [0.20, 0.62]
		1.2.3 Cohort studies (crude RR)	3	0.22 [0.14, 0.35]
		1.2.4 Cohort studies (adjusted RR)	3	0.55 [0.36, 0.84]
2.1 Anaemia in children aged 0-11yrs	2.1.1 Randomised controlled trials (adjusted OR)	1	0.52 [0.34, 0.80]	
	2.1.2 Case-control, cross-sectional and cohort studies (crude OR)	2	0.65 [0.33, 1.30]	
	2.1.3 Case-control, cross-sectional and cohort studies (adjusted OR)	1	0.56 [0.24, 1.27]	
2 Screening¹	2.2 Malaria infection	2.2.1 Randomised controlled trials (adjusted OR)	1	0.95 [0.63, 1.43]
		2.2.2 Case-control, cross-sectional and cohort studies (crude OR)	5	0.35 [0.13, 0.98]
		2.2.3 Case-control, cross-sectional and cohort studies (adjusted OR)	2	0.93 [0.82, 1.05]
	2.3 Clinical malaria	2.3.1 Case-control and cross-sectional studies (crude OR)	1	1.16 [0.82, 1.64]
		2.3.2 Cohort studies (crude RR)	5	0.71 [0.49, 1.04]
		2.3.3 Cohort studies (adjusted RR)	3	0.56 [0.46, 0.67]
3 Main wall material²	3.1 Anaemia in children	3.1.1 Case-control, cross-sectional and cohort studies (crude OR)	1	0.58 [0.33, 1.02]
		3.1.2 Case-control, cross-sectional and cohort studies (adjusted OR)	1	0.57 [0.29, 1.12]
	3.2 Malaria infection	3.2.1 Case-control, cross-sectional and cohort studies (crude OR)	12	0.57 [0.42, 0.78]
		3.2.2 Case-control, cross-sectional and cohort studies (adjusted OR)	7	0.73 [0.62, 0.85]
	3.3 Clinical malaria	3.3.1 Case-control and cross-sectional studies (crude OR)	7	0.63 [0.43, 0.93]
		3.3.2 Case-control and cross-sectional studies (adjusted OR)	1	0.16 [0.06, 0.44]
3.3.3 Cohort studies (crude RR)		1	2.07 [1.18, 3.63]	
3.3.4 Cohort studies (adjusted RR)		2	1.05 [0.48, 2.30]	
4 Main roof material²	4.1 Anaemia in children	4.1.1 Case-control, cross-sectional and cohort studies (crude OR)	1	0.71 [0.45, 1.12]
		4.2 Malaria infection	4.2.1 Case-control, cross-sectional and cohort studies (crude OR)	9
	4.2.2 Case-control, cross-sectional and cohort studies (adjusted OR)		6	0.83 [0.64, 1.08]
	4.3 Clinical malaria	4.3.1 Case-control and cross-sectional studies (crude OR)	4	0.86 [0.48, 1.53]
		4.3.2 Case-control and cross-sectional studies (adjusted OR)	1	0.30 [0.13, 0.66]
		4.3.3 Cohort studies (crude RR)	2	0.59 [0.52, 0.67]
4.3.4 Cohort studies (adjusted RR)		3	0.79 [0.70, 0.88]	
5 Main floor material²	5.1 Anaemia in children	5.1.1 Case-control, cross-sectional and cohort studies (crude OR)	1	0.78 [0.45, 1.34]
		5.2 Malaria infection	5.2.1 Case-control, cross-sectional and cohort studies (crude OR)	1
	5.2.2 Case-control, cross-sectional and cohort studies (adjusted OR)		2	0.74 [0.57, 0.96]
	5.3 Clinical malaria	5.3.1 Case-control and cross-sectional studies (crude OR)	1	0.19 [0.06, 0.57]
5.3.2 Cohort studies (adjusted OR)		1	0.81 [0.62, 1.06]	
6 Eaves³	6.1 Malaria infection	6.1.1 Case-control, cross-sectional and cohort studies (crude OR)	4	0.70 [0.58, 0.84]
		6.1.2 Case-control, cross-sectional and cohort studies (adjusted OR)	3	0.78 [0.70, 0.87]
	6.2 Clinical malaria	6.2.1 Case-control and cross-sectional studies (crude OR)	5	0.76 [0.55, 1.07]
		6.2.2 Case-control and cross-sectional studies (adjusted OR)	1	0.53 [0.36, 0.80]
6.2.3 Cohort studies (crude RR)		1	0.75 [0.50, 1.12]	
6.2.4 Cohort studies (adjusted RR)		2	0.71 [0.46, 1.11]	
7 Ceiling⁴	7.1 Clinical malaria	7.1.1 Case-control and cross-sectional studies (crude OR)	3	0.68 [0.56, 0.83]
		7.1.2 Case-control and cross-sectional studies (adjusted OR)	1	0.65 [0.46, 0.93]
8 Elevation⁵	8.1 Malaria infection	8.1.1 Case-control and cross-sectional studies (crude OR)	1	1.00 [1.00, 1.00]

¹Screened versus unscreened; ²Modern versus traditional main wall, roof and floor material: traditional homes were considered to have mud walls, a thatched roof and earth floors in sub-Saharan Africa (except in areas of high rainfall including Equatorial Guinea, where the basic wall material is typically concrete or wood [226]); mud or stone walls, a thatched, wood or mud roof and earth floors in North Africa; wood or bamboo walls, a thatched roof and wooden (stilted) floors in Southeast Asia [242]; mud or wood walls, a thatched roof and earth or wooden (stilted) floors in South Asia [243]; adobe or mud and wood walls, a thatched roof and earth floors in South America. ³Closed versus open eaves; ⁴Presence versus absence of a ceiling; ⁵Elevated versus non-elevated houses.

4.4. Discussion

In this systematic review and meta-analysis to assess whether modern housing is associated with a lower risk of malaria than traditional housing, 84 observational and six intervention studies were included. In eleven case-control, cohort and cross-sectional studies in East Timor, Egypt, Ethiopia, Greece, Malawi, Sri Lanka, Thailand, Uganda and Yemen, the odds of malaria infection were halved in modern *versus* traditional homes. In one case-control study in Mexico, the odds of clinical malaria were reduced by two thirds. In four cohort studies in Ethiopia, Tanzania and Uganda, the incidence of clinical malaria was halved in modern *versus* traditional homes.

Although house screening was the first intervention trialled against malaria [222], few intervention studies have rigorously evaluated the effect of housing on malaria. Observational studies were therefore also included, which were most likely subject to selection and measurement bias, low comparability between groups, residual confounding by wealth [6], and geographical clustering of socioeconomic status, house design and malaria. Although we found no evidence of publication bias across studies, we had limited power to detect publication bias due to the relatively small number of studies included [235]. Therefore it is highly possible that publication bias, selective outcome reporting, small-study effects, or selective analysis reporting were present across studies. Overall GRADE quality of evidence was judged to be 'very low' to 'low', indicating considerable uncertainty in the estimated effects. Despite this, the relative consistency of the size and direction of effect across studies and settings indicates some protection by modern housing, compared to traditional homes, in urban and rural settings in Africa, Asia and South America. Specifically, wall and roof materials other than traditional wood, mud and thatch, and modern house designs encompassing closed eaves, screened doors and windows, and ceilings, may help reduce mosquito house entry and malaria transmission, and therefore merit further field evaluation.

Good housing can help protect by blocking the entry routes of malaria vectors, which vary by species and region. Overall, the reduced prevalence and incidence of malaria in modern *versus* traditional homes indicates that this classification was a good proxy for overall ease of entry by mosquitoes across different settings. Closed eaves are likely to be protective in SSA since the primary African vector *Anopheles gambiae* s.l. locates hosts by following odour plumes close to the ground and flying upwards when a vertical surface is reached. Open eaves then funnel mosquitoes inside [240]. The presence of a ceiling possibly replicates the protective effect of closed eaves. Conversely, eaves may be less important in South East Asia, where vector entry differs. For example, open verandas are a key feature for house entry by *An. philippinensis* in

Laos PDR [228]. Screening doors and windows can help to directly block vector entry, while modern wall and roof materials may contain fewer gaps, alter the attractiveness of the interior environment to mosquitoes or provide fewer resting sites for mosquitoes than traditional materials such as mud or thatch. It has also been hypothesized that metal-roofed homes are hotter and less conducive for mosquito survival; in Tanzania, the mean physiological age of vectors and sporozoite rate was observed to be lower in more modern *versus* traditional villages [244]. Understanding the mechanism of protection of different house features against individual vectors is important for identifying synergy or discordance with IRS and LLINs.

Housing is incrementally improving across much of SSA as living standards increase. The present analysis suggests that modern house improvements should be further evaluated in relation to malaria, in addition to specific house modifications including screening. If effective, housing could help reduce reliance on insecticides by providing an additional and more permanent intervention where LLINs and IRS are compromised by behavioural and physiological resistant vectors [219]. Furthermore, since malaria has declined in many African countries, often prior to specific intervention, further research to evaluate the contribution of housing improvements and the expansion of urban environments less conducive to malaria transmission is advocated [6]. Improving the home environment aligns with integrated vector management and may help protect against other vector-borne diseases, such as filariasis, cutaneous leishmaniasis, Japanese encephalitis, and dengue, where vectors enter houses [245], and diarrhoeal disease, through better water, sanitation and hygiene (WASH). Since global housing programmes are key strategies of UN-HABITAT and Habitat for Humanity among other organisations, a pipeline for building malaria-safe homes already exists.

Improving housing will not be equally effective everywhere, since outdoor transmission can limit the efficacy of interventions centred on the home. Future research should address questions of equity by investigating whether mosquitoes diverted from improved houses may increase exposure among unprotected neighbours. Potentially damaging health effects must also be considered, such as an increased risk of respiratory diseases if airflow is restricted in the presence of certain cooking fuels. It is also shown here that the evidence base for housing needs strengthening, with only one intervention study that measured clinical outcomes [115]. Therefore further small-scale experimental studies to pinpoint exactly which house features can reduce vector entry cost effectively in different settings, RCTs with epidemiological outcomes, and concurrent studies addressing how to incorporate protective features into local house designs and building regulations are needed.

In conclusion, despite low quality evidence, the direction and consistency of effects indicate that housing is an important risk factor for malaria. Future research should evaluate the protective effect of both specific house features and incremental housing improvements associated with socioeconomic development. Investment in such research and in housing programmes should be considered a natural component of malaria control efforts and a close complement to IVM and WASH as part of long-term, sustainable development.

Acknowledgements

This work was supported by the Malaria Centre at the London School of Hygiene & Tropical Medicine; Leverhulme Centre for Integrative Research in Agriculture and Health; Research and Policy for Infectious Disease Dynamics (RAPIDD) programme of the Science and Technology Directorate, US Department of Homeland Security, the Fogarty International Center (US National Institutes of Health); the Bill & Melinda Gates Foundation (OPP1053338); Novartis Foundation for Sustainable Development; Medical Research Council and Department For International Development. We thank Yanfang Jiang and Margaux Mesle for their help translating papers.

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Student	Lucy S. Tusting
Principal Supervisor	Jo Lines
Thesis Title	Agriculture, development and malaria in rural Uganda

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Date: 30.7.15

Chapter 5. House structure and the risk of malaria in Uganda

Published as: Wanzira H, Tusting LS [equal contributors], Arinaitwe E, Maxwell K, Rek J, Bottomley C, Staedke SG, Kanya M, Dorsey G, Lindsay SW. Mind the gap: house structure and the risk of malaria in Uganda. *PLoS ONE* 2015; **10**: e0117396.

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ABSTRACT

Background: Good house construction may reduce the risk of malaria by limiting the entry of mosquito vectors. We assessed how house design may affect mosquito house entry and malaria risk in Uganda.

Methods: 100 households were enrolled in each of three sub-counties: Walukuba, Jinja district; Kihhi, Kanungu district; and Nagongera, Tororo district. CDC light trap collections of mosquitoes were done monthly in all homes. All children aged six months to 10 years (n=878) were followed prospectively for a total of 24 months to measure parasite prevalence every three months and malaria incidence. Homes were classified as modern (cement, wood or metal walls; and tiled or metal roof; and closed eaves) or traditional (all other homes).

Results: A total of 113,618 female *Anopheles* were collected over 6,765 nights. 6,816 routine blood smears were taken of which 1,061 (15.6%) were malaria parasite positive. 2,582 episodes of uncomplicated malaria were diagnosed after 1,569 person years of follow-up, giving an overall incidence of 1.6 episodes per person year at risk. The human biting rate was lower in modern homes than in traditional homes (adjusted incidence rate ratio (IRR) 0.48, 95% confidence interval (CI) 0.37–0.64, $p < 0.001$). The odds of malaria infection were lower in modern homes across all the sub-counties (adjusted odds ratio 0.44, 95%CI 0.30–0.65, $p < 0.001$), while malaria incidence was lower in modern homes in Kihhi (adjusted IRR 0.61, 95%CI 0.40–0.91, $p = 0.02$) but not in Walukuba or Nagongera.

Conclusions: House design is likely to explain some of the heterogeneity of malaria transmission in Uganda and represents a promising target for future interventions, even in highly endemic areas.

5.1. Background

The population of Africa is expected to double to nearly two billion between 2010 and 2040 and may reach three billion by 2070 [224]. The need to invest in improving and expanding housing options is therefore urgent. Previous studies have demonstrated the importance of house design as a determinant of malaria risk [116, 241, 232] and good house construction could prove an important future supplement to long-lasting insecticide-treated nets (LLINs) and indoor residual spraying (IRS) [221, 193].

House structure is expected to affect malaria transmission since 80–100% of transmission in sub-Saharan Africa occurs indoors [70]. *Anopheles gambiae* s.l., the major African malaria vector, enters houses at night through open eaves, the gap between the top of the wall and the roof [196]. Thus closing the eaves has been observed to be protective against malaria in Ethiopia [246] and The Gambia [114]. Screening external doors and windows is also a simple method to reduce indoor transmission [116, 241]. In a recent randomised controlled trial (RCT) in The Gambia, house screening was associated with a 50% reduction in indoor vector density and a similar 50% reduction in the risk of anaemia in young children [115]. Other potentially protective features include the replacement of thatched roofs with tiled or metal roofs, as observed in Tanzania [247], and the presence of ceilings, as observed in The Gambia [248] and Kenya [165].

In Uganda, new homes are typically constructed with metal roofs, brick or concrete walls and closed eaves replacing the traditional thatched roofs, mud walls and open eaves (Figure 5.1). In urban areas, homes are often built with well-fitted doors and windows to improve security and unscreened airbricks are frequently inserted over doors and windows to cool the interior of these buildings (Figure 5.2). Here we investigated whether modern architectural features are associated with reduced house entry by mosquitoes and malaria risk in children at three sites in Uganda with mixed housing and markedly different malaria transmission levels.



Figure 5.1. Traditional (left) and modern (right) houses in Nagongera, Uganda (S. Lindsay)



Figure 5.2. External (left) and internal (right) view of unscreened airbricks in Uganda

5.2. Methods

Study site: The study was carried out in Walukuba sub-county, Jinja district; Kihhi sub-county, Kanungu district and Nagongera sub-county, Tororo district, between August 2011 and September 2013. There are two rainy seasons (March to May; August to October). Walukuba (00°26'33.2"N, 33°13'32.3"E) is situated near Lake Victoria. Malaria transmission is low with an estimated annual *Plasmodium falciparum* entomological inoculation rate (aPfeIR) of 3.8 infective bites per person per year [174]. The primary malaria vector species is *An. arabiensis* (64%), the remainder being *An. gambiae* s.s. (36%) [174]. Kihhi (00°45'03.1"S, 29°42'03.6"E) is a rural setting in the highlands of western Uganda with moderate malaria transmission and an estimated aPfeIR of 26.6. The primary malaria vector species is *An. gambiae* s.s. (99%) [174]. Nagongera (00°46'10.6"N, 34°01'34.1"E) is a rural setting in south-eastern Uganda characterized by savannah grassland, cultivated crops and rocky outcrops. Malaria transmission is extremely high with an estimated aPfeIR of 125. The primary malaria vector species are *An. gambiae* s.s. (81.5%) and *An. arabiensis* (18.5%) [174]. Rainfall patterns are similar in the three study locations.

Recruitment of study participants: Before the start of the study, a census was conducted in all three sub-counties and a random sample of households selected for screening. From August 2011 to September 2011, children from 100 households randomly selected from the census survey were enrolled into a cohort study and followed for 24 months until September 2013 if

they met the following eligibility criteria: (1) aged six months to less than 10 years, (2) resident of the household selected for recruitment, (3) no intention to move out of the sub-county for the next two years, (4) agreement to attend the study clinic for any febrile illness, (5) agreement to avoid antimalarial medications administered elsewhere and (6) provision of written informed consent. Recruitment was dynamic such that children reaching six months of age and meeting the eligibility criteria were enrolled, and children were withdrawn when they reached eleven years of age. The sample size of 300 children for each site was calculated for a separate study comparing temporal changes in malaria incidence from the cohort studies with temporal changes in malaria test positivity rate from health facility based surveillance. The analysis described here is a secondary analysis making use of these data sets.

Baseline assessment and follow-up of study participants: At enrolment, a baseline clinical evaluation was conducted and study participants were given a LLIN (PermaNet[®], Vestergaard Frandsen, Switzerland). Parents of participants were requested that their children attend the designated study clinic, open seven days a week, for all healthcare needs. Subjects presenting with a fever or history of fever within the past 24 hours with a positive blood smear were diagnosed with malaria. Episodes of uncomplicated malaria were treated with artemether-lumefantrine and complicated episodes treated with quinine. New episodes of malaria were diagnosed by passive case detection and malaria episodes defined as any treatment for malaria. Routine visits were conducted at the study clinic every three months, with a standard evaluation including a thick blood smear to assess for parasitaemia.

Microscopy: Thick and thin blood smears were stained with 2% Giemsa and read blind. Blood smears were considered negative when the examination of 100 high power fields did not reveal asexual parasites. All slides were read twice and discrepancies resolved by a third reviewer. In addition, all positive blood smears with a parasite densities $\leq 20,000/\mu\text{l}$ based on the field readings were re-read by an expert microscopist based in Kampala and had to be confirmed to be considered positive in the final analyses.

Entomology: Detailed descriptions of the entomological studies are provided elsewhere [174]. In brief, CDC light trap collections were done monthly in each house for 24 months. Occupants were given a LLIN (PermaNet[®], Vestergaard Frandsen, Switzerland) and the light trap positioned with the light 1.5m from the floor near the foot of the bed. Collections were made between 19.00h and 07.00h the following morning. Specimens were sorted to species level and counted.

Household surveys: Each household was visited at baseline and a questionnaire administered to the head of the household to record data on features of the house (main materials of the wall, roof and floor), which were independently validated by field assistants, together with household demographics and proxy wealth indicators.

Statistical analysis: Data were collected using a paperless system for the household survey and using standardized case record forms entered into Microsoft Access for follow-up of study participants. Analyses were performed with Stata Version 13 (StataCorp, Texas). Missing data were excluded from the analysis.

Wealth index and household characteristics: Principal component analysis (PCA) was used to create a wealth index from 10 factors [249]: ownership of (1) mobile telephones, (2) radios, (3) clocks, (4) cupboards, (5) tables, (6) bicycles; (7) number of days that meat was consumed in the past week (<2 versus ≥ 2 days), (8) difficulty in getting food to eat (sometimes, often or always versus seldom or never), (9) toilet access (no facility, a composting toilet or uncovered pit latrine, versus a covered pit latrine or flush toilet) and (10) main mode of transport to the health facility (walking versus other). Within each study site households were ranked by wealth scores and site-specific tertiles created to provide a categorical measure of socioeconomic position (SEP). Household characteristics were compared between sites using the chi-square test.

Entomological and epidemiological outcomes: Main wall material, main roof material and eave type were used to classify homes as either modern (wood, cement or brick walls; and metal or tiled roof; and closed eaves) or traditional (all other homes). Negative binomial regression was used to model the relationship between household risk factors and the number of *Anopheles* caught per house by light trap catches, with the number of sampling nights included as an offset term in the model. The odds of malaria infection at the time of each routine clinic visit was modelled using logistic regression and negative binomial regression used to model the number of malaria cases per child. Robust standard errors were used to adjust for clustering due to household in both models. We estimated an incidence rate ratio (IRR) for the association between house type and human biting rate (HBR) adjusted for SEP; and an odds ratio (OR) and IRR for the association between house type and malaria adjusted for age, gender and SEP. The associations were analysed separately for each study site and Wald tests were used to test for effect modification by study site.

Ethics: Written informed consent was obtained in the appropriate language from guardians for the participation of their child and from an adult household member for the light trap catches and household surveys. Approval from local leaders was obtained before beginning activities. Ethics approval was provided by the Uganda National Council for Science and Technology; Makerere University School of Medicine Research and Ethics Committee; University of California, San Francisco Committee for Human Research; and the London School of Hygiene and Tropical Medicine Ethics Committee.

5.4. Results

Study population: In total 878 children were enrolled; 251 in Walukuba, 327 in Kihhi and 300 in Nagongera (Figure 5.3; Table 5.1). The mean age of participants during follow-up was five years and 428 (48.8%) were female. Overall, 103 of 300 (34.3%) homes were classified as modern (with cement, wood or metal walls, tiled or metal roofs and closed eaves), 114 (38.0%) had unscreened airbricks and 21 (7.0%) had screened airbricks. Homes in peri-urban Walukuba were generally of better quality than those in rural Kihhi and Nagongera (Table 5.1).

Wealth index: The first principal component explained 21.5% of the overall variability in the asset variables. The weight assigned to each variable was: radio ownership (0.43), table ownership (0.41), cupboard ownership (0.39), mobile ownership (0.34); frequency of problems satisfying food needs (0.33), toilet access (0.33), clock ownership (0.32), bicycle ownership (0.18), main mode of transport to health facility (0.14), and meat consumption (0.12).

HBR: 113,618 adult female *Anopheles* were collected over 6,765 nights of collection. Data were missing for one household. Overall, HBR was highest in Nagongera (43.3 adult female *Anopheles* per house per night) and lower in Kihhi (4.6) and Walukuba (1.1). In Kihhi and Nagongera, HBR was lower in homes with tiled or metal roofs and homes with cement, wood or metal walls (Table 5.2). In all sites HBR was lower in houses with closed eaves than houses with open eaves, and in houses with screened or unscreened airbricks compared to houses with no airbricks. There was no evidence that the association between house type and HBR varied with site. Controlling for site and SEP, HBR was 52% lower in modern homes compared with traditional homes (IRR 0.48, 95% confidence intervals (CI) 0.37–0.64, $p < 0.001$, Figure 5.4).

Parasite prevalence: 6,816 routine blood smears were taken of which 1,061 (15.6%) were positive. All children contributed at least one routine blood smear. *PfPR* was highest in Nagongera (28.7%) and lower in Kihhi (9.4%) and Walukuba (7.4%). The association between house type and odds of malaria infection varied by site ($p < 0.001$). Controlling for age, gender

and SEP, the odds of malaria infection were lower in children living in modern homes than in traditional homes in Walukuba (OR 0.35, 95%CI 0.13–0.92, $p=0.03$), Kihihi (OR = 0.27, 95%CI 0.10–0.71, $p=0.008$) and Nagongera (OR 0.59, 95%CI 0.38–0.90, $p=0.01$) (Table 5.3). Overall, controlling for age, gender, site and SEP, the odds of malaria infection were 56% lower in children living in modern homes (OR 0.44, 95%CI 0.30–0.65, $p<0.001$).

Incidence of clinical malaria: 2,582 episodes of uncomplicated malaria were diagnosed after 1,569 person years of follow-up, yielding an overall incidence of 1.6 episodes per person year at risk (PPY). Five participants were withdrawn immediately after screening and did not contribute person years at risk. Incidence was highest in Nagongera (2.8 episodes PPY) and lower in Kihihi (1.4) and Walukuba (0.4). The association between house type and malaria incidence varied by site ($p<0.001$). Controlling for age, gender and SEP, malaria incidence was 39% lower in children living in modern homes in Kihihi (IRR 0.61, 95%CI 0.40–0.91, $p=0.02$) but not in Walukuba or Nagongera (Table 5.4).

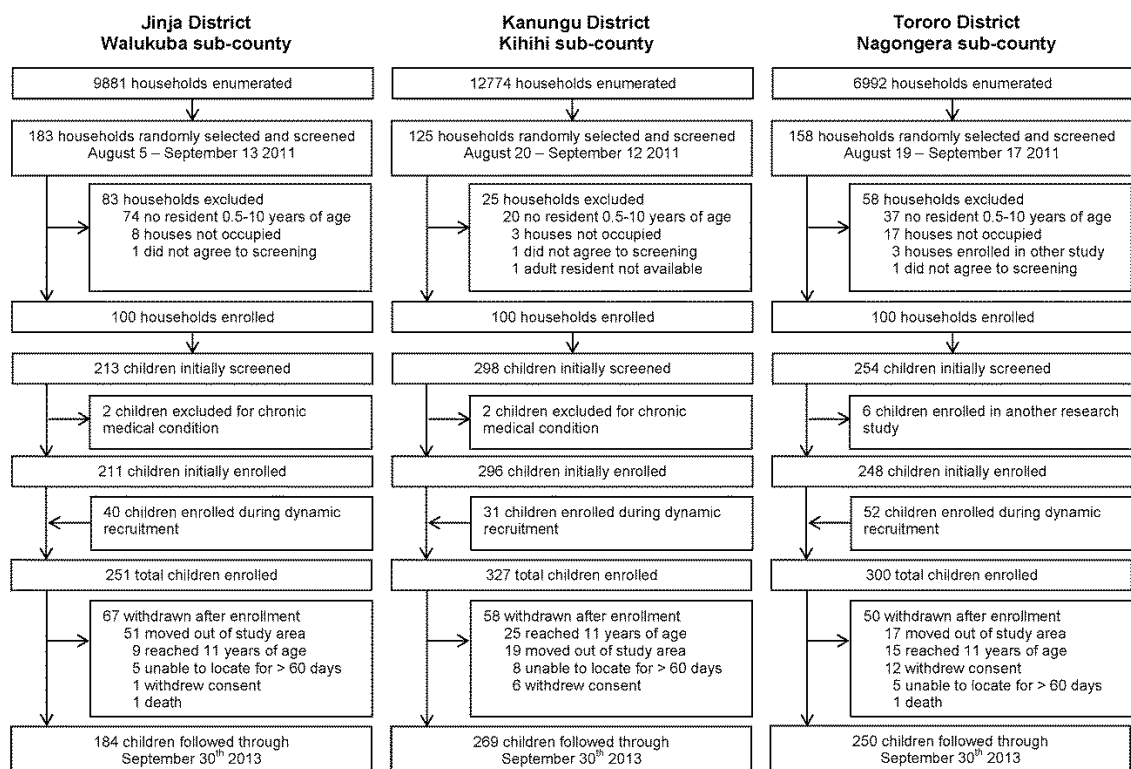


Figure 5.3. Study profile for a cohort study at three sites in Uganda

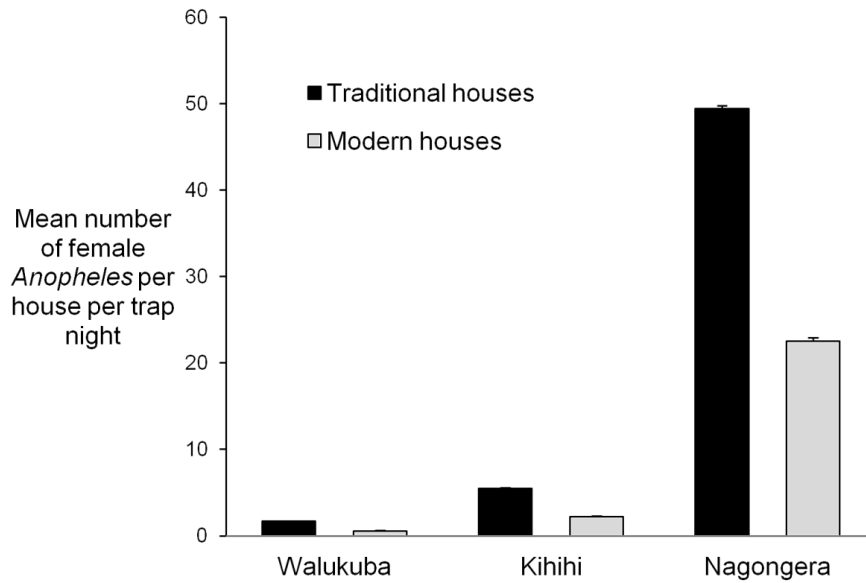


Figure 5.4. Mean human biting rate (*Anopheles* spp) in houses at three sites in Uganda. Modern houses were classified as those with a cement, wood or metal wall; tiled or metal roof and closed eaves. All other houses were classified as traditional. Error bars represent upper 95% confidence intervals.

Table 5.1. Characteristics of study participants and households at three sites in Uganda

Characteristic	All sites	Individual study sites			P	
		Walukuba	Kihihi	Nagongera		
Individual study participant level data						
Number of children	878	251	327	300	–	
Mean age in years during follow up (95% CI ^a)	5.4 (5.2–5.6)	5.0 (4.7–5.4)	5.6 (5.3–5.9)	5.4 (5.1–5.8)	0.06	
Female participants (%)	428 (48.8%)	127 (50.6%)	165 (50.5%)	136 (45.3%)	0.35	
Individual household level data						
Number of households	300	100	100	100	–	
Wealth index, stratified by study site (%)	Poorest tertile	34.7	34	36	34	0.98
	Medium tertile	34.3	35	35	33	
	Highest tertile	31.0	31	29	33	
Main floor material (%)	Earth, sand, dung or stones	69.7	48	77	84	<0.001
	Wood, bricks or cement	30.3	52	23	16	
Main roof material (%)	Thatched	17.7	2	13	38	<0.001
	Tiles or metal	82.3	98	87	62	
Main wall material (%)	Mud	60.7	35	70	77	<0.001
	Cement, wood or metal	39.3	65	30	23	
Eaves (%)	Open	33.7	28	25	48	0.001
	Closed	66.3	72	75	52	
Airbricks (%)	None	55.0	68	27	70	<0.001
	Unscreened	38.0	14	72	28	
	Screened	7.0	18	1	2	
House type (%)	Traditional	65.7	49	71	77	<0.001
	Modern ^b	34.3	51	29	23	

^aCI: Confidence interval.^bCement, wood or metal wall; tiled or metal roof and closed eaves.

Table 5.2. Association between household characteristics and the human biting rate at three sites in Uganda

Characteristic	Walukuba			Kihhi			Nagongera			
	HBR ^a (Total collection nights)	IRR (95% CI) ^b	p	HBR (Total collection nights)	IRR (95% CI) ^b	p	HBR (Total collection nights)	IRR (95% CI) ^b	p	
Wealth index, stratified by study site	1 st tertile	1.97 (692)	1	–	7.92 (830)	1	–	49.24 (787)	1	–
	2 nd tertile	0.75 (777)	0.30 (0.18–0.52)	<0.001	2.58 (795)	0.33 (0.20–0.56)	<0.001	40.57 (785)	0.79 (0.58–1.07)	0.13
	3 rd tertile	0.58 (715)	0.25 (0.14–0.43)	<0.001	2.78 (627)	0.38 (0.22–0.66)	0.001	40.02 (757)	0.76 (0.56–1.04)	0.09
Main floor material	Earth, sand, dung or stones	1.76 (1010)	1	–	5.32 (1778)	1	–	46.93 (1966)	1	–
	Wood, bricks or cement	0.49 (1174)	0.25 (0.16–0.40)	<0.001	1.93 (474)	0.38 (0.22–0.65)	0.001	23.74 (363)	0.49 (0.35–0.68)	<0.001
Main roof material	Thatched	1.17 (48)	1	–	8.95 (307)	1	–	54.38 (872)	1	–
	Tiles or metal	1.08 (2136)	1.07 (0.18–6.36)	0.94	3.92 (1945)	0.43 (0.22–0.86)	0.02	36.70 (1457)	0.65 (0.50–0.83)	0.001
Main wall material	Mud	1.65 (698)	1	–	5.52 (1636)	1	–	49.42 (1800)	1	–
	Cement, wood or metal	0.81 (1486)	0.63 (0.37–1.06)	0.08	2.18 (616)	0.40 (0.24–0.66)	<0.001	22.54 (529)	0.45 (0.34–0.58)	<0.001
Eaves	Open	1.73 (616)	1	–	7.63 (579)	1	–	53.86 (1109)	1	–
	Closed	0.83 (1568)	0.39 (0.23–0.67)	0.001	3.56 (1673)	0.45 (0.27–0.77)	0.004	33.74 (1220)	0.60 (0.48–0.77)	<0.001
Airbricks	None	1.39 (1456)	1	–	7.50 (608)	1	–	48.48 (1615)	1	–
	Unscreened	0.56 (321)	0.34 (0.17–0.68)	0.002	3.58 (1621)	0.48 (0.29–0.80)	0.005	33.44 (667)	0.68 (0.52–0.89)	0.004
	Screened	0.39 (407)	0.26 (0.14–0.49)	<0.001	0.43 (23)	0.06 (0.01–0.65)	0.02	6.21 (47)	0.13 (0.05–0.30)	<0.001
House type ^c	Traditional	1.68 (1010)	1	–	5.46 (1659)	1	–	49.42 (1800)	1	–
	Modern ^d	0.57 (1174)	0.49 (0.28–0.85)	0.01	2.21 (593)	0.54 (0.30–0.98)	0.04	22.54 (529)	0.45 (0.34–0.61)	<0.001

^aHBR: Human biting rate, adult female anopheles collected per house per night (total adult female anophelines caught / total nights of collection).

^bIRR: Incidence rate ratio; CI: Confidence interval.

^cIRR adjusted for socioeconomic position.

^dCement, wood or metal wall; tiled or metal roof and closed eaves.

Table 5.3. Risk factors for malaria infection in children aged 6 months to 10 years at three sites in Uganda

Characteristic	Walukuba			Kihhi			Nagongera			
	PR ^a (Total blood smears)	OR (95% CI) ^b	p	PR (Total blood smears)	OR (95% CI)	p	PR (Total blood smears)	OR (95% CI)	p	
Age at time of blood smear	6m to <3 years	5.3 (455)	1	-	6.0 (598)	1	-	18.5 (491)	1	-
	3 to <5 years	8.4 (441)	1.64 (0.88-3.06)	0.12	8.8 (543)	1.51 (0.88-2.61)	0.14	27.0 (514)	1.63 (1.13-2.35)	0.01
	5 to <11 years	8.0 (929)	1.55 (0.88-2.75)	0.13	10.9 (1470)	1.91 (1.17-3.12)	0.01	32.9 (1375)	2.15 (1.55-2.99)	<0.001
Gender	Female	6.4 (909)	1	-	7.9 (1274)	1	-	27.4 (1077)	1	-
	Male	8.4 (916)	1.35 (0.89-2.04)	0.16	10.8 (1337)	1.42 (0.97-2.08)	0.08	29.7 (1303)	1.12 (0.88-1.43)	0.37
Wealth index, stratified by study site	1 st tertile	8.4 (526)	1	-	13.5 (1001)	1	-	33.3 (771)	1	-
	2 nd tertile	7.0 (616)	0.82 (0.38-1.78)	0.62	7.8 (883)	0.54 (0.28-1.06)	0.07	26.6 (888)	0.72 (0.50-1.04)	0.08
	3 rd tertile	7.0 (683)	0.83 (0.31-2.18)	0.70	5.5 (727)	0.37 (0.20-0.71)	0.003	26.2 (721)	0.71 (0.47-1.07)	0.10
Main floor material	Earth, sand, dung or stones	10.0 (869)	1	-	10.6 (2130)	1	-	30.0 (2113)	1	-
	Wood, bricks or cement	5.0 (956)	0.48 (0.23-0.99)	0.05	3.7 (481)	0.33 (0.13-0.80)	0.01	18.4 (267)	0.53 (0.36-0.76)	0.001
Main roof material	Thatched	7.4 (27)	1	-	16.6 (314)	1	-	24.5 (918)	1	-
	Tiles or metal	7.4 (1798)	1.00 (0.34-2.92)	0.99	8.4 (2297)	0.46 (0.23-0.92)	0.03	31.3 (1462)	1.40 (1.05-1.87)	0.02
Main wall material	Mud	9.3 (589)	1	-	11.6 (1982)	1	-	30.5 (1977)	1	-
	Cement, wood or metal	6.5 (1236)	0.67 (0.33-1.37)	0.27	2.4 (629)	0.19 (0.07-0.49)	0.001	19.6 (403)	0.56 (0.37-0.84)	0.01
Eaves	Open	10.8 (518)	1	-	17.3 (648)	1	-	27.7 (1161)	1	-
	Closed	6.0 (1307)	0.53 (0.23-1.21)	0.13	6.7 (1963)	0.35 (0.20-0.60)	<0.001	29.5 (1219)	1.09 (0.80-1.49)	0.58
Airbricks	Unscreened	6.3 (256)	1	-	7.3 (1924)	1	-	27.3 (634)	1	-
	Screened	3.6 (331)	0.56 (0.13-2.54)	0.46	0 (10)	-	-	11.1 (18)	0.33 (0.07-1.66)	0.18
	None	8.6 (1238)	1.42 (0.43-4.67)	0.57	15.2 (677)	2.27 (1.30-3.98)	0.004	29.3 (1728)	1.11 (0.75-1.63)	0.61
House type ^c	Traditional	10.7 (857)	1	-	11.4 (2017)	1	-	30.5 (1977)	1	-
	Modern ^d	4.4 (968)	0.35 (0.13-0.92)	0.03	2.5 (594)	0.27 (0.10-0.71)	0.008	19.6 (403)	0.59 (0.38-0.90)	0.01

^aPR: Parasite rate (total positive blood smears / total blood smears); N: total blood smears.

^bOR: Odds ratio; CI: Confidence interval.

^cOR adjusted for age at the time of the blood smear, gender and socioeconomic position.

^dCement, wood or metal wall; tiled or metal roof and closed eaves.

Table 5.4. Risk factors for clinical malaria in children aged 6 months to 10 years at three sites in Uganda

Characteristic		Walukuba			Kihhi			Nagongera		
		Malaria incidence ^a (total person years)	IRR (95% CI) ^b	p	Malaria incidence (total person years)	IRR (95% CI)	p	Malaria incidence (total person years)	IRR (95% CI)	p
Mean age during follow-up	6m to <3 years	0.40 (106.0)	1	-	1.58 (139.4)	1	-	4.27 (110.8)	1	-
	3 to <5 years	0.62 (93.6)	1.59 (0.92-2.73)	0.10	1.77 (104.0)	1.10 (0.77-1.55)	0.61	3.64 (110.1)	0.86 (0.73-1.02)	0.08
	5 to <11 years	0.37 (223.1)	0.90 (0.61-1.34)	0.62	1.28 (352.9)	0.79 (0.60-1.03)	0.08	2.04 (328.8)	0.48 (0.40-0.58)	<0.001
Gender	Female	0.41 (209.8)	1	-	1.24 (290.4)	1	-	2.51 (248.2)	1	-
	Male	0.45 (212.8)	1.13 (0.73-1.74)	0.59	1.62 (305.9)	1.30 (1.01-1.68)	0.04	3.06 (301.5)	1.24 (1.03-1.49)	0.02
Wealth index, stratified by study site	1 st tertile	0.63 (120.8)	1	-	1.85 (227.5)	1	-	3.03 (178.0)	1	-
	2 nd tertile	0.40 (142.4)	0.63 (0.31-1.28)	0.20	1.54 (203.7)	0.84 (0.60-1.19)	0.33	3.06 (204.3)	1.00 (0.77-1.28)	0.98
	3 rd tertile	0.31 (159.4)	0.49 (0.27-0.87)	0.02	0.73 (165.1)	0.39 (0.26-0.60)	<0.001	2.27 (167.4)	0.72 (0.53-0.98)	0.04
Main floor material	Earth, sand, dung, stones	0.52 (201.0)	1	-	1.55 (486.8)	1	-	2.88 (487.3)	1	-
	Wood, bricks or cement	0.35 (221.6)	0.68 (0.40-1.17)	0.17	0.91 (109.5)	0.58 (0.39-0.86)	0.01	2.26 (62.4)	0.78 (0.49-1.24)	0.30
Main roof material	Thatched	0.63 (6.3)	1	-	2.63 (72.0)	1	-	3.14 (211.5)	1	-
	Tiles or metal	0.43 (416.3)	0.70 (0.49-1.02)	0.06	1.27 (524.4)	0.49 (0.31-0.76)	0.002	2.61 (338.1)	0.82 (0.66-1.02)	0.07
Main wall material	Mud	0.56 (135.0)	1	-	1.66 (453.6)	1	-	2.89 (455.6)	1	-
	Cement, wood or metal	0.37 (287.7)	0.65 (0.36-1.17)	0.15	0.71 (142.7)	0.42 (0.28-0.64)	<0.001	2.44 (94.1)	0.84 (0.57-1.24)	0.39
Eaves	Open	0.49 (120.5)	1	-	2.10 (148.9)	1	-	2.98 (267.9)	1	-
	Closed	0.41 (302.2)	0.81 (0.43-1.51)	0.50	1.21 (447.4)	0.59 (0.40-0.86)	0.01	2.65 (281.7)	0.89 (0.72-1.11)	0.30
Airbricks	Unscreened	0.43 (59.9)	1	-	1.15 (439.1)	1	-	2.66 (147.4)	1	-
	Screened	0.29 (76.7)	0.63 (0.23-1.77)	0.38	0.00 (2.1)	-	-	1.45 (4.1)	0.55 (0.21-1.43)	0.22
	None	0.47 (286.1)	1.03 (0.50-2.12)	0.93	2.26 (155.2)	1.92 (1.35-2.73)	<0.001	2.88 (398.1)	1.09 (0.83-1.43)	0.54
House type ^c	Traditional	0.53 (197.2)	1	-	1.63 (461.7)	1	-	2.89 (455.6)	1	-
	Modern ^d	0.35 (225.4)	0.80 (0.46-1.39)	0.43	0.74 (134.6)	0.61 (0.40-0.91)	0.02	2.44 (94.1)	0.90 (0.63-1.28)	0.55

^aMalaria incidence per person years (new malaria episodes/person years of observation)

^bIRR: Incidence rate ratio; CI: Confidence interval.

^cIRR adjusted for mean age during follow up, gender and socioeconomic position.

^dCement, wood or metal wall; tiled or metal roof and closed eaves.

5.4. Discussion

We investigated the association between house construction and malaria at three sites in Uganda: peri-urban Walukuba with low malaria transmission, rural Kihhi with moderate transmission and rural Nagongera with high transmission. Modern homes were associated with a 52% reduction in HBR after controlling for site and SEP. Similarly, the odds of malaria infection were 56% lower in children living in modern homes than those living in traditional homes, after controlling for age, gender, site and SEP. These results show that reducing vector biting rates by half is associated with a similar proportional reduction in malaria infection. A similar result was found in a RCT of house screening in The Gambia which showed that house screening reduced malaria transmission by half, with a similar reduction in malaria anaemia risk [115].

Our findings suggest that good house construction may help protect against malaria in Uganda by reducing house entry by vectors. HBR was highest in homes with mud walls, thatched roofs and open eaves, consistent with the house-entering behaviour of *An. gambiae*. This vector follows human odour plumes until it reaches an external house wall, flies upwards and, funnelled by the inclined roof, enters the house through open eaves [114, 196]. Homes with earth, sand, dung or stone flooring were also crudely associated with a higher HBR and odds of malaria infection than homes with wood, brick or cement floors, perhaps because they are more likely to contain moist, odorous convection currents. Surprisingly, HBR was higher in homes with no airbricks than homes with unscreened airbricks, most likely because houses with airbricks are typically those built in a more modern style, with fewer overall entry points. Screening air bricks with fly mesh to further reduce indoor mosquito density could be further investigated as a cheap and simple additional intervention in well-built homes.

Heterogeneity in malaria transmission at small spatial scales is not only driven by environmental factors such as proximity to larval habitats, but also wealth inequalities [250]. The odds of malaria infection are approximately doubled in the poorest children compared to the wealthiest children within a community [6]. While the exact mechanism for this is unknown, wealthier homes may have improved ownership and use of LLINs [105], better access to chemoprophylaxis and treatment [188], better nutrition and improved treatment-seeking behaviour and health expenditure [7], in addition to better housing [3]. Our findings are consistent with the hypothesis that housing may contribute to socioeconomic inequalities in malaria risk.

We also observed that the association between house type and malaria prevalence and incidence varied by site. This effect modification might be explained by differences in the

average quality of homes between sites and a community-level protective effect of good housing. Malaria transmission is generally lower in urban than rural Africa [36] because the built-up environment is less conducive to breeding by *An. gambiae*, urban populations generally have better access to prophylaxis and treatment and individual exposure to infectious bites declines with increasing population density [149, 36]. The lower HBR and associated burden of malaria observed in peri-urban Walukuba, compared to rural Kihhi and Nagongera, is consistent with the quality of homes in Walukuba being generally higher than the other sites.

Reducing the number of entry points into a house is not a panacea. Most obviously, interventions built into the home do not protect against outdoor transmission [251]. We observed an association between house type and malaria incidence only in Kihhi, where 99% of transmission is by *An. gambiae s.s.*, a highly endophagic vector. In contrast, no association was observed in Walukuba, where 64% of malaria vectors are the less endophagic *An. arabiensis*, nor in Nagongera, where 19% vectors are *An. arabiensis*. Screening interventions also may not be as effective against culicine mosquitoes as *An. gambiae*, reducing their potential appeal to homeowners. Moreover, restricting air flow in homes may increase the internal temperature and the risk from respiratory diseases, especially if wood is burned indoors [252]. However, houses with metal roofs, closed eaves, tightly fitting doors and windows and air bricks are considered desirable, and are being built today on a massive scale [221]. Screening should be further evaluated as a potentially simple and cheap means to reduce malaria risk.

Our findings may also not be generalisable to other countries with different house styles and vector ecology. Furthermore, the observed association between house type and malaria risk is not evidence of causality. Indeed, since the direct and indirect costs of malaria can contribute to poverty within a household [215], especially in low-income settings lacking social security systems, a high malaria burden could plausibly be associated with poorer housing, through its effect on household disposable income and the affordability of building materials. Yet the elevated HBR observed in homes with mud walls, thatched roofs and open eaves is consistent with a direct causal link between house quality and malaria transmission. Household welfare is important to quantify accurately, since house construction is related to wealth, however the ranking of households in our wealth index will have been affected by the indicators selected into the PCA [253]. House design was also assessed only at baseline, without measurement of incremental improvements subsequently accrued. Nonetheless our observations are consistent with an increasing body of work that demonstrates that house features affect mosquito-house entry [232, 221].

In conclusion, we provide evidence that house structure may explain some of the often marked heterogeneity of transmission in Uganda. Improving house design should be evaluated further as a potential malaria control intervention in SSA, even in areas of very high transmission.

Acknowledgements

We are grateful to the study participants and their families. We thank the Infectious Diseases Research Collaboration (IDRC) for administrative and technical support.

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Date: 30.7.15

Chapter 6. Measuring socioeconomic inequalities in relation to malaria risk: comparison of metrics in rural Uganda

Submitted as: Tusting LS, Rek JC, Arinaitwe E, Staedke SG, Kanya M, Bottomley C, Lines J, Johnston D, Dorsey G, Lindsay SW. Measuring socioeconomic inequalities in relation to malaria risk in Uganda.

ABSTRACT

Background: Poverty is an important risk factor for malaria. However, there is little consensus on how best to measure poverty in malaria studies in rural African communities. Here we evaluate the agreement between four indicators of socioeconomic position (SEP) and explore their relative strength in predicting malaria risk in children in Nagongera, Uganda.

Methods: Socioeconomic information was collected for 318 children living in 100 households, who were followed for 36 months. Mosquito density was measured using monthly light trap collection. Parasite prevalence was recorded routinely every three months and malaria incidence measured by passive case detection. SEP was determined using: (1) two wealth indices derived from principal component analysis, (2) income, (3) occupation and (4) education. Wealth Index I (reference) included asset ownership and access to infrastructure variables alone. Wealth Index II additionally included food security and house construction variables; which are often included in wealth indices but may directly affect malaria risk. Indicators were assessed in terms of: (1) relative agreement and (2) their prediction of malaria risk.

Results: Wealth Index I was strongly correlated with Wealth Index II and income but not occupation. In multivariate analysis, only Wealth Index II and income from remittances were associated with the human biting rate, only the wealth indices were consistently associated with parasite prevalence (highest vs lowest tertile Wealth Index I: adjusted odds ratio (aOR) 0.57, 95% confidence intervals (CI) 0.40-0.82, $p=0.003$; Wealth Index II: aOR 0.57, 95%CI 0.40-0.82, $p=0.002$) and only female caregiver's education was associated with malaria incidence (attended vs never attended school: adjusted incidence rate ratio 0.70, 95%CI 0.49-0.98, $p=0.04$). There was no consistent association between occupation and malaria outcomes.

Conclusions: In this setting, wealth indices, income and education were stronger predictors of socioeconomic differences in malaria risk than occupation. The wealth index was still a predictor of malaria risk after excluding variables directly associated with malaria, but the strength of association was lower.

6.1. Background

Malaria is closely associated with poverty, with the odds of malaria infection doubled on average in the poorest children within a community compared with the least poor [6].

Measuring socioeconomic position (SEP), the suite of social and economic factors that determine the position held by individuals and groups within a society [176, 171], is therefore critical both to studying the socioeconomic determinants of malaria and to most observational malaria research, since SEP confounds many relationships. However, as for many other health outcomes [254, 255], the relative strength of metrics for evaluating the association between SEP and malaria has been little considered.

SEP can be measured directly using household consumption, expenditure or income, or indirectly using proxy metrics such as wealth indices, occupation, household vulnerability and education [197]. Consumption is generally considered to be the 'gold standard' since it is the most direct indicator of SEP, is accurate to measure and is relatively stable over time, yet it is expensive to collect, requiring detailed data on rental income, reported household consumption and fees from durable items owned [256, 257]. Household income is another direct indicator of SEP, generally adjusted for household size and composition, but also requires lengthy interviewing, is difficult to measure when derived from multiple sources and is subject to temporal fluctuation [258, 259].

Wealth indices derived from assets have been developed as an alternative to consumption and are widely used as indirect metrics of SEP in malaria studies since they are simple to do and less subject to reporting biases. Wealth indices can have similar predictive values to consumption in estimating the relationship between SEP and health outcomes [249, 253, 260, 197]. However, findings can be affected by the weighting strategy and choice of included assets [178]. For example, the inclusion of assets in the wealth index that are associated directly with the outcome of interest can increase the association between SEP and the outcome of interest [253]. This is often relevant to malaria; for instance, house construction materials are sometimes included in wealth indices, especially if the Demographic and Health Survey (DHS) model is used [261]. Yet house construction may be independently assessed as a risk factor for malaria, since it can influence house entry by mosquito vectors [19]. SEP may also be measured indirectly using classes of occupation, as in the DHS [262], and education, typically by measuring years of formal education completed, qualifications attained or literacy [263, 264].

Previous studies of health inequalities have compared the household rankings produced by different SEP indicators [253, 178, 265-268] and evaluated the association of different indicators with specific health outcomes [178, 269-271]. However, to our knowledge, only one study has previously evaluated indicators for measuring socioeconomic inequalities in relation to malaria risk [272]. In that study, three indices were developed using data from 25 Tanzanian villages: a consumption index and two wealth indices derived from principal component analysis (PCA). Little difference was found between household rankings from the two wealth indices while a weak relationship was found between the wealth index and consumption index, with the households rankings based on PCA less discriminatory than those based on consumption. However, a higher score in both the consumption and wealth index was associated with a reduced risk of malaria infection, indicating that the wealth index was a reasonable empirical and logistical alternative to consumption in that context [272].

In the present study we evaluate the agreement between four indicators of socioeconomic position (SEP) and explore how the risk of malaria in children varies with these indicators in Nagongera, rural Uganda. The four indicators compared are: (1) two wealth indices derived from PCA, (2) income, (3) occupation and (4) female caregiver's education. To our knowledge, this is the first evaluation of metrics other than wealth indices and consumption indices for measuring the association between SEP and malaria.

6.2. Methods

Study site: The study was carried out between August 2011 and September 2014 in Nagongera sub-country, Tororo district, Uganda (00°46'10.6"N, 34°01'34.1"E). Rainfall is bimodal, with long rains from March to June and short rains from August to December. Malaria transmission is intense with an estimated annual *Plasmodium falciparum* entomological inoculation rate of 125 [174]. *Anopheles gambiae* sensu stricto (81.5%) and *An. arabiensis* (18.5%) are the primary vectors.

Data source: This study was part of a cohort study described elsewhere [174, 173]. All children aged six months to 10 years and their primary caregivers were enrolled from 100 randomly selected households in Nagongera in August-September 2011. Recruitment was dynamic, such that children reaching six months of age and meeting the eligibility criteria were enrolled and children reaching 11 years were withdrawn. Households with no remaining study participants were withdrawn and seven additional households recruited in September 2013. Participants were followed for all their health care needs at the designated study clinic in Nagongera for 36

months, until September 2014. Outcomes measured were: (1) human biting rate (HBR), measured by one night of CDC light trap catches per month in each home, (2) prevalence of parasitaemia measured routinely every three months and confirmed by microscopy and (3) incidence of all malaria episodes measured by passive case detection.

Household and women's surveys: Data on indicators of SEP were collected from three surveys: (i) a baseline household survey conducted at the time of enrolment, (ii) a second household survey conducted after 24 months of follow-up in September-October 2013 and (iii) a women's survey, administered as a separate structured questionnaire after the second household survey. Both household surveys were administered as a structured interview by trained study staff to one designated adult respondent from each household, if they met four inclusion criteria: (1) usual male or female resident, (2) present in the sampled household the night before the survey, (3) aged at least 18 years and (4) agreement to provide informed written consent. The women's survey was administered to all women of childbearing age (18-49 years), resident in each study household, who met three inclusion criteria: (1) usual female resident, (2) present in the sampled household the night before the survey, (3) agreement to provide informed written consent. Households were excluded if no adult respondent could not be located on more than three occasions over two weeks.

Variables for the wealth indices were collected in the first household survey (main mode of transport to the health facility) and in the second household survey (all other wealth index variables). House construction was recorded through separate house visits by the entomology field teams during 2013 and confirmed by the second household survey. Household income and occupation were measured in the second household survey. Educational status of each child's mother or the eldest female caregiver in each child's household was recorded in the women's survey.

Data analysis:

Data were collected using standardized case record forms entered into Microsoft Access for follow-up of study participants and using a paperless system for the household and women's surveys. Analyses were performed with Stata Version 13 (StataCorp, Texas).

Wealth indices: Two wealth indices were produced using PCA [249]. Overall there remains a paucity of underlying theory to support the choice of variables for PCA [259]. We based our collection of data on candidate PCA variables on a literature review, the 2006 Uganda

Demographic and Health Survey and the 2009 Uganda Malaria Indicator Survey [175, 273]. To avoid a narrow or skewed distribution of wealth index scores [274], we aimed to include a balance of variables on asset ownership and access to infrastructure [275].

For Wealth Index I, the following variables were included in the PCA: ownership of a (1) radio, (2) mobile telephone, (3) table, (4) cupboard, (5) clock and (6) sofa; (7) people per sleeping room; (8) access to an improved toilet and (9) main mode of transport to the health facility. Wealth indices often include food security and house construction variables [31], but these factors may be independently associated with malaria in the study area [22, 18]. Therefore, to evaluate whether including food security and house construction variables altered the association between the wealth index and malaria outcomes, Wealth Index II additionally included five variables: (10) main roof material, (11) main wall material, (12) main floor material, (13) frequency of meat consumption and (14) number of meals per day. Households were ranked by wealth scores and grouped into tertiles. This was done for both wealth indices to give two categorical measures of SEP. Standardised, continuous wealth index scores were created by subtracting mean index scores and dividing by the standard deviation. Additionally, the association between Wealth Index I and the five variables additionally included in Wealth Index II was assessed using Pearson's chi-square test.

Agreement between SEP indicators: Rankings of households by Wealth Index I and II were compared using kappa coefficients and Spearman rank correlation coefficients. Cross tabulations and Pearson's chi-square test were used to explore the associations between household-level indicators of SEP and tertiles of Wealth Index I.

Sensitivity of SEP indicators to malaria risk: Each indicator of SEP was evaluated as a predictor of HBR, parasite prevalence and incidence of clinical malaria. Negative binomial regression was used to model the number of *Anopheles* caught per household per night and the number of malaria cases per child with the number of catch nights and person years included as offset terms. The prevalence of malaria infection at the time of each routine clinic visit was modelled using logistic regression. First, a crude analysis was done in which the models for HBR included no covariates and the models for parasite prevalence and malaria incidence were minimally adjusted for age and gender. Second, to evaluate the relative sensitivity of SEP indicators to inequalities in malaria risk, all indicators of SEP were included in multivariable models for HBR, parasite prevalence and malaria incidence. In all models, robust standard errors were used to adjust for clustering at the household level.

Ethics: Ethical approval was given by the Uganda National Council for Science and Technology; Makerere University School of Medicine Research and Ethics Committee; University of California, San Francisco Committee for Human Research; and London School of Hygiene and Tropical Medicine Ethics Committee.

6.3. Results

Study population 333 total children in 107 total households were enrolled into the cohort study between August 2011 and September 2014. The mean age of study children during follow-up was 5.7 years and 153 (46%) were female. All households were surveyed at enrolment in the first household survey. Seven households were withdrawn and replaced immediately before the second household survey in September 2013, such that the second household survey collected data for 100 households and 318 (95%) children. 105 women were surveyed, such that data on female caregivers' education was collected for 301 (90%) children enrolled (Figure 6.1).

Wealth indices: In Wealth Index I (no housing or food security variables), the first principal component explained 29.3% of overall variability in the asset variables. Greatest weight was given to ownership of a cupboard (Table 6.1). In Wealth Index II (all variables), the first principal component explained 30.5% of the overall variability in the asset variables. Greatest weight was given to main floor material. Both indices were right-skewed, with wealth index scores ranging from -2.4 to 6.6 (Figure 6.2). Wealth Index I was strongly associated with the five variables additionally included in Wealth Index II: main roof material ($p=0.001$), main wall material ($p<0.001$), main floor material ($p<0.001$), frequency of meat consumption ($p<0.001$) and number of meals per day ($p<0.001$).

Agreement between SEP indicators: Ranking of households by scores from the two wealth indices was similar but not identical (Spearman's $\rho = 0.93$, $p<0.001$) as was the grouping of households into tertiles (Spearman's $\rho = 0.87$, $p<0.001$; $\kappa = 0.73$, $p<0.001$), with 82% of households placed into the same tertile by both wealth indices (Figure 6.3, Table 6.2). Households placed in higher tertiles of Wealth Index I (reference index) had greater income and better educated adult women than households in the lowest tertile (Table 6.2). However, there was no association between Wealth Index I and occupation.

Sensitivity of SEP indicators to malaria risk:

HBR: 124,746 adult female *Anopheles* were caught over 3,489 collection nights, yielding an overall HBR of 35.8 *Anopheles* per house per night. All households contributed at least one collection night. Controlling for all other SEP indicators, HBR was associated only with Wealth Index II (highest vs lowest tertile: adjusted incidence rate ratio (aIRR) 0.67, 95% confidence intervals (CI) 0.49-0.92, $p=0.01$) and income from remittances (received vs did not receive remittances in past 12 months: aIRR 0.67, 95% CI 0.47-0.96, $p=0.03$) (Table 6.3).

Parasite prevalence: 3,367 total routine blood smears were taken of which 1,037 (30.8%) were positive. All participants contributed at least one blood smear. Controlling for age, gender and all other SEP indicators, parasite prevalence was associated with only the wealth indices (highest vs lowest tertile of Wealth Index I: aOR 0.57, 95% CI 0.40-0.82, $p=0.003$; Wealth Index II: aOR 0.57, 95% CI 0.40-0.82, $p=0.002$) (Table 6.4). Parasite prevalence was not associated with income, occupation or education.

Incidence of clinical malaria: 2,399 episodes of uncomplicated malaria were diagnosed after 802 person years of follow-up, yielding an overall incidence of 3.0 episodes per person year at risk. *One participant was withdrawn immediately after enrolment and did not contribute person time.* Controlling for age, gender and all other SEP indicators, only female caregiver's education was associated with malaria incidence (attended school vs never attended school: aIRR 0.70, 95% CI 0.49-0.98, $p=0.04$). Malaria incidence was not associated with either wealth index nor income or occupation (Table 6.5).

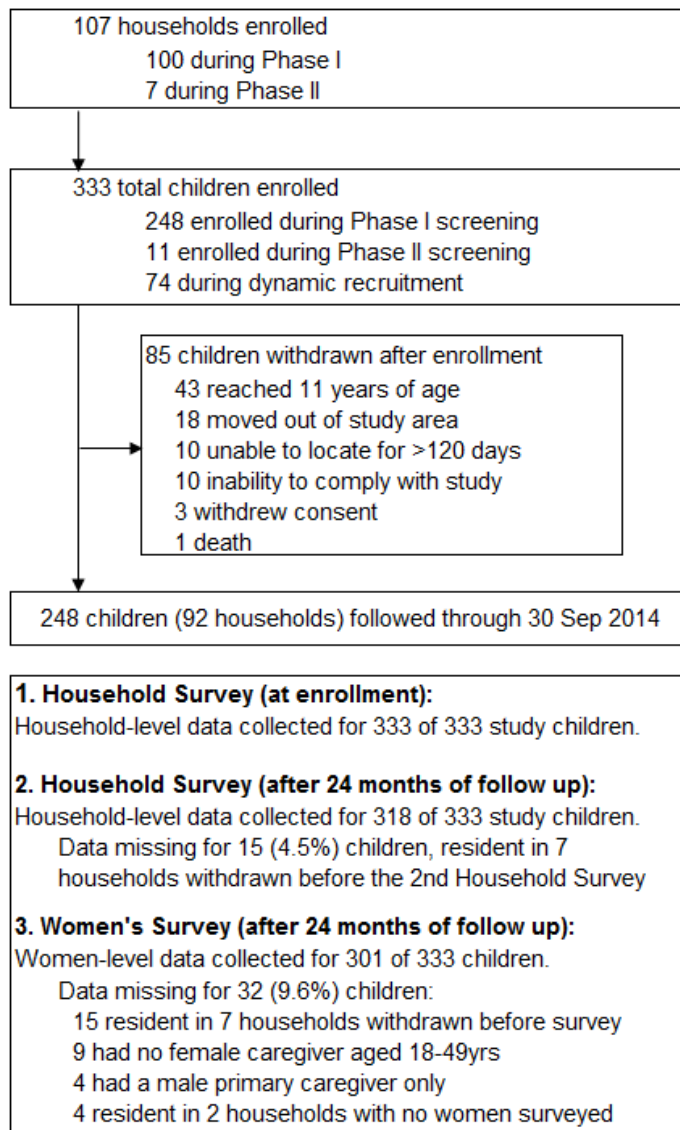


Figure 6.1. Study profile for a cohort of children followed for 36 months in Nagongera, Uganda

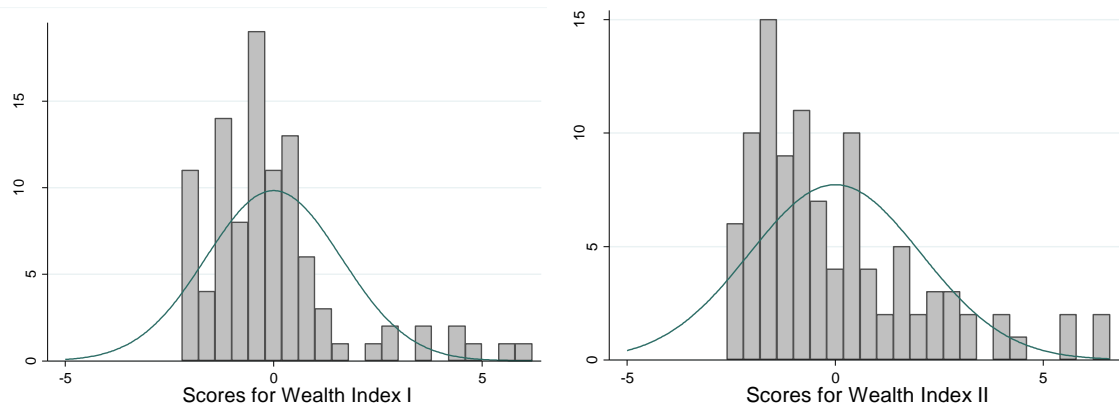


Figure 6.2. Distribution of wealth index scores from principal component analysis (PCA) in 100 households in Nagongera, Uganda.

Variables entered into the PCA for Wealth Index I (A): ownership of a (1) radio, (2) mobile telephone, (3) table, (4) cupboard, (5) clock and (6) sofa; (7) people per sleeping room; (8) access to an improved toilet facility and (9) main mode of transport to the health facility.

Additional variables entered for Wealth Index II (B): (10) main roof material, (11) main wall material, (12) main floor material, (13) frequency of meat consumption and (14) number of meals per day.



Figure 6.3. Association between scores from two wealth indices derived from principal component analysis in 100 households in Nagongera, Uganda.

Lines perpendicular to the axes represent cut-offs for tertiles of each wealth index.

Table 6.1. Variables included in two wealth indices for 100 households in Nagongera, Uganda and their impact on household wealth index score

Item	Proportion of households with item	Weight	
		Wealth index I ^a	Wealth index II ^b
Radio	0.53	0.29	0.18
Mobile telephone	0.61	0.30	0.27
Table	0.62	0.37	0.31
Cupboard	0.07	0.45	0.27
Clock	0.12	0.43	0.29
Sofa	0.05	0.41	0.31
≤2 people per sleeping room	0.23	0.19	0.14
Improved toilet	0.18	0.29	0.20
Transport to health facility other than walking	0.33	0.10	0.05
Tiled or metal roof	0.65	Not included	0.21
Cement or plaster wall	0.24	Not included	0.35
Wood, brick or cement floor	0.17	Not included	0.38
Meat eaten ≥3 days in the past week	0.40	Not included	0.26
≥3 meals per day in past week	0.28	Not included	0.33

^aWealth Index I: variables entered into principal component analysis (PCA): ownership of a (1) radio, (2) mobile telephone, (3) table, (4) cupboard, (5) clock and (6) sofa; (7) people per sleeping room; (8) access to an improved toilet facility and (9) main mode of transport to the health facility. Individual household wealth index scores are calculated by summing the coefficients of assets or characteristics possessed by each household.

^bWealth Index II: variables entered into PCA were those included in Wealth Index I in addition to: (10) main roof material, (11) main wall material, (12) main floor material, (13) frequency of meat consumption and (14) number of meals per day.

Table 6.2. Agreement between indicators of socioeconomic position in 100 households in Nagongera, Uganda

Indicator			All	Wealth Index I (reference) ^a			p
			tertile	Poorest	Middle	Highest	
Number of households			100	35	32	33	-
1. Wealth index	Wealth Index II ^b (%)	Poorest tertile	34	91.4	6.3	0.0	<0.001
		Middle tertile	34	8.6	75.0	21.2	
		Highest tertile	32	0.0	18.8	78.8	
	Wealth Index II ^b	Mean score (95% CI) ^c	100	-0.9	-0.1	1.0	<0.001
2. Income	Total income from agriculture in the past 12 months, UGX ^d (%)	<100,000	37	51.4	40.6	18.8	0.001
		100,000 - <300,000	35	37.1	40.6	28.1	
		≥300,000	27	11.4	18.8	53.1	
	Remittances received in the past 12 months (%)	No	85	94.3	87.5	72.7	0.04
		Yes	15	5.7	12.5	27.3	
3. Occupation	Main occupation of the household head (%)	Agriculture or unskilled	72	80.0	78.1	57.6	0.08
		Skilled	28	20.0	21.9	42.4	
	Main source of household income (%)	Agriculture or unskilled	80	85.7	84.4	69.7	0.27
		Skilled	16	11.4	15.6	21.2	
		Remittances or other	4	2.9	0.0	9.1	
Number of children			318	110	107	101	-
4. Education	Female caregiver ever attended school (%)	No	24.9	29.9	21.9	22.5	0.33
		Yes	75.1	70.1	78.1	77.6	
	Female caregiver's highest level of school completed (%)	None	24.9	29.9	21.9	22.5	0.003
		Incomplete 1 ^{iv}	55.2	62.6	52.1	50.0	
		1 ^{iv} or higher	19.9	7.5	26.0	27.6	

^aWealth Index I: variables entered into principal component analysis (PCA): ownership of a (1) radio, (2) mobile telephone, (3) table, (4) cupboard, (5) clock and (6) sofa; (7) people per sleeping room; (8) access to a toilet facility and (9) main mode of transport to the health facility.

^bWealth Index II: variables entered into PCA were those included in Wealth Index I in addition to: (10) main roof material, (11) main wall material, (12) main floor material, (13) meat consumption and (14) number of meals per day.

^cStandardised wealth index scores were created by subtracting mean index scores and dividing by the standard deviation. The p-value for this variable was calculated using analysis of variance.

^dUGX: Ugandan shilling

Table 6.3. Association between household-level indicators of socioeconomic position and the human biting rate in 100 households in Nagongera, Uganda

Characteristic			HBR ^a	Crude IRR (95% CI) ^b	p	Adjusted IRR (95% CI) ^c	p
1. Wealth index	Wealth Index I	Poorest tertile	41.5 (1136)	1	-	1	-
		Middle tertile	34.4 (1132)	0.86 (0.65-1.13)	0.27	0.88 (0.68-1.14)	0.34
		Highest tertile	28.8 (1110)	0.71 (0.54-0.93)	0.01	0.75 (0.56-1.02)	0.06
		Continuous score ^d	-	0.87 (0.77-0.99)	0.03	Not included	-
	Wealth Index II	Poorest tertile	40.8 (1124)	1	-	1	-
		Middle tertile	35.8 (1173)	0.90 (0.68-1.18)	0.44	0.93 (0.72-1.20)	0.58
		Highest tertile	27.9 (1081)	0.69 (0.52-0.91)	0.008	0.67 (0.49-0.92)	0.01
		Continuous score ^d	-	0.79 (0.71-0.89)	<0.001	Not included	-
2. Income	Total income from agriculture in past 12 months (UGX) ^e	<100,000	37.0 (1291)	1	-	1	-
		100,000 - <300,000	29.3 (1142)	0.80 (0.61-1.04)	0.10	0.77 (0.59-1.01)	0.06
		≥300,000	40.0 (910)	1.05 (0.79-1.40)	0.72	1.16 (0.86-1.58)	0.34
	Remittances received in the past 12 months	No	37.0 (2872)	1	1	1	-
		Yes	23.0 (506)	0.63 (0.46-0.86)	0.004	0.67 (0.47-0.96)	0.03
3. Occupation	Primary occupation of the household head	Agriculture, unskilled or cannot work	35.3 (2431)	1	1	1	-
		Skilled	34.1 (947)	0.95 (0.74-1.24)	0.72	0.98 (0.71-1.34)	0.89
	Main source of household income	Agriculture or unskilled	36.8 (2690)	1	-	1	-
		Skilled	30.0 (544)	0.82 (0.60-1.13)	0.23	0.83 (0.57-1.23)	0.36
		Remittances or other	19.2 (144)	0.53 (0.30-0.95)	0.03	0.80 (0.42-1.50)	0.48

^aHBR: Human biting rate: total female *Anopheles* / total collection nights. Total collection nights are shown in brackets.

^bIRR: Incidence rate ratio; CI: Confidence interval.

^cIRR adjusted for Wealth Index I and all other indicators of SEP, excluding Wealth Index II. The IRR for Wealth Index II was adjusted for all other indicators of SEP, excluding Wealth Index I.

^dStandardised wealth index scores were created by subtracting mean index scores and dividing by the standard deviation.

^eUGX: Ugandan shilling

Table 6.4. Association between indicators of socioeconomic position and malaria infection in children aged six months to 10 years in Nagongera, Uganda

Characteristic		% positive ^a	Crude OR (95% CI) ^b	P	Adjusted OR (95% CI) ^c	p	
Age at the time of the blood smear	6m to <3yrs	19.2 (657)	1	-	1	-	
	3 to <5 yrs	27.6 (699)	1.60 (1.18-2.18)	0.002	1.60 (1.16-2.20)	0.004	
	5 to <11 yrs	35.7 (2011)	2.34 (1.77-3.09)	<0.001	2.40 (1.83-3.17)	<0.001	
Gender	Female	29.9 (1518)	1	-	1	-	
	Male	31.5 (1849)	1.07 (0.86-1.35)	0.54	1.04 (0.82-1.30)	0.75	
1. Wealth index	Wealth Index I	Poorest	38.4 (1087)	1	1	-	
		Middle	29.6 (1170)	0.65 (0.48-0.87)	0.003	0.69 (0.51-0.94)	0.02
		Highest	25.3 (1010)	0.52 (0.35-0.78)	0.001	0.57 (0.40-0.82)	0.003
	Wealth Index II	Continuous score ^d	-	0.82 (0.64-1.04)	0.10	Not included	-
		Poorest	37.7 (1109)	1	-	1	-
		Middle	28.9 (1210)	0.63 (0.46-0.87)	0.004	0.64 (0.47-0.88)	0.005
		Highest	26.4 (948)	0.58 (0.40-0.84)	0.004	0.57 (0.40-0.82)	0.002
2. Income	Total income from agriculture in the past 12 months (Ugandan shillings)	<100,000	34.0 (1180)	1	1	-	
		100,000 - <300,000	29.7 (1136)	0.79 (0.56-1.11)	0.17	0.77 (0.55-1.09)	0.15
		≥300,000	28.0 (908)	0.75 (0.53-1.07)	0.12	0.87 (0.62-1.22)	0.43
	Remittances received in the past 12 months	No	32.2 (2847)	1	-	1	-
		Yes	23.8 (420)	0.62 (0.37-1.04)	0.07	0.65 (0.40-1.05)	0.08
3. Occupation	Primary occupation of the household head	Agriculture or unskilled	32.9 (2416)	1	1	-	
		Skilled	26.3 (851)	0.76 (0.51-1.15)	0.19	0.77 (0.55-1.08)	0.13
	Main source of household income	Agriculture or unskilled	32.1 (2635)	1	-	1	-
		Skilled	27.0 (497)	0.82 (0.48-1.41)	0.48	1.03 (0.58-1.81)	0.93
		Remittances or other	28.9 (135)	0.83 (0.33-2.07)	0.68	1.04 (0.49-2.20)	0.93
4 Education	Female caregiver ever attended school	No	33.4 (788)	1	1	-	
		Yes	30.4 (2296)	0.90 (0.65-1.25)	0.54	0.87 (0.59-1.29)	0.49
	Female caregiver's highest level of school completed	None	33.4 (788)	1	-	1	-
		Incomplete 1 ^{iv}	31.7 (1703)	0.96 (0.68-1.36)	0.83	1.26 (0.92-1.74)	0.16
		1 ^{iv} or higher	26.6 (593)	0.74 (0.48-1.15)	0.18	Omitted due to	-

^aPercentage of blood slides positive with malaria parasites. Total blood slides are shown in brackets. ^bOR: Odds ratio minimally adjusted for age at the time of the blood smear and gender; CI: Confidence interval. ^cOR adjusted for age at the time of the blood smear, gender, Wealth Index I and all other SEP indicators, excluding Wealth Index II. The OR for Wealth Index II was adjusted for age at the time of the blood smear, gender and all other indicators of SEP, excluding Wealth Index I. ^dStandardised wealth index scores were created by subtracting mean index scores and dividing by the standard deviation.

Table 6.5. Association between indicators of socioeconomic position and malaria incidence in children aged six months to 10 years in Nagongera, Uganda

Characteristic		Malaria incidence ^a	Crude IRR (95% CI) ^b	p	Adjusted IRR (95% CI) ^c	p	
Mean age during follow-up	6m to <3yrs	4.1 (134)	1	-	1	-	
	3 to <5 yrs	4.2 (177)	1.01 (0.85-1.19)	0.93	0.99 (0.82-1.20)	0.96	
	5 to <11 yrs	2.3 (491)	0.54 (0.46-0.65)	<0.001	0.54 (0.46-0.65)	<0.001	
Gender	Female	2.7 (361)	1	-	1	-	
	Male	3.2 (441)	1.13 (0.97-1.32)	0.12	1.14 (0.97-1.35)	0.11	
1. Wealth index Wealth Index I	Poorest	3.0 (258)	1	-	1	-	
	Middle	3.1 (280)	1.12 (0.90-1.40)	0.31	1.16 (0.93-1.43)	0.18	
	Highest	2.9 (241)	1.05 (0.83-1.34)	0.68	1.08 (0.86-1.37)	0.51	
	Continuous score ^d	-	0.95 (0.86-1.06)	0.35	Not included	-	
	Wealth Index II	Poorest	3.2 (264)	1	-	1	-
	Middle	2.9 (289)	1.03 (0.83-1.29)	0.77	1.10 (0.90-1.35)	0.33	
	Highest	2.9 (226)	1.00 (0.78-1.27)	0.98	1.04 (0.80-1.36)	0.75	
	Continuous score ^d	-	0.95 (0.84-1.07)	0.38	Not included	-	
2. Income	Total income from agriculture in the past 12 months (UGX) ^e	<100,000	3.1 (283)	1	-	1	-
		100,000 - <300,000	2.5 (270)	0.84 (0.66-1.06)	0.14	0.79 (0.62-1.00)	0.05
		≥300,000	3.5 (215)	1.13 (0.90-1.42)	0.29	1.11 (0.88-1.40)	0.37
	Remittances received in the past 12 months	No	3.1 (679)	1	-	1	-
		Yes	2.6 (100)	0.88 (0.65-1.20)	0.42	1.10 (0.76-1.57)	0.62
3. Occupation	Primary occupation of the household head	Agriculture or unskilled	3.0 (576)	1	-	1	-
		Skilled	3.0 (203)	0.93 (0.74-1.19)	0.58	0.90 (0.66-1.23)	0.51
	Main source of household income	Agriculture or unskilled	3.1 (628)	1	-	1	-
		Skilled	2.8 (118)	0.93 (0.70-1.23)	0.59	1.01 (0.69-1.48)	0.97
		Remittances or other	2.5 (33)	0.77 (0.43-1.36)	0.37	0.67 (0.38-1.19)	0.17
4. Education	Female caregiver ever attended school	No	3.5 (188)	1	-	1	-
		Yes	2.9 (546)	0.80 (0.67-0.95)	0.01	0.70 (0.49-0.98)	0.04
	Female caregiver's highest level of school completed	None	3.5 (188)	1	-	1	-
		Incomplete 1 ^f	3.0 (406)	0.83 (0.69-1.01)	0.06	1.26 (0.91-1.74)	0.16
		1 ^f or higher	2.4 (140)	0.69 (0.53-0.91)	0.008	Omitted due to	-

^aMalaria incidence: episodes per person years at risk. Total person years at risk shown in brackets. ^bIRR: Incidence rate ratio minimally adjusted for mean age during follow-up and gender; CI: Confidence interval. ^cIRR adjusted for mean age during follow-up, gender, Wealth Index I and all other SEP indicators, excluding Wealth Index II. The IRR for Wealth Index II was adjusted for mean age during follow-up, gender and all other indicators of SEP, excluding Wealth Index I. ^dStandardised wealth index scores were created by subtracting mean index scores and dividing by the standard deviation. ^eUGX: Ugandan shilling

6.4. Discussion

We compared two wealth indices and three additional indicators of SEP for measuring socioeconomic inequalities in malaria risk in children in a rural, high transmission area of Uganda. HBR was 29-31% lower in households in the highest tertile of Wealth Indices I and II, compared to the lowest tertile, and 37% lower in households that received any remittances in the past 12 months. However, after controlling for all other SEP indicators, only access to remittances and Wealth Index II (which included house construction and food security variables) were significantly associated with lower HBR. Controlling for age, gender and all other SEP indicators, the odds of malaria infection were 43% lower in children in the highest tertile of both Wealth Index I and II, compared to the lowest tertile, and malaria incidence was 30% lower in children whose primary female caregiver had attended school, compared to those whose caregiver had not. No association was found between occupation and malaria.

Since their early development and adoption by the DHS and World Bank [249, 276], wealth indices have become widely used to measure SEP in epidemiological studies in low and middle income settings [6]. While there is continuing debate over how well wealth indices agree with consumption [260], they are a pragmatic means to rapidly assess SEP and can theoretically represent long-term SEP, similar to consumption expenditure, because assets are relatively resilient to short-term economic shocks [197]. We observed that the wealth index was relatively sensitive to socioeconomic inequalities in HBR and parasite prevalence and indeed it is possible that this metric was less subject to measurement error than other metrics and more indicative of long-term living conditions [277]. The one previous comparison of indicators for measuring socioeconomic inequalities in malaria risk found that the wealth index was a reasonable alternative to consumption in rural Tanzania [272].

Although there is a paucity of underlying theory to guide the choice of included variables in wealth indices [259], the inclusion of assets with a direct association with the outcome of interest may increase the observed socioeconomic inequalities in health [253]. Furthermore, variables often included in the wealth index, such as house type, are sometimes evaluated independently as malaria risk factors [19]. We therefore sought to evaluate how the choice of variables included in the wealth index affected the association with malaria outcomes. Household rankings from the two wealth indices were highly correlated, but controlling for other SEP indicators, only the wealth index that included house construction and food security variables was associated with HBR. House structure may also explain part of the association between SEP and malaria in Nagongera since it is both a malaria risk factor [18] and associated with relative wealth, so it is plausible that its inclusion strengthens the association between

the wealth index and malaria risk and that there is a trade-off between house type and SEP in the model. Previous wealth indices based on assets alone [13] and on assets and food security [18] in the same district were not significantly associated with parasite prevalence.

We observed that female caregiver's education was better able to predict differences in malaria incidence than other metrics of SEP. Good education is commonly associated with improved health outcomes elsewhere [278, 270] and generally considered to be a useful metric of SEP since it is a proxy for knowledge-based assets and can be strongly related to other measures of SEP such as income and occupation [264, 197]. However education was not associated with HBR nor parasite prevalence and the epidemiological meaning of this remains unclear. The use of education as a metric of SEP can be complicated by changes in the cost, ease and social expectations of educational attendance over time [197]. While we restricted our analysis to female education only, removing gender differences, variation across women's age groups or ethnic groups may have persisted, making it difficult to identify variation in malaria risk reflecting education alone.

We found no association between agricultural income and malaria, but we observed that HBR was lower in households that had received remittances in the past 12 months. We also observed that both agricultural income and access to remittances were strongly associated with the reference wealth index. It is plausible that income may be a reasonable proxy for underlying SEP but that our specific measures of income were inadequate to fully detect differences in malaria risk related to SEP. Income is difficult to measure in low income settings such as Nagongera, due to multiple household income sources, home production and seasonal or annual variation in income [197]. Thus we simply estimated the total estimated income from the sale of crops and livestock and recorded whether or not households had access to remittances. Our approach did not account for other income sources and this, together with measurement error due to recall bias, unwillingness to divulge income and interviewing only the household head, may help explain the inconsistent association with malaria outcomes [258]. Of course, our findings may alternatively reflect a scenario of no underlying relationship between income and malaria, if a lack of cash income is not a barrier to having those characteristics that offer some protection against malaria.

We did not observe any association between malaria infection risk and occupation, when classed as unskilled and agricultural *versus* skilled. Occupational life can be complex and therefore difficult to measure in low-income settings since people often have casual, seasonal, or multiple jobs [187]. In Nagongera, where households predominantly rely on smallholder

farming and small home enterprises, further differentiation between commercial and subsistence farmers may have been needed to determine underlying SEP. For example, the DHS typically classifies households using occupation-based social class measures that include subdivisions of types of agricultural activity [262].

Overall, our study supports the continued use of wealth indices as a pragmatic approach to estimating SEP in malaria studies. While we did not compare the wealth index with consumption, the wealth index was consistently more sensitive to inequalities in malaria risk than income and occupation. However, there remains a need to better understand how to select and weight the included variables. While the inclusion of variables directly associated with the outcome may inflate health inequalities [253], such variables may be an important part of what makes wealth protective. Moreover, the inclusion or exclusion of different variables can improve understanding of the causal pathway between SEP and a health outcome [253]. However, it may be pragmatic to remove from the wealth index any variables being investigated as exposures of interest. Individual studies should consider what is appropriate for the study setting and design.

Our study has a number of limitations. First, to avoid excessive questioning we did not evaluate consumption, yet this is the gold standard measure of SEP [197]. Second, metrics such as income and occupation may be subject to measurement error due to recall bias, inaccurate reporting during lengthy interviews and social desirability bias when asking questions related to socioeconomic conditions. Third, our findings may not be generalizable outside the study population in Nagongera. For example, in generating both wealth indices the smallest weight was assigned to mode of transport to the health facility, possibly reflecting reimbursement of clinic travel expenses to study participants. Additionally, we compared two wealth indices only, limiting the conclusions that may be drawn. Fourth, we used PCA as a weighting strategy, but this was originally designed for use with continuous data. We also did not analyse other weighting strategies, such as factor or multiple correspondence analysis, but a recent study concluded that variable coding may be more important than the weighting strategy in improving wealth index agreement with consumption [268]. Finally, variables used to construct the wealth index were collected at more than one time point. However, we consider household assets to be relatively stable over time [197].

In conclusion, wealth indices, income and education were stronger predictors of socioeconomic differences in malaria risk than occupation in this setting. The wealth index was

still a predictor of malaria risk after excluding variables directly associated with malaria, but the strength of association was lower.

Acknowledgements

We are grateful to the study participants and their families. We thank the Infectious Diseases Research Collaboration (IDRC) for administrative and technical support. This work was supported by NIH/NIAID (U19AI089674); Leverhulme Centre for Integrative Research in Agriculture and Health; Research and Policy for Infectious Disease Dynamics (RAPIDD) programme of the Science and Technology Directorate, US Department of Homeland Security, the Fogarty International Center (US National Institutes of Health); Bill & Melinda Gates Foundation (OPP1053338) and the Malaria Centre at the London School of Hygiene & Tropical Medicine.

Chapter 7. Poverty, livelihoods and rural differentiation: Identifying indicators of agricultural success among smallholder farmers in rural Uganda

ABSTRACT

Background: In settings where agriculture is a major source of livelihood in rural sub-Saharan Africa, quantifying relative agricultural success can help to understand differences in socioeconomic position (SEP). A qualitative study was conducted to identify indicators of relative agricultural success among smallholder farmers in Nagongera, eastern Uganda.

Methods: In-depth interviews (IDIs) were conducted with one adult respondent in each of 25 households, randomly selected from 100 households enrolled into an epidemiological cohort study. IDIs were structured around five domains: (1) land use and ownership, (2) farm labour and householder occupations, (3) type of farming and the degree of capitalisation, (4) farm income and market engagement and (5) off-farm linkages. Ten farms belonging to IDI respondents were additionally mapped using a geographical positioning system.

Results: All households interviewed (n=25) cultivated land. Agriculture was the primary source of livelihood for 68% (17) of households and 32% (8) households reported additional income from other sources, suggesting that poverty reduction was driven by 'accumulation from below'. Between households, there was considerable heterogeneity in farming scale, inputs, capitalisation and market engagement. Ten farms were included in the agricultural land survey. Measured cultivated land area ranged from 0.2 to 6.5 hectares per household. Farming was mainly done by hand without heavy equipment, with ox-ploughs, pesticides and fertiliser sometimes used. 32% (12) of households hired external farm labour. Home consumption was the primary reason for cultivating crops, but all households reported marketing some produce.

Conclusions: Occupation groups are unlikely to differentiate between rural households universally engaged in agriculture and overall production is difficult to measure. However, cultivated land area, farm labour hire and use of capital inputs are relatively heterogeneous and therefore may be useful indicators for quantifying relative agricultural success in Nagongera. Five modified domains of indicators of agricultural success are proposed for Nagongera: (1) land ownership and area cultivated, (2) farm labour, (3) capitalisation and inputs, (4) yields and productivity and (5) market engagement.

7.1. Background

While 48% of Africans were still living on incomes below the international poverty line of US\$ 1.25 per day in 2010 [163], Africa is developing rapidly, with gross domestic product (GDP) growth during 2000-2010 increasing at double the rate of the 1980s and 1990s [162]. The middle class (arguably those living on US\$ 2-20 per day) is expected to grow from 355 million people in 2010 (34% of the total population) to 1.1 billion (42%) in 2060 [162]. The importance of sustaining this development to further reduce income poverty, hunger, lack of shelter and ill health is undisputed [77].

Our understanding of poverty in sub-Saharan Africa (SSA) has advanced in the past two decades [279, 32]. At the micro-level, development is generally accepted to involve a reduction in livelihood vulnerability, changes in livelihoods activities (see footnote²) and increasingly higher incomes through a shift towards more productive activities [179]. In rural areas, such activities are typically grounded in agriculture, possibly with diversification into non-agricultural activities, although there can be a complex relationship between the two [280-283]. While agriculture makes varying contributions to African GDP at the macro-level [163], it remains the backbone of many developing rural economies and important as a source of employment and self-employment in both rural and urban areas [33].

Although the rural African population is often viewed as a homogeneous class, there are important patterns of differentiation. Broadly, the rural poor can be differentiated into: (1) a small stratum of commercial smallholders and large-scale farmers; and (2) a growing class that survives through cultivation of small plots of land and wage labour [284] but these two groups encompass many classes of farmers with different objectives, constraints and reproduction systems [285, 284, 286]. For example, farmers may be surviving (farming for subsistence, not to a surplus), accumulating assets through farming (through produce sales or employing labour) or diversifying outside farming (supplementing farm income by other means) [34, 283]. To understand rural differentiation and differences in socioeconomic position (SEP) in settings where agriculture is a major livelihood, it is necessary to examine relative agricultural success [287]. Agricultural success reflects the degree to which smallholder farmers have successfully derived a living from the land, possibly also using agricultural income to upscale other enterprises [33, 287].

²A livelihood is 'the activities, the assets and the access that jointly determine the living gained by an individual or household'. Livelihood diversification is 'the process by which households construct a diverse portfolio of activities and social support capabilities for survival and in order to improve their standard of living.' Ellis, F., *Rural livelihood diversity in developing countries: evidence and policy implications*, in *Natural Resource Perspectives*. 1999, Overseas Development Institute: London.

Relative agricultural success in rural SSA can be approximated using metrics such as farm size, production performance and labour hire [286, 186] or using the so-called 'livelihoods' approach that examines the processes of accumulation, production and social reproduction that enable people to pursue different livelihood strategies [179, 32, 34, 288]. Categories based on farm size are commonly used to classify farmers on a continuum from landless workers to large-scale farmers, reflecting two main sources of landholding inequality: (1) inequality between social extremes (large cultivators versus smallholders) and (2) inequality within the large class of smallholders who cultivate a wide range of land area that supports variable production levels [286]. The main limitations to using farm size as a measure of relative success are twofold. First, farm size is relative and must be contextualised, since land area cultivated generally declines with greater soil fertility [289]. Second, farm size does not necessarily reflect productivity and other income sources, thus is not a consistent and accurate indicator of wealth [186]. Differentiation between farmers can also be based on production performance (also referred to as land productivity or yield) and the degree of reliance on external labour, although such measures can be affected by unmeasured external environmental conditions and temporary contingencies [286, 186].

An alternative approach to gauging relative agricultural success is the 'livelihoods' approach, which examines the strategies by which people gain a living [290-292]. Basic livelihood strategies involve crop and livestock production, with possible diversification into activities that generate additional income by producing non-agricultural goods [182]. Where there is high natural resource potential, crop farming is typically important to poor people's livelihoods, providing opportunities for 'hanging in' (i.e. maintaining livelihood levels), 'stepping up' (investing in assets to expand current activities and increase production and income) and 'stepping out' (accumulating resources to move into different activities with higher returns) [179, 32]. Where the local economy is dynamic, there is more scope to 'step up' and 'step out' through unskilled labour and petty trading [32]. Examination of these factors enables an understanding of the processes of accumulation and production that underpin socioeconomic differences. This approach has been applied in Zimbabwe where livelihood strategies were found to fit into categories of 'hanging in', 'stepping up', 'stepping out' and 'dropping out' [293, 32] and separately into categories of 'back-foot', 'crisis', 'survivalist' and 'accumulation' [34, 288].

In practice, empirical studies of rural differentiation typically apply a combination of these approaches. In Senegal, Oya applied five criteria to differentiate between farmers: (1) labour

relations (percentage of labour done by wage labourers), (2) patterns of land use and ownership (land purchases and proportion of land leased), (3) degree of capitalisation or means of production (including light or heavy machinery, draught animals, transport); (4) education (personal achievement and investment in children's education) and (5) surplus use patterns (balance between consumer (luxury) durable goods and means of production [186, 286]. In Zimbabwe, Scoones undertook a household ranking exercise to understand local perceptions of social and economic differentiation. Local indicators of 'success' focused on market engagement, home infrastructure and capital equipment, labour hiring, off-farm linkages and non-material indicators such as farming knowledge and skills. Success ranks correlated with a range of indicators derived from survey data, including asset ownership, production, sales and income [34].

This chapter describes qualitative research to identify indicators of relative agricultural success in Nagongera sub-county, eastern Uganda, to better understand heterogeneity in SEP. The overall aim of this formative work was to shape the design of the main household survey (Chapter 8). Poverty levels in Uganda are high, with 65% of the population living on less than US\$ 2 per day in 2009 and a mean gross domestic income per capita of US\$ 572 during 2009-2013 [163]. The economy is agriculture-based: the net output of agriculture equated to 24% of GDP and the agricultural sector provided two-thirds of total employment in 2010 [163]. Building on work by Oya [286] and Scoones [34], in-depth interviews (IDIs) were conducted to examine the suitability of indicators within five domains of agricultural success: (1) land use and ownership, (2) farm labour and householder occupations, (3) type of farming and the degree of capitalisation, (4) farm income and market engagement and (5) off-farm linkages.

7.2. Methods

Study area and population: The study was carried out in April-May 2013 in Nagongera sub-county, Tororo district, Uganda (00°46'10.6"N, 34°01'34.1"E). The population is rural, the major ethnic groups being the Japadhola, Iteso, Basamia, Bagwere and Banyoli. Rainfall is bimodal, with long rains from March to June and short rains from August to December. The area is characterised by low-lying agricultural land, with rocky hills and a sandy loam soil of medium to low fertility. Agriculture is the major livelihood, the staple food crops being cassava, maize, beans, sorghum, millet and groundnuts.

Study design: The study was nested within a malaria surveillance cohort study, described elsewhere [173] Briefly, 100 randomly selected households were enrolled in August-

September 2011 and eligible household members were followed for all their health care needs at the designated study clinic in Nagongera for 36 months, until September 2014.

Household selection: Guided by previous studies in Tororo [13], Kabale [294] and Hoima districts [270], principal component analysis (PCA) was used to create a wealth index from ten variables measured in the cohort study baseline survey: ownership of (1) mobile telephones, (2) radios, (3) bicycles, (4) clocks, (5) cupboards and (6) tables; (7) main roof material; (8) main floor material; (9) total number of sleeping rooms and (10) access to a toilet facility. Households were ranked by the resulting scores and divided into tertiles to provide a categorical measure of SEP. Nine households were randomly selected from the lowest tertile and eight from each of the middle and highest tertiles, using computer software, to give a total sample of 25 households.

IDIs and farm surveys: Recommendations of the Consolidated Criteria for Reporting Qualitative Studies (COREQ) were followed [295] (Appendix 7). IDIs were conducted with a designated adult respondent by a trained female Ugandan social scientist with a bachelor's degree (LIT) in the appropriate language (Japhadola, Kiswahili or English), if the respondent met the following eligibility criteria: (1) aged at least 18 years, (2) usual resident of a study household and (3) agreed to provide informed written consent. Research aims were fully explained to each participant. The facilitator was experienced in IDIs, familiar with the study site but unknown to participants. Interview times were arranged several days beforehand in person and IDIs carried out at participants' homes by LIT also in the presence of the study community liaison officer and LST. IDIs lasted approximately 30-45 minutes and were structured using a standard topic guide based around five domains: (1) land use and ownership, (2) farm labour and householder occupations, (3) type of farming and the degree of capitalisation, (4) farm income and market engagement and (5) off-farm linkages. Responses were noted throughout in English and IDIs were recorded. Contact summaries were completed immediately after each IDI. A transcript of each IDI was produced and translated into English using a standard notation system by LIT. Transcriptions were proof-read against the audio file by the transcriber and sections read by LST to check for any areas of confusion or unclear terminology. Translation of the audio files into English followed a meaning-based approach. During the IDIs it was ascertained whether households grew crops and ten contiguous farms were mapped by walking the perimeter of each farm plot with a hand-held GPS device (Forerunner 305[®], Garmin International Inc, KA).

Data analysis: Initial analysis of the IDIs was conducted using notes taken during the IDIs and contact summaries. Translations were read to understand the general flow of discussion and responses grouped under the five domains of interest, using Microsoft Excel. The analysis was based on thematic content, with high-level concepts interpreted for each domain [296].

Shapefiles for farm perimeters were extracted from the GPS using Garmin Training Centre® (Garmin International Inc, KA) and imported into the Intelligent Precision Farming Toolbox® (Courtyard Partnership, UK) to calculate the total area of land cultivated by each household.

Ethics: Ethical approval for the study was given by the Uganda National Council for Science and Technology (UNCST); Makerere University School of Medicine Research and Ethics Committee (SOMREC); University of California, San Francisco Committee for Human Research (UCSF-CHR); and London School of Hygiene and Tropical Medicine Ethics Committee. Prior to the start of the study, the Community Advisory Board was informed of the study and methodology. Informed written consent was obtained for all participants.

7.3. Results

Study participants: All respondents agreed to participate. Of the 25 adult respondents included in the IDIs, 56% (n=14) of respondents were female. 32% (8) had received no formal education, 40% (10) had been educated to the primary level and 28% (7) to the secondary level. 32% (8) were aged less than 30 years, 16% (4) were aged 31-40 years and 52% (13) were aged over 40 years.

Summary of findings: All households interviewed (n=25) cultivated land surrounding or near to the home. Agriculture was found to be the primary livelihood for 68% (17) households and 32% (8) households reported additional income from other occupations. 20% (5) households had access to remittances. Farming was largely done by hand without heavy equipment, with ox-ploughs occasionally hired or owned. 32% (12) of households hired external farm labour. The primary reason for cultivating crops was home consumption, but 72% (18) of households reported marketing at least some farm produce routinely and 28% (7) households reported marketing their produce at times of greater need. Ten farms were surveyed. Cultivated land area ranged from 0.2 to 6.5 ha (measured) and 0.0 to 2.8 ha (self-reported) (Figure 7.1).

1. Land use and ownership: All households interviewed (n=25) owned or hired land for cultivation. 40% (10) owned the land under cultivation in its entirety and 60% (15) also leased some land. Inheritance was a common route to owning land: *'It is our ancestral land'* (126003301); *'That land belongs to my husband's birth land'* (117010301); *'They farm there in*

the order in which they were born' (134002901) and also a reason for limited land: *'The boys are many. If they had not married then I would be having a lot of it [land] but they have touched [used] some of it'* (135002401). Land was generally located immediately surrounding the home but sometimes also further afield (i.e. different village or sub-county). Land further afield was either inherited (and often in the care of relatives) or hired for growing a specific crop, often rice or maize.

2. Farm labour and household occupations: Farming was the sole livelihood for 68% (17) of households, while 32% (8) of households reported that at least one member of their household had an occupation outside the home farm. These other occupations included work in a restaurant, external farm labour, building, selling eggs and fish, teaching and tailoring. Household farm labour was generally composed of adult women or both adult women and men, with supplementary help from children during school holidays: *'When they return for holidays they help me to farm'* (134002901). 32% (12) of households routinely or occasionally hired farm labour from outside the household. Workers were typically paid in cash or in kind, through the reciprocal exchange of produce and services: *'He gives me produce; when he grows maize he gives me maize and when he grows millet he also gives me millet'* (135002401).

3. Type of farming and degree of capitalisation: Households grew a wide diversity of crops: 'kalini' (upland rice), maize, millet, rice and sorghum; pulses: beans ('ojanjo'), mbalayo peas and pigeon peas; root crops: cassava, groundnuts, sweet potato and yams ('opele'); fruit and vegetables: apple, avocado, banana, guava, jackfruit, mango, passion fruit, pineapple, plantain ('pendi'), pumpkin and tomato; and other crops in small quantities including coffee, sugarcane, grass (for thatching), 'muzizi', saisal (for rope production) and simsim. Staples were beans, cassava, groundnuts, maize, millet, rice, sorghum and sweet potato. 52% (13) households reported using pesticides; 24% (6) reported applying fertiliser, typically manure or mulch; 32% (8) reported hiring an ox-plough and 4% (1) reported owning an ox-plough.

4. Farm income and market engagement: 72% (18) of households reported marketing at least some farm produce routinely, while seven households reported only marketing their produce at times of greater need, for example when cash was required for health care, school fees or for special social occasions: *'Everyone grows crops for consumption but I only get some to sell when faced with a problem'* (135002401). Crops appeared more likely to be sold regularly than livestock, which in many households were kept as insurance: *'They help me [solve] when I get a*

problem; I can get it and turn it into money' (119000901); *'When there is a challenge I use [livestock] like for [buy] uniforms which you are supposed to buy within the first week'* (111008001). Produce was typically sold directly to local traders, at the local market or trading centre, to the Nagongera village rice mill and in one case, Tororo town market. Some interviewees readily reported their farm income, with a range of annual incomes reported up to ≈ US\$ 350. However some women whose husbands sold produce did not know their annual income and others were reticent about divulging this information: *'I don't know because I am not the one who receives it'* (111007302).

5. Off-farm linkages: 80% (20) of households had no access to remittances and five households were sometimes sent money by relatives: *'There are times when my daughter who is a health worker sends us some money to support me'* (134002901). Remittances were used for school fees, health care, groceries and household consumables.

Limitations to production and success: Reported limitations to crop yields were: (1) diseases such as cassava mosaic virus (*'At the moment cassava is affected by mosaic when you uproot it you find it blackish and very bitter'* (119000901)); (2) poor soil (*'I over cultivate it, its fertility has reduced'* (136003102); *'nutrients are not there because we have over planted things'* (134011901)); (3) limited land (*'It is not enough and the means to acquire more are still lacking'* (128001701); *'The land is inadequate'* (111007302)); (4) rain or hail damage to crops (*'But there is rain that falls with hailstones...That kind [of rain] can destroy things [crops]'* (122007301); *'Sometimes it rains and floods and spoils the crops; the crops become reddish'* (136003102)); (5) consumption by pests or livestock (*'The crops of nowadays are very affected with pests'* (134011901)) and (6) lack of seeds or other inputs (*'It can be easy for me if I got the seeds of the crops to grow'* (103017501)).

When asked why some farmers were more successful than others, respondents cited land size and inputs (*'Where they farm is big and they also add in fertility'* (119000901); *'But the other [successful] people have plenty of land on which they grow those things'* (112000801) and access to credit groups (*'When they [farmers] harvest then they pay back NAADS [National Agricultural Advisory Service]'* (137004001)). Some farmers reported that ill-health was an impediment to success (*'It is because there are people who have aged [old] so their health cannot allow them [to farm]'* (137004001); *'I broke here [shows me leg and one pelvic] I have a problem with farming'* (134010901); *'We get illnesses like flu, some malaria'* (128001701)).

7.4. Discussion

In this formative study, IDIs were conducted with 25 adult respondents in Nagongera, a rural, agrarian sub-county in eastern Uganda, to identify indicators of relative agricultural success appropriate for understanding heterogeneity in SEP. Agriculture was found to be a critical livelihood among surveyed households, consistent with Ugandan national employment statistics [175]. However, there was considerable variation in measured farm size and reported crop types and yields, inputs, capitalisation, market engagement and reported incomes. While most households were accumulating assets through farming, a few households seemed to be purely surviving whereas others had diversified outside farming into wage labour, trade and teaching. This finding is consistent with the 'differentiation' approach, which roughly categorises farmers as surviving (farming for subsistence, not to a surplus), accumulating assets through farming (through produce sales or labour hire) or diversifying outside farming (where farm income is supplemented by other means), as observed in many rural African settings [297]. Since some level of participation in the agricultural sector was almost universal, poverty reduction appears to be driven via 'accumulation from below', in which the majority of people are engaged in agriculture, with capital accumulation through surplus production [34, 179, 183].

To explore the relevance of difference indicators of relative agricultural success in Nagongera, IDIs were structured around five domains, based on previous work by Oya [33, 287] and Scoones [34]: (1) land use and ownership, (2) farm labour and householder occupations, (3) type of farming and the degree of capitalisation, (4) farm income and market engagement and (5) off-farm linkages. Within each domain, considerable variation in responses was observed, but particularly in reported land area, labour hire and use of capital inputs. Many respondents reported shortages in land, with plots sometimes scattered over a wide area outside the home village. Land fragmentation stems from a land inheritance system that successively divides land over generations, typical of many SSA settings including Rwanda [289] and Nigeria [298].

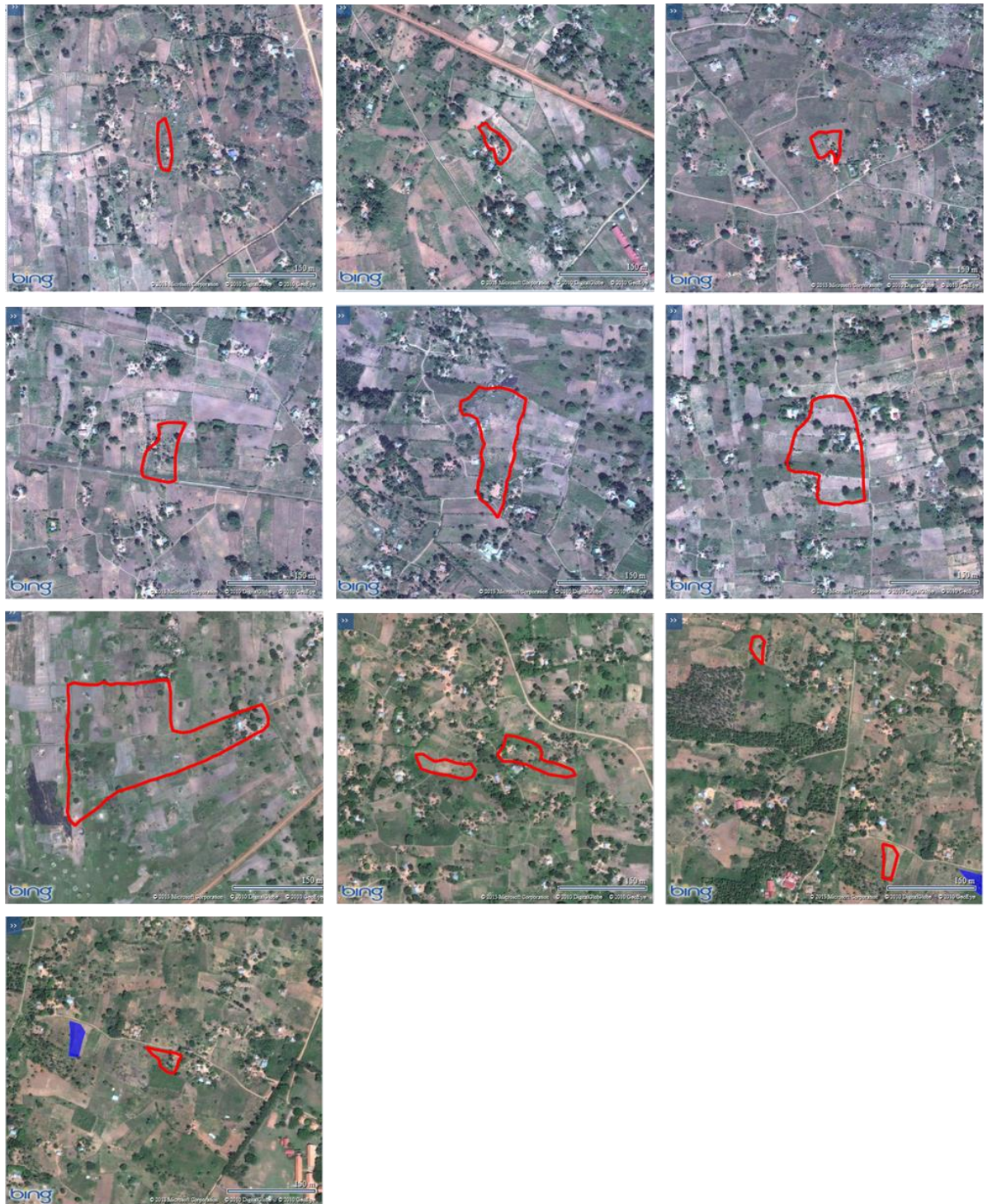


Figure 7.1. Aerial maps of ten farms surveyed in Nagongera, Uganda.

Area within red border denotes land under cultivation by each household. Blue shaded areas denote neighbouring farms also surveyed. Cultivated land area ranged from 0.2 to 6.5 ha (measured) and 0.0 to 2.8 ha (self-reported).

Since farm size was reported as a key determinant of production, land area cultivated may be an informative indicator of relative agricultural success (although the discrepancies between measured and self-reported land area highlight the caution needed in interpreting survey results). Agriculture was the primary occupation, since all households reported cultivating crops. Some households had additional income sources outside the home farm, but these were often agriculture-based (e.g. egg sales and farm labour). This homogeneity in occupation may cause simple occupation categories to mask patterns of differentiation [285, 284, 286].

Considerable diversity was observed in inputs and capitalisation; specifically in the proportion of households reporting hired external farm labour, using fertiliser and pesticides and accessing an ox-plough, suggesting that these variables may be good indicators of relative agricultural success. There was also variation in the types and quantities of crops being grown. For example, only a small number of households grew rice, which was agreed to be highly profitable. However, quantifying crop yields is complex and subject to recall and reporting bias. Interestingly, land availability was one of the factors most consistently reported as limiting production. While it is commonly held that productivity decreases with increasing farm size, a study in Senegal found that the scale of production (measured using farm size, metric tons produced and the proportion of produce marketed) was correlated with better productivity performance, indicating a virtuous circle between expanded accumulation and efficiency [286].

Based on these observations, five modified domains of agricultural success indicators are proposed for Nagongera: (1) land area cultivated, (2) farm labour, (3) capitalisation and inputs, (4) yields and productivity and (5) market engagement. These modified domains reflect the limitations of occupation categories for distinguishing between households universally engaged in agriculture and the difficulty in measuring crop yields. In addition, it is recognised that off-farm linkages (access to remittances) may best be measured as an independent determinant of SEP. Within the modified domains, indicators that may be particularly useful for identifying relative agricultural success include cultivated land area, farm labour hire and the use of capital inputs.

This study also did not assess the scope for agricultural development intervention in Nagongera, but participants described limitations to crop yields and productivity that imply yield gaps. Agricultural production in East Africa has been estimated to be less than a quarter of its potential, leading to calls for 'more nuanced policy-making to boost smallholder farm

output, requiring better knowledge of individual farm households and the constraints they face' [299]. In Nagongera, reported limitations to production included land access, lack of credit to buy seeds and seedlings, damage by pests and heavy rainfall. While the provision of additional land in a densely populated areas is unfeasible, access to credit or advisory groups such as NAADS may enable greater inputs. Furthermore, education for farmers could encourage the adoption of more sophisticated techniques, for example through Farmer Field Schools, which have been successfully piloted in Busia, Kaberamaido and Soroti districts [300]. It was also reported that ill-health was common, which can be an impediment to agricultural productivity through: (1) reductions in the work effort and (2) reduced investments in agriculture. When margins of survival are narrow, short periods of illness that coincide with or delay planting or harvesting can have catastrophic economic effects, sometimes exacerbated by the need to pay for health care. By incurring costs which deplete household cash reserves, ill-health may also reduce local demand for produce [301].

The study was subject to a number of limitations, including recall bias and unwillingness to share information during IDIs, particularly with respect to land ownership and household income. In some cases female respondents were also ignorant of income, since male relatives took responsibility for the sale of produce. This highlights the difficulty of obtaining accurate data on household income. Bias may also have been introduced by the presence of study staff in the communities; several participants requested seeds, money or other help. While households were selected randomly from three tertiles of SEP, the small sample limited scope for formally assessing whether different variables were associated with SEP.

In conclusion, while some households have diversified into non-agricultural activities, agriculture remains a critical livelihood in Nagongera, consistent with poverty reduction being largely driven by accumulation from below. Relative agricultural success may be an important metric for understanding rural differentiation and heterogeneity in SEP in Nagongera and best indicated by cultivated land area, farm labour hire and use of capital inputs.



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Student	Lucy S. Tusting
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Thesis Title	Agriculture, development and malaria in rural Uganda

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Stage of publication	Not yet submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived and designed the study with guidance from others, collected the socioeconomic data, analysed the data (excluding the spatial analysis) and wrote the first draft of the paper.
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Student Signature:

Date: 30.07.2015

Supervisor Signature:

Date: 30.7.15

Chapter 8. Why is malaria a disease of poverty? Evidence from rural Uganda

Prepared as: Tusting LS, Reik JC, Arinaitwe E, Staedke SG, Kanya M, Bottomley C, Cano JO, Johnston D, Lines J, Dorsey G, Lindsay SW. Why is malaria a disease of poverty? Evidence from rural Uganda.

ABSTRACT

Background: Malaria control and sustainable development are linked, but implementation of 'intersectoral' interventions is limited by a poor understanding of the causal pathways between poverty and malaria. We investigated the relationships between socioeconomic position (SEP), potential determinants of SEP, and malaria in Nagongera, rural Uganda.

Methods: Socioeconomic information was collected for 318 children aged six months to 10 years living in 100 households, who were followed for 36 months. Mosquito density was recorded using monthly light trap collections. Parasite prevalence was measured every three months and malaria incidence determined by passive case detection. First, we evaluated the association between success in smallholder agriculture (the primary livelihood source) and SEP. Second, we explored socioeconomic risk factors for human biting rate (HBR), parasite prevalence and incidence of clinical malaria, and spatial clustering of socioeconomic variables. Third, we investigated the role of selected factors in mediating the association between SEP and malaria.

Findings: Relative agricultural success was associated with higher SEP. In turn, high SEP was associated with lower HBR (highest *versus* lowest wealth index tertile: incidence rate ratio 0.71, 95% confidence intervals (CI) 0.54-0.93, $p=0.01$) and lower odds of malaria infection in children (highest *versus* lowest wealth index tertile: adjusted odds ratio 0.52, 95%CI 0.35-0.78, $p=0.001$), but SEP was not associated with clinical malaria incidence. Mediation analysis suggested that part of the total effect of SEP on malaria infection risk was explained by house type (24.9%, 95%CI 15.8–58.6%) and food security (18.6%, 95%CI 11.6–48.3%); however, the assumptions of the mediation analysis may not have been fully met.

Interpretation: Housing improvements and agricultural development interventions to reduce poverty merit further investigation as intersectoral interventions against malaria.

8.1. Background

As attention shifts to the Sustainable Development Goals, malaria control is at a pivotal juncture. While the disease remains a major public health problem, the past fifteen years have seen a 30% fall in annual global incidence [1]. This progress has been achieved mainly with long-lasting insecticide-treated nets (LLINs) and indoor residual spraying (IRS), yet future progress may be hampered by insecticide resistance in mosquitoes [2]. Since malaria is a disease of poverty and underdevelopment, sustainable control may need a broader approach, embracing non-health sectors including agriculture, water and sanitation and housing [6]. Indeed, social and development-related environmental changes are thought to have contributed to malaria elimination in the USA and Europe [107]. Reflecting this, the 2013 *Multisectoral Action Framework for Malaria* outlined practical steps to target the social and environmental determinants of malaria [3]. Additionally the World Health Organization's new *Global Technical Strategy for Malaria* [4] and the complementary Roll Back Malaria action plan both seek to link malaria control with sustainable development [5].

Yet despite support for intersectoral malaria control, we lack specific knowledge of how to target interventions. Indeed, the *Multisectoral Action Framework for Malaria* states 'there is a need to better understand causality, including identifying those intersectoral interventions that have the greatest impact on malaria' [3]. While the odds of malaria infection or clinical malaria are on average doubled in the poorest children within a community [6], we have only a weak understanding of the underlying causal pathways between household-level poverty and malaria. Wealth may help to protect through better access to health care, LLIN coverage, treatment-seeking behaviour, housing quality and food security among other variables [19, 21, 7], but the relative contributions of these factors are unknown. Furthermore, although malaria is associated with poverty, few malaria studies have considered the determinants of rural poverty itself, limiting the evidence on the potential overlap between development initiatives and malaria control [3]. Here we aim to address these knowledge gaps through a novel, interdisciplinary investigation of the association between socioeconomic position (SEP), its determinants, and malaria among children in Nagongera, Uganda, a rural area with high malaria transmission levels.

8.2. Methods

Study site: The study was carried out between August 2011 and September 2014 in Nagongera sub-country, Tororo, Uganda (00°46'10.6"N, 34°01'34.1"E). Rainfall is bimodal and malaria transmission intense with an estimated annual *Plasmodium falciparum* entomological inoculation rate of 125 [174]. Smallholder agriculture is the primary livelihood source.

Cohort study: This study was part of a cohort study described elsewhere [174, 173]. All children aged six months to 10 years and their primary caregivers were enrolled from 100 randomly selected households in August-September 2011. Recruitment was dynamic; eligible children reaching six months were enrolled and children reaching 11 years were withdrawn. Households with no remaining study participants were withdrawn and replaced. Participants were followed for all healthcare needs at the study clinic for 36 months, until September 2014. All study participants were provided a LLIN at enrolment and compliance was >99% by self-report at the time of routine clinic visits. Outcomes measured were: (1) indoor human biting rate (HBR), measured by monthly CDC light trap catches in each home, (2) prevalence of parasitaemia measured routinely every three months by microscopy and (3) incidence of all malaria episodes measured by passive case detection.

Conceptual framework: Collection of socioeconomic data was guided by a pre-defined conceptual framework, hypothesising that: (1) relative agricultural success is associated with higher SEP (Panel 2), (2) high SEP is associated with a lower risk of malaria and (3) the association between SEP and malaria is mediated by treatment-seeking behaviour, house type and food security among other factors (Figure 8.1).

Household and women's surveys: Socioeconomic data were collected through three surveys. Household-level variables were collected through two household surveys: the first at enrollment and the second after 24 months of follow-up in September-October 2013. Both surveys were administered as a structured interview to one designated respondent per household, meeting four inclusion criteria: (1) usual resident, (2) present the previous night, (3) aged ≥ 18 years and (4) informed written consent. Data at the level of each child's mother or female caregiver were collected in a women's survey, administered as a separate structured questionnaire after the second household survey to all women meeting four inclusion criteria: (1) usual resident, (2) present the previous night, (3) age 18-49 years, (4) informed written consent. Households were excluded if no adult respondent could be located on more than three occasions over two weeks.

Data analysis: Data were collected using standardized case record forms entered into Microsoft Access for follow-up of study participants and using a paperless system for the socioeconomic surveys.

Wealth index: Principal component analysis (PCA) was used to create a wealth index from nine variables:[302] ownership of (1) mobile telephones, (2) radios, (3) clocks, (4) cupboards, (5) sofas and (6) tables; (7) number of people per sleeping room, (8) access to an improved toilet and (9) main mode of transport to the health facility. Households were ranked by wealth scores and grouped into tertiles to give a categorical measure of SEP.

There were four components to the analysis that evaluated: (1) the association between agricultural success and SEP, (2) risk factors for HBR, parasite prevalence and incidence of clinical malaria, including SEP, (3) spatial clustering of socioeconomic variables and (4) mediators of the association between SEP and parasite prevalence.

(1) Association between agricultural success and SEP: Agricultural success was estimated using indicators within five domains, after Oya [186] and Scoones [34] (Figure 8.1): (1) land area cultivated, (2) farm labour, (3) capitalisation (access to advanced means of production, such as pesticides or heavy machinery), (4) productivity and (5) market engagement (proportion of produce sold *versus* used for own consumption). Cross tabulations and Pearson's chi-square test were used to explore the associations between indicators of agricultural success, wealth index tertiles and food security.

(2) Risk factors for malaria: For each risk factor, including SEP, we modelled its association with HBR, parasite prevalence and incidence of clinical malaria. Negative binomial regression was used to model the number of *Anopheles* caught per household per night and the number of malaria cases per child with the number of catch nights and person years included as offset terms. The odds of malaria infection at the time of each routine clinic visit were modelled using logistic regression. For the clinical outcomes (parasite prevalence and malaria incidence), age and gender were included in the model as covariates and robust standard errors were used to adjust for repeat measures (clustering) at the household level.

(3) Spatial analysis of socioeconomic variables: Spatial autocorrelation (clustering) of three socioeconomic variables (cultivated land area, wealth index scores and house type) was explored at global scale using univariate Moran's *I* and at local scale using univariate Anselin Moran's *I* (Appendix 8).

(4) Mediation of the association between SEP and malaria: We calculated the effect of SEP on malaria infection risk that is mediated through treatment-seeking behaviour, house type and

food security using the algorithm described by Imai [303] (Figure 8.1). This algorithm makes two ignorability assumptions [303] which in practice will hold if there is no unmeasured confounding of the association between exposure and mediator, exposure and outcome or mediator and outcome, and there is no reverse causation (Appendix 9).

Ethics: Ethical approval for the study was given by the Uganda National Council for Science and Technology; Makerere University School of Medicine Research and Ethics Committee; University of California, San Francisco Committee for Human Research and London School of Hygiene and Tropical Medicine Ethics Committee.

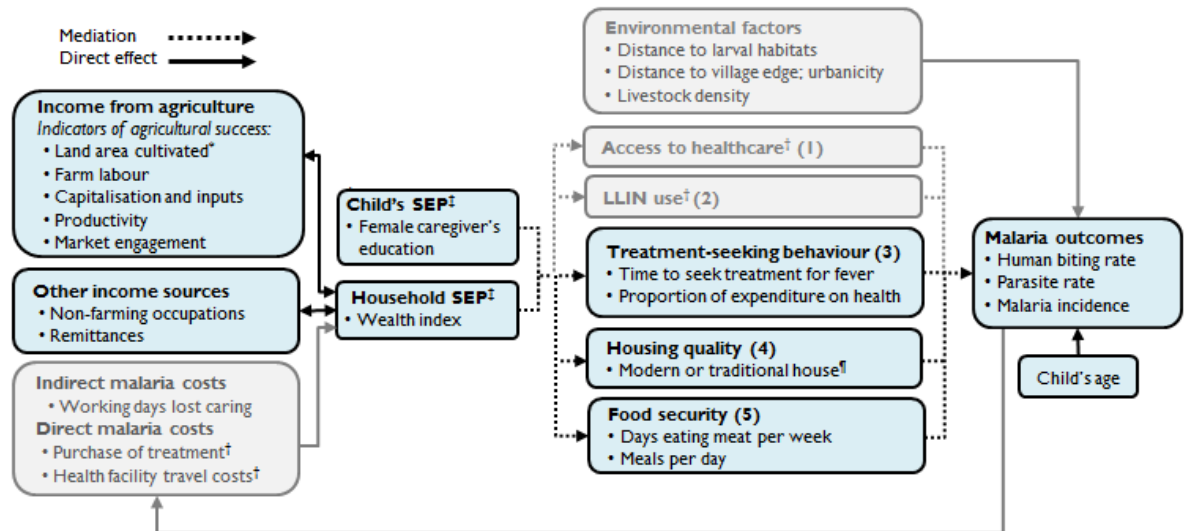


Figure 8.1. Conceptual framework for the relationship between relative agricultural success, socioeconomic position (SEP) and malaria in Nagongera, Uganda

In sub-Saharan Africa, the odds of malaria infection are on average halved in children with the highest SEP within a community, compared to children with lowest SEP [6]. Household SEP may be approximated using a wealth index and personal SEP approximated using the education level of female caregivers.[‡] Wealthier children are hypothesised to have a lower risk of malaria due, among other factors, to: (1) greater disposable income, that makes prophylaxis, treatment and transport to clinics more affordable and therefore improves access to health care [7], (2) greater ownership and use of LLINs [8-11], stemming from greater affordability of LLINs and education [7, 12, 13], (3) improved healthcare-seeking behaviour among caregivers [14, 15] (though the evidence is inconsistent [16, 17]), (4) better housing, which lowers the risk of exposure to malaria vectors indoors [18, 19] and (5) greater food security, which reduces undernutrition and protein-energy malnutrition and possibly subsequent susceptibility to malaria infection and progression to severe disease [20-23] (though the evidence is inconsistent [24, 25]). Modern houses[¶] were defined as those with cement, wood or metal walls; and tiled or metal roof; and closed eaves. All other houses were classified as traditional. Access to healthcare[†] and LLIN use[†] were not hypothesised to be associated with SEP in this study population, since LLINs and all healthcare were provided free of charge. Other household-level risk factors for malaria include distance to larval habitats [26], distance to village periphery [27], urbanicity [28] and the density of livestock nearby [29]; which were outside the scope of this study. In turn, malaria imposes costs that can cause poverty, but this feedback loop was not analysed in this study [30, 31]. Heterogeneity in SEP is hypothesised to be driven largely by relative success in smallholder agriculture, since agriculture is the primary livelihood source in Nagongera. There are many other determinants of SEP that are well studied outside the health sphere [32-34], but we include here only non-agricultural income and access to remittances. Cultivated land area* is included as an indicator of relative agricultural success, but may also be a determinant of relative agricultural success among other factors which are outside the scope of this study. This conceptual framework is not an exhaustive representation of all malaria risk factors, confounders, mediators and causal associations, but includes only those analysed in this study. The conceptual framework adds greater complexity to those by de Castro [31] and Somi [30], which primarily demonstrate bi-directionality, while this study is chiefly interested in dissecting the strands of the poverty-to-malaria direction.

8.3. Results

Study population: 333 total children in 107 total households were enrolled between August 2011 and September 2014 (Figure 8.2). The mean age of study children during follow-up was 5.7 years and 153 (46%) were female.

Wealth index: The first principal component explained 29.3% of overall variability in the asset variables. The weight assigned to each variable was: cupboard ownership (0.45), clock ownership (0.43), sofa ownership (0.41), table ownership (0.37), mobile ownership (0.30), toilet access (0.29), radio ownership (0.29), people per sleeping room (0.19), mode of transport to health facility (0.10). Wealthier households generally sought treatment for fever faster and had better education, housing and food security than poorer households (Table 8.1).

Association between agricultural success and SEP: All households grew crops and agriculture was the primary source of income for 74% of households. Wealthier households cultivated more land and had higher agricultural income, compared to the lowest tertiles. Wealthier households and those with larger farms also employed more farm labour, were more likely to use an oxplough, owned more tropical livestock units and sold a greater proportion of their crops than poorer households and those with smaller farms (Table 8.2). Households with larger farms reported fewer problems getting food to eat ($p=0.001$) and ate meat more frequently ($p=0.002$).

Risk factors for malaria:

HBR: 124,746 adult female *Anopheles* were caught over 3,489 collection nights, yielding an overall HBR of 35.8 *Anopheles* per house per night. HBR was 29% lower in the wealthiest households (highest versus lowest wealth index tertile: incidence rate ratio (IRR) 0.71, 95% confidence intervals (CI) 0.54-0.93, $p=0.01$) and 47% lower in households with good house construction, controlling for household SEP (modern versus traditional housing: adjusted IRR 0.53, 95% CI 0.40-0.69, $p<0.001$) (Table 8.3).

Malaria infection: 3,367 total routine blood smears were taken of which 1,037 (30.8%) were positive. All participants contributed at least one smear. Controlling for age and gender, the odds of infection were 49% lower in children living in modern housing (modern versus traditional housing: adjusted odds ratio (OR) 0.51, 95% CI 0.36-0.71, $p<0.001$), 48% lower in wealthier children (highest versus lowest wealth index tertile: adjusted OR 0.52, 95% CI 0.35-

0.78, $p=0.001$) and 36% lower in children with good food security (meat eaten 3-7 *versus* 0-2 days per week: adjusted OR 0.64, 95% CI 0.47-0.88, $p=0.007$) (Table 8.4).

Incidence of clinical malaria: 2,399 episodes of uncomplicated malaria were diagnosed after 802 person years of follow-up, yielding an overall incidence of 3.0 episodes per person year at risk. One participant was withdrawn immediately after enrolment without contributing person time. Controlling for age and gender, malaria incidence was 31% lower among children with better-educated female caregivers (completed at least primary *versus* no education: adjusted IRR 0.69, 95% CI 0.53-0.91, $p=0.008$). Malaria incidence was not associated with any other risk factors explored (Table 8.4).

Spatial analysis of socioeconomic variables: Across the whole study area, there was no evidence of clustering of cultivated land area, house type or wealth index (Appendix 8). However, there was local clustering of these three variables, with a cluster of modern housing and high wealth index scores in study houses located in a small town (Nagongera) at the south east of the study area (Figure 8.3).

Mediation of the association between SEP and malaria: There was evidence that the total effect of SEP on malaria infection risk in children was partly explained by differences in house quality (24.9%, 95% CI 15.8% – 58.6%) and food security (18.6%, 95% CI 11.6% – 48.3%) in wealthier and poorer homes, but no evidence of mediation by health expenditure (Table 8.5).

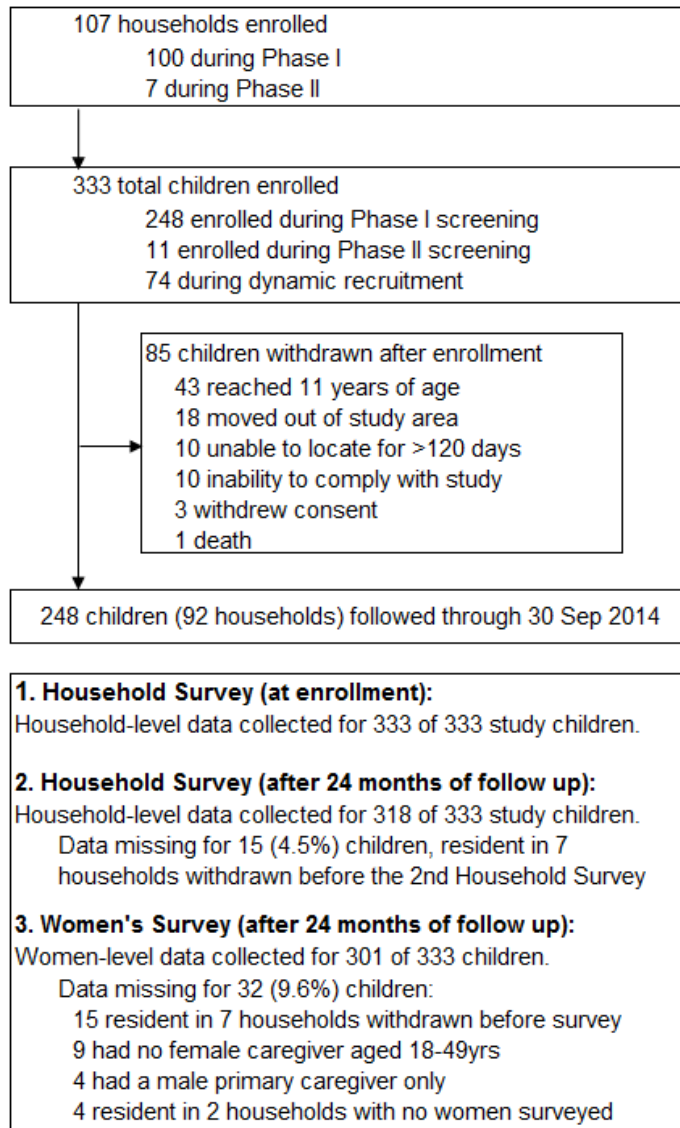


Figure 8.2. Study profile for a cohort of children followed for 36 months in Nagongera, Uganda

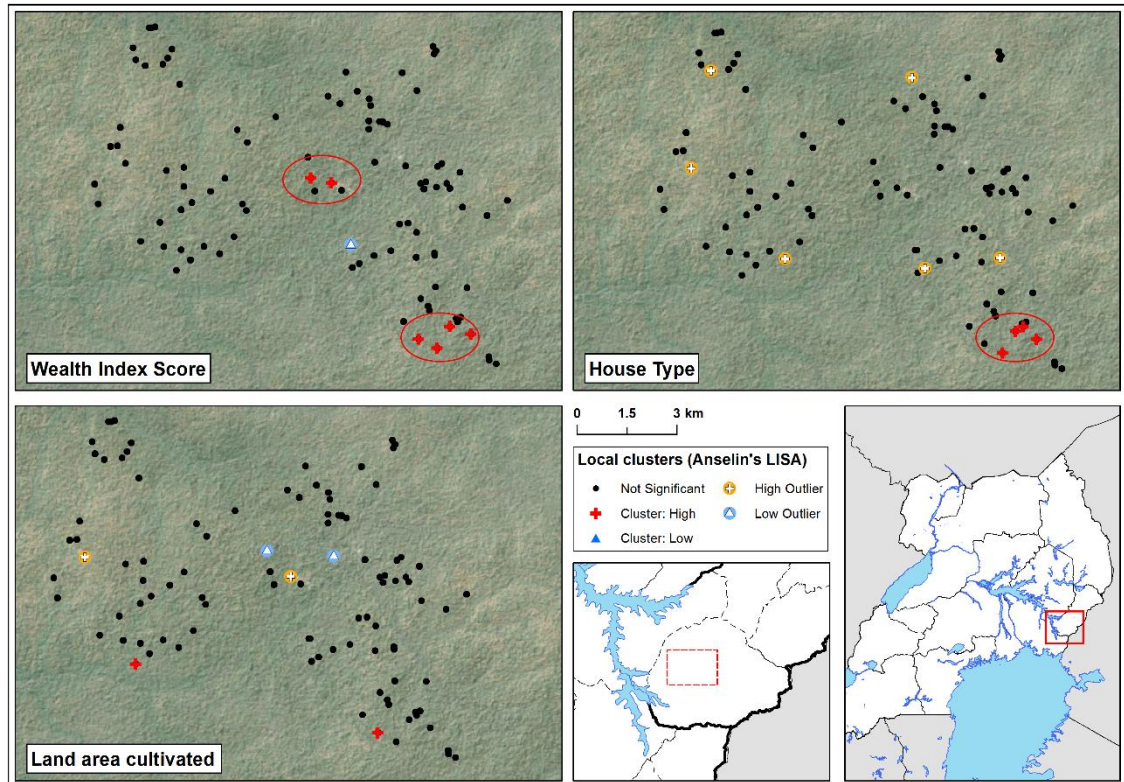


Figure 8.3. Local cluster maps of wealth index score, house type (modern *versus* traditional) and cultivated land area in 100 households in Nagongera, Uganda.

Maps show results from univariate Local Indicator of Spatial Association analysis [304]. A cluster of high wealth index scores overlapping with a cluster of modern housing is seen in the south-east of the study area. Houses were classified as modern (cement, wood or metal walls; and tiled or metal roof; and closed eaves) or traditional (all other houses).

Table 8.1. Characteristics of study participants and households in Nagongera, Uganda

Characteristic	Tertile of wealth (%)			
	Low	Middle	High	p
Characteristics of children (N=333)				
Mean age during follow up in years	5.6	5.6	5.8	0.61
Female	41.8	45.8	50.5	0.45
Female caregiver completed at least primary education ^a	7.5	26.0	27.6	0.003
Female caregiver seeks fever treatment on same day ^b	28.8	8.2	42.0	<0.001
Characteristics of households (N=100)				
Distance to nearest health facility <3 km	54.3	40.6	48.5	0.53
Health expenditure ≥25% of total household expenditure	8.6	6.3	18.2	0.26
Modern house ^c	0.0	25.0	48.5	<0.001
Meat eaten ≥3 days per week	17.1	37.5	66.7	<0.001
Meals per day ≥3	2.9	28.1	54.6	<0.001
Land area cultivated ≥1.6 ha ^d	28.6	34.4	60.6	0.02

^aData on caregiver's education collected for 301 of 333 (90%) children.

^bData on caregiver's treatment-seeking behaviour collected for 191 of 333 (57%) children.

^cModern house: Cement, wood or metal wall; tiled or metal roof and closed eaves. Traditional house: all other houses.

^dHa = hectare; 1.6ha = 4 acres

Table 8.2. Association between agricultural success, cultivated land area and household socioeconomic position in 100 households in Nagongera, Uganda

Indicator	Land area cultivated (%)			Wealth index tertile (%)			
	<1.6 ha ^a N=59	≥1.6 ha N=41	P	Poorest N=35	Middle N=32	Highest N=33	P
<i>Land area cultivated</i>							
Land area cultivated (≥1.6 ha vs <1.6ha) ^a	-	-	-	28.6	34.4	60.6	0.02
Land ownership (all owned vs part rented)	35.6	51.2	0.12	45.7	34.4	45.5	0.57
<i>Farm labour</i>							
Hired farm labour	50.9	61.0	0.32	42.9	43.8	78.8	0.004
Total number of farm workers (≥6 people vs 0-5 people)	25.4	51.2	0.008	17.1	31.3	60.6	0.001
<i>Capitalisation and inputs</i>							
Ox-plough used, past 12 months	33.9	73.2	<0.001	34.3	40.6	75.8	0.001
Pesticides and herbicides used, past 12 months	69.5	78.1	0.34	65.7	75.0	78.8	0.46
Access to credit for agriculture	15.3	29.3	0.09	17.1	18.8	27.3	0.55
<i>Productivity</i>							
TLU ^b per household member (≥0.05 vs <0.05 TLU per person)	33.9	61.0	0.007	37.1	34.4	63.6	0.03
<i>Market engagement</i>							
Total income from crop sales, past 12 months ^c	27.1	51.2	0.002	20.0	31.3	60.6	0.01
Total income from crop and livestock sales, past 12 months ^d	18.6	40.0	0.001	11.4	18.8	53.1	0.001
Proportion of crops sold (≥25% vs <25%)	22.0	48.8	0.005	17.1	31.3	51.5	0.01
<i>Non-agricultural income</i>							
Main source of household income ^e	-	-	-	11.4	15.6	21.2	0.27
Remittances received, past 12 months	-	-	-	5.7	12.5	27.3	0.04

^aHa = hectare; 1.6ha = 4 acres.

^bTropical Livestock Units (TLUs) are a standardised method for quantifying livestock. One TLU corresponds approximately to 250kg animal weight and total TLUs are calculated by assigning region-specific weights to different livestock types. The following weights were assigned, after Chilonda and Otte: 0.5 per cattle, 0.1 per goat, 0.01 per poultry or rabbit [305].

^cTotal income from all crop sales in the past 12 months: ≥200,000 versus <200,000 Ugandan shillings (UGX).

^dTotal income from crop and livestock sales in the past 12 months: ≥300,000 versus <300,000 UGX.

^eMain source of household income: skilled labour versus remittances, agriculture or manual labour.

Table 8.3. Socioeconomic risk factors for human biting rate in 100 households in Nagongera, Uganda

Characteristic		HBR (Total collection nights) ^a	IRR (95% CI) ^b	p
Wealth index tertile	Poorest	41.5 (1136)	1	0.01
	Middle	34.4 (1132)	0.86 (0.65-1.13)	
	Highest	28.8 (1110)	0.71 (0.54-0.93)	
House type ^c	Traditional	40.5 (2690)	1	<0.001
	Modern ^d	19.9 (799)	0.53 (0.40-0.69)	

^aHBR: Human biting rate: total adult female *Anopheles* caught / total days of collection.

^bIRR: Incidence rate ratio; CI: Confidence interval.

^cIRR for this variable was adjusted for socioeconomic position.

^dModern house: Cement, wood or metal wall; tiled or metal roof and closed eaves. Traditional house: all other houses.

Table 8.4. Socioeconomic risk factors for malaria in children aged six months to 10 years in Nagongera, Uganda

Characteristic		Malaria infection			Incidence of clinical malaria		
		PR (Total blood smears) ^a	OR (95% CI) ^b	p	Malaria incidence (total person years) ^c	IRR (95% CI) ^d	p
Mean age during follow-up	6m to <3yrs	19.2 (657)	1		4.1 (134)	1	
	3 to <5yrs	27.6 (699)	1.60 (1.18-2.18)	<0.001	4.2 (177)	1.01 (0.85-1.19)	<0.001
	5 to <11yrs	35.7 (2011)	2.34 (1.77-3.09)		2.3 (491)	0.54 (0.46-0.65)	
Gender	Female	29.9 (1518)	1	0.54	2.7 (361)	1	0.12
	Male	31.5 (1849)	1.07 (0.86-1.35)		3.2 (441)	1.13 (0.97-1.32)	
Wealth index tertile	Lowest	38.4 (1087)	1		3.0 (258)	1	
	Middle	29.6 (1170)	0.65 (0.48-0.87)	0.001	3.1 (280)	1.12 (0.90-1.40)	0.66
	Highest	25.3 (1010)	0.52 (0.35-0.78)		2.9 (241)	1.05 (0.83-1.34)	
Female caregiver's level of education	None	33.4 (788)	1		3.5 (188)	1	
	Incomplete 1 ^{ry}	31.7 (1703)	0.96 (0.68-1.36)	0.21	3.0 (406)	0.83 (0.69-1.01)	0.005
	1 ^{ry} or higher	26.6 (593)	0.74 (0.48-1.15)		2.4 (140)	0.69 (0.53-0.91)	
Distance to health facility	3-6km	33.4 (1994)	1	0.07	2.9 (474)	1	0.56
	0-2km	27.1 (1373)	0.75 (0.55-1.02)		3.1 (328)	1.06 (0.87-1.29)	
Time for female caregiver to seek treatment for fever	≥1 day	29.5 (1434)	1	0.55	3.3 (342)	1	0.31
	Same day	27.5 (509)	0.86 (0.51-1.42)		2.5 (120)	0.87 (0.67-1.13)	
Proportion of household expenditure on health	<25%	31.0 (3059)	1	0.65	3.1 (730)	1	0.15
	25-50%	34.1 (208)	1.15 (0.63-2.10)		2.0 (49)	0.73 (0.48-1.12)	
House type ^e	Traditional	32.9 (2794)	1	<0.001	3.0 (665)	1	0.67
	Modern	20.4 (573)	0.51 (0.36-0.71)		2.7 (136)	0.93 (0.68-1.28)	
Days eating meat per week	0-2 days	34.6 (2123)	1	0.007	3.0 (507)	1	0.71
	3-7 days	24.7 (1144)	0.64 (0.47-0.88)		2.9 (271)	0.96 (0.77-1.20)	
Meals per day	2 meals	33.1 (2439)	1	0.05	3.0 (581)	1	0.78
	3-4 meals	25.6 (828)	0.72 (0.52-1.00)		2.9 (197)	0.96 (0.75-1.24)	

^aPR: *Plasmodium falciparum* parasite rate: total positive blood smears / total blood smears.

^bOR: Odds ratio adjusted for age at the time of the blood smear and gender. CI: Confidence interval.

^cMalaria incidence per person year: total malaria episodes / total person years at risk.

^dIRR: Incidence rate ratio adjusted for mean age during follow-up and gender.

^eModern house: Cement, wood or metal wall; tiled or metal roof and closed eaves. Traditional house: all other houses.

Table 8.5. Mediation analysis of the association between socioeconomic position and malaria infection in children aged six months to 10 years in Nagongera, Uganda

Mediating variable	Risk difference (95% CI) ^a , high versus low SEP ^b			Proportion of total effect of SEP that occurs through mediator, % (95% CI)
	Direct effect of SEP	Effect of SEP through mediator	Total effect of SEP	
Treatment-seeking behaviour ^c	-11.3 (-18.0, -5.0)	0.0 (-0.9, 0.8)	-11.3 (-18.0, -5.1)	0.0 (0.0, 0.0)
House type ^d	-8.6 (-15.6, -2.1)	-2.9 (-5.5, 0.8)	-11.5 (-18.1, -4.9)	24.9 (15.8, 58.6)
Food security ^e	-9.2 (-16.9, -2.2)	-2.1 (-5.3, 0.0)	-11.4 (-18.4, -4.4)	18.6 (11.6, 48.3)

^aRisk difference adjusted for gender, age (<5yrs vs 5-11yrs) and clustering at the household level.

^bSEP: household socioeconomic position, modelled as a binary variable (middle and highest wealth index tertiles versus lowest wealth index tertile).

^c≥25% vs <25% total household expenditure spent on health. Health expenditure was used as a proxy for treatment-seeking behaviour since data on caregiver's treatment-seeking behaviour were available for 191 of 333 (57%) children only.

^dHouse type: modern (cement, wood or metal walls; and tiled or metal roof; and closed eaves) versus traditional (all other houses).

^eFood security: Meat consumed 3-7 days versus 0-2 days per week.

8.4. Discussion

We conducted a novel investigation of the association between SEP, its determinants, and malaria in children in a rural high-transmission setting in Uganda. Households with greater agricultural success had higher SEP. In turn, households and children of higher SEP were exposed to a 29% lower HBR and 48% lower odds of malaria infection than the poorest. Finally, there is evidence that the association between SEP and malaria infection was mediated partly by house type and food security. Our findings concur with observations elsewhere in SSA that malaria prevalence is on average doubled in the children of lowest SEP within communities [6]. The influence of socioeconomic factors may be as important to malaria today in Uganda as it was previously North America and Europe [107].

To our knowledge, the present study is the first to use mediation analysis to explore the causal pathways by which poverty may cause malaria. The analysis suggests firstly that house type can explain part of the association between SEP and malaria infection risk, consistent with previous observations that well-built housing, with closed eaves and modern wall and roof materials, is associated with lower malaria risk through reduced mosquito house entry [18, 19]. Second, we observed that food security may also mediate the poverty-malaria association. Good nutrition may help protect against malaria in Nagongera, since stunting (an indicator of chronic malnutrition) is associated with a higher incidence of clinical malaria in children in the study district [22]. Yet overall the evidence on nutrition and malaria remains mixed [24] and our measure of food security may have been a better proxy for SEP than nutritional status. There was no evidence of mediation by health expenditure, nor was health expenditure an individual risk factor for malaria. Health expenditure may be a poor proxy for treatment-seeking behaviour. Alternatively, health expenditure may have been altered after two years of study participation in which all medications were provided by the health centre.

Identifying potential mediating factors between SEP and malaria provides evidence of a biologically plausible mechanism for causality, yet the mediation analysis accounted for less than half of the association between poverty and malaria, suggesting that other mediators remain unaccounted for. Additionally, the assumptions underlying the mediation analysis may not have been fully met. For example, the costs of malaria can cause poverty [30, 31] and the relationship between SEP and malaria may be confounded by environmental factors such as distance to larval habitats is possible (alternatively, location might lie on the causal pathway between SEP and malaria). While we aimed to omit from the wealth index variables directly associated with malaria [302], some of the included assets may have been associated with both SEP and house type (e.g. sofa ownership or toilet access).

To identify potential overlap between development interventions and malaria control, we sought to better understand heterogeneity in SEP in the study area. Overall we detected a socioeconomic gradient large enough to be associated with variation in malaria risk. In turn, this gradient was associated with relative agricultural success, consistent with agriculture being a major livelihood source in Nagongera as in much of rural Africa [34, 179]. We also observed that wealthier households had larger farms. While wealthier households may invest more in agriculture and other enterprises, land access may constrain productivity in Nagongera due to land fragmentation stemming from the division of land over generations. This fragmentation will likely continue as the Ugandan population expands from 39 million to an estimated 104 million, 2014-2050 [306]. Elsewhere in SSA, poverty has been linked to lower vegetation index scores (NDVI), remoteness and poor soil fertility [307].

By examining the relationship between poverty and malaria, we can identify practical steps towards intersectoral intervention. First, there may be an overlap between poverty reduction and malaria control [6]. Thus, where agriculture is an important livelihood source, interventions such as Farmer Field Schools (a group-based education approach) might be targeted to increase production and marketing capacity while incorporating training in Integrated Pest and Vector Management [301]. If land access constrains productivity, diversification into activities providing non-agricultural income may be necessary. Second, since house quality is associated with malaria risk [115, 19], coordination with housing programmes such as UN-Habitat can encourage 'healthy' new housing and ensure that microfinancing for incremental housing improvements includes health education [221]. Third, should good nutrition be protective against malaria, nutrition-sensitive interventions – including those related to agriculture and food security – may be complementary to malaria control.

Our study has a number of limitations. First, the mediation analysis was based on untestable assumptions, which limits the strength of the findings. Second, the conceptual framework was not an exhaustive representation and we were unable to investigate all pathways linking SEP and malaria, all potential determinants of poverty nor co-endemic health outcomes [179, 34, 217]. Indeed, the mediation analysis suggests that some of these other pathways are important yet missing from the analysis. Third, the wealth index is an imperfect metric and its representation of underlying SEP is influenced by the variables included [302]. Fourth, our spatial analysis modelled few variables relevant to malaria. Despite the methodological challenges, we believe our analysis offers insight into the complex relationship between poverty and malaria and a framework for future interdisciplinary research.

In conclusion, housing improvements and agricultural development interventions to reduce poverty merit further investigation as intersectoral interventions against malaria. Further interdisciplinary research will be needed to fully understand the complex pathways between socioeconomic development and malaria and to identify non-traditional interventions for sustainable malaria control.

Acknowledgments

This work was supported by the Leverhulme Centre for Integrative Research in Agriculture and Health; US National Institutes of Health (U19AI089674); Research and Policy for Infectious Disease Dynamics (RAPIDD) programme of the Science and Technology Directorate, US Department of Homeland Security, the Fogarty International Center (US National Institutes of Health); and the Bill & Melinda Gates Foundation (OPP1053338). We thank the Infectious Diseases Research Collaboration for administrative and technical support and the Malaria Centre at the London School of Hygiene & Tropical Medicine.

Chapter 9. Discussion

9.1. Overview

This thesis has used secondary data from two systematic reviews, together with socioeconomic data collected for children followed for 36 months in rural Uganda, to investigate the household-level association between poverty and malaria. The overall goal was to guide future research into reducing malaria alongside socioeconomic development. This research was motivated by the recognition that coordination with non-health sectors, including water and sanitation, urban planning and housing, is needed for long-term, sustainable intervention against malaria – but that our ability to target such intervention is limited first by a poor understanding of the causal pathways linking poverty and malaria and second by a lack of consideration of the determinants of poverty in rural Africa within malaria studies. This thesis aimed to address both limiting factors.

9.2. Summary of findings

Chapter 2 proposed a conceptual framework of the hypothesized causal pathways between SEP and malaria. These hypotheses were that:

- 1) Since agriculture is the main livelihood in Nagongera, agricultural success is a key determinant of household SEP;
- 2) There is an association between low SEP and increased malaria risk, regardless of the direction of causality;
- 3) The association between SEP and malaria is mediated by (i) treatment-seeking behaviour, (ii) housing quality and (iii) food security among other factors;
- 4) Poor housing quality is associated with increased malaria risk after controlling for SEP, through the effect on mosquito house entry.

The remaining chapters tested these hypotheses through two systematic reviews and meta-analyses and through the collection of socioeconomic data for a cohort of 318 children resident in 100 households who were followed for 36 months in Nagongera, Uganda.

Chapter 3 systematically reviewed the evidence for the association between poverty and malaria in sub-Saharan Africa (SSA). Malaria has long been recognized as a ‘disease of poverty’, yet the only previous review (non-systematic) of published evidence for the relationship between poverty and malaria found mixed evidence of any association [105]. In the present study, of 4,696 studies reviewed, 15 studies were identified as eligible for inclusion. In the meta-analysis of both crude and adjusted results, there was strong evidence that the odds of malaria infection were approximately doubled in the poorest children, compared with the

least poor children (crude odds ratio (OR) 1.66, 95% confidence intervals (CI) 1.35 to 2.05, $p < 0.001$, $I^2 = 68\%$; adjusted OR 2.06, 95% CI 1.42 to 2.97, $p < 0.001$, $I^2 = 63\%$), an effect consistent across subgroups [6]. Thus, Chapter 3 provides direct evidence in support of Hypothesis 2, that there is an association between low SEP and increased malaria risk, regardless of the direction of causality.

Chapter 4 systematically reviewed the evidence for the association between house construction and malaria across SSA, Asia and South America and was the first systematic review of this relationship [19]. Of 15,526 studies screened, 90 were included in a qualitative synthesis and 53 reported epidemiological outcomes, included in a meta-analysis. Residents of modern houses had 47% lower odds of malaria infection compared to traditional houses (adjusted OR 0.53, 95% CI 0.42-0.67, $p < 0.001$, five studies) and a 45-65% lower odds of clinical malaria (case-control studies: adjusted OR 0.35, 95% CI 0.20-0.62, $p < 0.001$, one study; cohort studies: adjusted incidence rate ratio (IRR) 0.55, 95% CI 0.36-0.84, $p = 0.005$, three studies). Evidence of a high risk of bias was found within studies. Overall, despite low quality evidence, the direction and consistency of effects indicated housing as an important risk factor for malaria.

Chapter 5 also investigated the association between housing and malaria, but specifically at three sites in Uganda: Walukuba, Jinja district; Kihhihi, Kanungu district; and Nagongera, Tororo district [18]. Data were analysed from a cohort study that prospectively followed all children aged six months to ten years ($n = 878$) for a total of 24 months to measure parasite prevalence every three months and malaria incidence, and that conducted CDC light trap collections of mosquitoes monthly in all homes. Homes were classified as modern (cement, wood or metal walls; and tiled or metal roof; and closed eaves) or traditional (all other homes). The human biting rate (HBR) was lower in modern homes than in traditional homes (adjusted IRR 0.48, 95% CI 0.37-0.64, $p < 0.001$). The odds of malaria infection were lower in modern homes across all the sub-counties (adjusted OR 0.44, 95% CI 0.30-0.65, $p < 0.001$), while malaria incidence was lower in modern homes in Kihhihi (adjusted IRR 0.61, 95% CI 0.40-0.91, $p = 0.02$) but not in Walukuba or Nagongera. The results indicated that house design is likely to explain some of the heterogeneity of malaria transmission in Uganda and may represent a promising target for future intervention, even in highly endemic areas.

Taken together, the findings of Chapters 4 and 5 provide evidence in support of Hypothesis 4, that poor housing quality is associated with increased malaria risk after controlling for SEP, through its effect on mosquito house entry.

Since poverty is associated with malaria, but there is little consensus on how to measure poverty in malaria studies, **Chapter 6** explored the agreement between four indicators of socioeconomic position (SEP) and evaluated how HBR, parasite prevalence and malaria incidence varied with these four indicators of SEP in 318 children followed for 36 months in Nagongera, Uganda. SEP was determined using: (1) two wealth indices derived from principal component analysis, (2) income, (3) occupation and (4) female caregiver's education. Wealth Index I (reference index) included asset ownership and access to infrastructure variables alone. Wealth Index II additionally included food security and house construction variables; factors that are often included in wealth indices but that may directly affect malaria risk. This was the first evaluation of metrics beyond wealth and consumption indices for measuring the association between SEP and malaria. Overall, the wealth index still predicted malaria risk after excluding variables directly associated with malaria, but the strength of association was lower. In this setting, wealth indices, income and education were stronger predictors of socioeconomic differences in malaria risk than occupation.

One objective of this thesis was to explore potential determinants of SEP in Nagongera, to identify overlap between poverty reduction and malaria interventions. In agrarian settings where agriculture is the major source of livelihood, quantifying relative agricultural success is important to understand differences in SEP. **Chapter 7** therefore describes a qualitative study to identify indicators of relative agricultural success among smallholder farmers in Nagongera, Uganda. In-depth interviews were conducted with one adult respondent in each of 25 households, randomly selected from 100 households enrolled into a cohort study. All households interviewed (n=25) cultivated land. Agriculture was the primary source of livelihood for 68% (17) of households and 32% (8) households reported additional income from other sources, suggesting that poverty reduction was driven by 'accumulation from below', in which the majority of people are engaged in agriculture, with capital accumulation through surplus production. Between households, there was considerable heterogeneity in farming scale, inputs, capitalisation and market engagement. The findings indicated that occupation groups are unlikely to differentiate between rural households universally engaged in agriculture and that overall production is difficult to measure. There appeared to be heterogeneity in cultivated land area, farm labour hire and use of capital inputs, which may be appropriate indicators of relative agricultural success in Nagongera.

Chapter 8 presents the final synthesis in which the relationships between SEP, potential determinants of SEP, and malaria were evaluated in Nagongera, Uganda. Relative agricultural success was found to be associated with high SEP. In turn, high SEP was associated with lower

HBR (highest versus lowest wealth index tertile: adjusted IRR 0.71, 95% CI 0.54-0.93, $p=0.01$) and lower odds of malaria infection in children (highest versus lowest wealth index tertile: adjusted OR 0.52, 95% CI 0.35-0.78, $p=0.001$), but SEP was not associated with incidence of clinical malaria. At a local level, clustering of cultivated land area, wealth index and house type was detected. Local clustering of HBR and parasite prevalence relative to the wealth index was also detected. There was evidence that part of the total effect of SEP on malaria infection risk was mediated by house type (24.9%, 95% CI 15.8% – 58.6%) and food security (18.6%, 95% CI 11.6% – 48.3%). Since these factors accounted for less than half of the association between SEP and malaria, other mediators may remain unaccounted for, though it is unclear what these may have been. The findings indicate that housing improvements and agricultural development interventions to reduce poverty merit further investigation as intersectoral interventions against malaria.

Taken together, the findings of Chapters 7 and 8 are consistent with Hypothesis 1, that relative agricultural success is a key determinant of household SEP in Nagongera. First, heterogeneity in SEP was closely associated with relative agricultural success (Chapter 8). This is consistent with the observation that agriculture is the primary livelihood source in Nagongera (Chapter 7) as observed in other African settings [34, 179, 183]. Within the conceptual framework, it was originally hypothesised that cultivated land area was one of a series of indicators appropriate for measuring relative agricultural success in Nagongera. However, cultivated land area was found to be individually associated with nearly all other indicators of agricultural success (Chapter 8) and with SEP, indicating that poverty may be more common in those with small farms. While this provides no evidence of causality from land access to agricultural success and SEP (indeed, wealthier households may invest more in farming), it is plausible that land access is a key constraint to productivity since land fragmentation is highly prevalent in Nagongera.

To our knowledge, the present study is the first to use mediation analysis to explore the causal pathways by which poverty may increase malaria risk. First, we observed that house type may explain part of the association between SEP and malaria infection risk. Studies elsewhere in Uganda [18] and SSA [19] have observed that well-built housing, with closed eaves and modern wall and roof materials, is associated with lower malaria risk through reduced house entry by mosquito vectors, and that measures of higher urbanicity in Uganda can be associated with lower HBR [28]. Second, we found that food security (access to sufficient food) may also mediate the association between poverty and malaria. Good nutrition may help protect against malaria in Nagongera since a previous study in the same district found that stunting, an indicator of chronic malnutrition, was associated with a higher incidence of clinical malaria in

children [22]. Yet overall the evidence on nutrition and malaria remains mixed [24, 25] and our finding should be interpreted with caution since our measure of food security may have acted more as a proxy for SEP than nutritional status [197]. There was no evidence of mediation by health expenditure, nor was health expenditure an individual risk factor for malaria. Health expenditure may be a poor proxy for treatment-seeking behaviour. Alternatively, health expenditure may have been altered after two years of study participation in which all medications were provided by the health centre.

Collectively, the findings of Chapters 3-8 indicate that socioeconomic factors are important to malaria epidemiology today in Uganda and elsewhere in SSA, as they were historically in Europe and North America among other factors. This thesis makes a step towards identifying entry points for intersectoral intervention, yet also confirms the great complexity of the relationship between development and malaria. This complexity is evidenced by the mediation analysis, which indicated that many variables may explain why the poorest children within communities have a greater risk of malaria than the least poor. Fully disentangling these mediators may never be possible – but this study provides a first step.

9.3. Study limitations

While study limitations are discussed in individual chapters, four major limitations are reiterated here. First, central to this thesis was the strong assumption of no reverse causality from malaria to SEP. This assumption was inherent in the interpretation of results from the systematic review and meta-analysis of SEP and malaria (Chapter 3) and central to the methods used to analyse the mediation pathway between SEP and malaria (Chapter 8). Reverse causality from malaria to poverty is highly probable; findings from Tanzania indicate that the direct and indirect costs of malaria can induce poverty within households [30, 31]. Reverse causality from malaria to SEP also complicates the interpretation of the observation that well-built, modern housing is associated with decreased malaria risk (Chapters 4-5), since a high malaria burden could plausibly be associated with poorer housing through its effect on household disposable income and the affordability of building materials. Nevertheless, the elevated HBR observed in homes with mud walls, thatched roofs and open eaves provides a plausible biological explanation for the effect of house quality on malaria transmission.

Two studies in Tanzania have investigated two-way causality using instrumental variable (IV) probit regression, whereby an association between a chosen IV (a factor that causally affects the exposure, but has no effect on the outcome except through the exposure, and does not share any common causes with the outcome) and the outcome of interest provides evidence

of a causal relationship [30, 31]. This method was not possible here due to the lack of a suitable IV. That this thesis does not directly address reverse causality is arguably its greatest weakness. Yet the chief objective was to dissect the strands of the poverty-to-malaria direction, rather than to demonstrate bi-directionality. In some respects the study complements the work of de Castro [31] and Somi [30], for example by building additional complexity into the conceptual framework (Figure 0.1) than those outlined previously [30, 31] and by providing a biologically plausible explanation for the poverty-to-malaria direction.

A second major limitation is the inherent difficulty in measuring SEP – and the residual confounding by SEP of the association between housing and malaria that may ensue. The wealth index is strongly influenced by the choice of included variables; for example, previous wealth indices based on assets alone [13] and on assets and food security [18] in the same district of Uganda were not found to be significantly associated with parasite prevalence. Though the wealth index compares favourably with other SEP indicators and is widely used, the inconsistency associated with the choice of included variables highlights its limitations. Residual confounding by wealth of the association between housing and malaria is plausible: while we broadly aimed to omit from the wealth index factors directly associated with malaria (e.g. house construction materials), some variables included may have been associated with both SEP and house type (e.g. sofa ownership, toilet access or people per sleeping room). This makes it difficult to identify the relative contribution of SEP and housing to malaria risk (Chapter 8). Residual confounding by wealth may also have accounted for the finding that food security part mediated the association between SEP and malaria.

Third, although the conceptual framework was developed using an extensive literature review, it is not an exhaustive representation and was thus subject to initial bias (knowledge of the investigator). Ongoing bias, whereby certain factors are given prominence and others are ignored, was also likely since not all pathways outlined within the framework were investigated, either due to homogeneity in some variables, such as LLIN use, or due to logistical constraints to measuring some variables, including ecological factors such as distance to water bodies, elevation and vegetation, nor did we model seasonal variation in our outcomes of interest, which is a key consideration [308]. A major assumption underlying the mediation analysis of the pathway from SEP to malaria (Chapter 8) was of no unmeasured confounding, yet confounding of the relationship between SEP and malaria by environmental factors such as distance to larval habitats and residence on the periphery of the village, among other variables, is possible [27]. Furthermore, the effects of co-endemic diseases and health outcomes was not accounted for [217].

A final major limitation was that the sample size (300 children per site) was calculated to compare temporal changes in malaria incidence from the present cohort with temporal changes in malaria test positivity rate from health facility based surveillance in Walukuba sub-county, Jinja district; Kihhi sub-county, Kanungu district and Nagongera sub-county, Tororo district. The analysis described in Chapter 5 was a secondary analysis making use of the cohort study datasets and Chapters 6-8 collected additional data for the Nagongera cohort. Thus the study was not powered for the specific analyses undertaken.

Collectively these issues highlight the difficulties in appropriately measuring SEP, the complexity of the relationship between SEP and malaria and some of the methodological challenges in elucidating this relationship. The strength of the findings from observational studies of this kind is low. However, this thesis provides a framework for further research.

9.4. Future directions

Over the course of this PhD, it has become increasingly recognised in the mainstream that international development and malaria control are linked and can be mutually supportive. In 2013, RBM and the United Nations Development Programme (UNDP) published a *Multisectoral Action Framework for Malaria*, advocating for greater coordination with non-health sectors to control malaria [3], that drew on the systematic review of socioeconomic development presented in Chapter 3. Within the Roll Back Malaria Partnership, a new work stream on 'Housing and malaria' was established in 2014 [309]. These advances reflect the growing momentum behind the concept of integrated vector management, which acknowledges that vector-borne disease can be controlled through non-health interventions [76] and is being re-encouraged through updated manuals [310]. More recently, the new *WHO Global Technical Strategy (GTS) For Malaria 2016-2030* recognises that 'efforts to prevent and control malaria contribute to and benefit from sustainable development' and that 'collaboration with non-health sectors needs to be augmented. National malaria programmes should become an integral part of poverty-reduction strategies, national development plans and regional development cooperation strategies' [4]. Complementary to the GTS, the RBM Second Global Malaria Action Plan (GMAP-2) *Towards a Malaria-Free World: A Global Case for Investment and Action 2016–2030* advocates a multisectoral approach towards malaria. At a higher level globally, the new Sustainable Development Goals (SDGs) acknowledge that ill health remains a significant cause and a consequence of poverty [77].

While it is encouraging that high-level support for intersectoral malaria control has built momentum, the evidence underpinning current recommendations remains thin. As already

discussed, this partly stems from a poor understanding of the causal relationship between poverty and malaria, meaning that the relative impact of targeting specific factors – such as housing, education, land use or nutrition – remains unknown [3]. A paucity of truly interdisciplinary research has limited our knowledge of the potential overlap between international development efforts and malaria control and thus our power to advocate for help from the development sector. Specifically, while recognising that malaria is a ‘disease of poverty’, malaria experts do not fully understand theories of poverty reduction, nor are we wholly aware of the development interventions deployed by other sectors. The evidence for intersectoral malaria control also remains weak since ‘development’ is difficult to randomise as an intervention. Of course, there are examples of non-randomised intervention studies to test ‘development’ interventions, yet the effects of individual components within a multiple-intervention package are difficult to measure. This issue was inherent in the Millennium Villages Project, a non-randomised controlled assessment of an integrated, multisectoral approach to rural development, conducted in nine developing countries, which claimed to provide proof-of-concept that such an approach could reduce all-cause mortality in children [311].

By exploring the association between SEP and malaria, the underlying causal pathway between the two, and the potential determinants of SEP in Nagongera, Uganda, this thesis has identified two areas of potential overlap between development and malaria that merit future study. First, poverty reduction may be central to long-term, sustainable malaria control. Poverty reduction is complex, but a local understanding can help identify potential synergy between poverty reduction interventions and malaria control. For example in Nagongera, where poverty reduction may be related to agricultural success, farmers’ assets and capital might be improved through Farmer Field Schools, a group-based education approach to help farmers improve crop yields [301, 312]. The findings of this study were also consistent with cultivated land area being a key constraint to productivity, i.e. that the poorest people are likely to have the smallest farms. Land fragmentation is extensive in Nagongera, the product of an inheritance system that successively divides land over generations, typical of many SSA settings including nearby Rwanda [289]. Since Uganda has one of the highest fertility rates worldwide (5.9 children per woman in 2014) with a projected population increase from 38.8 million in 2014 to 104.1 million in 2050 [306], this process is likely to continue. Thus, more intensive farming or diversification into non-agricultural activities may become increasingly critical. Second, improving housing has great potential as an intersectoral intervention against malaria. We observed that modern housing is associated with an approximately 50% reduction in mosquito house entry and malaria risk, and that house design may explain part of the

association between SEP and malaria. Studies elsewhere in Uganda [18] in other African settings have observed that well-built housing, with closed eaves, modern wall and roof materials and screened doors and windows, is associated with lower malaria risk, through reduced house entry by mosquito vectors [19].

To achieve truly intersectoral malaria control, there are two requirements. First, we must pinpoint exactly which aspects of development (for example housing, food security or education) have the greatest impact on malaria and design and test interventions accordingly, in collaboration with other academic disciplines and sectors. Second, we must use the resulting data to advocate at the highest government levels. The GTS and AIM are helpful stepping stones, but they are targeted at health experts. Direct advocacy of the case for intersectoral malaria control to African leaders, for example through the African Leaders Malaria Alliance, and to ministers of agriculture and forestry, housing and urban planning among others is critical, as demonstrated in Khartoum (Panel 1.1). For example, once we have established which house features are most important for mosquito house entry in different settings and have conducted qualitative studies to design cheap, locally appropriate and protective housing and randomised controlled trials to evaluate the impact on epidemiological and entomological outcomes, we must work with UN agencies and organisations including UNDP, UN-Habitat and Habitat for Humanity International to advocate that governments integrate these house designs within housing programmes. Additionally there is huge potential to enlist the private sector in intersectoral malaria control by appealing to multinational businesses that uphold corporate social responsibility [313].

In conclusion, interdisciplinary research is critical to fully understand the complex pathways between development and malaria, in order to identify sustainable methods of control. Housing improvements and agricultural development interventions to reduce poverty merit specific investigation as intersectoral interventions against malaria.

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Appendices

Appendix 1. Constructing a human development index (HDI) of income and education

The human development index of income and education was calculated using the 'Build Your Own Index' tool available from the United Nations Development Programme website [1]. The index is the geometric mean of normalized indices of income (2011 Gross National Income (GNI) per capita in purchasing power parity terms (constant international 2005 US\$)) and education (expected years of schooling as of 2011 (of children); mean years of schooling as of 2011 (of adults)). Sub-indices (dimension indices) for each of the three components were created by setting minimum and maximum values for each component. Maximum values were set to the observed value of the indicators from the included countries between 1980 and 2010. Minimum values were set to those deemed to be subsistence values or 'natural' zeros; 0 years for both education variables and US\$163 for per capita GNI. The minimum value for education is set at 0 years since societies can subsist without formal education, while a basic income is necessary for survival; US\$163 is the lowest value recorded from any country (Zimbabwe 2008, corresponding to less than 45 cents per day). Dimension indices were then calculated as follows:

$$\text{Dimension index} = \frac{\text{actual value} - \text{minimum value}}{\text{maximum value} - \text{minimum value}}$$

For education, the geometric mean of the two subcomponents was taken, and the above equation applied to create the dimension index. The HDI was then calculated as the geometric mean of the two dimension indices [2]:

$$(I_{\text{Education}}^{1/3} \cdot I_{\text{Income}}^{1/3})$$

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Appendix 3.1. Characteristics of studies included in a meta-analysis of socioeconomic position and malaria

Table A3.1.1 Characteristics of included studies

Reference	Study site	Study design	Study size	Participants	Recruitment of participants	Exposure	Outcome	Comparison	Measure of effect	Crude effect (95% CI)	Adjusted effect (95% CI)	Factors adjusted for	Reason for exclusion from quantitative analysis
<i>Studies included in the quantitative analysis</i>													
Al-Taiar et al., 2009 ¹	Yemen	Case-control	628	Children aged 6 months - 10 years	Recruited from health centres	Low v high SEP	Clinical malaria (parasitaemia plus fever)	Age-matched healthy community controls	OR	1.76 (1.21-2.57)	n/a	n/a	n/a
Baragatti et al., 2009 ²	Burkina Faso	Cross-sectional	3354	Children aged 6 months - 12 years	Randomly sampled from community	Family has irregular land tenure v regular land tenure	P/PR	None	OR	2.07 (1.10-3.88)	1.85 (1.17-2.92)	Age, land tenure, building density, equipment, education, bed net use, season	n/a
Clarke et al., 2001 ³	The Gambia	Cross-sectional	1196	Children aged 6 months - 5 years	Cluster-sampled from 48 villages	'Poor' v 'less poor'	P/PR	None	OR	2.34 (1.35-4.05)	n/a	n/a	n/a
Custodio et al., 2009 ⁴	Equatorial Guinea	Cross-sectional	552	Children aged 0-5 years	Randomly sampled from community	Low v high SEP	P/PR	None	OR	1.49 (0.98-2.25)	n/a	n/a	n/a
Gahutu et al., 2011 ⁵	Rwanda	Cross-sectional	749	Children aged 0-5 years	Randomly selected from villages, health centre and district hospital	Low household income (<5000 Rwandan Franks (RwF)) v high income (>=5000 RwF)	P/PR	None	OR	1.59 (1.05-2.40)	n/a	n/a	n/a
Ghebreyesus et al., 2000 ⁶	Ethiopia	Cross-sectional	2114	Children aged 0-10 years	Randomly sampled from community	House does not own radio v household does own radio	Incidence of clinical malaria (parasitaemia plus fever)	None	OR	0.97 (0.60-1.59)	n/a	n/a	n/a

Table A3.1.1 Characteristics of included studies (continued)

Reference	Study site	Study design	Study size	Participants	Recruitment of participants	Exposure	Outcome	Comparison	Measure of effect	Crude effect (95% CI)	Adjusted effect (95% CI)	Factors adjusted for	Reason for exclusion from quantitative analysis
Koram et al., 1995 ⁷	The Gambia	Case-control	768	Children aged 3 months - 10 years	Recruited from three health centres	Family does not own a refrigerator v family does own refrigerator	Clinical malaria (parasitaemia plus fever)	Age, date and neighbourhood matched healthy controls	OR	2.30 (1.44-3.75)	2.58 (1.46-4.45)	Place of residence, travel history, ownership of housing plot, house type, crowding, mother's knowledge of malaria, insecticide use, medicine use	n/a
Krefis et al., 2010 ⁸	Ghana	Cross-sectional	1,496	Children aged <15 years	Recruited when visiting major hospital for medical care	Low v high SEP	Clinical malaria (parasitaemia plus fever)	None	OR	n/a	1.79 (1.32-2.44)	Age, sex, ethnicity, number of children in family, mother's age, place of residence	n/a
Ong'Echa et al., 2006 ⁹	Kenya	Case control	374	Children aged 0-3 years Cerebral malaria and children with previous hospital visits excluded.	Recruited when visiting district hospital with symptoms of malaria.	Parents are farmers v parents are not farmers	Clinical malaria (parasitaemia plus fever)	Healthy controls recruited from MCH clinic	OR	3.85 (1.64-9.09)	0.92 (0.41-2.04)	child risk factors, nutritional factors, house type, mosquito control measures	n/a
Pullan et al., 2010 ¹⁰	Uganda	Cross-sectional	1770	Children aged 5-15 years	Selected from all households of district	Lowest SEP quintile v highest	P/PR	None	OR	1.25 (0.74-2.13)	n/a	n/a	n/a
Ronald et al., 2006 ^{11*}	Ghana	Cross-sectional	296	Children aged 1-9 years	Randomly sampled from community	Decreasing household SEP	P/PR	None	OR	3.22 (1.95-5.32)	3.95 (2.26-6.90)	Age, travel to rural areas	n/a

Table A3.1.1 Characteristics of included studies (continued)

Reference	Study site	Study design	Study size	Participants	Recruitment of participants	Exposure	Outcome	Comparison	Measure of effect	Crude effect (95% CI)	Adjusted effect (95% CI)	Factors adjusted for	Reason for exclusion from quantitative analysis
Slutsker et al., 1996 ¹²	Malawi	Cross-sectional	3915	Infants aged 0-3 months	Infants' mothers were enrolled into a chemoprophylaxis study at four ante-natal clinics	Low v high or medium SEP	PfPR	None	OR	1.80 (1.30-2.10)	n/a	n/a	n/a
Villamor et al., 2003 ¹³	Tanzania	Cross-sectional	687	Children aged 6 - 60 months	Children enrolled in a vitamin A supplementation trial admitted to hospital with pneumonia	No electricity at home v electricity at home	PfPR	None	OR	1.84 (1.23-2.76)	n/a	n/a	n/a
Winskill et al., 2011 ^{14*}	Tanzania	Cross-sectional	1438	Children aged 6 months - 13 years	Randomly selected from 21 hamlets	Decreasing household SEP	PfPR	None	OR	1.15 (0.94-1.39)	n/a	n/a	n/a
Yamamoto et al., 2010 ¹⁵	Burkina Faso	Case-control	283	Children aged 0-9 years	Recruited by passive case detection at central laboratory	Low v high SEP	Clinical malaria (parasitaemia plus fever)	Age, sex, ethnicity and residence matched controls from DSS database	OR	0.47 (0.20-1.08)	n/a	n/a	n/a
<i>Studies excluded from quantitative analysis</i>													
Clark et al., 2008 ¹⁶	Uganda	Cohort	558	Children aged 1-10 years	Recruited from a census population in one parish	1st and 2nd quintiles (lowest) v 4th wealth quintile (highest)	Incidence of clinical episodes of malaria per person-year at risk	None	RR	2.04 (1.54-2.70)	1.30 (0.96-1.79)	Age, sickle cell trait, G6PD deficiency in females, bednet use, household crowding, distance from swamp	Not possible to calculate OR

Table A3.1.1 Characteristics of included studies (continued)

Reference	Study site	Study design	Study size	Participants	Recruitment of participants	Exposure	Outcome	Comparison	Measure of effect	Crude effect (95% CI)	Adjusted effect (95% CI)	Factors adjusted for	Reason for exclusion from quantitative analysis
Klinkenberg et al., 2006 ¹⁷	Ghana	Cross-sectional	1744	Children aged 6–60 months	Randomly sampled from communities near (<1000m) and less near (>1000m) agricultural sites in Accra	SEP is below mean for the city	PfPR	None	Paper gives insufficient information	n/a	n/a	n/a	Not possible to calculate OR
Kreuels et al., 2008 ¹⁸	Ghana	Cohort	535	Children aged 2 - 4 months	Recruited from nine villages visiting health centre with no chronic diseases. Followed up to 24 months.	Family does not have good financial situation v family has good financial situation	Clinical malaria (parasitaemia plus fever)	None	Incidence rate ratio	1.59 (1.33-1.89)	1.52 (1.27-1.82)	Sex, ethnicity, birth season, sickle cell trait, mother's education, mother's occupation, knowledge of malaria, protective measures	Not possible to calculate OR
Matthys et al., 2006 ¹⁹ *	Côte d'Ivoire	Cross-sectional	672	Children aged 0-15 years	Selected from farming and non-farming households	Low v high SEP	PfPR	None	OR	n/a	2.44 (0.88-10.00)	Age, agricultural zone, crops grown, irrigation, staying overnight in temporary farm hut, distance to permanent ponds and fish ponds.	Bayesian Credible Intervals given only
Pullan et al., 2010 ²⁰ *	Uganda	Cross-sectional	1844	Children aged 5 - 15years.	All residents of four villages asked to participate; 78% included overall.	Decreasing household SEP	PfPR	None	OR	n/a	2.27 (0.88-25.00)	Age, bed net use	Bayesian Credible Intervals given only

OR= Odds ratio. PfPR=*Plasmodium falciparum* parasite rate. RR=risk ratio. SEP=socioeconomic position. *Socioeconomic position analysed as a continuous variable.

References to Appendix 3.1

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Appendix 3.2. Risk of bias assessment for studies included in a meta-analysis of socioeconomic position and malaria

Table A3.2.1 Risk of bias assessment for studies included in a meta-analysis of socioeconomic position and malaria: case-control studies

Reference	Selection				Comparability	Exposure		Overall quality assessment score (of a maximum of 8)
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	
Al-Taiar et al., 2009	* Yes, with independent validation	* Consecutive or obviously representative series of cases	* Community controls	* No history of disease	Study does not control for other factors	Interview not blinded to case/control status	* Yes	5
Koram et al., 1995	* Yes, with independent validation	* Consecutive or obviously representative series of cases	* Community controls	* No history of disease	* * Study controls for insecticide use, place of residence, travel history, ownership of housing plot, house type, crowding, mother's knowledge of malaria, medicine use	Interview not blinded to case/control status	* Yes	7
Ong'Echa et al., 2006	* Yes, with independent validation	* Consecutive or obviously representative series of cases	Hospital controls	* No history of disease	* * Study controls for mosquito control measures, house type, wasting, parents' education	Interview not blinded to case/control status	* Yes	6
Yamamoto et al., 2010	* Yes, with independent validation	* Consecutive or obviously representative series of cases	* Community controls	No description of source	Study does not control for other factors	Interview not blinded to case/control status	* Yes	4

Table A3.2.2 Risk of bias assessment for studies included in a meta-analysis of socioeconomic position and malaria: cross-sectional studies

Reference	Selection		Comparability	Exposure	Overall quality assessment score (of a maximum of 5)
	Representativeness of the sample	Ascertainment of exposure	Comparability of groups on the basis of the design or analysis	Assessment of outcome	
Baragatti et al., 2009	* Somewhat representative of the average child in the community	* Structured interview	** Study controls for age, land tenure, building density, equipment, education, bednet use, season	* Independent blind assessment	5
Clarke et al., 2001	* Truly representative of the average child in the community	* Structured interview	Study does not control for other factors	* Independent blind assessment	3
Custodio et al., 2009	* Truly representative of the average child in the community	* Structured interview	Study does not control for other factors	* Independent blind assessment	3
Gahutu et al., 2011	* Truly representative of the average child in the community	* Structured interview	Study does not control for other factors	* Independent blind assessment	3
Ghebreyesus et al., 2000	Selected group of children (from villages near dams)	* Structured interview	Study does not control for other factors	* Independent blind assessment	2
Krefis et al., 2010	* Somewhat representative of the average child in the community	* Structured interview	** Study controls for age, sex, ethnicity, number of children in family, mother' age, place of residence	* Independent blind assessment	5
Pullan et al., 2011	* Truly representative of the average child in the community	* Structured interview	Study does not control for other factors	* Independent blind assessment	3
Ronald et al., 2006	* Truly representative of the average child in the community	* Structured interview	* Study controls for age, travel to rural areas	* Independent blind assessment	4
Slutsker et al., 1996	* Somewhat representative of the average child in the community	* Structured interview	Study does not control for other factors	* Independent blind assessment	3
Villamor et al., 2003	* Somewhat representative of the average child in the community	No description	Study does not control for other factors	* Independent blind assessment	2
Winskill et al., 2011	* Truly representative of the average child in the community	* Structured interview	Study does not control for other factors	* Independent blind assessment	3

Appendix 3.3. Assessment of publication bias in a systematic-review and meta-analysis of socioeconomic position and malaria.

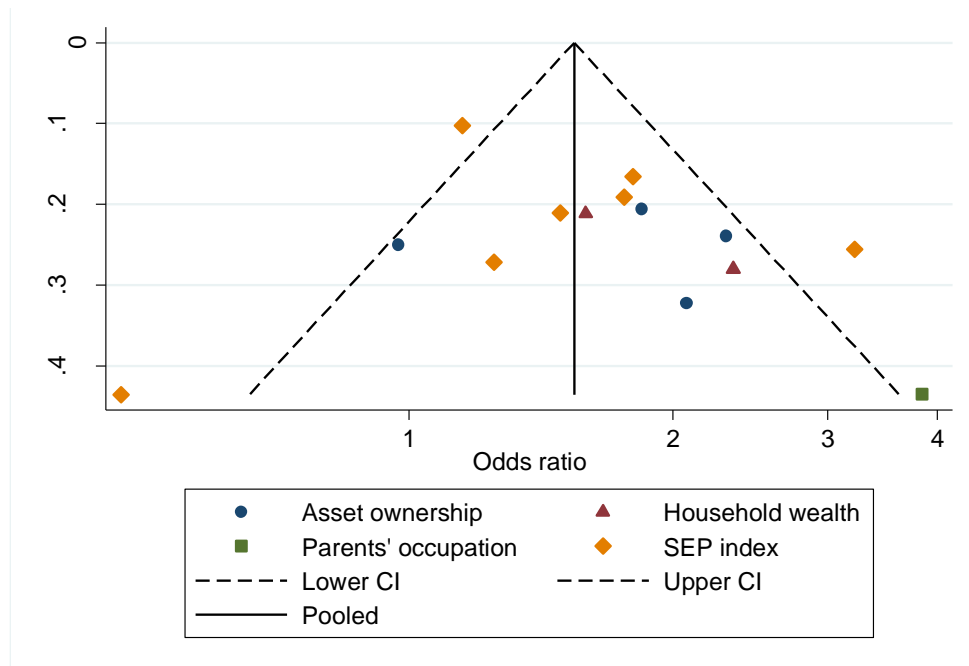


Figure A3.3.1 Funnel plot to assess publication bias in a systematic-review and meta-analysis of socioeconomic position and malaria (studies reporting crude results).
Plot shows study size as a function of effect size for studies included in the meta-analysis.

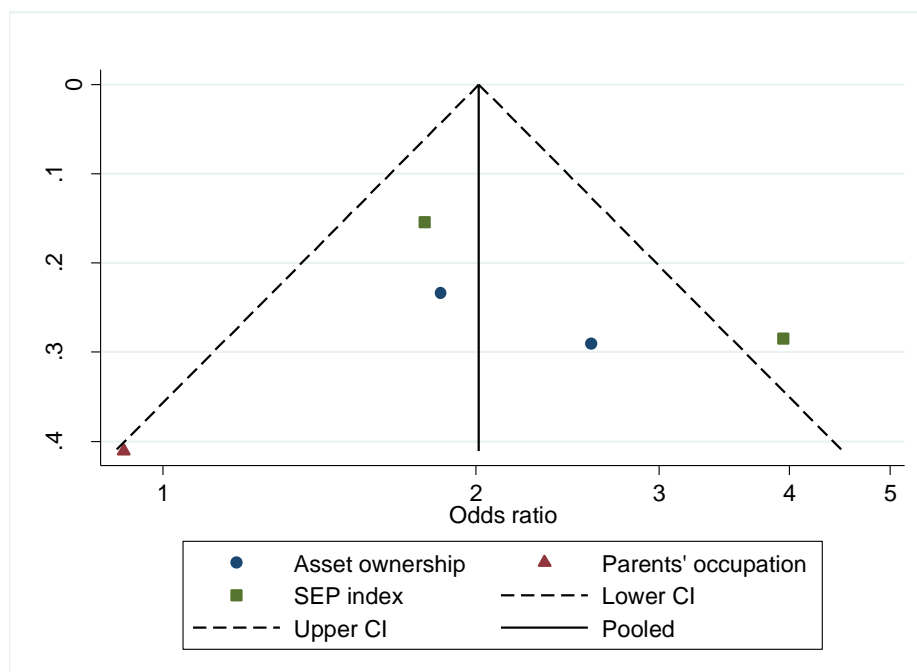


Figure A3.3.2 Funnel plot to assess publication bias in a systematic-review and meta-analysis of socioeconomic position and malaria (studies reporting adjusted results).
Plot shows study size as a function of effect size for studies included in the meta-analysis.

Appendix 4.1. Search strategy in PubMed for a systematic review of housing and malaria.

Search date December 13, 2013

1. Malaria (Medical Subject Headings (MeSH) term)
2. Anopheles (MeSH term)
3. Mosquito Control (MeSH term)
4. Plasmodium (MeSH term)
5. Disease vectors (MeSH term)
6. Insect vectors (MeSH term)
7. Entomology (MeSH term)
8. Malaria (text word)
9. Mosquito* (text word)
10. Anophel* (text word)
11. Entomologic* (text word)
12. Parasitemi* (text word)
13. Parasitaemi* (text word)
14. Plasmodium (text word)
15. 1 or 2 or 3 or 4 or 5 or 6 or 7
16. 8 or 9 or 10 or 11 or 12 or 13 or 14
17. 15 or 16
18. Housing (MeSH term)
19. Architecture as topic (MeSH term)
20. Hous* (text word)
21. Home (text word)
22. Homes (text word)
23. Hut (text word)
24. Huts (text word)
25. Shelter (text word)
26. Shelters (text word)
27. Building* (text word)
28. Dwelling* (text word)
29. Eave* (text word)
30. Wall (text word)
31. Walls (text word)
32. Air brick* (text word)
33. Airbrick* (text word)
34. Roof (text word)
35. Roofing (text word)
36. Door (text word)
37. Doors (text word)
38. Window* (text word)
39. Ceiling* (text word)
40. Stilt (text word)
41. Stilts (text word)
42. 18 or 19
43. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
44. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
45. 42 or 43 or 44
46. 17 and 45

Appendix 4.2. Characteristics of studies included in a systematic review of housing and malaria

Table A4.2.1 Characteristics of intervention studies included in the quantitative analysis (n=6)

Reference	Kampango 2013 ¹	Kirby 2009 ²	Massebo 2013 ³	Mng'ong'o 2011 ⁴	Njie 2009 ⁵	Ogoma 2010 ⁶
Trial design	Randomised controlled study (pilot)	Randomised controlled study	Randomised controlled study (pilot)	Randomised controlled study (pilot)	Randomised cross-over study (pilot)	Non-randomised cross-over study (pilot)
Age	n/a	6 months to 10 years	n/a	n/a	n/a	n/a
Sex	n/a	Any	n/a	n/a	n/a	n/a
Sample size for primary and secondary outcomes	Density of adult anophelines: 16 houses	Anaemia prevalence in children: 755 children in 500 houses. Density of adult anophelines: 500 houses (100 per year in the full screening arm, 100 per year in the ceiling arm, 50 per year in the control arm)	Indoor density of adult anophelines: 40 households (20 in the screened arm and 20 in the control arm)	Density of adult anophelines: 321 houses (231 in treatment arm and 90 in control arm)	Density of adult anophelines: 12 houses	Density of adult anophelines: 4 local houses (one block) and 4 experimental huts (one block)
Intervention	Screening of gables ends and eaves	House screening	House screening	House screening with repellent plants	Screening of eaves	House screening
Details of the intervention	Four experimental rounds: one house randomly assigned control and three houses assigned screening of gables with old bednets, untreated shade cloth or deltamethrin-impregnated shade cloth for 2wks; followed by screening gables and eaves for 1wk	Houses were randomised to one of three arms: (1) no screening, (2) screened ceilings or (3) full screening (screened doors, windows and closed eaves using a mixture of sand, rubble and cement as is normal local practice).	Doors and windows were screened with metal mesh and eaves closed with mud.	Screening of house entry points by planting the densely foliated repellent plant <i>Lantana camara</i> around houses	In the first of two four-week intervention periods, 6 of 12 houses (with no windows and screened doors) were randomly selected and eaves blocked. Before the second period, 6 homes with blocked eaves had them opened, and 6 homes with open eaves had them closed.	Four repetitions of four experimental treatments over four nights in each block. No screening on the first night; on the subsequent three nights three of the four houses in each block had three identical treatments, changed each night (screening the eaves, windows and then doors).
Duration of intervention	3 weeks	6 months in each study year	Two months	10 months	4 weeks	16 days
Co-interventions	None	None. 30% slept under ITNs	Untreated bednets	None	Door screening	Untreated bednet
Co-interventions equal?	n/a	n/a	Yes	n/a	Yes	Yes
Outcomes included in the review	1. Density of adult anophelines , measured by nightly CDC light trap collections.	1. Anaemia prevalence in children , measured by cross-sectional surveys pre- and post-intervention. 2. Density of adult mosquitoes , measured by fortnightly CDC light trap collections. 3. Parasite prevalence , measured by RDTs in pre/post cross-sectional surveys.	1. Density of adult anophelines , measured by CDC light trap collections on four consecutive nights every second week in all households over 2m	1. Density of adult anophelines , measured by ≈8 CDC light trap collections across all houses per week.	1. Density of adult anophelines , sampled using CDC light trap collections one night every two weeks.	1. Density of adult anophelines , measured by nightly CDC light trap collections.
Continent	Africa	Africa	Africa	Africa	Africa	Africa
Country	Mozambique	The Gambia	Ethiopia	Tanzania	The Gambia	Tanzania
Urban or rural	Rural	Rural	Rural	Rural	Rural	Rural
Primary vectors	<i>An. funestus</i> , <i>An. gambiae</i> s.l	<i>An. gambiae</i> s.s., <i>Anopheles arabiensis</i>	<i>An. arabiensis</i>	<i>An. gambiae</i> s.l; <i>An. funestus</i> s.s.	<i>An. gambiae</i> s.s., <i>Anopheles arabiensis</i>	<i>An. gambiae</i> s.l; <i>An. funestus</i> s.s.
Transmission	Not reported	Moderate	Moderate	High	Moderate	High
Funding	Bill & Melinda Gates Foundation	Medical Research Council (UK)	Centre for International Health	Xerox Foundation	Medical Research Council (UK)	Valent Bioscience, CDC, USAID, Addessium Foundation, Wellcome Trust

Pilot study: study with less than one year or transmission season of baseline data and/or intervention implemented for less than one year or transmission season; CDC: Centers for Disease Control and Prevention; OR: Odds ratio; IRR: Incidence rate ratio; ITN: Insecticide-treated net.

Table A4.2.2 Characteristics of observational studies included in the quantitative analysis (n=66)

Study	Country	Setting	Primary vectors	Transmission	LLIN coverage	IRS coverage	Study design	Study size	Age group	Recruitment of participants	Control group	Follow – up	Outcomes included
Abe 2009 VNM⁷	Vietnam	Rural	<i>An. dirus</i>	Low	50.4% coverage (any net)	Not reported	Cross-sectional	682	All ages	Community: All inhabitants of one village were surveyed	n/a	n/a	Malaria infection (microscopy)
Adiamah 1993 GMB⁸	The Gambia	Peri-urban	<i>An. gambiae s.l.</i>	Moderate	29% coverage (any bednet)	Not reported	Case-control	253	<10 yrs	Health facility: Children with mild malaria attending district hospital, age-matched as controls for children with severe malaria	Community controls: healthy, resident >500m from the cases, age-matched	n/a	Mild malaria (parasitaemia plus fever, microscopy); density of adult Anophelines (geometric mean number adult Anopheles per light trap catch)
Al-Mekhlafi 2011 YEM⁹	Yemen	Rural	<i>An. arabiensis</i> , <i>An. culicifacies</i>	Low	Not reported overall	Not reported overall	Cross-sectional	287	All ages	Health facility: febrile patients presenting	n/a	n/a	Malaria infection (microscopy)
Al-Taïar 2009 YEM¹⁰	Yemen	Rural	<i>An. arabiensis</i>	Low	8% coverage in study children (any net)	Not reported overall	Case-control	628	6m – 10 yrs	Health facility: Recruited consecutively from health centres; only one child per family was recruited	Community controls: age- and area of residence matched, healthy (no malaria infection or history of malaria in past 6 months), selected randomly from same community	n/a	Clinical malaria (microscopy)
Animut 2013¹¹	Ethiopia	Rural	<i>An. arabiensis</i>	Not reported	Not reported	Not reported	Cohort	Pyrethrum spray catch: 10 randomly selected houses on 2 nights per village per month	n/a	Randomly sampled from 3 villages	n/a	24 months	Density of <i>An. arabiensis</i> (mean number <i>An. arabiensis</i> per pyrethrum spray catch)
Asante 2013 GHA¹²	Ghana	Urban and rural	Not stated	High	47%	Not reported	Cohort	1855	0–12 months	Health facilities: infants born to all mothers with and without placental malaria resident in 42 communities	n/a	12 months	Clinical malaria (RDT and microscopy; ACD through monthly home visits and PCD at clinics)
Barber 1935 GRC¹³	Greece	Rural	<i>An. elutus</i> , <i>An. maculipennis</i>	Low	Not reported	Not reported	Cross-sectional (clinical data); cohort (entomological data)	461 houses	1–11 months	All children aged 1–11 months resident in five villages (clinical data); all households in five villages (entomological data)	n/a	18 months	Malaria infection (microscopy); density of adult anophelines (mean number <i>An. elutus</i> and <i>An. maculipennis</i> per resting catch)

Table A4.2.2 Characteristics of observational studies included in the quantitative analysis (n=66) (continued)

Study	Country	Setting	Primary vectors	Transmission	LLIN coverage	IRS coverage	Study design	Study size	Age group	Recruitment of participants	Control group	Follow – up	Outcomes included
Bosman 1992¹⁴	Republic of Guinea	Urban and rural	<i>An. gambiae s.l.</i>	High	Not reported	Not reported	Cross-sectional	44 pyrethrum spray catches in three villages	n/a	Not reported	n/a	n/a	Density of adult Anophelines (August monthly mean number adult Anopheles per pyrethrum spray catch)
Bradley 2013 GNQ¹⁵	Bioko, Equatorial Guinea	Rural, coastal	<i>An. funestus</i> , <i>An. gambiae</i>	High	5%	Not reported	Cross-sectional (repeat surveys)	22726	2–14 years	Randomly sampled from census survey	n/a	n/a	Malaria infection (RDT)
Briggs–Watson 1940 USA¹⁶	USA	Rural	<i>An. quadrimaculatus</i>	Low	Not reported	Not reported	Cross-sectional	1118 individuals (143 individuals)	All ages	Purposefully selected from community	n/a	n/a	Malaria infection (microscopy)
Brooker 2004 KEN¹⁷	Kenya	Rural, highland	<i>An. gambiae s.l.</i>	Low	3%	Not reported	Case-control	284	7–18 years (school age)	Recruited using active case detection from three schools over 10 weeks	Age- and school-matched children with absence of symptoms or no parasitaemia	n/a	Clinical malaria (microscopy)
Burkot 1989¹⁸	Papua New Guinea	Rural	<i>An. punctulatus</i>	High	88% reported sleeping under any net	Not reported	Cross-sectional	195 houses	n/a	Households selected from eight villages (not stated how)	n/a	12 months	Human biting rate (mean number of Anopheles per human landing catch)
Butraporn 1986 THA¹⁹	Thailand	Rural	Not stated	High	60% report regular use of bednet	Not reported	Case-control	698	All ages	Systematically sampled from list of malaria-positive cases residing in nine villages	Community controls (selection not described), matched on age, sex, village of residence	n/a	Malaria infection
Charlwood 2003²⁰	Sao Tome	Peri-urban	<i>An. gambiae</i>	Not reported	Not reported	Not reported	Cross-sectional	22 landing catches in homes at ground level; 8 inside houses built on stilts	n/a	Not stated	n/a	n/a	Human biting rate (mean number of Anopheles per man hour of collection (HLC))
Coleman 2010 ZAF²¹	South Africa	Urban	<i>An. arabiensis</i>	Low	17% report sleeping under any net	68%	Case-control	212 households	All ages	Households with at least one confirmed malaria case in study area within study period	Community controls (three nearest households to case households with no confirmed malaria during the same period)	n/a	At least one confirmed case of clinical malaria in household

Table A4.2.2 Characteristics of observational studies included in the quantitative analysis (n=66) (continued)

Study	Country	Setting	Primary vectors	Transmission	LLIN coverage	IRS coverage	Study design	Study size	Age group	Recruitment of participants	Control group	Follow – up	Outcomes included
Coogle 1927 ²²	USA	Rural	<i>An. quadrimaculatus</i>	Low	Not reported	Not reported	Cohort	208 (estimated)	n/a	Purposefully selected from the community	n/a	Not reported	Density of adult anophelines (mean number <i>An. quadrimaculatus</i> per home)
Dahesh 2009 EGY ²³	Egypt	Rural, lowland	<i>Not stated</i>	Not reported	Not reported	Not reported	Cohort	333	All ages	All inhabitants of one village	n/a	n/a	Malaria infection
Danis–Lozano 2007 MEX ²⁴	Mexico	Rural	<i>An. pseudopunctipennis</i> ; <i>An. albimanus</i> .	Low	54% study participants reported always sleeping under net	Not reported	Case–control	357	All ages	Recruited from 60 villages by active case detection and by passive case detection at health facilities from community health workers or health clinics	Community controls, age–matched to within 5 years, resident in the study area, with no parasitaemia and no antibodies to <i>P. vivax</i>	n/a	Clinical malaria (microscopy)
de Almeida 2010 TLS ²⁵	East Timor	Rural	<i>Not stated</i>	Low	49% study participants reported sleeping under a bednet	Not reported	Cross–sectional	216	All ages	All inhabitants of 71 households (selection not described) were sampled	n/a	n/a	Malaria infection (microscopy)
De Beudrap 2011 UGA ²⁶	Uganda	Urban and rural	<i>Not stated</i>	Moderate	45–65% households reported using at least one net	Not reported	Cross–sectional	1325	0–5 years	20 children randomly selected from each of 33 villages	n/a	n/a	Malaria infection (microscopy and RDT)
Ekpenyong 2008 NGA ²⁷	Nigeria	Rural	<i>Not stated</i>	High	3% reported sleeping under bednet	Not reported	Cross–sectional	1296	4–15 years	36 children randomly selected from six randomly selected schools every month for six months	n/a	n/a	Malaria infection (microscopy)
Ernst 2009 KEN ²⁸	Kenya	Rural, highland	<i>An. gambiae</i> s.s.	Low	4% reported sleeping under bednet	Not reported	Case–control	1468	All ages	Individuals presenting to two health centres with malaria symptoms and positive blood smear	Community controls: selected from census, matched by area of residence and age category, with no malaria symptoms the previous month and no history of confirmed malaria in the study period	n/a	Clinical malaria (microscopy)

Table A4.2.2 Characteristics of observational studies included in the quantitative analysis (n=66) (continued)

Study	Country	Setting	Primary vectors	Transmission	LLIN coverage	IRS coverage	Study design	Study size	Age group	Recruitment of participants	Control group	Follow – up	Outcomes included	
Gamage–Mendis 1991²⁹	Sri Lanka	Rural	<i>An. subpictus</i> , <i>An. culicifacies</i>	Moderate	7% use of bednets	Not reported	Cohort	279 PSC in 146 houses	n/a	Randomly selected from one village	n/a	12 months	Indoor resting density (geometric mean number of <i>Anopheles</i> per trap per night)	
Geissbuhler 2007³⁰	Tanzania	Urban and rural	<i>An. gambiae</i> s.s., <i>An. arabiensis</i> , <i>An. merus</i>	Moderate	83% reported sleeping under a net	Not reported	Cross-sectional	216 houses (1 night long HLC in each)	n/a	Selected from households enrolled as sentinel sites for UMCP	n/a	10 weeks	Human biting rate (mean number of bites received by those sleeping indoors (HLC))	
Ghebreyesus 2000 ETH³¹	Ethiopia	Rural, highland	<i>An. arabiensis</i>	Low	Not reported	Not reported	Cohort	2114	0–10 years	All children aged 0–10 years resident in six villages	n/a	12 months	Clinical malaria (microscopy)	
Guthman 2001 PER³²	Peru	Rural	<i>An. albimanus</i> ; <i>An. pseudopunctipennis</i> ; <i>An. calderoni</i>	Low	35% reported sleeping under bednet the previous night	3% in past 6 months	Case–control	1292	All ages	All individuals with malaria symptoms and malaria infection within a community, detected by active case detection	Community controls: age-, sex- and village-matched, with no malaria infection or history of malaria in past 28 days	n/a	12 months	Clinical malaria (microscopy)
Hagmann 2003 STP³³	Principe	Urban and rural	<i>An. gambiae</i>	Moderate	54% reported using bednets		Cross-sectional	1062	All ages	All inhabitants of six communities	n/a	n/a	Malaria infection (microscopy)	
Haque 2013 BGD³⁴	Bangladesh	Rural	<i>An. baimai</i> ; <i>An. minimus</i> s.l.; <i>An. annularis</i>	High	71% households owned at least 0.5 nets per person	Not reported	Cohort	1634 (households)	Households	All households in all 54 villages in one administrative area	n/a	24 months	At least one malaria case per household detected by passive case detection at health facilities	
Hiscox 2013³⁵	Lao PDR	Rural	<i>An. philippinensis</i> , <i>An. nivipes</i> , <i>An. aconitus</i>	Not reported	Not reported	Not reported	Cross-sectional	192 households (96 modern; 96 traditional)	n/a	Randomly selected from census of all households in study area	n/a	n/a	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	
Hustache 2007 GUF³⁶	French Guiana	Rural, forest	<i>An. darlingi</i>	Moderate	70% children reported sleeping under bednets	Not reported	Cohort	369	0–5 years	All children aged 0–5 years in one village	n/a	12 months	Clinical malaria (microscopy)	

Table A4.2.2 Characteristics of observational studies included in the quantitative analysis (n=66) (continued)

Study	Country	Setting	Primary vectors	Transmission	LLIN coverage	IRS coverage	Study design	Study size	Age group	Recruitment of participants	Control group	Follow – up	Outcomes included
Kaur 2009 MYS³⁷	Malaysia	Rural, forest	<i>An. maculatus</i>	Moderate	95% people reported always sleeping under ITN	91% in the past yer	Cross-sectional	520	All ages	Residents of 10 villages randomly selected from 19 villages in one district	n/a	n/a	Malaria infection (microscopy)
Kirby 2008³⁸	The Gambia	Rural	<i>An. gambiae</i> s.s., <i>An. arabiensis</i> , <i>An. melas</i>	Moderate	Not reported	Not reported	Cross-sectional	976 houses (with sentinel LTC in 4 additional houses to adjust for nightly density variation)	n/a	Randomly selected from 46 residential DSS blocks in town and 22 satellite villages	n/a	n/a	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)
Konradsen 2003 LKA³⁹	Sri Lanka	Rural	<i>An. culicifacies</i> , <i>An. subpictus</i>	Not reported	Very low'	Aprox 82% 'good' coverage	Cohort	2640 collections in 473 houses (indoor resting densities sampled fortnightly)	n/a	New 10% sample of houses from 7 contiguous villages randomly selected every fortnight	n/a	30 months	Presence (vs absence) of <i>An. subpictus</i> in each collection (pyrethrum spray catch)
Koram 1995 GMB⁴⁰	The Gambia	Peri-urban	<i>An. gambiae</i> s.s.	Moderate	32% reported using bednets	Not reported	Case-control	768	3m to 10 years	Children presenting to clinic with mild malaria	Community controls: age-matched, randomly selected from compound at least 400m from case compound	n/a	Clinical malaria (microscopy)
Kreuels 2008 GHA⁴¹	Ghana	Rural	<i>An. gambiae</i> s.s., <i>An. arabiensis</i> , <i>An. funestus</i>	High	31% reported using bednet	Not reported	Cohort	535	3 months to 2 years	Participants enrolled into a randomised, double-blind, placebo-controlled study of IPTi	n/a	21 months	Clinical malaria (microscopy)
Lindsay 1988⁴²	The Gambia	Rural	<i>An. gambiae</i> s.s., <i>An. arabiensis</i>	Not reported	Not reported	Not reported	Cohort	Not reported	n/a	Selected from 4 hamlets	n/a	6 months	Density of adult Anophelines (mean number of <i>Anopheles</i> per night)
Lindsay 1995⁴³	The Gambia	Rural	<i>An. gambiae</i> s.s., <i>An. arabiensis</i>	High	90% (children, any net)	Not reported	Cohort	381 bednets in use in one village	n/a	140 bednets sampled randomly every three weeks from bednets of all 381 children aged 0–7 years in one village	n/a	18 months	Density of of adult anophelines (mean number <i>An. gambiae</i> s.l. caught under bednets)

Table A4.2.2 Characteristics of observational studies included in the quantitative analysis (n=66) (continued)

Study	Country	Setting	Primary vectors	Transmission	LLIN coverage	IRS coverage	Study design	Study size	Age group	Recruitment of participants	Control group	Follow – up	Outcomes included
Liu 2014 TZA ⁴⁴	Tanzania	Rural	<i>An. gambiae</i> s.l.; <i>An. arabiensis</i>	Moderate	57% household ownership	Not reported	Cohort	435 houses	2 months – 2 years	Randomly selected from participants of IPTi trial	n/a	22 months	Clinical malaria (microscopy); density of adult anophelines (mean number of <i>Anopheles</i> collected per household)
Magalhaes 2012 AGO ⁴⁵	Angola	Rural	Not stated	Moderate	28% mothers owned bednets	Not reported	Cross-sectional	2265	≤15 years	Households randomly selected from DSS administrative area	n/a	n/a	Malaria infection (RDT)
Maheu–Giroux 2010 PER ⁴⁶	Peru	Rural, forest	<i>An. darlingi</i>	Low	Not reported	Not reported	Cohort	1018	All ages	All households within catchment of health facility sampled, 90% consented to provide data	n/a	30 months	Incidence of clinical malaria (microscopy, retrospective passive case detection)
Malik 2003 SDN ⁴⁷	Sudan	Urban	<i>An. arabiensis</i>	Moderate	11% households used bednets	Not reported	Cross-sectional	8092	All ages	Households randomly selected from three administrative areas and surveyed in three surveys	n/a	n/a	Malaria infection (microscopy)
Mmbando 2011 TZA ⁴⁸	Tanzania	Rural	Not stated	High	'High'	Not reported	Cross-sectional	12298	0–19 years	Randomly selected from 14 villages	n/a	n/a	Malaria infection (microscopy)
Mutuku 2011 ⁴⁹	Kenya	Rural	<i>An. funestus</i> ; <i>An. gambiae</i> s.s.; <i>An. arabiensis</i>	Moderate	68% coverage of all sleeping places (any net)	Not reported	Cohort	1777 collections in 20 houses sampled weekly	n/a	Randomly selected from two villages	n/a	89 weeks	Density of adult Anophelines (pyrethrum spray catch)
Nahum 2010 BEN ⁵⁰	Benin	Peri-urban	<i>An. gambiae</i> s.s.; <i>An. melas</i>	Moderate, seasonal	55% children slept under a bednet	Not reported	Cohort	553	6 months to 5 years	All eligible children from households enumerated in census survey	n/a	18 months	Clinical malaria (microscopy)
Oesterholt 2006 TZA ⁵¹	Tanzania	Rural	<i>An. arabiensis</i>	Low	Not reported	Not reported	Cohort	3388	All ages	All inhabitants of one village included; cases identified by passive case detection at clinic	n/a	12 months	Clinical malaria (fever plus parasitaemia, microscopy)

Table A4.2.2 Characteristics of observational studies included in the quantitative analysis (n=66) (continued)

Study	Country	Setting	Primary vectors	Transmission	LLIN coverage	IRS coverage	Study design	Study size	Age group	Recruitment of participants	Control group	Follow – up	Outcomes included
Ong'Echa 2006 KEN ⁵²	Kenya	Rural	<i>An. gambiae</i> s.s.; <i>An. arabiensis</i> ; <i>An. funestus</i>	High	35% households reported using bednets	Not reported	Case–control	374	0–3 years	Children attending district hospital with malaria symptoms and positive smear	Hospital controls: recruited from MCH clinic at the same hospital during presentation for EPI vaccinations, malaria–negative smear and no history of fever or diarrhoea in past 14 days	n/a	Malaria anaemia, malaria infection
Osterbauer 2012 UGA ⁵³	Uganda	Rural	Not stated	High	34% study participants reported sleeping under ITN the previous night	None	Cross–sectional	600	4–6 months	Recruited using convenience sampling at antenatal clinic in district hospital	n/a	n/a	Malaria infection (microscopy)
Ouma 2007 KEN ⁵⁴	Kenya	Urban and peri–urban	Not stated	High	32% women used ITN in pregnancy	Not reported	Cross–sectional	685	15–45 years	First ANC attenders at district hospital screened for folic acid supplementation trial	n/a	n/a	Malaria infection (microscopy)
Pardo 2006 GNQ ⁵⁵	Bioko, Equatorial Guinea	Urban and rural	<i>An. gambiae</i> s.s.; <i>An. funestus</i>	High	38% slept under any net	78%	Cross–sectional	433	0–5 years	Randomly selected from the community	n/a	n/a	Malaria infection (microscopy)
Peterson 2009a ETH ⁵⁶	Ethiopia	Peri–urban	<i>An. arabiensis</i>	Low	3% households owned a ITN at baseline	Not reported	Cohort	294 (households; with 1367 individuals)	>1 year	Random sampling of every fourth house in city administrative unit	n/a	4 months	Clinical malaria (microscopy)
Peterson 2009b ETH ⁵⁷	Ethiopia	Peri–urban	<i>An. arabiensis</i>	Low	4% compounds owned an ITN	Not reported	Cohort	1187 (compounds; with 8008 individuals)	>1 year	All compounds within one city administrative unit	n/a	4 months	Clinical malaria (microscopy)
Rulisa 2013 RWA ⁵⁸	Rwanda	Rural	Not stated	Moderate	97% people reported sleeping under bednet	94% (self report)	Cross–sectional	520 (households; with 2634 individuals)	All ages	Households in which one member presented at study health facility with fever or history of fever	n/a	n/a	At least one malaria infection in household (microscopy)
Russell 2013 ⁵⁹	Tanzania	Rural	<i>An. arabiensis</i> , <i>An. gambiae</i> s.s	High	Number of bednets in use per person ranged from 0.44 to 0.63 in high density clusters	Not reported	Cohort	72 houses sampled monthly	n/a	Randomly selected from two villages	n/a	12 months	Density of adult <i>An. gambiae</i> s.l. (CDC light trap)

Table A4.2.2 Characteristics of observational studies included in the quantitative analysis (n=66) (continued)

Study	Country	Setting	Primary vectors	Transmission	LLIN coverage	IRS coverage	Study design	Study size	Age group	Recruitment of participants	Control group	Follow – up	Outcomes included
Sintasath 2005 ERI ⁶⁰	Eritrea	Rural; highland and lowland	<i>An. arabiensis</i>	Low	Not reported	39% villages were covered	Cross-sectional	2779 households	All ages	Randomly selected from villages in six zobas that were selected due to greater ecological diversity and population density	n/a	n/a	At least one malaria infection in household (RDT)
Siri 2010 KEN ⁶¹	Kenya	Urban to semi-rural	<i>Not stated</i>	High	46% children slept under bednet the previous week	Not reported	Case-control	906	0–7 years	Children admitted to district hospital inpatient ward with malaria anaemia and high parasitaemia	Community controls: Healthy respondents to a concurrent citywide knowledge, attitude, and practice survey; aged 0–7 years	n/a	Malaria anaemia (microscopy)
Temu 2012 MOZ ⁶³	Mozambique	Rural	<i>An. gambiae</i> , <i>An. funestus</i>	High	23% children slept under ITN	65% children lived in homes with IRS	Cross-sectional	8338	1–15 years	Surveyed as part of a Malaria Indicator Survey at 19 sentinel sites	n/a	n/a	Malaria infection (RDT)
Townes 2013 MWI ⁶⁴	Malawi	Rural	<i>An. funestus</i> , <i>An. gambiae</i> s.s., <i>An. arabiensis</i>	High	53% households at least one bednet	Not reported	Cross-sectional	390	4 months to 5 years	All children aged 4 months to 5 years resident in 10 randomly selected villages	n/a	n/a	Malaria infection (RDT)
Van der Hoek 2003 LKA ⁶⁵	Sri Lanka	Rural	<i>An. culicifacies</i>	Low	6% participants reported sleeping under a bednet in the past 2 weeks	None	Case-control	875	All ages	Inhabitants of seven villages who attended district hospital or mobile clinic with positive blood smear	Community controls: randomly selected from census of same villages who did not report a malaria episode in previous two weeks	n/a	Malaria infection (microscopy)
Wanzirah 2015 ⁶⁶ (published since search)	Uganda	Rural	<i>An. gambiae</i> s.s., <i>An. arabiensis</i>	Moderate to high	99% reported sleeping under any net the previous night	None	Cohort	300 households	n/a	100 households randomly selected from census population in each of three sites	n/a	24 months	Clinical malaria (microscopy); malaria infection (microscopy); human biting rate (mean number of <i>Anopheles</i> per household per night)
Winskil 2011 TZA ⁶⁷	Tanzania	Rural	<i>An. gambiae</i> s.l.	High	46% slept under ITN	Not reported	Cross-sectional	1438	6 months –13 years	All eligible residents of five villages	n/a	n/a	Malaria infection (microscopy)

Table A4.2.2 Characteristics of observational studies included in the quantitative analysis (n=66) (continued)

Study	Country	Setting	Primary vectors	Transmission	LLIN coverage	IRS coverage	Study design	Study size	Age group	Recruitment of participants	Control group	Follow – up	Outcomes included
Wolff 2001 MWI ⁶⁸	Malawi	Rural	Not stated	Moderate	Not reported	Not reported	Cross-sectional	318	0–5 years	Residents of randomly selected houses built by Habitat for Humanity International and the closest traditional house to each	n/a	n/a	Malaria infection (microscopy)
Woyessa 2013 ETH ⁶⁹	Ethiopia	Rural	Not stated	Low	29% households own at least one ITN	Some coverage	Cross-sectional	3398	All ages	Households randomly selected from six administrative areas	n/a	n/a	Malaria infection (microscopy)
Yamamoto 2010 BFA ⁷⁰	Burkina Faso	Peri-urban	Not stated	High	49% participants resided in households reporting use of ITNs	Not reported	Case-control	283	0–9 years	Children presenting to district health facility with fever and parasitaemia	Community controls: age, sex, ethnicity and residence matched, selected from DSS database	n/a	Clinical malaria (microscopy)
Ye 2006 BFA ⁷¹	Burkina Faso	Rural, peri-urban	Not stated	High	53% reported use of any net	Not reported	Cross-sectional	661	6 months – 5 years	Randomly selected using cluster sampling from four DSS sites	n/a	n/a	Malaria infection (microscopy)
Yukich 2013 ETH ⁷²	Ethiopia	Urban and rural	<i>An. arabiensis</i>	Low–moderate	42% participants lived in homes owning at least one ITN, 19% used a ITN the previous night	Not reported	Case-control	560	≥18 years	Individuals presenting at local health facility with fever and malaria infection	Individuals presenting at same health facility without malaria infection	n/a	Malaria infection (microscopy and RDT)
Zhou 2007 ⁷³	Kenya	Rural, highland	<i>An. gambiae</i> s.s., <i>An. funestus</i>	High	Not reported	Not reported	Cohort	871 houses	n/a	Households randomly selected from two areas of 3x3km and 4x4km	n/a	9 months	Density of adult anophelines (mean number of <i>An. gambiae</i> s.s. per house (pyrethrum spray catch))

CDC: Centers for Disease Control and Prevention; OR: Odds ratio; IRR: Incidence rate ratio; RDT: Rapid diagnostic test; ITN: Insecticide-treated net; LLIN: Long-lasting insecticide-treated net; IRS: Indoor residual spraying; PCD: Passive case detection; ACD: Active case detection; SES: socioeconomic status.

Table A4.2.3 Characteristics of observational studies excluded from the quantitative analysis (n=18)

Study	Country	Setting	Primary vectors	Transmission	LLIN coverage	IRS coverage	Study design	Study size	Age group	Recruitment of participants	Control group	Follow-up	Reason for exclusion from quantitative analysis
Ayele 2012 ETH⁷⁴	Ethiopia	Rural, highland	<i>Not stated</i>	Low	Not reported	Not reported	Cross-sectional	5708 households	Not stated	224 clusters of 25 households randomly selected from census	n/a	n/a	Confidence intervals cannot be replicated; data reporting not accurate
Ayele 2013 ETH⁷⁵	Ethiopia	Rural, highland	<i>Not stated</i>	Low	Not reported	Not reported	Cross-sectional	5708 households	Not stated	224 clusters of 25 households randomly selected from census	n/a	n/a	Confidence intervals cannot be replicated; data reporting not accurate
Bell 1997⁷⁶	Solomon Islands	Urban, coastal	<i>An. farauti s.l., An. punctulatus, An. koliensis</i>	Moderate	29.5% (any net); 12.7% (ITN)	Not reported	Cross-sectional	309	>=16 years	Every second outpatient from study health facilities recruited if consent given and aged at least 16 yrs	n/a	n/a	No confidence intervals given; direction of comparison unclear
Cano 2006⁷⁷	Equatorial Guinea	Rural	<i>An. gambiae s.s., An. moucheti, An. carnevalei</i>	High	31% slept under bednet (any)	Not reported	Cohort	One village with 37 households, each of which was surveyed 6–8 times over the collection period	n/a	Two sentinel houses were purposefully selected; 5 light traps were circulated among the remaining households	n/a	42 days	Regression coefficients given only
de Barros 2011⁷⁸	Brazil	Rural	<i>An. darlingi</i>	Not reported	4% families reported sleeping under nets	Not reported	Cohort	333	All ages	All residents of a side road	n/a	30 months	Regression coefficients only
Kibret 2010⁷⁹	Ethiopia	Rural, semi-arid	<i>An. arabiensis, An. pharoensis</i>	Moderate	Not reported	Not reported	Cross-sectional	2435	All ages	Households randomly selected from two villages	n/a	n/a	Regression coefficients only
Lwetoijera 2013 TZA⁸⁰	Tanzania	Rural	<i>An. gambiae s.l., An. funestus</i>	Not reported	100% households owned treated nets, 32% households owned mainly ITNs	Not reported	Cohort	72 randomly selected houses each month	n/a	Randomly selected from two villages each month	n/a	48 months	Regression coefficients given only
Mala 2011⁸¹	Kenya	Rural	<i>An. arabiensis</i>	Not reported	Not reported	Not reported	Cohort	20 houses	n/a	10 houses randomly selected from each of two sites	n/a	22 months	Regression coefficients given only

Table A4.2.3 Characteristics of observational studies excluded from the quantitative analysis (n=18) (continued)

Study	Country	Setting	Primary vectors	Transmission	LLIN coverage	IRS coverage	Study design	Study size	Age group	Recruitment of participants	Control group	Follow – up	Reason for exclusion from quantitative analysis
Manah 2012 ^{82, 83}	Malaysia	Rural	<i>Not stated</i>	Low	Not reported	Not reported	Case–control	332	All ages	All malaria cases notified to the district health office within study period	Age– and sex–matched controls	n/a	House structure described as a risk factor for malaria infection but no data given
Muturi 2008	Kenya	Rural	<i>An. arabiensis</i> , <i>An. pharoensis</i>	Not reported	Not reported	Not reported	Cohort	30 houses	n/a	Randomly selected from 3 study sites	n/a	12 months	Regression coefficients given only
Nkwo–Akenji 2006 ⁸⁴	Cameroon	Rural	<i>An. gambiae</i> ; <i>A. funestus</i>	High	Not reported	Not reported	Cross–sectional	208	0–14 years	Selected from community (not stated how)	n/a	n/a	Confidence intervals not reported
Palsson 2004 ⁸⁵	Guinea Bissau	Peri–urban	<i>An. gambiae</i> s.l., <i>An. squamosus</i>	Moderate	94% people reported sleeping under nets (any)	Not reported	Cohort	30 houses sampled three times during each rainy season	n/a	10 houses selected from each of three areas (not stated how)	n/a	26 months (rainy season only)	Regression coefficients given only
Somi 2007 ⁸⁶	Tanzania	Rural	<i>Not stated</i>	High	50% people reported sleeping under any net, 18% under an ITN	Not reported	Cross–sectional	2318 (household; with 7657 individuals)	All ages	Households randomly selected from two DSS sites	n/a	n/a	Regression coefficients only
Somi 2008 ⁸⁷	Tanzania	Rural	<i>Not stated</i>	High	79% people reported sleeping under any net, 27% under an ITN	Not reported	Cross–sectional	557 (households; with 2034 individuals)	All ages	Households randomly selected from two DSS sites	n/a	n/a	Regression coefficients only
Subramanian 1991 ⁸⁸	India	Rural	<i>An. fluviatilis</i>	Moderate	Not reported	Not reported	Cohort	1461	All ages	All inhabitants of one village	n/a	12 months	Insufficient data reported
Sur 2006 IND ⁸²	India	Urban	<i>An. stephensi</i>	Low	Very low	None	Cohort	60452	All ages	Individuals reporting to a study health post with fever were screened; denominator was total population from census	None	12 months	Relative risk reported only
Tilaye 2007 ETH ⁸⁹	Ethiopia	Urban	<i>Not reported</i>	Not reported	38% individuals belonged to households owning at least one bednet	18% individuals lived in homes with IRS in preceding year	Cross–sectional	734	All ages	Residents of households selected by multi–stage cluster sampling from three randomly selected administrative areas	n/a	n/a	House features included do not represent a comparison of modern versus traditional
Van der Hoek 1998 LKA ⁹⁰	Sri Lanka	Rural	<i>An. culicifacies</i>	Moderate	9% (any net)	90%	Cohort	280	All ages	All inhabitants of one village	n/a	12 months	Relative risk reported only

ITN: Insecticide-treated net; LLIN: Long-lasting insecticide-treated net; IRS: Indoor residual spraying; PCD: Passive case detection; ACD: Active case detection; SES: socioeconomic status; DSS: Demographic Surveillance System

References to Appendix 4.2

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Appendix 4.3. Risk of bias assessment for a systematic review of housing and malaria

Table A4.3.1 Risk of bias assessment for studies included in the quantitative analysis (intervention studies, n=6)

Reference	Allocation sequence generation	Allocation concealment	Baseline outcome measurements	Baseline features	Incomplete outcome data	Length of follow up	Blinding (performance)	Blinding (detection)	Contamination	Selective outcome reporting	Recruitment bias
Kampango 2013	Low	High	Unclear	Unclear	Low	High	High	High	Low	Low	Low
	Intervention randomly allocated	Patients and investigators could foresee assignment	No baseline measurement of outcome	No information reported	Low missing data	Follow up period less than one year or transmission season	Performance bias possible due to knowledge of the allocated interventions	Primary outcomes not assessed blinded.	Unlikely that the control group received the intervention	All pre-specified outcomes are reported	No change in size or number of clusters after randomisation
Kirby 2009	Low	High	Low	Low	Low	Low	High	Low	Low	Low	Low
	Intervention randomly allocated	Patients and investigators could foresee assignment	Outcomes were measured pre intervention and adjusted for in analysis	Baseline characteristics of the study and control areas are reported and similar	Low missing data, balanced across groups	Follow up period at least one transmission season	Performance bias possible due to knowledge of the allocated interventions	Primary outcomes assessed blinded	Unlikely that the control group received the intervention	All pre-specified outcomes are reported	No change in size or number of clusters after randomisation
Massebo 2013	Low	High	Low	Low	Low	High	High	High	Low	Low	Low
	Intervention randomly allocated	Patients and investigators could foresee assignment	Outcomes were measured pre intervention and no important differences were present	Baseline characteristics of the study and control areas are reported and similar	No missing data	Follow up period less than one year or transmission season	Performance bias possible due to knowledge of the allocated interventions	Primary outcomes not assessed blinded.	Unlikely that the control group received the intervention	All pre-specified outcomes are reported	No change in size or number of clusters after randomisation
Mng'ong'o 2011	Low	High	Unclear	High	Unclear	Low	High	High	Low	Low	Low
	Houses selected in stepwise fashion starting from random point	Patients and investigators could foresee assignment	No baseline measurement of outcome	Differences between control and intervention areas	No information reported	Follow up period at least one transmission season	Performance bias possible due to knowledge of the allocated interventions	Primary outcomes not assessed blinded.	Unlikely that the control group received the intervention	All pre-specified outcomes are reported	No change in size or number of clusters after randomisation
Njie 2009	Low	High	Unclear	Unclear	Low	High	High	High	Low	Low	Low
	Intervention randomly allocated	Patients and investigators could foresee assignment	No baseline measurement of outcome	No information	Low missing data	Follow up period less than one year or transmission season	Performance bias possible due to knowledge of the allocated interventions	Primary outcomes not assessed blinded.	Unlikely that the control group received the intervention	All pre-specified outcomes are reported	No change in size or number of clusters after randomisation
Ogoma 2010	Unclear	High	Unclear	Unclear	Low	High	High	High	Low	Low	Low
	No information reported	Patients and investigators could foresee assignment	No baseline measurement of outcome	No information reported	Low missing data	Follow up period less than one year or transmission season	Performance bias possible due to knowledge of the allocated interventions	Primary outcomes not assessed blinded.	Unlikely that the control group received the intervention	All pre-specified outcomes are reported	No change in size or number of clusters after randomisation

Table A4.3.2 Risk of bias assessment for studies included in the quantitative analysis (case–control studies, n=14)

Reference	Selection				Comparability	Exposure			Overall quality assessment score (max 9)
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non–response rate	
Adiamah 1993	Yes, with independent validation *	Consecutive or obviously representative series of cases *	Community controls *	No clinical malaria *	Study controls for age *	Structured interview and direct observation where blind to case/control status *	Yes *	Not described	7
Al–Tair 2009	Yes, with independent validation *	Consecutive or obviously representative series of cases *	Community controls *	No history of malaria in past 6 months *	Study controls for age, location, area of residence, khat trees, larval habitats, IRS, history of travel**	Interview not blinded to case/control status	Yes *	Non respondents described	7
Brooker 2004	Yes, with independent validation *	Consecutive or obviously representative series of cases *	Community controls *	No malaria infection *	Study controls for age *	Structured interview where blind to case/control status *	Yes *	Not described	7
Butraporn 1986	Yes, record linkage	Consecutive or obviously representative series of cases *	Community controls *	No malaria infection *	Study controls for age, gender *	Structured interview where blind to case/control status *	Yes *	Not described	6
Coleman 2010	Yes, record linkage	Consecutive or obviously representative series of cases *	Community controls *	Households with no confirmed case of clinical malaria during the study period *	Study controls for household wealth *	Structured interview where blind to case/control status *	Yes *	Not described	6
Danis–Lozano 2007	Yes, with independent validation *	Potential for biases (not all incident cases were recruited, without explanation)	Community controls *	No malaria infection *	Study controls for age, village, occupation **	Structured interview where blind to case/control status *	Yes *	Rate different and no designation	7
Ernst 2009	Yes, record linkage	Consecutive or obviously representative series of cases *	Community controls *	No malaria symptoms or history of malaria (however not slide confirmed negative)	Study controls for age, study site **	Interview not blinded to case/control status	Yes *	Same rate for both groups *	6
Guthman 2001	Yes, with independent validation *	Consecutive or obviously representative series of cases *	Community controls *	No clinical malaria or infection*	Study controls for age, gender, area of residence, age of house, IRS in past six months, distance to nearest canal, agricultural work, education level **	Structured interview where blind to case/control status *	Yes *	No description	8
Koram 1995	Yes, with independent validation *	Consecutive or obviously representative series of cases *	Community controls *	No clinical malaria *	Study controls for age *	Structured interview and direct observation *	Yes *	No description	7
Ong'Echa 2006	Yes, with independent validation *	Consecutive or obviously representative series of cases *	Hospital controls	No malaria infection or history of fever in past 14 days *	Study controls for age, axillary temperature $\geq 37.5^{\circ}\text{C}$, wasting, caretaker education, occupation of household head and mother, bednet use, mosquito coil use **	Structured interview; blinding not described	Yes *	Same rate for both groups *	7
Siri 2010	Yes, with independent validation *	Consecutive or obviously representative series of cases *	Community controls *	No high parasitaemia or malaria anaemia *	Study controls for age, mosquito coils, bednet ownership, sleeping in rural area, household head gender, wealth, land ownership, domestic animals in residence, crowding, urbanisation **	Direct observation and interview not blind to case/control status	No	No description	6

Table A4.3.2 Risk of bias assessment for studies included in the quantitative analysis (case–control studies, n=14) (continued)

Reference	Selection				Comparability	Exposure			Overall quality assessment score (max 9)
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Van der Hoek 2003	Yes, record linkage	Consecutive or obviously representative series of cases *	Community controls *	No malaria infection	Study controls for age, gender, distance to stream, distance to cattle shed, use of bednets, pyrethrum coils and traditional fumigants, IRS **	Direct observation; not clear whether blinded to case/control status	Yes *	No description	5
Yanamoto 2010	Yes, record linkage	Consecutive or obviously representative series of cases *	Community controls *	No description of malaria infection status	Study design controls for age *	Direct observation *	Yes *	No description	5
Yukich 2013	Yes, record linkage	Consecutive or obviously representative series of cases *	Hospital controls	No malaria infection *	Study does not control for other factors	Structured interview where blind to case/control status *	Yes *	No description	4

ITN: Insecticide-treated net; LLIN: Long-lasting insecticide-treated net; IRS: Indoor residual spraying

Table A4.3.3 Risk of bias assessment for studies included in the quantitative analysis (cross-sectional studies, n=31)

Reference	Selection		Comparability	Exposure	Overall quality assessment score (max 5)
	Representativeness of the sample	Assessment of outcome	Comparability of groups on the basis of the design or analysis	Ascertainment of exposure	
Abe 2009	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study controls for age, numebr of family members, bednet use**	Structured interview*	5
Al-Makhlafi 2011	Somewhat representative of the average individual or household in the community *	Independent blind assessment *	Study does not control for other factors	Structured interview*	3
Barber 1935	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study does not control for other factors	Direct observation *	3
Bosman 1992	No description of the derivation of the sample	Independent blind assessment *	Study does not control for other factors	Secure record *	2
Bradley 2013	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study controls for age, year of survey, spray coverage, net use, socioeconomic status, living in an urban area, crowding, eaves and screening **	Secure record *	5
Briggs-Watson	No description of the derivation of the sample	Independent blind assessment *	Study does not control for other factors	Direct observation *	2
Burkot 1989	No description of the derivation of the sample	Independent blind assessment *	Study does not control for other factors	Direct observation *	2
Charlwood 2003	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study does not control for other factors	Direct observation *	3
Dahesh 2009	No description of the derivation of the sample	Independent blind assessment *	Study does not control for other factors	Structured interview *	2
de Almeida 2010	No description of the derivation of the sample	Independent blind assessment *	Study does not control for other factors	Structured interview *	2
de Beaudrap 2010	Somewhat representative of the average individual or household in the community (children aged 0–5 years) *	Independent blind assessment *	Study controls for age, weight-for-age, socioeconomic status, education level of household head, latitude, altitude, bednet use **	Structured interview *	5
Ekpenyong 2008	Somewhat representative of the average individual or household in the community (school children) *	Independent blind assessment *	Study does not control for other factors	Structured interview *	3
Geissbuhler 2007	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study does not control for other factors	Direct observation *	3
Hagmann 2003	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study does not control for other factors	Structured interview *	3
Hiscox 2013	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study controls for village, location of kitchen, wall material, veranda style, presence of animals *	Visual observation *	4
Kaur 2009	Somewhat representative of the average individual or household in the community (77.5% response rate) *	Independent blind assessment *	Study controls for age, protective clothing, going out at night, ever staying in another village **	Structured interview *	5

Table A4.3.3 Risk of bias assessment for studies included in the quantitative analysis (cross-sectional studies, n=31) (continued)

Reference	Selection		Comparability	Exposure	Overall quality assessment score (max 5)
	Representativeness of the sample	Assessment of outcome	Comparability of groups on the basis of the design or analysis	Ascertainment of exposure	
Kirby 2008	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study controls for distance to nearest pit latrine, horses in compound, eave type, crowding, churai in room *	Visual observation *	4
Magalhaes 2012	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study does not control for other factors	Structured interview *	3
Malik 2003	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study controls for age, gender, season, bednet use, distance to health facility, indoor breeding, region, IRS **	Structured interview *	5
Mmbando 2011	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study controls for age, bednet use, socioeconomic status, passive case detection, altitude, season **	Structured interview *	5
Osterbauer 2012	Selected group (infants recruited at antenatal clinic)	Independent blind assessment *	Study controls for age, HIV-exposure at birth, period of enrollment, gender, mother's age, bednet use, trimethoprim-sulphamethoxazole prophylaxis **	Structured interview *	4
Ouma 2007	Selected group (women attending antenatal clinic)	Independent blind assessment *	Study controls for age, ethnicity, area of residence, spending night in malarious area, trimester, bednet use, treatment of bednet **	Structured interview *	4
Pardo 2006	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study does not control for other factors	Structured interview *	3
Rulisa 2013	Selected group (households in which one member presented to health facility with fever)	Independent blind assessment *	Study controls for gender, age, positivity of study index case, bednet ownership, main roof material, presence of open water vessel, vegetation around home, electricity **	Structured interview *	4
Sintasath 2005	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study controls for ecological strata, eaves, IRS, distance to river, rainfall *	Structured interview *	4
Temu 2012	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study controls for age, socioeconomic status, year of survey **	Structured interview *	5
Townes 2013	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study does not control for other factors	Structured interview *	3
Winskill 2012	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study does not control for other factors	Structured interview *	3
Wolff 2001	Selected group (households who received Habitat for Humanity homes and their neighbours)	Independent blind assessment *	Study controls for water source, occupation, education, malaria knowledge, waste disposal method *	Structured interview *	3
Woyessa 2013	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study does not control for other factors	Structured interview *	3
Ye 2006	Truly representative of the average individual or household in the community *	Independent blind assessment *	Study controls for site, presence of larval habitat, well and animal enclosure, bednet use *	Structured interview *	4

ITN: Insecticide-treated net; LLIN: Long-lasting insecticide-treated net; IRS: Indoor residual spraying

Table A4.3.4 Risk of bias assessment for studies included in the quantitative analysis (cohort studies, n=21)

Reference	Selection			Comparability	Exposure			Overall quality assessment score (max 9)
	Representativeness of the sample	Selection of the non-exposed cohort	Assessment of outcome	Comparability of groups on the basis of the design or analysis	Ascertainment of exposure	Was follow-up at least one transmission season or year?	Adequacy of follow up of cohorts	
Animut 2013	Truly representative of the average individual or household in the community *	Drawn from the same community as the exposed cohort *	Independent blind assessment *	Study does not control for other factors	Direct observation *	Yes *	Complete follow up *	6
Asante 2013	Somewhat representative of the average individual or household in the community (infants only) *	Drawn from the same community as the exposed cohort *	Independent blind assessment *	Study controls for age, mother's gravidity, primagravidae, wealth, maternal anaemia, urban or rural, distance to health facility, ITN use, malaria exposure score (based on sibling and neighbour malaria antibody) **	Direct observation *	Yes *	Subjects lost to follow up unlikely to introduce bias – small number lost (83.2%) *	8
Coogle 1927	No description of the derivation of the cohort	No description of the derivation of the unexposed cohort	No description	Study does not control for other factors	No description	No description	No statement	0
Gamage–Mendis 1991	Truly representative of the average individual or household in the community *	Drawn from the same community as the exposed cohort *	Independent blind assessment *	Study does not control for other factors	Direct observation *	Yes *	No statement	5
Ghebreyesus 2000	Somewhat representative of the average individual or household in the community (children aged 0–10 years) *	Drawn from the same community as the exposed cohort *	Independent blind assessment *	Study adjusts for age, sex, time at risk, eave type, presence of windows, number of sleeping rooms, livestock ownership, radio ownership, water source, use of irrigated land **	Structured interview *	Yes *	Complete follow up *	9
Haque 2013	Truly representative of the average individual or household in the community *	Drawn from the same community as the exposed cohort *	Record linkage *	Study controls for bednet ratio, house density, distance to nearest streams, elevation *	Visual observation *	Yes *	No statement	6
Hustache 2007	Somewhat representative of the average individual or household in the community *	Drawn from the same community as the exposed cohort *	Record linkage *	Study does not control for other factors	Direct observation *	Yes *	No statement	5
Konradsen 2000	Truly representative of the average individual or household in the community *	Drawn from the same community as the exposed cohort *	Independent blind assessment *	Study does not control for other factors	Direct observation *	Yes *	Complete follow up *	6
Kreuels 2008	Somewhat representative of the average individual or household in the community (infants enrolled into IPTi trial) *	Drawn from the same community as the exposed cohort *	Independent blind assessment *	Study controls for village of residence *	Structured interview *	Yes *	No statement	6
Lindsay 1988	No description of the derivation of the cohort	Drawn from the same community as the exposed cohort *	No description	Study does not control for other factors	No description	Yes *	No statement	2

Table A4.3.4 Risk of bias assessment for studies included in the quantitative analysis (cohort studies, n=21) (continued)

Reference	Selection			Comparability	Exposure			Overall quality assessment score (max 5)
	Representativeness of the sample	Selection of the non-exposed cohort	Assessment of outcome	Comparability of groups on the basis of the design or analysis	Ascertainment of exposure	Was follow-up at least one transmission season or year?	Adequacy of follow up of cohorts	
Lindsay 1988	Truly representative of the average individual or household in the community *	Drawn from the same community as the exposed cohort *	Independent blind assessment *	Study does not control for other factors	Direct observation *	Yes *	Complete follow up *	6
Liu 2014	Somewhat representative of the average individual in the community (infants enrolled into IPTi trial) *	Drawn from the same community as the exposed cohort *	Independent blind assessment *	Study controls for age, mother's education, wealth index, bednet and repellent use, water source, electricity, urban or rural, IPTi trial arm **	Direct observation *	Yes *	Complete follow up *	8
Maheu-Giroux 2009	Somewhat representative of the average individual in the community (90% residents consented to participate) *	Drawn from the same community as the exposed cohort *	Record linkage *	Study does not control for other factors	Structured interview *	Yes *	Follow up rate <80% and no description of those lost	5
Mututi 2008	Truly representative of the average individual or household in the community *	Drawn from the same community as the exposed cohort *	Independent blind assessment *	Study does not control for other factors	Direct observation *	Yes *	Complete follow up *	6
Nahum 2010	Truly representative of the average individual or household in the community *	Drawn from the same community as the exposed cohort *	Independent blind assessment *	Study controls for sex, site, bed type, bednet use, pirogue, fishing net *	Structured interview *	Yes *	Subjects lost to follow up unlikely to introduce bias (small number lost) *	7
Oesterholt 2006	Truly representative of the average individual or household in the community *	Drawn from the same community as the exposed cohort *	Record linkage *	Study adjusts for age *	Structured interview *	Yes *	Complete follow up *	7
Peterson 2009a	Truly representative of the average individual or household in the community *	Drawn from the same community as the exposed cohort *	Record linkage *	Study does not control for other factors	Structured interview *	No	No statement	4
Peterson 2009b	Truly representative of the average individual or household in the community *	Drawn from the same community as the exposed cohort *	Record linkage *	Study controls for bednet ownership, vegetation in compound, distance to larval habitats, temperature, rainfall, larval densities*	Direct observation *	No	No statement	5
Russell 2013	Truly representative of the average individual or household in the community *	Drawn from the same community as the exposed cohort *	Independent blind assessment *	Study does not control for other factors	Direct observation *	Yes *	Complete follow up *	6
Wanzirah 2015	Truly representative of the average individual or household in the community *	Drawn from the same community as the exposed cohort *	Independent blind assessment *	Study controls for age, gender, household wealth **	Direct observation *	Yes *	Subjects lost to follow up unlikely to introduce bias (>80% follow-up)*	8
Zhou 2007	Truly representative of the average individual or household in the community *	Drawn from the same community as the exposed cohort *	Independent blind assessment *	Study does not control for other factors	Direct observation *	Yes *	Complete follow up *	6

ITN: Insecticide-treated net; LLIN: Long-lasting insecticide-treated net; IRS: Indoor residual spraying; IPTi: intermittent preventive treatment in infants.

Appendix 4.4. Funnel plots to assess publication bias in the meta-analysis of modern versus traditional housing.

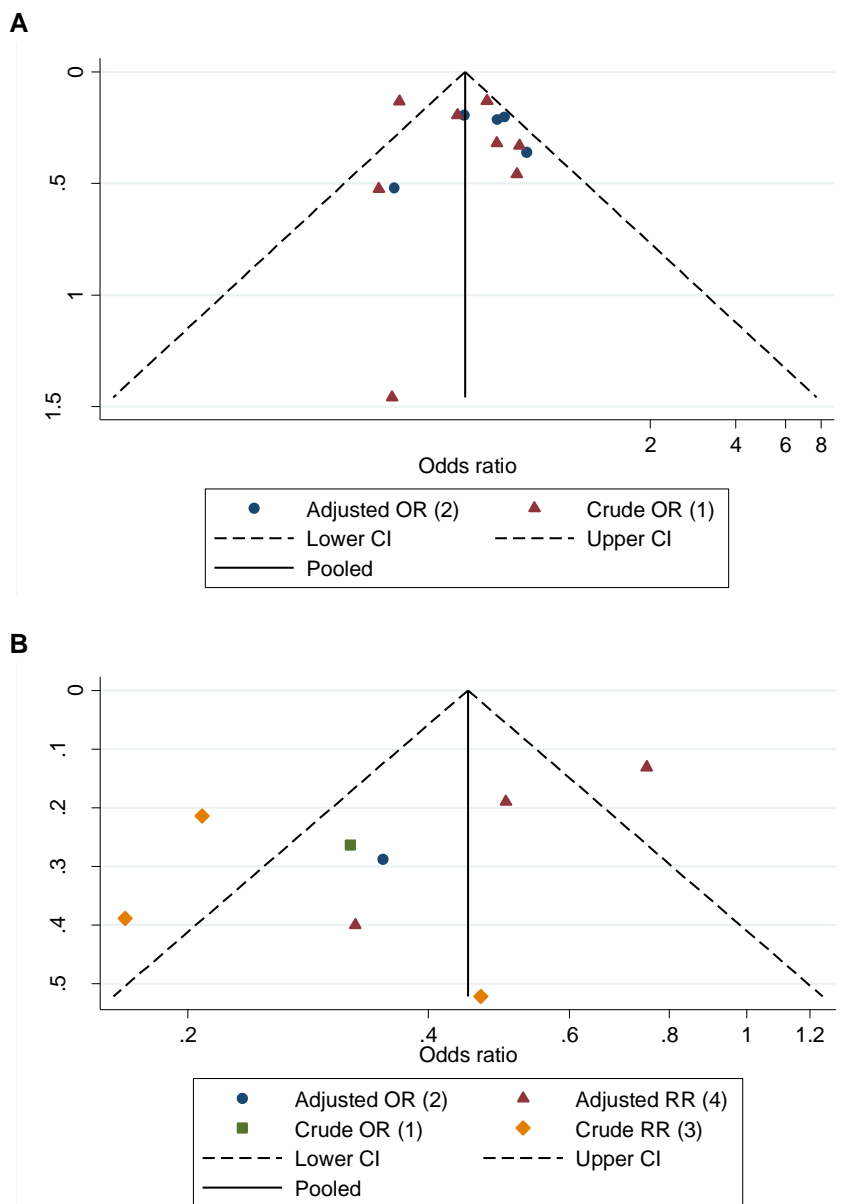


Figure A4.4.1 Funnel plots to assess publication bias in the meta-analysis of modern versus traditional housing.

Plots show study size as a function of effect size for studies included. Asymmetry is indicative of publication bias, selective outcome reporting, small-study effects, or selective analysis reporting. (A) Studies reporting malaria infection. 1: Case-control, cross-sectional and cohort studies: crude odds ratio, 2: Case-control, cross-sectional and cohort studies: adjusted odds ratio. (B) Studies reporting clinical malaria. 1: Case-control and cross-sectional studies (crude odds ratio), 2: Case-control and cross-sectional studies (adjusted odds ratio), 3: Cohort studies (crude rate ratio), 4: Cohort studies (adjusted rate ratio).

Appendix 4.5. Association between house construction and entomological outcomes in a meta-analysis of housing and malaria

Table A4.5.1. Association between house construction and entomological outcomes (intervention studies)

Study reference	Design	Intervention (type of screening)	Comparison	Outcome	Measurement of outcome	Mean density or rate				Measure of effect	
						Pre-intervention		Post-intervention			
						Control	Treatment	Control	Treatment		
Massebo 2013	RCS (pilot)	Full	Screening vs no screening	HBR	Mean number <i>An. arabiensis</i> per CDC light trap per night	20.1 (10.9–29.3)	20.3 (12.8–27.8)	7.9 (6.5–10.1)	4.8 (3.9–6.2)	Abundance ratio	0.61 (0.44–0.83)
Mng'ong'o 2011	RCS (pilot)	Full	Lantana plant vs no Lantana plant	HBR	Mean number adult anophelines per CDC light trap per night	n/a	n/a	–	–	Crude IRR	0.54 (0.40–0.73)
Mng'ong'o 2011	RCS (pilot)	Full	Lantana plant vs no Lantana plant	HBR	Mean number adult anophelines per CDC light trap per night	n/a	n/a	–	–	IRR adjusted for smoke stains	0.503 (0.380–0.667)
Ogoma 2010	Non-randomised cross-over study (pilot study)	Eaves	Screened eaves vs no screening	HBR	Mean number <i>An. gambiae</i> s.l. per CDC light trap per night	n/a	n/a	80.0 (4–630)	59.0 (9–415)	Relative Rate	0.91 (0.84–0.98)
Ogoma 2010	Non-randomised cross-over study (pilot)	Windows	Screened windows vs no screening	HBR	Mean number <i>An. gambiae</i> s.l. per CDC light trap per night	n/a	n/a	80.0 (4–630)	80.0 (15–370)	Relative Rate	0.98 (0.94–1.02)
Ogoma 2010	Non-randomised cross-over study (pilot)	Door	Screened doors vs no screening	HBR	Mean number <i>An. gambiae</i> s.l. per CDC light trap per night	n/a	n/a	80.0 (4–630)	96.0 (17–700)	Relative Rate	1.03 (0.97–1.09)
Kirby 2009	RCS	Ceiling	Ceiling vs no screening	HBR	Mean number <i>An. gambiae</i> s.l. per CDC light trap per night	n/a	n/a	37.5 (31.6–43.3)	19.1 (16.1–22.1)	Ratio of means for total <i>An. gambiae</i> s.l. over all trapping visits, adjusted for location, year, SES, wall material, horses, people in house	0.60 (0.46–0.80)
Kirby 2009	RCS	Full	Full vs no screening	HBR	Mean number <i>An. gambiae</i> s.l. per CDC light trap per night	n/a	n/a	37.5 (31.6–43.3)	15.2 (12.9–17.4)	Ratio of means for total <i>An. gambiae</i> s.l. over all trapping visits, adjusted for location, year, SES, wall material, horses, people in house	0.46 (0.34–0.63)
Kirby 2009 (2006 data)	RCS	Ceiling	Ceiling vs no screening	EIR	Measured using CDC light traps	n/a	n/a	2.27 (1.38–3.16)	1.14 (0.85–1.42)	Abundance ratio	0.50 (0.32–0.79)
Kirby 2009 (2006 data)	RCS	Full	Full vs no screening	EIR	Measured using CDC light traps	n/a	n/a	2.27 (1.38–3.16)	0.77 (0.57–0.96)	Abundance ratio	0.34 (0.21–0.54)
Kirby 2009 (2007 data)	RCS	Ceiling	Ceiling vs no screening	EIR	Measured using CDC light traps	n/a	n/a	1.35 (0.74–1.97)	0.90 (0.22–1.57)	Abundance ratio	0.67 (0.28–1.58)

Table A4.5.1. Association between house construction and entomological outcomes (intervention studies) (continued)

Study reference	Design	Intervention (type of screening)	Comparison	Outcome	Measurement of outcome	Mean density or rate				Measure of effect	
						Pre-intervention		Post-intervention			
						Control	Treatment	Control	Treatment		
Kirby 2009 (2007 data)	RCS	Full	Full vs no screening	EIR	Measured using CDC light traps	n/a	n/a	1.35 (0.74–1.97)	0.42 (0.24–0.63)	Abundance ratio	0.31 (0.16–0.59)
Kampango 2013	RCS (pilot)	Eaves	Gables screened with local cloth vs no screening	HBR	Mean number <i>An. funestus</i> per CDC light trap per night	n/a	n/a	43.4 (38.0–49.6)	13.0 (10.7–15.7)	Crude IRR	0.3 (0.25–0.37)
Kampango 2013	RCS (pilot)	Full	Gables screened with local cloth vs no screening	HBR	Mean number <i>An. gambiae</i> s.l. per CDC light trap per night	n/a	n/a	6.88 (4.98–9.51)	2.13 (1.48–3.08)	Crude IRR	0.31 (0.19–0.50)
Njie 2009	Randomised cross-over study (pilot)	Eaves	Screened eaves vs no screening	HBR	Mean number <i>An. gambiae</i> s.l. per CDC light trap per night	n/a	n/a	6.1 (3.5–10.0)	2.1 (1.3–3.1)	Percent reduction	0.34 (0.18–0.67)
Njie 2009	Randomised cross-over study (pilot)	Screened eaves	Screened eaves vs no screening	Adult density	Odds of finding <i>An. gambiae</i> in house (CDC light trap)	n/a	n/a	–	–	OR adjusted for trapping week, crossover group, numbers of horses and cows in compounds	0.34 (0.20–0.56)

Table A4.5.2. Association between house construction and entomological outcomes (observational studies)

Reference	House feature	Specific comparison	Outcome	Mean density or rate		Measure of effect	Crude results	Adjusted results	Factors adjusted for
				Exposed	Unexposed				
Barber 1935	House type	New (tiled roof, ceiling, non-leaky) vs old (thatched roof, reed or no ceiling, in poor condition)	Density of adult anophelines (mean number <i>An. elutus</i> and <i>An. maculipennis</i> per resting catch)	6.8	9.4	None reported	–	–	n/a
Bosman 1992	House type	Modern vs traditional	Density of adult Anophelines (August monthly mean number adult Anopheles per pyrethrum spray catch)	–	–	None reported	–	–	n/a
Gamage–Mendis 1991	House type	Poor vs good	Indoor resting density (geometric mean number of <i>Anopheles</i> per trap per night)	3.42	1.95	None reported	–	–	n/a
Hiscox 2013	Village type	Modern vs traditional homes	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	0.72 (0.45–1.14)	–	n/a
Konradsen 2000	House type	Poor vs good	Presence (vs absence) of <i>An. culicifacies</i> in each collection (pyrethrum spray catch)	–	–	OR	1.6 (1.1–2.1)	–	n/a
Konradsen 2000	House type	Poor vs good	Presence (vs absence) of <i>An. subpictus</i> in each collection (pyrethrum spray catch)	–	–	OR	1.4 (1.1–1.7)	–	n/a
Liu 2014	House type	Highest quintile of housing index compared to lowest quintile (based on roof, wall and floor material, ceiling, eaves, screening)	Density of adult anophelines (mean number of <i>Anopheles</i> collected per household)	–	–	IRR	0.334 (0.228–0.489)	0.571 (0.373–0.874)	Cattle near house, water source, electricity, urban or rural
Mutuku 2011	House type	Poor vs good	Density of adult Anophelines (pyrethrum spray catch)	–	–	IRR	1.07 (0.72–1.44)	–	n/a
Wanzirah 2015	House type	Modern vs traditional	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	–	0.48 (0.37–0.64)	Study site, household wealth
Coogle 1927	Screening	Screened vs unscreened	Density of adult anophelines (mean number <i>An. quadrimaculatus</i> per home)	2.2	–	None reported	–	–	n/a
Geissbuhler 2007	Screening	No ceiling and unscreened windows vs ceiling and screened windows	Human biting rate (mean number of bites received by those sleeping indoors (HLC))	4.4	2.3	None reported	–	–	–
Zhou 2007	Screening	No screening vs screening	Density of adult anophelines (mean number of <i>An. gambiae</i> s.s. per house (pyrethrum spray catch))	4.15 (3.95–5.35)	2.92 (2.08–3.76)	OR (proportion houses with <i>An. gambiae</i> s.s.)	1.04 (1.01–1.07)	–	n/a
Zhou 2007	Screening	No screening vs screening	Density of adult anophelines (mean number of <i>An. funestus</i> per house (pyrethrum spray catch))	0.52 (0.37–0.67)	0.44 (0.29–0.59)	OR (proportion houses with <i>An. funestus</i>)	1.14 (1.09–1.20)	–	n/a

Table A4.5.2. Association between house construction and entomological outcomes (observational studies) (continued)

Reference	House feature	Specific comparison	Outcome	Mean density or rate		Measure of effect	Crude results	Adjusted results	Factors adjusted for
				Exposed	Unexposed				
Adiamah 1993	Main wall material	Mud vs brick/concrete	Density of adult Anophelines (geometric mean number adult <i>Anopheles</i> per light trap catch)	24.6	15.5	None reported	–	–	n/a
Hiscox 2013	Main wall material	Other vs wood	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	1.83 (1.14–2.93)	2.35 (1.30–4.23)	Village, location of kitchen, veranda style, presence of animals
Kirby 2008	Main wall material	Mud vs cement	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	5.36 (3.92–7.31)	1.44 (1.10–1.87)	Distance to nearest pit latrine, horses, eave type, crowding, churai in room
Zhou 2007	Main wall material	Mud vs brick	Density of adult anophelines (mean number of <i>An. gambiae</i> s.s. per house (pyrethrum spray catch))	4.16 (3.24–5.08)	0.86 (0.53–1.19)	OR (proportion houses with <i>An. gambiae</i> s.s.)	1.34 (1.29–1.40)	–	n/a
Zhou 2007	Main wall material	Mud vs brick	Density of adult anophelines (mean number of <i>An. funestus</i> per house (pyrethrum spray catch))	0.53 (0.37–0.65)	0.22 (0.06–0.38)	OR (proportion houses with <i>An. funestus</i>)	1.87 (1.70–2.04)	–	n/a
Wanzirah 2015	Main wall material	Cement, wood or metal vs mud	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	–	0.63 (0.48–0.84)	Study site, household wealth
Hiscox 2013	Main roof material	Other vs iron	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	0.49 (0.16–1.44)	–	n/a
Kirby 2008	Main roof type	Thatch vs metal	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	1.15 (0.94–1.41)	–	n/a
Wanzirah 2015	Main roof material	Tiles or metal vs thatch	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	–	0.72 (0.52–1.00)	Study site, household wealth
Zhou 2007	Main roof material	Grass thatch vs iron sheet	Density of adult anophelines (mean number of <i>An. gambiae</i> s.s. per house (pyrethrum spray catch))	4.26 (3.15–5.37)	2.00 (1.33–2.67)	OR (proportion houses with <i>An. gambiae</i> s.s.)	1.15 (1.12–1.19)	–	n/a
Zhou 2007	Main roof material	Grass thatch vs iron sheet	Density of adult anophelines (mean number of <i>An. funestus</i> per house (pyrethrum spray catch))	0.39 (0.27–0.51)	0.61 (0.39–0.83)	OR (proportion houses with <i>An. funestus</i>)	0.75 (0.71–0.79)	–	n/a
Wanzirah 2015	Main floor material	Woods, bricks or cement vs earth, sand, dung or stones	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	–	0.42 (0.32–0.55)	Study site, household wealth
Adiamah 1993	Eaves	Presence vs absence of eaves	Density of adult Anophelines (geometric mean number adult <i>Anopheles</i> per light trap catch)	29.3	14.6	None reported	–	–	n/a
Animut 2013	Eaves	Open vs closed eaves	Density of <i>An. arabiensis</i> (mean number <i>An. arabiensis</i> per CDC light trap per house)	0.97 (0.60–1.34)	0.66 (0.43–0.88)	Abundance Ratio	1.5 (0.9–2.4)	–	n/a

Table A4.5.2. Association between house construction and entomological outcomes (observational studies) (continued)

Reference	House feature	Specific comparison	Outcome	Mean density or rate		Measure of effect	Crude results	Adjusted results	Factors adjusted for
				Exposed	Unexposed				
Animut 2013	Eaves	Open vs closed eaves	Density of <i>An. arabiensis</i> (mean number <i>An. arabiensis</i> per pyrethrum spray catch)	5.67 (4.22–7.12)	0.77 (–0.15–1.69)	None reported	7.4 (2.2–24.4)	–	n/a
Kirby 2008	Eaves	Closed vs open	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	0.38 (0.32–0.46)	–	n/a
Kirby 2008	Eaves	Continuous variable (eave gap size)	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	1.06 (1.04–1.08)	0.71 (0.60–0.85)	Distance to nearest pit latrine, horses, main wall material, crowding, churai in room
Lindsay 1988	Eaves	Open vs closed	Density of adult Anophelines (mean number of <i>Anopheles</i> per night)	–	–	Percent reduction	43.2	–	n/a
Lindsay 1995 (wet season)	Eaves	Open vs closed	Density of of adult anophelines (mean number <i>An. gambiae</i> s.l. caught under bednets)	–	–	Percent increase	–	10 (0–21)	Store room, bednets tucked, fire, ceiling
Russell 2013	Eaves	Closed vs open	Density of aduly <i>An. gambiae</i> s.l. (CDC light trap))	31.25% households in low anopheline density cluster (Z scores <1.96) had closed eaves vs 0% houses in high anopheline density cluster (Z scores >1.96)					
Wanzirah 2015	Eaves	Closed vs open	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	–	0.58 (0.45–0.74)	Study site, household wealth
Adiamah 1993	Ceiling	No ceiling vs ceiling	Density of adult Anophelines (geometric mean number adult <i>Anopheles</i> per light trap catch)	20.5	10.7	None reported	–	–	n/a
Lindsay 1995 (wet season)	Ceiling	Ceiling present vs absent	Density of adult anophelines (mean number <i>An. gambiae</i> s.l. caught under bednets)	–	–	Percent decrease	–	13 (1–25)	Store room, bednets tucked, fire, open eaves
Burkot 1989	Elevation	Houses built on stilts vs at ground level	Human biting rate (mean number of <i>Anopheles</i> per human landing catch)	50.8 (SD 46.9)	166 (SD 125)	None reported	–	–	–
Charlwood 2003	Elevation	Ground level homes vs homes built on stilts	Human biting rate (mean number of <i>Anopheles</i> per man hour of collection (HLC))	3.58 (2.9–4.4)	2.38 (1.7–3.3)	Abundance Ratio	1.5 (1.0–2.2)	–	n/a
Charlwood 2003	Elevation	Ground level homes vs homes built on stilts	Human biting rate (mean number of <i>An. gambiae</i> per light trap per night)	–	–	None reported	–	–	n/a
Hiscox 2013	Elevation	Continuous variable (height on stilts)	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	1.00 (0.99–1.00)	–	n/a
Animut 2013	Windows	Present vs absent	Density of <i>An. arabiensis</i> (mean number <i>An. arabiensis</i> per CDC light trap per house)	0.27 (–0.04–0.60)	1.02 (0.78–1.27)	Abundance Ratio	0.3 (0.1–0.9)	–	n/a

Table A4.5.2. Association between house construction and entomological outcomes (observational studies) (continued)

Reference	House feature	Specific comparison	Outcome	Mean density or rate		Measure of effect	Crude results	Adjusted results	Factors adjusted for
				Exposed	Unexposed				
Animut 2013	Windows	Present vs absent	Density of <i>An. arabiensis</i> (mean number <i>An. arabiensis</i> per pyrethrum spray catch)	1.95 (0.72–3.18)	2.35 (1.30–3.39)	Abundance Ratio	0.8 (0.4-1.8)	–	n/a
Hiscox 2013	Doors and windows	Other covering vs resettlement style shutters	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	1.23 (0.75–2.01)	–	n/a
Hiscox 2013	Doors and windows	Open vs resettlement style covers	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	0.87 (0.25–3.12)	–	n/a
Animut 2013	Roof condition	Hole present vs absent	Density of <i>An. arabiensis</i> (mean number <i>An. arabiensis</i> per pyrethrum spray catch)	4.81 (3.31–6.31)	1.17 (0.24–2.10)	Abundance Ratio	4.1 (1.8-9.5)	–	n/a
Animut 2013	Roof condition	Hole present vs absent	Density of <i>An. arabiensis</i> (mean number <i>An. arabiensis</i> per CDC light trap per house)	1.12 (0.75–1.50)	0.61 (0.38–0.83)	Abundance Ratio	1.8 (1.1-3.0)	–	n/a
Animut 2013	Wall condition	Hole present vs absent	Density of <i>An. arabiensis</i> (mean number <i>An. arabiensis</i> per CDC light trap per house)	0.77 (0.54–1.01)	0.67 (0.32–1.02)	Abundance Ratio	1.1 (0.6-2.1)	–	n/a
Animut 2013	Wall condition	Hole present vs absent	Density of <i>An. arabiensis</i> (mean number <i>An. arabiensis</i> per pyrethrum spray catch)	3.27 (2.22–4.32)	0.73 (–0.48–1.94)	Abundance Ratio	4.5 (0.9-23.4)	–	n/a
Hiscox 2013	Veranda style	Closed vs open	Human biting rate (mean number of <i>Anopheles</i> per CDC light trap per night)	–	–	IRR	0.32 (0.18–0.58)	0.51 (0.23–1.11)	Village, location of kitchen, wall material, presence of animals

CDC: Centers for Disease Control and Prevention; OR: Odds ratio; IRR: Incidence rate ratio; SES: socioeconomic status

Appendix 5. STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Incl.
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Yes
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes
Methods			
Study design	4	Present key elements of study design early in the paper	Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Yes
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	n/a
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	n/a
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	n/a
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes
Bias	9	Describe any efforts to address potential sources of bias	Yes
Study size	10	Explain how the study size was arrived at	Yes
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Yes
		(b) Describe any methods used to examine subgroups and interactions	Yes
		(c) Explain how missing data were addressed	Yes
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	n/a
		(e) Describe any sensitivity analyses	n/a

Appendix 5. STROBE Statement—checklist of items that should be included in reports of observational studies (continued)

	Item No	Recommendation	Incl.
Results			Manuscript page #
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes Figure 5.3
		(b) Give reasons for non-participation at each stage	Figure 5.3
		(c) Consider use of a flow diagram	Figure 5.3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes Table 5.1
		(b) Indicate number of participants with missing data for each variable of interest	Yes
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Yes
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	Tables 5.2-5.4
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	n/a
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	n/a
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 5.2-5.4
		(b) Report category boundaries when continuous variables were categorized	Tables 5.2-5.4
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Tables 5.2-5.4
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes

Appendix 7. Consolidated criteria for reporting qualitative studies (COREQ)

Adapted from:

Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Eq Health Care* 2007; **19**: 349-357.

Item	Guide questions/description	Reported in section
Domain 1: Research team and reflexivity		
<i>Personal Characteristics</i>		
1. Inter viewer/facilitator	Which author/s conducted the inter view or focus group?	Methods
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	Methods
3. Occupation	What was their occupation at the time of the study?	Methods
4. Gender	Was the researcher male or female?	Methods
5. Experience and training	What experience or training did the researcher have?	Methods
<i>Relationship with participants</i>		
6. Relationship established	Was a relationship established prior to study commencement?	Methods
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Methods
8. Interviewer characteristics	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	n/a
Domain 2: study design		
<i>Theoretical framework</i>		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Methods
<i>Participant selection</i>		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Methods
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	Methods
12. Sample size	How many participants were in the study?	Results
13. Non-participation	How many people refused to participate or dropped out? Reasons?	Results
<i>Data collection</i>		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Methods
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	Methods
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Results
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Methods, p5
18. Repeat interviews	Were repeat inter views carried out? If yes, how many?	n/a
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	Methods
20. Field notes	Were field notes made during and/or after the interview or focus group?	Methods
21. Duration	What was the duration of the inter views or focus group?	Methods
22. Data saturation	Was data saturation discussed?	n/a
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	n/a
Domain 3: analysis and findings		
<i>Data analysis & reporting</i>		
24. Number of data coders	How many data coders coded the data?	Methods
25. Description of the coding tree	Did authors provide a description of the coding tree?	n/a
26. Derivation of themes	Were themes identified in advance or derived from the data?	Methods
27. Software	What software, if applicable, was used to manage the data?	Methods
28. Participant checking	Did participants provide feedback on the findings?	n/a
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Results
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Results
31. Clarity of major themes	Were major themes clearly presented in the findings?	Results
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Results

Appendix 8. Implementation of spatial autocorrelation analysis

Spatial autocorrelation (clustering) of three socioeconomic variables (cultivated land area, wealth index scores and house type) was explored at global scale using univariate Moran's I [1] and at local scale using univariate Anselin Moran's I [2]. The global Moran's I estimates the degree of correlation between neighbours over the whole study area, whereas Anselin Moran's I measures local clustering [2].

Spatial autocorrelation statistics depend on the definition of neighbourhood relationships through which the spatial configuration of the sampled subpopulation was defined prior to analysis. Delaunay triangulation was used to set up a neighbourhood matrix of sampling units (households). This method is commonly applied to construct neighbours on point features by creating Voronoi triangles [3]. A mesh of non-overlapping triangles is created from feature centroids; features associated with triangle nodes that share edges are neighbours (Figure A8.1). The sum of weights for a given distance class decreases for large distance classes, and a bias may arise from the fact that only observations at the edge of the sampled population can contribute to the estimates for larger distances. We therefore limited the description of the spatial structure to half the maximum distance between households (around 7.3 km for the study area) [4]. We also standardized the spatial weights so that all weights summed to unity within a group of neighbours (row standardisation). The estimate of spatial autocorrelation can be biased when the data are not normally distributed [5]. Accordingly, cultivated area cultivated was transformed by a cubic root function to approach a Gaussian distribution.

Cluster analysis: Moran's I [1] was used to account for the global spatial autocorrelation of socioeconomic variables. For the Moran's I statistic, the sum of covariations between the sites for the distance $d(i,j)$ was divided by the overall number of sites $W(d_{i,j})$ within the distance class $d(i,j)$. Thus, the spatial autocorrelation coefficient for a distance class $d(i,j)$ was the average value of spatial autocorrelation at that distance.

$$I = \frac{n}{S_p} \frac{\sum_{i=1}^n \sum_{j=1}^n W_{ij} (\gamma_i - \bar{\gamma})(\gamma_j - \bar{\gamma})}{\sum_{i=1}^n (\gamma_i - \bar{\gamma})^2}, \text{ where}$$

n = the sample size

$$W_{ij} = \begin{cases} 1 & \text{if sites } i, j \text{ are neighbours} \\ 0 & \text{otherwise} \end{cases} = \text{row-standardized spatial weights matrix of sites } i \text{ and } j$$

$$S_p = \sum_{i=1}^n \sum_{j=1}^n W_{i,j} = \text{sum of the number of sampling locations per distance class,}$$

γ_i = the value at household i ; $\bar{\gamma}$ = global mean value

The actual value for Moran's I was then compared with the expected value under the assumption of complete randomisation.

$$E(I) = -\frac{1}{n-1}$$

Moran's *I* values may range from -1 (disperse) to +1 (clustered). A Moran's *I* value of 0 suggests complete spatial randomness. To verify that the value of Moran's *I* was significantly different from the expected value, a Monte Carlo randomisation test was applied with 9,999 permutations to achieve highly significant values. This statistic is a global statistic in that it averages all cross outcomes over the entire domain. A local version, called Local Indicator of Spatial Association (LISA) or Anselin Local Moran's *I* [2] allows us to test for statistically significant local spatial clusters, including the type and location of these clusters. It is calculated as follows:

$$I_i(d) = \frac{(y_i - \bar{y})}{\frac{1}{n} \sum_{i=1}^n (y_i - \bar{y})} \sum_{j=1}^n W_{ij}(d) (y_j - \bar{y}), \text{ where}$$

$W_{ij}(d)$ is the row-standardized weights matrix given a local neighbourhood search radius d . The neighbourhood definitions were the same as the global statistics were applied. Unlike the global Moran's *I*, which has the same expected value for the entire study area, the expected value of local Moran's *I* varies for each sampling location because it is calculated in relation to its particular set of neighbours.

$$E(I_i) = -\frac{1}{n-1} \sum_{j=1}^n W_{i,j}$$

The significance of the local Moran's *I* was calculated using a randomisation test on the Z-score with 9,999 permutations to achieve highly significant values. Positive spatial autocorrelation occurs when, for example, a household with a specific outcome value is surrounded by neighbouring households with similar outcome value (low-low, high-high), thus forming a spatial cluster.

Results of the global analysis are shown in Table A8.1.

Table A8.1. Global univariate and bivariate Moran's *I* values for socioeconomic variables and malaria outcomes in 100 households in Nagongera, Uganda

Outcome/spatially lagged variable	Moran's <i>I</i>	z-score	p-value
<i>Global univariate analysis</i>			
Wealth index score	0.07	1.42	0.16
Land area cultivated	-0.04	-0.55	0.58
House type ^a	-0.01	-0.05	0.96

^aHouse type: modern (cement, wood or metal walls; and tiled or metal roof; and closed eaves) or traditional (all other homes). All other variables were modelled as continuous.

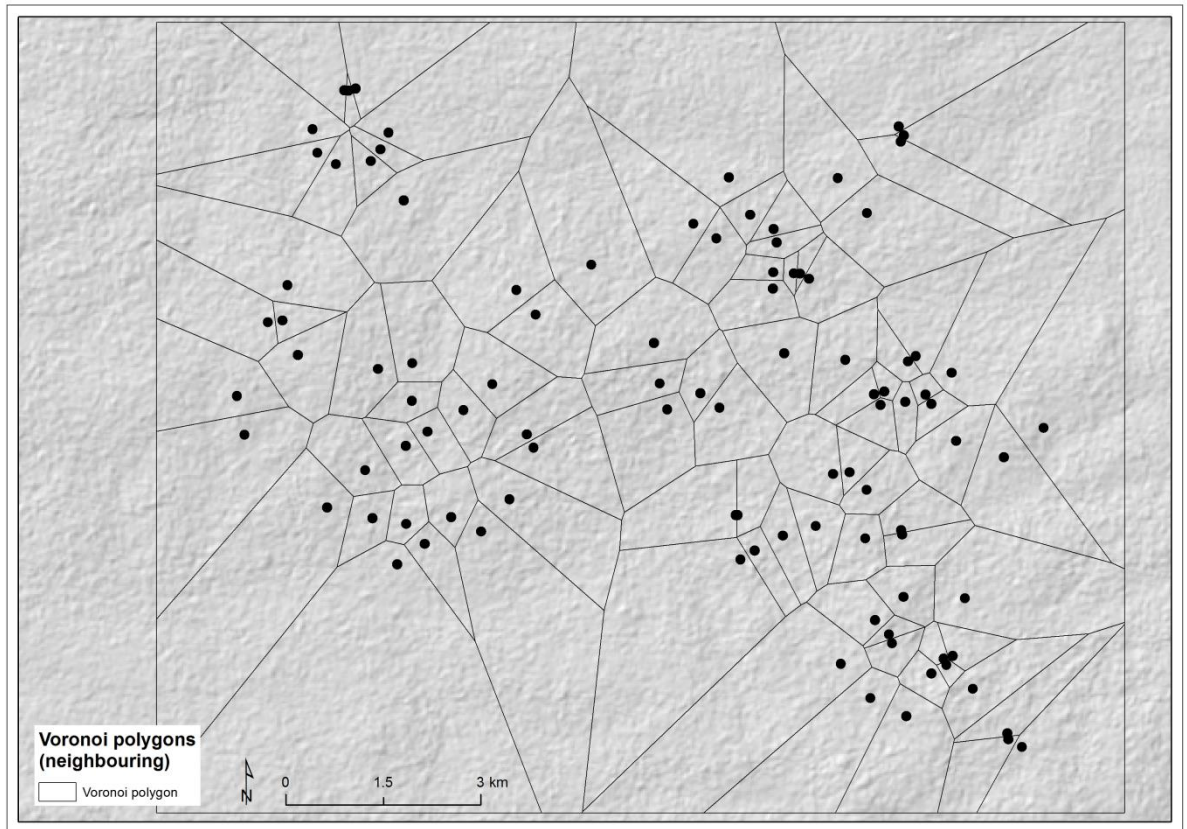


Figure A8.1. Neighbourhood matrix performed based on Delaunay triangulation to model the spatial relationship between households within the study area.

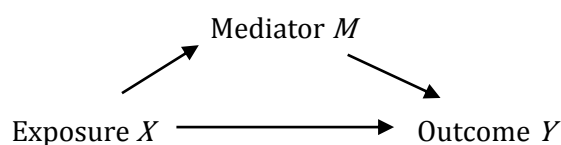
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Appendix 9. Mediation analysis

Background

While much of epidemiology is focused on establishing a causal effect between exposure and outcome, it is sometimes necessary to understand the pathways that explain an effect. A mediating variable, M , helps to explain the relationship between exposure, X , and outcome, Y . Mediation analysis is a causal inference approach that seeks to quantify the part of the total effect of X on Y that is explained by the effect through M (the indirect effect), in relation to the effect that does not occur through M (the direct effect):



In Chapter 8 it is hypothesised that the relationship between socioeconomic position (SEP) (X) and malaria infection risk in children (Y) is mediated partly by three variables (M): house type, food security and caregiver's treatment-seeking behaviour. Assuming causality in the SEP-to-malaria direction, we aimed to quantify the proportion of the total effect of SEP on malaria infection that was mediated by each of these three variables.

Approaches to mediation analysis

A simple approach to mediation analysis is to fit two regression models for: (i) the effect of X on Y , adjusting for measured confounders, and (ii) the effect of X on Y , adjusting for measured confounders and M . An observed reduction in the magnitude of the effect estimate in the second model may be interpreted as evidence of mediation by M ; in other words, that M explains part of the association between X and Y . This approach has been applied to study the causal pathway from SEP and TB for example [1], but does not allow quantification of the indirect effect.

Traditionally, methods to quantify indirect effects have used structural equation models or path analysis [2, 3]. Assuming that all the effects in a directed acyclic graph can be represented by linear regression, effects in parallel can be combined by addition and effects in sequence can be combined by multiplication [3, 4]. Thus, the indirect effect is the product of the effect of the exposure on the mediator and of the effect of the mediator on the outcome. The total effect is the direct effect plus the indirect effect. This approach has been extended to enable the calculation of direct and indirect effects in non-linear models [5, 6]. However, when these

standard regression approaches are applied, the direct effect is interpreted as if the mediator were fixed at the same value for all units [7, 8], which is not always the case in reality.

Newer methods allow for variation between subjects in the level at which the mediator is controlled. In other words, the direct effect is able to express what would happen if the mediator was fixed to the level natural in the absence of any intervention [8]. Practical methods to estimate such effects range from methods to allow for exposure-mediator interaction and other non-linearities [9, 10], to direct modelling of direct and indirect effects [11]. In this study, we apply the Monte Carlo simulation approach described by Imai [12]. This approach is flexible in being able to accommodate linear and nonlinear relationships, parametric and nonparametric models, continuous and discrete mediators, and various types of outcome variables. Using the algorithm described by Imai, we calculated the average causal mediation effects as follows:

1. Fit parametric models for the observed mediating and outcome variables.
2. Simulate model parameters from their sampling distributions.
3. Repeat the following three steps:
 - a. *Simulate the potential values of the mediator:* Two potential values of the mediator are generated, each based on the mediator model, one under exposure and one under non-exposure.
 - b. *Simulate the potential outcomes given the simulated values of the mediator:* For each exposure status two potential values of the outcome are generated, each based on the outcome model, one using the mediator value under exposure and one using the mediator value under non-exposure.
 - c. *Compute the causal mediation effects:* The difference is taken between the two outcome predictions under exposure and the two outcome predictions under non-exposure. These differences are then averaged across all study units.
4. Compute summary statistics: The point estimate of the average causal mediation effect and its uncertainty estimates are computed from the distribution of mediation effects.

The algorithm by Imai requires two sequential ignorability assumptions [12, 13]: (i) conditional on the observed pretreatment covariates, the treatment is independent of all potential values of the outcome and mediating variables and (b) the observed mediator is independent of all potential outcomes given the observed treatment and pretreatment variables. In practice, these will hold only if there is no unmeasured confounding of the association between

exposure and mediator, exposure and outcome or mediator and outcome, and there is no reverse causality. We implemented the algorithm using the *medeff* command [14] in Stata13 (StataCorp, Texas), with 1000 simulations, to calculate the effect of SEP on malaria infection risk mediated by treatment-seeking behaviour, house type and food security. Age and gender were included as covariates and we adjusted for clustering at the level of the household.

Limitations

While the identification of potential mediators between SEP and malaria provides evidence of a biologically plausible mechanism for causality, the mediation analysis had a number of limitations. First, it is unlikely that the assumption of no reverse causality was met. Reverse causality from malaria to poverty in Nagongera is highly probable, since the direct and indirect costs of malaria can cause poverty within households as observed in Tanzania [15, 16]. Second, it is not possible to exclude the possibility of unmeasured confounding between exposure and mediator and between mediator and outcome. In particular, the assumption that the mediator is ignorable given observed treatment and pretreatment confounders (i.e. that among children in the same category of SEP and with the same pretreatment characteristics, the mediator can be regarded as if it were randomised) is very strong. Even in randomised studies it is always possible that there is unmeasured confounding between mediator and outcome. In our study there may have been confounding of the association between house type and malaria, for example, by distance of house to village periphery among numerous other factors [17]. Furthermore, using the Imai algorithm it is not possible to control for confounders of the mediator-outcome relationship, even if these are measured, without an additional assumption [12]. Therefore, regardless of the number of pretreatment confounders measured, it is difficult to establish the ignorability of the mediator.

Third, the conceptual framework used to guide the analysis was not an exhaustive representation of all mediating pathways and confounders. Indeed, the mediation analysis investigated only three potential mediators of the SEP-malaria relationship and accounted for less than half of the total effect. This suggests that other mediating factors were unaccounted for. Finally, it is not clear that the study was adequately powered for the mediation analysis, the sample size (N = 300) being calculated to compare temporal changes in malaria incidence from the cohort with temporal changes in malaria test positivity rate from health facility based surveillance [18].

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