The Impact of Vector Control for Malaria on Lymphatic Filariasis in Tanzania

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

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July 2018

Abstract

In Tanzania, lymphatic filariasis (LF) caused by the filarial worm *W. bancrofti* is co-endemic with malaria and shares common mosquito vectors of the *Anopheles* species. LF mapping to estimate prevalence in 2004 determined the entire country was LF-endemic. However, by 2009 it was questionable whether LF transmission persisted in some districts that had not yet initiated mass drug administration (MDA) to interrupt transmission. Over the same period, national scale-up in distribution of insecticide-treated nets (ITNs) and focalised scale-up of indoor residual spraying (IRS) was underway. These interventions aimed at reducing vector populations should plausibly facilitate interruption of LF transmission, however this has not been thoroughly investigated in Tanzania. This research project sought to 1) examine predicted LF risk and trends in vector control coverage on a national scale in Tanzania, 2) investigate vector control coverage on a local scale in the Lake Zone of Tanzania, and 3) assess LF exposure and its predictors in the Lake Zone. First, secondary data analyses confirmed the risk of LF is highly variable throughout Tanzania. Nationally, household ITN ownership increased from 38% in 2007-08 to 92% in 2011-12 but decreased to 65% in 2015-16 based on Demographic and Health Survey (DHS) and Malaria Indicator Survey (MIS) data. Focalised scale-up of IRS in the Lake Zone followed the same trend (4% to 12% to 5%, respectively). Spatial analysis of ITN ownership and IRS coverage revealed significant hotspots of low and high vector control coverage. Second, in the Lake Zone, three cross-sectional household surveys conducted in six villages found a significant overall decrease in household net ownership from 73% to 50% between 2011-2013. Scale-up of IRS reached 94% of households surveyed in targeted villages by 2013. Notably, IRS was found to be significantly negatively associated with net ownership. Third, children 2-7 years of age in the six villages were sampled for the presence of antibodies to the *W. bancrofti* antigen Wb123. Baseline Wb123 seroprevalence varied markedly by village, ranging from 7% to 52%. Overall, a significant decrease in Wb123 seroprevalence from 28% in 2011 to 18% in 2013 was observed. Household net ownership was found to be significantly associated with the decline in Wb123 seropositivity. However, trends in net ownership and Wb123 seroprevalence at the village-level were variable. This study documents positive antibody responses to Wb123 in children born during the study, indicating recent LF exposure in a region considered to not have ongoing LF transmission. Notwithstanding the variable coverage and decline in net ownership in some villages, net ownership was found to be significantly associated with LF exposure. These findings underscore the potential for vector control to contribute to reductions in LF transmission and the need for increased coordination between malaria and LF programmes.

Dedication

I dedicate this entire endeavour to my father-in-law,

Dean F. Cornwell, PhD (1948-2015).

You were with me on this from the beginning, “Cuz”.

I only wish you were here to share the end.

In loving memory of my niece,

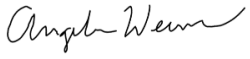
Ciara Ava O’Driscoll (2005-2017)

Declaration

I hereby certify that this dissertation constitutes my own product, that where the language of others is set forth, quotation marks so indicate, and that appropriate credit is given where I have used the language, ideas, expressions or writings of another.

I declare that the dissertation describes original work that has not previously been presented for the award of any other degree of any institution.

Signed,



Angela Weaver

Acknowledgements

To my Tanzanian colleagues, Asante kwa kunipa moyo kama mdogo wako mpendwa. I have learned so much from you all and I will always consider Tanzania a second home. This work would not have been possible without the support and friendship of my dear sister Dr. Upendo Mwingira. I am also grateful to Dr. Mwele Malecela for providing guidance and assistance throughout this process, including concerns for my safety when I was six months pregnant in the field.

Many thanks to the staff of the NTD Programme in Dar es Salaam, including Dr. Wilfred Lazaro, Dr. Maria Chikawe (rest in peace), Cecilia Uisso, Irene Mremi, as well as Grades Stanley, Dr. Kaatano, and the staff from NIMR Mwanza, including Emmanuel Masini, Joyce Machange, Judith Dotto, and all the support staff and laboratory technicians who assisted with the field work. I am also grateful to Deo Mtundu for his assistance with data management.

I am deeply grateful to the communities in Tanzania that participated in this work.

To my primary supervisor, Dr. Louise Kelly-Hope, I'm not sure I would have ever completed this effort without your support, words of encouragement, and frank advice. You've kept me calm when I needed it most. I would also like to thank my second supervisor, Dr. Martin Donnelly, for his critical feedback and support.

I am grateful to the members of my advisory committee at LSTM, Dr. Hilary Ranson and Dr. Charles Wondji, for their thoughtful feedback and guidance. I would also like to thank Dr. Moses Bockarie, Dr. Benjamin Koudou, and Dr. Greg Devine for their early supervision and support, as well as the support staff at LSTM, including the PGR team. I am appreciative to Rinki Deb for helping me navigate initial ethical clearance at LSTM. I am indebted to Dr. Hannah Betts for her thoughtful input and guidance on spatial and statistical analysis. Finally, I would like to express my gratitude to my examiners Dr. Lisa Reimer and Dr. Deirdre Hollingsworth for their thoughtful assessment and feedback.

I have been inspired by many people in my professional life and have been fortunate to work directly with some of the 'NTD giants' in the field. Thank you to Dr. Eric Ottesen, Dr. David Molyneux, Dr. Lorenzo Savioli, Dr. Dirk Engels, and Dr. Uche Amazigo for providing me with encouragement to purse a PhD in the first place, and for inspiring me to focus it on a disease affecting neglected populations. I am forever grateful to Dr. Murray Trostle for mentoring me, encouraging my confidence, and expecting greater things from me. I am also thankful

for the support of Dr. Christy Hanson who was a wonderful mentor and encouraged my further education.

I would like to express my sincere appreciation for the financial support provided from the Bill and Melinda Gates Foundation through the Taskforce for Global Health/NTD Support Centre to complete the field and laboratory work for this project. I am indebted to the folks at the Taskforce for administrative support, technical guidance, and statistical expertise, including: Dr. Pat Lammie, Dr. Katie Gass, Andrew Majewski, Waithera Kagira-Watson, Kira Barbre, Julie Kenyon, Wendi McAfee, and Nikita McCage. I was lucky to have gotten to know Dominique Kylem and am grateful for his support in the early stages of this project. I am indebted to Dr. Eric Ottesen, who has provided thoughtful guidance and mentorship to me throughout this entire process.

LSTM also provided financial support for this project, including field costs and travel funding, for which I am very appreciative.

I was honoured to complete the laboratory portion of my work in the Williams Lab at Smith College in Massachusetts, USA. I am thankful to Dr. Steve Williams and Nils Pilotte for the warm welcome and for providing guidance and support. I'm indebted to Ashanta Ester for helping me re-learn my way around a laboratory and to both she and Brian Abrams for the time and effort spent processing samples.

This endeavour involved coordination with and guidance from many additional people and organizations in Tanzania. I am grateful for the inputs and support from Dr. Mahdi Ramsan and Dr. Fabrizio Molteni from RTI, Dr. Prosper Chaki and his colleagues at Ifakara Health Institute, Peter McElroy from CDC/Tanzania, and Dr. Jeremiah Ngondi from Envision/RTI.

Love and gratitude to my sister, Lori O'driscoll, for always supporting me no matter what. Cheers to my Huns in Australia for keeping me sane the past few years - Vicci, Alana, Mel, Celia, and Adriana. I'd also like to thank my dear friend Megan Fotheringham for her friendship and support over the years. Thank you also to my parents for their love and encouragement along the way.

To my mother-in-law, Barb – you have been a lifesaver. Thank you for supporting me and our family, especially in the last few weeks before submission. Without you the laundry would have spilled over and I wouldn't have been able to find the sink – or my sanity. I truly appreciate your willingness to travel all the way to Australia to help and am grateful for the precious time you spent with Ella and Maxton.

Babu, I can't forget you. You have been a light when it was dark, a friend, an adopted father, a colleague, and a wonderful travel companion. There are simply not enough bottles of red in the world to express my gratitude for our friendship.

To my little Aussie darlings, Ella and Maxton – fortunately you are young enough that you won't remember the many hours I spent away from you to work on "my book". I love you both with all my heart and it is my hope that one day you will read this and be inspired by your mum.

To Brian, my love and partner in all things worth pursuing, a mere thank you is simply not enough. So…let's go have a picnic.

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AFRO	Regional Office for Africa, World Health Organization
CDC	Centres for Disease Control and Prevention
CI	confidence interval
DBS	dried blood spot
DDT	dichloro-diphenyl-trichloroethane
DHS	Demographic and Health Survey
ELISA	enzyme-linked immuno-sorbent assay
EU	evaluation unit
GAHI	Global Atlas of Helminth Infections
GIS	geographic information system
GPELF	Global Programme to Eliminate Lymphatic Filariasis
GPS	global positioning system
ICT	immunochromatographic test
ITN	insecticide-treated net
IRS	indoor residual spraying
IU	implementation unit
IVM	integrated vector management
LF	lymphatic filariasis
LLIN	long-lasting insecticidal net
LSTM	Liverpool School of Tropical Medicine
MDA	mass drug administration
MIS	Malaria Indicator Survey
MoHCDGEC	Ministry of Health Community Development, Gender, Elderly and Children
MOHSW	Ministry of Health and Social Welfare
NIMR	National Institute of Medical Research
NMCP	National Malaria Control Program
NTD	neglected tropical disease
PMI	President's Malaria Initiative
RPRG	Regional Programme Review Group
SD	standard deviation
SES	socioeconomic status
TAS	transmission assessment survey
TNVS	Tanzania National Voucher Scheme
UCC	universal coverage campaign
Wb	*Wuchereria bancrofti*
WPRO	Western Pacific Regional Office, World Health Organization
WHA	World Health Assembly
WHO	World Health Organization

Chapter One

Introduction

1.1 Background

Since the launch of the Global Programme to Eliminate Lymphatic Filariasis (GPELF) in 2000, concerted advocacy efforts have increased awareness of lymphatic filariasis (LF) and boosted global funding to target its elimination (Linehan et al., 2011; Molyneux, Hotez, & Fenwick, 2005). Over 6.7 billion LF treatments have been delivered to more than 850 million at-risk individuals worldwide (WHO, 2017c). Due to these efforts, almost 500 million people no longer require LF treatment and several endemic countries have met World Health Organization (WHO) validation criteria for eliminating LF as a public health problem (WHO, 2017c).

These are tremendous achievements, especially for a disease that has long been considered 'neglected'; however, there are challenges that need to be addressed if the global target of LF elimination is to be achieved. Three of these challenges include:

1. **The need for alternative elimination strategies in some settings.** The main strategy of the GPELF is the delivery of preventive chemotherapy through a strategy of mass drug administration (MDA) (WHO, 2010c). By 2016, six of the 52 LF-endemic countries requiring MDA had not yet started and 16 had yet to reach all areas where MDA is required (WHO, 2017c). Moreover, not all LF-endemic countries implementing MDA are achieving adequate coverage (WHO, 2017c). In settings where populations requiring treatment are not being reached, alternative strategies may be required to interrupt LF transmission or to accelerate it (Bockarie, Pedersen, White, & Michael, 2009; Kelly-Hope, Molyneux, & Bockarie, 2013). Vector control has been recognized as one potential alternative or supplemental strategy in the GPELF (Bockarie, Kelly-Hope, Rebollo, & Molyneux, 2013; Irvine et al., 2015). Yet, the vast majority of vector control activities in LF-endemic areas of Africa are implemented by malaria programmes (WHO, 2011a). Furthermore, malaria and LF programmes are rarely coordinated and the impact of vector control on LF is not routinely monitored (WHO, 2013a).

2. **The need for more sensitive diagnostics.** Sensitive and specific diagnostics are required to guide LF programmatic decisions – particularly decisions regarding when to start and stop MDA and how to conduct post-MDA surveillance. The availability of sensitive field-friendly rapid antigen tests have been critical to establishing where to start and when to stop MDA (WHO, 2012b); however, they may not be able to meet the changing needs of the GPELF, particularly as LF programmes enter a post-

treatment surveillance phase (Won, Robinson, et al., 2018). Increasingly, antibody testing is being considered for its potential to guide LF programmes, primarily because antibody responses to *W. bancrofti* usually precede detection of antigen, making them early indicators of exposure (Kubofcik, Fink, & Nutman, 2012; Washington et al., 2004). One of the primary limitations of antibody tests is that they do not distinguish between current and past infection; however, detection of antifilarial antibodies in young children has been proposed as an early indicator of LF exposure, and therefore ongoing transmission (Steel, Kubofcik, Ottesen, & Nutman, 2012; Weil & Ramzy, 2007). Newer antibody assays show promise, including minimal to no cross reactivity with other filarial species which was another limitation of LF antibody testing to date (Steel et al., 2013); however, additional research is needed to inform the development of programmatic guidelines for their appropriate application (de Souza et al., 2017).

3. **The need to address small foci of infection.** LF is a highly focal disease and its distribution can vary considerably even within relatively small geographic areas (Fox & King, 2013; Melrose, 2004; Plucinski et al., 2018). The WHO LF mapping strategy that has been used to map thousands of districts since 2000 was designed to quickly and conveniently assess where active transmission is occurring, and thus, where MDA is required (Gass et al., 2017; WHO, 2000). However, the heterogeneity of LF has implications for this approach, particularly in low prevalence settings in which small foci of LF transmission may be missed (Drexler et al., 2012). In addition to the *detection* of small foci is the need to better understand the potential *implications*. It has been argued that small endemic foci may threaten long-term LF elimination; however, the risk posed by such foci remains unclear (Harris & Wiegand, 2017).

1.2 Rationale

At the time this study was conceived, almost every district in Tanzania was considered LF-endemic and in need of MDA based on LF mapping completed by 2004. Yet, by 2011, there was uncertainty regarding whether MDA was indeed required in all areas that had not yet been reached with treatment. As the LF Programme began planning for a substantial scale up of MDA, this uncertainty had important implications for programmatic decisions due to the expense of scaling-up mass treatment in such a large country.

One of the geographical areas with an uncertain LF situation at the time was the Lake Zone around Lake Victoria. LF mapping had indicated that the Lake Zone required MDA, but MDA

had not yet taken place due to prioritization of other geographic areas. At the same time, large-scale vector control interventions were being planned for the Lake Zone. This presented an opportunity to assess evidence of ongoing LF transmission and evaluate the potential impact of vector control on LF transmission.

Furthermore, this study presented an opportunity to consider the global challenges outlined above in the context of rapidly expanding programmes for both vector control for malaria and MDA for LF.

1.3 Aim

The overall aim of this research was to assess evidence of LF transmission and investigate the impact of vector control for malaria on LF transmission in Tanzania.

1.4 Overall Objectives

1. To examine predicted LF risk and trends in vector control coverage on a national scale in Tanzania
2. To investigate trends in vector control coverage on a local scale in the Lake Zone of Tanzania
3. To assess LF exposure, and thereby potential ongoing transmission, and its predictors in the Lake Zone of Tanzania.

These overall objectives take into consideration the challenges identified above by incorporating the following aspects into the research: monitoring the impact of vector control as a supplemental strategy in the absence of MDA, utilization of one of the newest serologic tools to detect LF exposure, and consideration of these factors in an area of low LF risk that may include localized foci of LF transmission.

1.5 Thesis Organisation

Following the Introduction (**Chapter 1**), the Literature Review (**Chapter 2**) provides an overview of LF and its transmission and detection, followed by a summary of the GPELF. The chapter concludes with a synopsis of the LF Programme in Tanzania.

Chapter 3 takes a national view of LF risk and vector control coverage in Tanzania. Large population-based surveys and existing modelled data were used to elucidate a general picture of LF risk, ITN ownership, and IRS coverage throughout the country. Case studies explore in greater detail the potential implications of vector control hotspots on LF

transmission in two different geographic settings in relation to factors such as the changing distribution of mosquito species and the emergence of insecticide resistance.

Chapter 4 considers a narrower geographic focus and examines net ownership and IRS coverage in the Lake Zone of Tanzania, parts of which have received intensified vector control as the focus of the IRS programme.

To investigate the potential implications of net ownership and IRS on LF transmission, **Chapter 5** examines evidence that LF transmission is occurring in the Lake Zone and investigates the potential impact of vector control on LF exposure in young children.

Chapter 6 brings this information together and considers various themes that have emerged in the research. Recommendations for programmatic actions and future research are also put forth.

Chapter Two

Literature Review

2.1 Overview of Lymphatic Filariasis

2.1.1 Introduction

LF, also known as elephantiasis, is a parasitic disease caused by infection with filarial parasites of the nematode species *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori* (Sasa, 1976). It is spread to humans by the bite of infected mosquitoes, predominately of the genera *Anopheles*, *Aedes*, *Culex* and *Mansonia* (Edeson & Wilson, 1964). Infection is usually acquired in childhood after repeated exposure, but clinical symptoms, including temporary or permanent disability, usually do not occur until adulthood (Witt & Ottesen, 2001).

LF is classified as a neglected tropical disease (NTD) by the WHO (WHO, 2010a). It is one of the leading causes of disability worldwide (WHO, 1995, 2012a) and is most commonly found among the world's poorest and most neglected populations (Molyneux et al., 2005). As a result, its clinical complications can contribute to a vicious cycle of poverty in already vulnerable populations (Haddix & Kestler, 2000). In 2014, WHO classified 73 countries as endemic for the disease and estimated that approximately 1.1 billion people residing in these countries are at risk (WHO, 2015).

2.1.2 Lymphatic Filariasis in History

It is surprising that such a pervasive disease has been 'neglected' for so long, especially given its well-documented history. LF is commonly referred to as an 'ancient' disease because it is thought to have existed since the beginnings of recorded history as evidenced by its description in historical writings (Addiss, 2005; Manning, 2000). The swellings of the extremities and genitalia that are characteristic of chronic infection with LF are described in many ancient texts (Rajan, 2000). The Sushruta Samhita, a medical textbook compiled by the Indian physician Sushruta in 70 AD, includes a description of a disease that is believed to be LF (Laurence, 1967; Rajan, 2000). Evidence of its existence in the 10th century is found in the Arabic writings of the Persian physician Rhazes, and the Persian physician Avicenna wrote of its presence in Alexandria (Rajan, 2000). The shame and stigma still associated with the disease today was evident in ancient societies. Routh and Bhowmik (1993) report that the disease was considered as an "opprobrium artis medicae" – the disgrace or infamy attached to conduct viewed as grossly shameful by society. Indeed, references in Buddhist texts between 600 and 250 BCE indicate that people with deformity from the disease were inauspicious and not allowed to enter the priesthood (Laurence, 1967). Such stigma persisted into the 16th century when writings from visitors to Malabar (present day Kerala, India) documented the swollen lower limbs characteristic of the disease, which became known as

the “curse of St. Thomas” (Laurence, 1970). Laurence (1970) also reports that these descriptions from Malabar include speculation that water in coconut plantations was (at least one) cause of the disease. Interestingly, this is an area with *Mansonia* mosquitoes, vectors of LF caused by *Brugia malayi* (Hoti et al., 2001). The damp conditions and vegetation of the coconut plantations referred to in these accounts would indeed have been ideal for the *Mansonia* life cycle. Even today, Kerala remains endemic for LF caused by *Brugia malayi* (Nujum et al., 2014).

It was in the eighteenth and nineteenth centuries that Western civilizations became aware of LF as colonialism brought Western physicians into contact with the tropical diseases present in the colonies (Rajan, 2000). Jean-Nicolas Demarquay, a French physician working in Havana, Cuba, is thought to have provided the first Western description of filariasis in 1863, including sketches of microfilariae he observed through microscopic examination of fluid from a hydrocele (Rajan, 2000). The later decades of the nineteenth century saw significant advancements in the understanding of the disease, particularly from physician-scientists working in India, China, and Australia. The Brazilian physician Otto Wucherer, for whom the predominant form of LF *Wuchereria bancrofti* is named, is credited with discovering microfilariae in chylous urine in 1868 (Routh & Bhowmik, 1993). In 1872, Timothy Lewis discovered microfilariae in peripheral blood from a Bengali seaman cook in Calcutta, India (Routh & Bhowmik, 1993). In 1876 while working in Brisbane, Australia, Joseph Bancroft was the first to observe the adult female worm - in a lymphatic abscess of the arm; he also obtained four live adults worms from a patient with a hydrocele of the spermatic cord (Cobbold, 1877). Each of these discoveries helped to establish the association between elephantiasis and its now known clinical manifestations hydrocele, chylocele, and chyluria (Routh & Bhowmik, 1993).

It is Sir Patrick Manson, a Scottish physician, who made perhaps the greatest advancements in our early understanding of the disease and its transmission. Working in China between 1875-1879, Manson was the first to describe “filarial periodicity”, a phenomenon in which microfilariae appear “in countless swarms in the cutaneous circulation during the night, and disappear from it during the day” (Manson, 1899). He also described the location of microfilaria when they are absent from the peripheral blood at night. He concluded that the majority are lodged in the deep veins of the body and especially concentrated in the blood vessels of the lungs (Manson, 1899). Manson also correctly inferred from his observations in humans that a blood sucking arthropod was involved in the transmission of the disease and he later demonstrated that the mosquito harbours the parasite and aids in its development

to an infective form ("Dr. Manson's Recent Researches on Filarial Disease," 1883). Working under Manson, parasitologist George Low demonstrated in 1900 that infective stage larvae are present in the proboscis of the mosquito, helping to support the hypothesis that infective larvae were transmitted from the mosquito to the host during a blood meal (Low, 1900).

These early discoveries were undoubtedly significant and foundational. Advancements in the first half of the twentieth century led to further understanding of the aetiology, biology, and transmission of the disease (Routh & Bhowmik, 1993). Later, studies in vector biology were greatly facilitated by the selection of a strain of *Aedes aegypti* susceptible to both *B. malayi* and *B. pahangi*, which offered a model mosquito for further research (Bartholomay & Christensen, 2002; MacDonald, 1962). By the early 1970s, the development of a laboratory host for *Brugia* species, the Mongolian gerbil *Meriones unguiculatus*, enabled further studies that increased our understanding of the mosquito-parasite relationship (Ash & Riley, 1970). Advances in molecular biology and genomics, including the development of genomic and cDNA libraries from filarial parasites helped to overcome additional limitations, including the dearth of available parasite material for study and the limited ability to maintain filarial parasites experimentally in only a few primate species (Ottesen, 1994). Advances in parasitology, diagnostics, immunology, genetics, pathogenesis of disease, and drug development have further expanded our knowledge and spurred the development of improved therapeutic strategies and prevention programs.

2.1.3 Epidemiology

Of the three species of filarial worms that cause LF, *Wuchereria bancrofti* is the most predominant, accounting for approximately 90% of infections worldwide (WHO, 1992). Infections with *W. bancrofti* are referred to as bancroftian filariasis and are geographically widespread, occurring in the hot and humid tropical regions of Africa, Asia, the Americas and the Pacific (Simonsen, Fischer, Hoerauf, & Weil, 2014). Two other species of filarial worms account for the remaining infections: *Brugia malayi*, which is limited to south Asia and the Pacific, and *Brugia timori*, a less common species limited to Timor and the neighbouring islands of Indonesia (Fischer, Supali, & Maizels, 2004). These latter infections are referred to as brugian filariasis.

WHO estimates that approximately 67 million people worldwide are infected with filarial parasites (WHO, 2017b). However, the epidemiology of LF varies significantly among the regions of the world. Southeast Asia and Africa bear the greatest proportion of the global population requiring preventive chemotherapy for LF. Only five countries in the South-East

Asia Region are considered LF-endemic, but this includes a population of almost 450 million people that require treatment (WHO, 2017c). Whereas in WHO/AFRO, approximately 371 million people require treatment, but they are dispersed throughout 32 LF-endemic countries (WHO, 2017c).

The remaining global burden is concentrated in the western pacific, a portion of the Americas, and the eastern Mediterranean. Eleven countries in the Western Pacific Region of WHO (WPRO) are considered LF-endemic with 14.7 million people requiring treatment (WHO, 2017c). However, many of these are island nations with relatively small populations. Although significant progress in eliminating LF has been made among some of these smaller island populations, several endemic countries within the region have made limited progress. Papua New Guinea, for example, accounts for 90% of the population requiring mass treatment in the Pacific sub-region of WPRO (WHO, 2015), but it reported that only 2.1% of its population requiring treatment was reached in 2016 (WHO, 2017c).

The WHO Region of the Americas has four endemic countries, including Guyana, Brazil, Dominican Republic, and Haiti (WHO, 2015). Within these four countries, Haiti accounts for almost 90% of the population requiring treatment (approximately 7 million people) (WHO, 2016a).

Finally, in the WHO Eastern Mediterranean Region, only Sudan and South Sudan are considered endemic, with populations of 13.4 and 1.7 million people requiring treatment, respectively (WHO, 2017c). However Sudan reported reaching less than 7% of its population requiring treatment in 2016 (WHO, 2017c).

Figure 2.1 shows the global distribution of LF and status of MDA (preventive chemotherapy) in 2016, as reported to WHO.

The geographic distribution of LF is strongly associated with poverty (Durrheim, Wynd, Liese, & Gyapong, 2004; Galvez Tan, 2003; Gyapong, Gyapong, Evans, Aikins, & Adjei, 1996). Along with other NTDs, populations at greatest risk within endemic countries include the 'poorest of the poor' who live on less than $2 US a day (Hotez, Fenwick, Savioli, & Molyneux, 2009; Molyneux et al., 2005). NTDs tend to cluster in geographic regions, with individuals commonly co-infected with more than one disease (Hotez et al., 2009). Populations living in rural areas and poor urban areas of endemic countries are at greatest risk (Hotez et al., 2007).

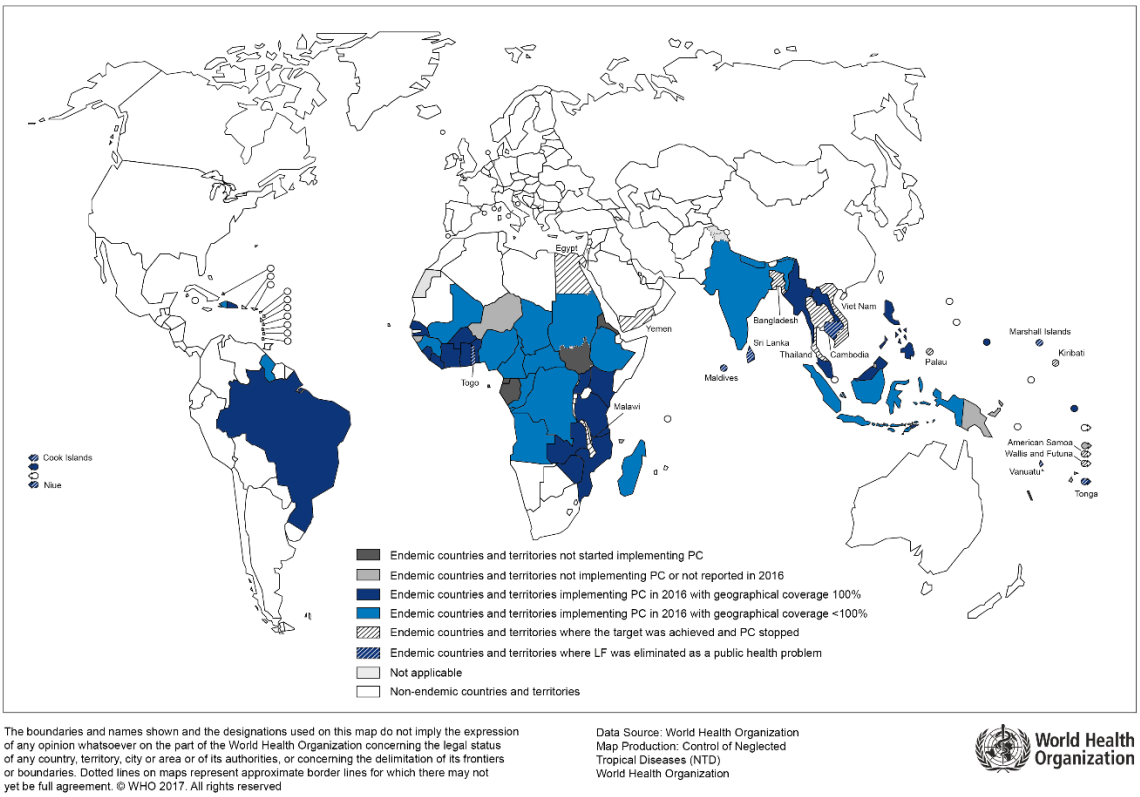


Figure 2.1 Global Distribution of LF and Status of MDA (preventive chemotherapy) in Endemic Countries, 2016 (Source: World Health Organization, 2017)

2.1.4 Aetiology and Morphology

The species of human filarial worms that cause LF (*W. bancrofti, B. malayi, and B. timori*) are members of the phylum Nematoda (Inglis, 1983), class Secernentea and order Spirurida (Anderson, 2000). Adult worms are pale, thread-like, unsegmented and reside in the lymphatic vessels of the human host (DeVries, 2005; Scott, 2000; Simonsen et al., 2014). Adult male worms of *W. bancrofti* measure approximately 4 cm in length and 50 mm in diameter (Araujo et al., 1995; Scott, 2000). Female worms are markedly larger than males, ranging in length from approximately 6-10 cm and 200 µm in diameter (Nanduri & Kazura, 1989; Scott, 2000). Both sexes are transversally striated on their exterior surface with periodic annulations (Araujo et al., 1995). The significance of irregularly distributed spherical protuberances on the exterior surface of both sexes is unknown (Araujo et al., 1995; Scott, 2000). Adult worms typically live for seven to ten years (Nanduri & Kazura, 1989), and it is estimated that the reproductive life span of adult *W. bancrofti* worms is four to eight years (Kazura, 2002; Michael et al., 2004). This has important implications for LF control measures, as will be discussed later. Sexually mature adults undergo ovoviviparous reproduction resulting in the release of thousands of microfilariae (first stage larvae) following fertilization (Nanduri & Kazura, 1989; Scott, 2000). Microfilariae retain their egg membrane as a

protective sheath and are approximately 260 µm long and 8 µm in diameter (Schacher, 1962; Simonsen et al., 2014; Wu, Preston, & Bianco, 2008). Following release from the female worm, these first stage larvae (L1) exit the lymphatic circulation, pass through the thoracic duct, and enter the peripheral circulation of the human host (Kazura, 2002; Scott, 2000; Simonsen et al., 2014). The life span of microfilariae is estimated to be one year or less and their densities in the blood are usually between 1-1,000 per mL of blood (Kazura, 2002; Simonsen et al., 2014).

2.1.5 Parasite Life Cycle

Lymphatic filariae have a biphasic life cycle (Figure 2.2). Larval development takes place in the intermediate mosquito host and larval and adult development take place in the definitive human host (Scott, 2000). There are no free-living forms of the parasite (Scott, 2000). Non-human hosts do not appear to be an important reservoir of human filariasis (Kazura, 2002), however both cats and Mongolian jirds can be infected with *Brugia* species (Ash & Riley, 1970; Palmieri et al., 1985).

Microfilariae released by the female adult worm as first stage larvae (L1) enter peripheral circulation within humans, where they become available for uptake and ingestion by female mosquitoes during a blood meal (Scott, 2000; Simonsen et al., 2014).

As Sir Patrick Manson first described in 1899, microfilariae follow a 24-hour periodic cycle in the peripheral blood with densities fluctuating throughout the day (Manson, 1899). This adaptation is thought to be associated with the biting times of the predominant vectors in a given geographical area (Hawking, 1975; Manson, 1899), which presumably increases the likelihood of microfilariae being ingested and transmitted (Simonsen et al., 2014). There are several forms of periodicity depending on which time of day microfilarial density in the peripheral blood is highest. *W. bancrofti* and *B. malayi* show 'nocturnal periodicity' in most areas of the world, with peak microfilarial density occurring in peripheral blood during the night, usually highest between 10 PM and 2 AM, and none to low density during the day (Sasa, 1976; Simonsen, Niemann, & Meyrowitsch, 1997). Night biting mosquito vectors predominate in these areas. Less common are strains of *W. bancrofti* and *B. malayi,* principally found in the Pacific, that exhibit continuous densities of microfilariae in the peripheral blood with higher density during the day or night. In this case, 'diurnally sub-periodic' refers to strains with higher densities during in the day, while 'nocturnally sub-periodic' refers to strains with higher densities during the night (Simonsen et al., 2014). Frank Hawking, father of renowned theoretical physicist Stephen Hawking, established the basis of

this phenomenon and associated it with the increase of microfilariae in the lungs during the day and their distribution in peripheral blood during the night (Hawking, 1965, 1967, 1975). Periodicity has been shown to be associated with the host rather than external stimuli such as night and day. For example, inversion of a person's sleep cycle leads to inversion of the microfilarial cycle (Hawking, 1965).

Once ingested by a susceptible mosquito species, microfilariae travel through the foregut to the midgut where they penetrate the single cell layer of the midgut wall to enter the haemolymph using piercing stylets (Bartholomay & Christensen, 2002; Kaslow & Welburn, 1996). Exsheathment of microfilariae is essential for further development in the mosquito (Kaslow & Welburn, 1996) and it has been shown to occur occasionally in the midgut (Christensen & Sutherland, 1984), in the hemocoel (Chen & Shih, 1988), or during penetration of the midgut wall (Agudelo-Silva & Spielman, 1985).

Migrating through the haemocoel, microfilariae eventually reach the thoracic flight muscles, where they shorten to a "sausage" form that is 240 to 250 µm in length (Nanduri & Kazura, 1989). Differentiation of the oesophagus, intestine and rectum occurs following a set of programmed cell divisions (Schacher, 1962). The next developmental stage occurs from 6-10 days post-infection when the first stage larvae (L1) moult to the second stage larvae (L2) (Scott, 2000). At this stage the larvae elongate, the gut develops further, and the genital primordium is formed (Schacher, 1962; Scott, 2000). A second moult, from second stage to third stage larvae (L3), occurs within the thoracic muscles 1-3 days later (11 to 13 days post-infection) (Scott, 2000). This transition from L2 to L3 larvae means the mosquito now has the *capacity* to transmit filarial infection to humans (Kazura, 2002). The L3 larvae migrate from the flight muscles to the head tissues of the mosquito 1-2 days later (Scott, 2000). Mature infective larvae are slender and measure approximately 1.4 to 2 mm long (Nanduri & Kazura, 1989). Once at the head, L3 larvae position themselves within the mouthparts of the mosquito where they can exit via the proboscis during a blood feeding (Bartholomay & Christensen, 2002; Scott, 2000). It takes approximately 10 to 14 days once ingested for microfilaria to mature to infective larvae (Nanduri & Kazura, 1989); however, the rates of larval development within the mosquito fluctuate with temperature (Simonsen et al., 2014).

Unlike malaria parasites, infective filarial larvae are not injected with saliva into the host when the mosquito feeds (Bartholomay & Christensen, 2002). Rather, they must actively escape the proboscis and are deposited on the skin where they can survive for sufficient time under moist conditions to enable them to enter the host (Anderson, 2000; Ewert, 1967; Scott, 2000). Infection in humans is initiated when third stage larvae (L3) enter the skin via the

puncture site, hair follicles, or other abrasions (Bartholomay & Christensen, 2002; Scott, 2000). The process of penetrating local connective tissue is facilitated by the release of proteases and other enzymes by the L3 (Maizels, Gomez-Escobar, Gregory, Murray, & Zang, 2001). Approximately 8 days post-infection, L3 have homed to the lymph vessels and undergo an additional moult, shedding their cuticle to become fourth stage larvae (L4) (Kazura, 2002; Scott, 2000). Initially L4 are approximately 3 to 6 mm in length, however, over the next 2-12 months they undergo significant growth as they develop into sexually mature male and female worms that reside in the lymphatic vessels (Kazura, 2002; Scott, 2000). Adult females can remain reproductively active for more than five years (Vanamail et al., 1996). After fertilization, zygotes develop into microfilariae over a three week period (Scott, 2000) and appear in the blood after a minimum of 3 months in *B. malayi* and 8 months in *W. bancrofti* (Simonsen et al., 2014).

2.1.6 Infection and Clinical Disease

Infection with LF can result in asymptomatic, acute, and chronic conditions, though it should be noted there is not necessarily a linear progression from an asymptomatic to a chronic state (Kumaraswami, 2000). A significant proportion of infected individuals have no apparent clinical signs or symptoms (Ottesen, 1980). The most common acute manifestations of the disease include acute filarial lymphangitis and acute dermatolymphangioadenitis (ADLA) resulting from secondary bacterial infections, while the most common chronic manifestations include hydrocele and lymphoedema, which can progress to elephantiasis (Dreyer, Medeiros, et al., 1999).

Most infected individuals show no obvious clinical symptoms of disease and have therefore traditionally been classified as ‘asymptomatic’ (Ottesen, 1984). This may include individuals with detectable levels of microfilaremia (‘asymptomatic microfilaraemics’), as well as individuals who are amicrofilaraemic but antigenemia-positive, indicating the presence of adult worms without detectable circulating juveniles (Weil et al., 1996).

Infected persons may be microfilaraemia-negative but antigenemia-positive if they are infected with only single sex worms incapable of reproduction, if the female worms present are not capable of reproduction because they are not yet sexually mature, or if the density of microfilaria is too low to be detected (Njenga, Wamae, Mwandawiro, & Molyneux, 2007).

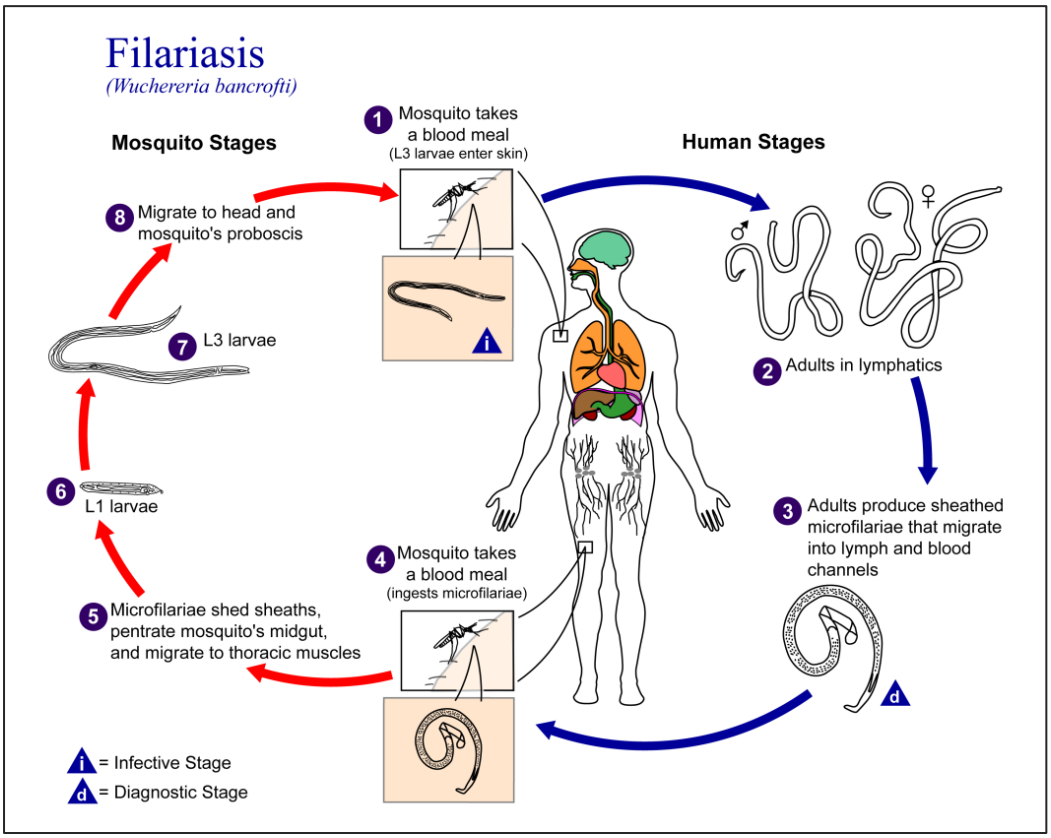


Figure 2.2 Biphasic Life Cycle of *Wuchereria bancrofti* (Source: CDC, 2010)

Infected individuals in the 'asymptomatic' category typically remain unaware of their infection status and may remain free of obvious signs of pathology for years or even decades (Ottesen, 1992). This was previously thought to represent a benign phase of the disease; however, studies of animal models in the 1980s demonstrated that adult worms can produce significant damage to the lymphatic system before inflammatory responses or obvious symptoms are seen (Freedman et al., 1994). Indeed, Dreyer and colleagues reported that renal abnormalities (haematuria and proteinuria) in asymptomatic microfilaraemics are quite common (Dreyer et al., 1992).

Diagnostic studies in the 1990s advanced our understanding of the relationship between the parasite and the progression of disease in humans. *In situ* studies utilizing ultrasonography and lymphoscintigraphy confirmed that, similar to animal models, subclinical abnormalities do occur in the absence of noticeable clinical symptoms in humans (Amaral et al., 1994; Dissanayake, Watawana, & Piessens, 1995; Freedman et al., 1994, 1995; Suresh et al., 1997). Amaral et al. (1994) used ultrasound to locate live adult *W. bancrofti* in the scrotal lymphatics of asymptomatic microfilaremic men around which they observed abnormal dilation of lymphatic channels. Freedman et al. (1994, 1995) used lymphoscintigraphy, an imaging technique in which small amounts of radiotracers are injected into the skin to enable

visualization of the lymphatic system and observed widespread lymphatic abnormalities in asymptomatic microfilaremic individuals. Dissanayake and colleagues (1995) reported subclinical lymphatic damage in the limbs of asymptomatic individuals. Suresh et al. (1997) confirmed the sonographic findings of Amaral et al. of adult worms in the scrotal lymphatic vessels, though they reported a higher sensitivity of diagnosis in mild infections than Amaral et al., which they attributed to the use of techniques that enabled better visualization of the lymphatics. Prior to these discoveries, it had been hypothesized that early lymphatic pathology resulting from LF was due mainly to the host inflammatory response (Ottesen, 1992); however, these studies suggested an alternative – that adult worms themselves induce the lymphatic dilation and dysfunction seen in early stage pathology (Ottesen, 1992, 1994).

LF infection is often acquired in childhood (Witt & Ottesen, 2001). In some areas endemic with *W. bancrofti*, up to one-third of children as young as four are infected, though few children with antigenemia are shown to have microfilaraemia, indicating that the intensity of infection requires time to increase to detectable levels (Lammie et al., 1998; Simonsen, Lemnge, Msangeni, Jakobsen, & Bygbjerg, 1996). Despite the absence of apparent clinical disease symptoms in children, studies utilizing ultrasonography and lymphoscintigraphy have demonstrated that subclinical lymphatic damage may begin at a young age (Dreyer, Norões, et al., 1999; Dreyer, Figueredo-Silva, Carvalho, Amaral, & Ottesen, 2001; Shenoy et al., 2008). Of promising note, the drug regimens used in mass treatment programs in *B. malayi* endemic areas of India have been shown to reverse subclinical damage in children (Shenoy et al., 2009).

Overt clinical disease usually begins to appear in early adulthood (Addiss & Brady, 2007). The mere presence of *living* adult worms in the lymphatic system does not appear to result in major histological changes (Pfarr, Debrah, Specht, & Hoerauf, 2009). However, *death* of adult worms triggers lymphangitis (inflammation of lymphatic vessels) and lymphadenitis (inflammation of lymph nodes), depending on worm location (Jungmann, Figueredo-Silva, & Dreyer, 1991). These conditions can cause localized pain and swelling and lead to underlying damage and dysfunction of the lymphatic system, which compromises lymphatic defences and increases an individual's susceptibility to recurrent (secondary) bacterial infection (Addiss & Brady, 2007; Dreyer, Medeiros, et al., 1999). Secondary bacterial infections, which are common in the lower limbs and often enter the body through a visible distal site of entry, provoke one of the most common symptoms of LF - ADLA (Dreyer, Medeiros, et al., 1999). ADLA events (also known as 'acute attacks') are associated with local pain, swelling, fever

and chills, and usually last for about a week but often recur several times per year (Simonsen et al., 2014; WHO, 2013b). Although swelling usually subsides after each attack, repeated episodes of ADLA contribute to progression to chronic lymphoedema and its more advanced form elephantiasis (Kumaraswami, 2000; Pani et al., 1995; Simonsen et al., 2014). In addition to the limbs, lymphoedema and elephantiasis can include swelling of the arms, breasts, and genitals (Addiss & Dreyer, 2000). The recommended treatment for lymphoedema and elephantiasis focuses on hygiene, skin care to prevent secondary bacterial infections, exercise, and elevation of affected limbs (Addiss & Brady, 2007).

The most common chronic manifestation of bancroftian filariasis in men is hydrocele, or scrotal swelling (Gyapong, Webber, Morris, & Bennett, 1998). Hydrocele is caused by the accumulation of fluid in the cavity of the tunica vaginalis (WHO, 2013b). Inflammatory responses following the death of adult worms living in the intrascrotal lymphatic vessels cause obstruction and scrotal nodule formation, multiple episodes of which can lead to the development of chronic hydrocele (Noroes et al., 2003). The recommended treatment for extensive hydrocele is hydrocelectomy (Addiss & Dreyer, 2000).

The patterns of both acute and chronic clinical manifestations of LF vary from one endemic area to another and differ based on the causative parasite (Sasa, 1976). For example, hydrocele is only found in areas endemic for *W. bancrofti*, and lymphoedema of the legs and arms appears to be more common but less severe in areas endemic for *B. malayi* compared to *W. bancrofti* (Fischer et al., 2004; Simonsen et al., 2014).

It should be noted that other clinical conditions can also result from LF, however, these conditions are less common than those discussed here and currently lack public health approaches to address them. These conditions include chyluria, tropical pulmonary eosinophilia, adenopathy, haematuria, lymphocele, and scrotal lymphoedema (Addiss & Brady, 2007; Simonsen et al., 2014). WHO recommends that these clinical conditions be treated with standard clinical and referral practices (WHO, 2013b).

2.1.7 Vectors

Four genera of mosquitoes play a significant role in the transmission of LF in humans, namely *Anopheles*, *Aedes*, *Culex*, and *Mansonia* (Zagaria & Savioli, 2002). Over 70 species and subspecies of mosquitoes have been recognized as vectors and their respective contribution to transmission varies by region (Scott, 2000; Simonsen et al., 2014).

The primary vectors of *W. bancrofti* are *Culex* mosquitoes in most urban and semi-urban areas, *Anopheles* in rural areas of Africa and elsewhere, and *Aedes* in the Pacific islands (Sasa,

1976). For *B. malayi*, *Mansonia* species serve as the primary vectors, while the only known mosquito vector for *B. timori* is *An. barbirostris* (Atmosoedjono, Partono, & Dennis, 1977; Sasa, 1976).

Culex mosquitoes transmit only the nocturnally periodic form of *W. bancrofti* but are the most widely distributed vector of LF globally (Manguin, Bangs, Pothikasikorn, & Chareonviriyaphap, 2010). *Culex quinquefasciatus* is the principle vector species in urban and semi-urban areas of South Asia, tropical regions of Africa, the Middle East, and in the Americas (Simonsen et al., 2014; Zagaria & Savioli, 2002). *Culex* breed in still water, including artificial containers and catchment basins, as well as large bodies of permanent water (Rozendaal, 1997). *Cx. quinquefasciatus* especially prefers to breed in polluted waters containing organic material, as is found in pit latrines, septic tanks, abandoned wells, and areas with poor drainage and sanitation. These breeding sites are often found in urban areas and are increasing as a result of rapid urbanization in many areas (Chavasse, Lines, Ichimori, & Marijani, 1995). *Cx. quinquefasciatus* is mainly domestic and bite throughout the night, both indoors and outdoors. They tend to rest during the day, in both indoor and outdoor environments (Rozendaal, 1997) .

Anopheles mosquitoes are known vectors for the nocturnally periodic forms of *W. bancrofti*, *B. malayi*, and *B. timori* (Zagaria & Savioli, 2002). In Africa, where *W. bancrofti* is endemic, *Anopheles* spp. are the primary vectors in most rural areas, with *An. funestus* and members of the *An. gambiae* complex serving as the most important vectors in these areas (Scott, 2000). Night-biting *Anopheles* are the main vectors for nocturnally periodic *W. bancrofti* in Papua New Guinea and in areas of Indonesia (Simonsen et al., 2014). The periodic form of *B. malayi* is transmitted by several species of *Anopheles* in South Asia, the most widespread being *An. barbirostris*, *An. campestris*, and *An. donaldi* (WHO, 2002). *An. barbirostris* is the only known mosquito vector of *B. timori*, which is nocturnally periodic and found only in the Alor, Timor and Flores islands of Indonesia (Atmosoedjono et al., 1977). *Anopheles* can be found in a wide range of habitats in both rural and urban areas (Sasa, 1976). For example, *An. funestus* prefer larger, more permanent or semi-permanent bodies of fresh water, particularly among the vegetation on the edges of ponds, swamps, and lakes, while *An. gambiae* can be found in drainage systems, rice fields, and puddles (Awolola, Oduola, Obansa, Chukwurar, & Unyimadu, 2007; Fillinger, Sonye, Killeen, Knols, & Becker, 2004; Leeson, 1937). *Anopheles* mosquitoes are both endophagic and exophagic night-biters, and are both endophilic and exophilic, feeding on both humans and animals, depending on species (Rozendaal, 1997).

Aedes mosquitoes transmit the sub-periodic forms of *W. bancrofti* and *B. malayi* in parts of South East Asia and in the South Pacific. *Ae. Polynsiensis* is the predominant vector of sub-periodic *W. bancrofti* in the Polynesian Islands (Zagaria & Savioli, 2002). Aedes prefer smaller bodies of water and can be found in both natural and artificial habitats. For example, *Ae. Polynsiensis* in Polynesia breed in both natural sites such as crab holes as well as artificial containers (Burkot et al., 2007).

Mansonia mosquitoes transmit both *W. bancrofti* and *B. malayi*. For *B. malayi* in South Asia, this includes both the sub-periodic form often found in dense swampy forest areas, as well as the periodic form (Simonsen et al., 2014). *Mansonia* also serve as a minor vector of *W. bancrofti* in limited areas of Africa, Papua, and the Americas (Zagaria & Savioli, 2002). *Mansonia* are found in swampy areas, and other areas containing vegetation where they can lay their eggs in masses under hanging plants or floating vegetation (Rozendaal, 1997). Vegetation is also required for larval and pupal development. They tend to be night-biters, are mainly exophagic, and usually rest indoors following a blood meal (Rozendaal, 1997).

The significant variation in mosquito species that transmit LF to humans and their relative distribution determines the epidemiological characteristics of the disease in a given geographical area (Snow & Michael, 2002). This variation complicates control and elimination efforts. Vector control strategies, for example, must be tailored to the biological behaviour of the relevant species (Ottesen, 2006). As discussed below, vector distribution also relates to transmission patterns and ultimately to the potential effectiveness of control efforts focused on preventive chemotherapy.

2.1.8 Determinants of Transmission

The transmission of LF is less efficient than that of other vector-borne diseases, such as dengue and malaria, and the reasons for this are multifaceted (Rozendaal, 1997).

Transmission is influenced by the life cycle requirements of the parasite, various aspects of the host-parasite relationship, prevalence and intensity (density) of microfilaria in the human host, the density of mosquitos in a community and their interaction with human hosts, as well as various facets of the parasite-mosquito relationship that influence vector capacity (Bockarie et al., 2009; Sasa, 1976; Snow, Bockarie, & Michael, 2006; Southgate & Bryan, 1992). These dynamics contribute to the potential for successful control and elimination programs (Manguin et al., 2010; Partono, 1984).

As discussed previously, the life cycle of filarial parasites requires both an intermediate mosquito host and a definitive human host for both larval and adult development,

respectively (Scott, 2000). The life cycle overall is fairly long, with estimates ranging from 7-10 years for the lifespan of adults worms (Nanduri & Kazura, 1989), of which approximately 4-8 years are reproductively active (Kazura, 2002; Michael et al., 2004). Despite the longevity of adult worms, they do not replicate themselves within the human host, meaning that the adult worm burden depends on the intensity of exposure to infective larvae and the only way for parasite loads to increase is through accumulated exposure and infection (Kazura, 2002; Maizels et al., 2001).

Both the uptake of microfilariae by the mosquito and the efficiency with which they ultimately develop into infective L3-stage larvae play important roles in transmission dynamics (Scott, 2000). The greater the number of infected human hosts with sufficient levels of circulating microfilariae in their peripheral blood and the higher the biting rate of the mosquito, the greater the likelihood that the mosquito will ingest microfilariae (Snow & Michael, 2002). Uptake is therefore dependent on the prevalence and intensity of infection in the community, with mosquito infection rates increasing with higher levels of parasitaemia (Piessens & Partono, 1980). Additionally, annual infective biting rate and annual transmission potential have been shown to be positively associated with microfilariae rate and density in the community (Kazura et al., 1997).

Once microfilariae are ingested by the mosquito, their development is dependent on a number of morphological, physiological, and biochemical factors, many of which limit transmission (Bartholomay & Christensen, 2002). As noted previously, microfilariae do not multiply within the mosquito vector. As a result, their likelihood of being transmitted in an infective form to a human host is limited by the number of microfilariae ingested (Snow & Michael, 2002). Additionally, the environment microfilariae encounter within the mosquito influences successful development to the infective stage (WHO, 2013a). Such environments differ by mosquito genus and ultimately influence patterns of transmission. In *Anopheles* mosquitoes, as the number of ingested microfilariae increases, the proportion of microfilariae that reach the infective L3 stage *increases*. This is known as 'facilitation' and its implication is that lower densities of microfilariae are associated with a lower rate of L3 development (de Souza et al., 2012; Snow et al., 2006; Southgate & Bryan, 1992). The opposite is seen in *Aedes* and *Culex* mosquitoes, where, as the number of ingested microfilariae increases, the proportion of microfilariae that reach the infective L3 stage *decreases*. This is known as 'limitation' and its implication is that low densities of microfilariae have a higher chance of survival to the infective stage (de Souza et al., 2012; Snow et al., 2006; Southgate & Bryan, 1992).

Facilitation and limitation have consequences for control strategies and the potential impact of intervention programs. The rationale for the strategy of MDA, which will be discussed later, is based on the effectiveness of vectors to transmit infection at low levels of microfilaraemia (de Souza et al., 2012). This strategy aims to reduce microfilarial density below a critical level at which the parasite population dies out. Reaching this critical level is more difficult for *Aedes* and *Culex* mosquitoes than for *Anopheles* mosquitoes. As a result, interrupting transmission of LF may be easier in regions in which *Anopheles* are the primary vector versus areas where *culicines* are the primary vectors (Taylor, Hoerauf, & Bockarie, 2010).

Finally, it should also be noted that local environmental conditions also affect patterns of LF transmission. Factors such as temperature, humidity, rainfall, soil type, and other conditions that affect breeding sites can also influence the life cycle and survivability of adult mosquitoes (WHO, 2013a). Mosquitoes that die before infective stage larvae have had a chance to develop (approximately ten days) cannot play a role in the transmission cycle.

2.1.9 Diagnostic Tools

A shift from individual diagnosis to large-scale monitoring and evaluation of at-risk populations has become increasingly important to guide LF programmes (Molyneux, 2009; Ramzy, 2002). Fortunately, a reliance on less sensitive and often onerous diagnostic methods has given way to more practical applications that are more suited to field settings (Owusu et al., 2015; Ramzy, 2002; Weil & Ramzy, 2007).

In the context of implementing a national LF program, there are several critical programmatic steps that must be undertaken in order to initiate and eventually cease MDA (WHO, 2011b). These programmatic steps will be discussed in the next section on the GPELF. Here, the diagnostic tests currently in use within the GPELF are summarized.

2.1.9.1 Detection of Microfilariae

Blood films are a method of direct detection of microfilariae in the peripheral blood of a human host, thereby providing definitive proof of infection in an individual (Simonsen et al., 2014). Detection of microfilariae within a community can provide data on infection prevalence, parasite density and community microfilarial load (Weil & Ramzy, 2007). The technique most often employed utilizes microscopic examination of Giemsa-stained thick blood smears prepared using capillary blood collected by finger-prick (Melrose, 2004). Blood films have generally been accepted as a diagnostic tool in the field because they utilize a relatively inexpensive technique and do not require sophisticated laboratory equipment;

however, in the numbers often required, they can be quite labour intensive (Melrose, 2004; Sasa, 1976; Weil & Ramzy, 2007). Furthermore, detection of microfilariae requires skilled microscopists to perform consistently in field settings (Weil, Lammie, & Weiss, 1997). Additionally, where microfilariae are nocturnally periodic, blood must be collected when microfilariae are at their peak densities in the peripheral blood, which generally occurs overnight between the hours of 10 pm and 2 am (Sasa, 1976). One of the primary limitations of blood films as a programmatic tool is their lack of sensitivity to detect active infections when microfilarial density is low (Eberhard & Lammie, 1991). As a result, individuals with low microfilarial counts or those with amicrofilaraemic infections may be missed and communities with active transmission may be misclassified as non-endemic since the true burden of infection may be underestimated (Lammie, Hightower, & Eberhard, 1994; Turner, Copeman, Gerisi, & Speare, 1993; Weil & Ramzy, 2007). Such communities could pose a risk for ongoing transmission; consequently, exclusive reliance on microfilarial testing to make programmatic decisions is not recommended (Weil & Ramzy, 2007). The limitations of detecting microfilariae using microscopy prompted the development of alternative methods of diagnosis, including immunological and molecular tests, as discussed below (Weil et al., 1997).

2.1.9.2 Detection of Circulating Filarial Antigens

As discussed previously, antigenemia is a marker of active filarial infection and antigen levels are related to the number of adult filarial worms in the host (Weil et al., 1996, 1999; Weil, Malane, Powers, & Blair, 1985; Weil, Ogunrinade, Chandrashekar, & Kale, 1990; Weil & Ramzy, 2007). Circulating filarial antigen tests detect antigens released by adult *W. bancrofti* worms in human blood (Weil & Ramzy, 2007). Unlike microfilaraemia, antigen levels do not significantly fluctuate based on time of day, so antigen testing can be conducted during the day or night (Moulia-Pelat et al., 1993). Testing for adult worm antigen is more sensitive than microfilariae detection; it has been demonstrated that at least one-third of all infections would be missed if only blood films are utilized (Witt and Ottesen, 2001). Both laboratory and rapid diagnostic methods are available to detect antigen from *W. bancrofti*, however rapid tests have become more common due to their utility in the field (Weil & Ramzy, 2007). The laboratory method involves detection using the antigen enzyme-linked immunosorbent assay (ELISA). The most accepted assay is the Og4C3, which uses monoclonal antibody raised against *Onchocerca gibsoni antigen* (Chanteau et al., 1994). The Og4C3 assay has been shown to have high sensitivity and specificity for *W. bancrofti* (Chanteau et al., 1994; Lammie et al., 1994). Rapid diagnostic methods have become the globally accepted tool for mapping

bancroftian filariasis, primarily due to their ease of use in the field and their comparable sensitivity with the ELISA (Weil et al., 2013). Until recently the only commercially available immunochromatography card test (ICT) available to detect *W. bancrofti* was the BinaxNOW Filariasis test (Alere Scarborough, Maine, United States), which utilizes finger-prick blood that can be sampled at any time of day (Weil et al., 1997). The ICT does not require skilled microscopists, laboratory equipment, or electricity (Weil & Ramzy, 2007). The main limitation of the ICT has been its cold chain requirements (2-8° C), relatively short shelf-life (3 months at ambient temperatures), and cost (Rebollo & Bockarie, 2014; Weil & Ramzy, 2007). Additionally, in order to avoid false-positive tests, the results must be read at exactly 10 minutes due to the instability of the card (Simonsen & Magesa, 2004; Weil et al., 2013). Recognizing these limitations, a new point-of-care rapid test strip, the Alere Filariasis Test Strip (FTS), was developed and shown to have increased sensitivity over the ICT in field studies (Weil et al., 2013). The ICT has been used extensively to map LF, and both the ICT and FTS are currently being used as programmatic monitoring tools within the GPELF (WHO, 2016b). However, antigen detection only reveals infection after adult parasites have developed and these tests have been shown to have reduced sensitivity following multiple rounds of MDA (Gounoue-Kamkumo et al., 2015; Njenga, Wamae, Njomo, Mwandawiro, & Molyneux, 2008). It is widely recognized that a sensitive and specific diagnostic tool that can detect early *exposure* to LF is required for the later stages of the GPELF when monitoring of transmission and of possible recrudescence following discontinuation of MDA becomes critical (Gass et al., 2012; Weil & Ramzy, 2007).

2.1.9.3 Detection of Antifilarial Antibodies

The potential of antibody testing for programmatic use has improved significantly in recent years as more sensitive tests that detect IgG4 subclass antibodies to recombinant filarial antigens have replaced earlier tests based on detection of IgG antibodies to native parasite antigens that were less sensitive and/or specific and lacked standardization (Simonsen et al., 2014; Weil et al., 2011; Weil & Ramzy, 2007). For bancroftian filariasis, one of the more promising assays has been an ELISA that detects antibodies to the recombinant filarial antigen Bm14. Bm14 has been shown to have high sensitivity and specificity to antibodies induced by *W. bancrofti* (Lammie et al., 2004; Ramzy et al., 1995; Weil et al., 2011). However, it cross-reacts with antibodies in serum or plasma from individuals infected with loiasis and onchocerciasis, diseases which are often co-endemic with LF (Lammie et al., 2004; Weil et al., 2011). More recently, a serological assay based on the *W. bancrofti* infective larval (L3) antigen Wb123 using the Luciferase Immunoprecipitation System (LIPS) was developed

(Kubofcik, Fink, & Nutman, 2012). Wb123 was shown to be highly sensitive, and importantly, overcomes a major limitation of the Bm14, demonstrating minimal to no cross reactivity with other filarial species (Kubofcik et al., 2012). Two rapid tests for Wb123 have been developed and tested - a rapid IgG4 ELISA and a lateral-flow strip immunoassay. The ELISA was shown to have a sensitivity of 93% and specificity of 97%, while the lateral-flow strip was shown to have 92% and 96%, respectively (Steel et al., 2013).

Increasingly, the detection of antifilarial antibodies is becoming recognized as a potentially meaningful indicator for LF programmes (Dewi et al., 2015; Hamlin et al., 2012; Lau et al., 2014; Mladonicky et al., 2009; Plucinski et al., 2018; Sullivan et al., 2016; Won, Robinson, et al., 2018; Won, Sambou, et al., 2018). This is partly because measures of antibody responses are more sensitive than antigen detection and because antibody responses to *W. bancrofti* usually precede detection of antigen, making them early indicators of exposure and infection (Kubofcik, Fink, & Nutman, 2012; Washington et al., 2004). Additionally, although antibody tests do not distinguish between current and past infection, detection of antifilarial antibodies in young children may provide the earliest indicator of LF exposure, and therefore ongoing transmission (Steel, Kubofcik, Ottesen, & Nutman, 2012; Weil & Ramzy, 2007). Antibody testing may offer new approaches to post-MDA surveillance for *W. bancrofti* since the absence of antibodies in young children born after MDA has stopped could confirm the absence of ongoing transmission (Ramzy et al., 2006; Weil et al., 2011; Weil & Ramzy, 2007). It has also been suggested that the Wb123 ELISA could be used to map LF in areas where *W. bancrofti* status is unknown (Steel et al., 2013).

2.2 The GPELF

In 1993, the International Taskforce for Disease Eradication classified LF as 'potentially eradicable' based in large part on the availability of drug treatments that showed promise for interrupting transmission (Centers for Disease Control and Prevention, 1993). In 1997, World Health Assembly Resolution (WHA) 50.29 recognized "the human suffering, social stigma and costs to society associated with lymphatic filariasis" and urged Member States and the global community to increase efforts to eliminate the disease as a public health problem (World Health Assembly, 1997). WHO subsequently launched the GPELF in 2000, with a goal of eliminating the disease as a public health problem by 2020 (WHO, 2010c).

2.2.1 Strategy

The WHO-endorsed strategy to achieve the goal of LF elimination is depicted in Figure 2.3. The specific approaches to treatment, including the drugs administered and monitoring and

evaluation criteria, differ slightly depending on the species of filarial worm targeted and factors such co-endemicity with onchocerciasis and loiasis. This overview focuses on the strategies for programmes targeting *W. bancrofti* in areas without loiasis.

The overall GPELF approach is two-pronged: 1) to interrupt transmission of the disease, and 2) to alleviate the suffering of affected populations (WHO, 2010c). Currently, the primary intervention to target interruption of transmission is MDA – a mass treatment approach in which all eligible individuals in affected communities are treated with safe and effective drugs, usually once per year (WHO, 2006). The drug regimen utilized depends on the presence of other diseases. Ivermectin and albendazole are co-administered once a year in areas co-endemic for onchocerciasis. In areas without onchocerciasis, diethylcarbamazine plus albendazole are co-administered (WHO, 2011b). Long-term pharmaceutical donation programmes provide the majority of the drugs required within the GPELF (WHO, 2017a).

The programmatic steps involved in the MDA component are discussed in detail in the next section. The second component, morbidity management and disability prevention (MMDP), is recognized as an important component of the LF elimination strategy but will not be elaborated upon since it is outside the scope of this research project.

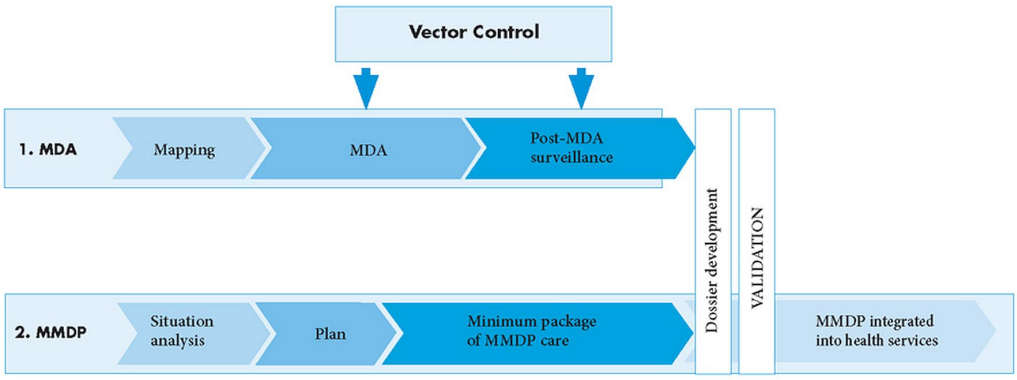


Figure 2.3 GPELF Strategy to Eliminate LF (Source: WHO, 2016)

WHO defines elimination of LF as a public health problem as "reduction in measurable prevalence of infection in endemic areas below a target threshold at which further transmission is considered unlikely even in the absence of MDA" (WHO, 2011b). To achieve this milestone, endemic countries are encouraged to implement the programmatic steps outlined below. It should be noted that although vector control is mentioned in the GPELF strategy and WHO has encouraged its use as supplemental approach to MDA in some

circumstances, most LF programmes lack the resources to do so and have remained focused on the MDA strategy (WHO, 2013a).

2.2.2 Programmatic Steps in the GPELF

Mapping

Areas suspected of being LF-endemic must be mapped to determine whether active LF transmission is occurring and MDA is required (WHO, 2011b). For *W. bancrofti*, mapping is conducted using rapid antigen tests (the ICT, or more recently the FTS) to measure antigenemia at the appropriate administrative level, usually the district (WHO, 2010b). The administrative level at which MDA is implemented is referred to by WHO as an implementation unit (IU). In AFRO, the predominant strategy utilized has been "rapid mapping" in which antigenemia surveys of 50-100 people greater than 15 years of age in two villages most likely to have ongoing transmission in an IU were conducted (WHO, 2000). This sampling strategy does not measure the prevalence of antigenemia throughout the IU; it is intended to provide a quick estimate of antigenemia in the two villages surveyed, which serve as an indication of the endemicity status of the entire IU (WHO, 2011b). If antigenemia is equal to or greater than 1%, the entire IU is designated as requiring MDA (WHO, 2011b) .

MDA

The entire population of an IU that has been designated as LF-endemic is considered to be at risk and MDA is targeted to the entire eligible population (certain individuals such as pregnant women, children under 90 cm in height, and the severely ill are excluded) (WHO, 2011b).

Several important monitoring and evaluation activities take place during the MDA period. Drug coverage after every MDA is used to monitor implementation, and at least one post-MDA coverage survey is suggested. Additionally, sentinel and spot-check sites are assessed before the first and sixth rounds of MDA, at a minimum, to determine the effectiveness of the intervention (WHO, 2011b).

The drugs used in MDA are microfilaricides (they act on microfilariae rather than adult worms); thus, five annual rounds of MDA are targeted to account for the approximate reproductive lifespan of an adult worm (Gyapong, Kumaraswami, Biswas, & Ottesen, 2005). Once five rounds of annual MDA are conducted, with each round achieving drug coverage of at least 65% of the total population, a transmission assessment survey (TAS) is undertaken to determine if the level of infection has been reduced such that transmission is likely no

longer sustainable (WHO, 2011b). The area selected for the TAS is designated as an evaluation unit (EU) and may consist of more than one IU or part of a single IU.

To implement a TAS, WHO currently recommends surveying children 6-7 years of age for antigenemia with the ICT or FTS since antigenemia in this age group would be an indicator of infections occurring since MDA was stopped (WHO, 2011b). School-based surveys are recommended where the net primary-school enrolment ratio is greater than or equal to 75% in the EU. Where it is not, community-based surveys are recommended. Detailed guidelines for conducting a TAS including survey design and sample size calculations are available for programmes. Ultimately, *in W. bancrofti* areas where *Anopheles* or *Culex* is the main vector, the target threshold is <2% antigenemia prevalence in the EU (WHO, 2011b). A critical cut-off value for the number of antigen-positive children determines if the EU "passes" the TAS. MDA can be stopped if the TAS is passed. If the number of antigen-positive children is greater than the critical cut-off number, MDA should be continued for at least two additional rounds before reassessment occurs (WHO, 2011b).

Post-MDA Surveillance

WHO advises that infection levels be monitored for at least five years after MDA has been stopped and suggests repeating a series of two post-MDA TAS approximately 2-3 years after the previous TAS (WHO, 2011b).

Validation

Once a country determines it has achieved the elimination criteria, they can submit a validation dossier that enables WHO to validate their claim of LF elimination as a public health problem (WHO, 2011b). According to WHO, validation is not a permanent state and does not represent an end to programme activities (WHO, 2017d). WHO advises that programmes continue surveillance for LF after validation, however no specific post-validation surveillance guidelines have been developed.

2.2.3 GPELF Progress

The GPELF has undertaken dramatic scale-up of MDA since its launch in 2000. Over 6.7 billion cumulative treatments have been delivered to over 850 million people (WHO, 2017c). Over 1,000 TAS have been implemented with a pass rate of 91.9%, and based on these results, WHO has concluded that approximately 500 million people no longer require LF treatment (WHO, 2017c). WHO has validated 11 countries as having achieved elimination of LF as a public health problem. Togo is the only country in AFRO to have done so; the other countries

include: Cambodia, Cook Islands, Egypt, Maldives, Marshall Islands, Niue, Sri Lanka, Thailand, Tonga, and Vanuatu (WHO, 2018).

Despite this tremendous success, LF will not be eliminated globally as a public health problem by the target date of 2020 (WHO, 2017c). There are a number of challenges to overcome before LF elimination can be achieved. Some of these are programmatic in nature; for example, LF programmes need to ensure effective coverage is reached in each round of MDA. Failing to do so results in the need for additional rounds of MDA, which requires more resources. In 2016, 22% of the IUs conducting MDA globally failed to achieve effective coverage (WHO, 2017c). However, in some cases, challenges exceed the capacity of individual LF programmes to address and require further research to inform strategies to address them. For example, it is not clear why some EUs fail a TAS even if they have achieved effective coverage of MDA for five years (WHO, 2017c). Additionally, as more countries enter post-MDA and post-validation surveillance phases, the need for effective and standardized approaches to monitor for and respond to resurgence of transmission is urgently needed (Harris & Wiegand, 2017; Joseph, 2010; Lau, Won, Lammie, & Graves, 2016; Sheel et al., 2018; Won, Sambou, et al., 2018). These and other challenges are described further in the relevant chapters of this thesis.

2.3 Lymphatic Filariasis in Tanzania

2.3.1 Historical Evidence of LF

Written accounts of LF in Tanzania date back to the early 1900s (Malecela, Kilima, & Mackenzie, 2008) and throughout the middle of the 20th century, several researchers documented the presence of LF infection in humans and mosquitoes on the Mainland (Jordan, 1955b; Nelson, Heisch, & Furlong, 1962; Smith, 1955). These early surveys indicated that LF in Tanzania was most prevalent in the coastal areas, in much of the Southern Province, and in the areas to the south of Lake Victoria and north of Lake Nyasa (Jordan, 1955a). Jordan (1956) undertook several studies of LF around Lake Victoria in the 1950's and reported that no filariasis could be found to the northeast and east of the Lake, but that it was endemic in the areas south and southeast of the Lake. Jordan also undertook one of the earliest attempts to eradicate LF in Tanzania, partly in response to the fact that hydrocele was one of the most common surgical conditions reported by hospitals at the time (Jordan, 1959). His eradication pilot took place on Ukara Island in Lake Victoria, where village-level prevalence of microfilaraemia ranging from 7-40% had previously been documented (Smith, 1955). Incidentally, one of the study sites included in the current research project (Bwisya) is located

on Ukara Island. Research on LF in Tanzania continued in the subsequent decades, including control efforts in Tanga and Zanzibar, however, large-scale efforts were not realised until much later (Malecela et al., 2008).

2.3.2 Launch of the National LF Elimination Programme

The National Lymphatic Filariasis Elimination Programme (NLFEP) was launched in Tanzania in 2000, following the WHA Resolution on LF in 1997. Precipitated by the availability of donated albendazole and ivermectin from major pharmaceutical companies, MDA began later that year, treating 45,000 people in endemic areas of the Coast Region (Kisoka et al., 2014; M N Malecela et al., 2009). From 2000-2008, the NLFEP focused on the completion of rapid mapping of LF to document the burden of disease and MDA was gradually expanded - but limited by a lack of resources. In 2009, with an infusion of resources for the control and elimination of NTDs, the NLFEP was integrated into the newly formed Neglected Tropical Disease Control Programme (NTDCP).

Since 2009, there has been a substantial scale-up of MDA for LF in Tanzania. According to WHO, national coverage of LF MDA (the proportion of the population requiring MDA for LF in the country) increased from 0.3% in 2000 to 85.5% in 2016, and by 2013, MDA was being implemented in all IUs considered to require it – targeting over 14 million people (WHO, 2016a). Notably, effective coverage of MDA was 95.7% in 2016, indicating the quality of the programme (WHO, 2016a). It is projected that by the end of 2019, 100% of the LF endemic districts in Tanzania will be under post-MDA surveillance (Envision, 2017). This projection assumes timely and successful completion of TAS. Unfortunately, more recently there have been several failed TAS in Tanzania (WHO, 2017c), underscoring the complexities of implementing the final stages of an elimination programme.

Chapter Three

The Spatial-Temporal Scale-Up of Vector Control Interventions in Tanzania: Potential Impact on the Lymphatic Filariasis Programme

3.1 Introduction

Malaria and LF contribute the greatest global burden of disease among the vector borne diseases and result in detrimental consequences for the world's most vulnerable populations (Hotez, Fenwick, Savioli, & Molyneux, 2009; van den Berg, Kelly-Hope, & Lindsay, 2013). In 2015, over 90% of the world's 212 million malaria cases occurred in Africa, where more than 395 million people were also at risk for LF (WHO, 2016a, 2016c).

There has been a dramatic scale-up of vector control interventions to prevent malaria across Africa in recent years (Kelly-Hope, Molyneux, & Bockarie, 2013). The most common interventions deployed are ITNs/long-lasting insecticidal nets (LLINs) (Lengeler, 2004) and IRS (Pluess, Tanser, Lengeler, & Sharp, 2010). In 2000, the proportion of households in sub-Saharan Africa with at least one ITN was only 3% (WHO, 2011b). By 2015 the proportion had increased to 79%, with 178 million ITNs distributed by manufacturers that year alone (WHO, 2016c). IRS has also been scaled-up, though to a lesser extent than ITNs, with approximately 49 million people in the WHO/AFRO region reportedly protected by IRS in 2015 (WHO, 2016c).

In many parts of Africa, particularly in rural areas, LF and malaria are co-endemic and transmitted by the same primary vector – *Anopheles* mosquitoes (Molyneux & Zagaria, 2002; Sasa, 1976). Malarial control efforts aimed at reducing vector populations should plausibly have an impact on both diseases. Indeed, this has been documented in several studies (Ashton et al., 2011; Bockarie, Tavul, Kastens, Michael, & Kazura, 2002; Bøgh, Pedersen, Mukoko, & Ouma, 1998; Burkot et al., 1990; Pedersen & Mukoko, 2002; Rebollo et al., 2015; Richards et al., 2013; Webber, 1979). Yet, the impact of vector control interventions for malaria on LF transmission is not routinely measured and programmes targeting these diseases are rarely implemented together (Stone, Lindsay, & Chitnis, 2014).

In Tanzania, a significant scale-up of vector control interventions undertaken by the NMCP has occurred since 2004 when the initial phase of the Mainland's ITN strategy (2004-2008) was launched. This scale-up has occurred alongside expanded efforts by the National NTD Programme to eliminate LF through MDA. It is possible that vector control interventions are facilitating interruption of LF transmission in some areas of Tanzania. If so, this could have major implications for the LF Programme. However, this possibility has not been thoroughly explored.

3.2 Aim

The aim of this chapter is to investigate the potential impact of vector control for malaria on LF in different LF transmission zones of Tanzania.

3.3 Objectives

- To examine historic LF prevalence in Tanzania and summarize regional levels of LF risk.
- To identify geographical patterns of ITN and IRS coverage in Tanzania by evaluating spatial clustering and mapping hotspots over time.
- To assess the overlap of regional LF risk and ITN and IRS coverage.
- To examine the potential impact of ITN and IRS coverage on LF transmission in two geographic areas of Tanzania with varying LF Risk, ITN and IRS coverage, and explore the possible influence of mosquito species distribution and insecticide resistance in these areas (brief case studies).

3.4 Methods

3.4.1 Study Site

The study area comprised Mainland Tanzania which has a total land area of 883,600 square kilometres and borders 8 countries and the Indian Ocean (National Bureau of Statistics (NBS), 2016). The climate varies from temperate in the highlands to tropical along the coast. Most of the country experiences a long dry season from May to October followed by rains from November to May. Coastal areas and the north-eastern highlands and Lake Victoria Basin experience long rains (masika) from March to May and short rains (mvuli) from October to December (MoHCDGEC et al., 2016; Rowhani, Lobell, Linderman, & Ramankutty, 2011). At the time this study was initiated, Mainland Tanzania was divided into 21 regions comprised of 114 districts; however, as of the 2012 census it consists of 25 regions and 185 districts (NBS and Office of Chief Government Statistician (OCGS), 2014). A zonal map of the country is provided in Figure 3.1. Zones are not official administrative units in Tanzania, however they are used in DHS surveys and by some Ministries within the government because they are useful for describing sub-national trends.

Figure 3.1 Map of Tanzania Identifying Zones (black labels) and Regions (white labels). Adapted from the Tanzania DHS/MIS 2015-16.

3.4.2 Study Population

Mainland Tanzania has a population of approximately 43.6 million people, with an average intercensal growth rate of 2.7% (National Bureau of Statistics, 2013). The population is highly dispersed and predominately rural with a life expectancy at birth (in 2012) of 61 years. Infant mortality has decreased from 115 deaths per 1,000 live births in 1988 to 46 deaths per 1,000 live births in 2012. Similarly, under-five mortality decreased from 191 to 67 deaths per 1,000 live births in the same period. Maternal mortality was estimated to be 432 deaths per 100,000 births in 2012 (NBS, 2013). In 2012, it was estimated that 68% of the population of Tanzania lived below the international poverty line of US $1.25 per day (UNICEF, 2012). As shown in Figure 3.2, malaria is endemic throughout most of the country, with an overall prevalence of 7.3% among children 6-59 months of age (MoHCDGEC et al, 2017).

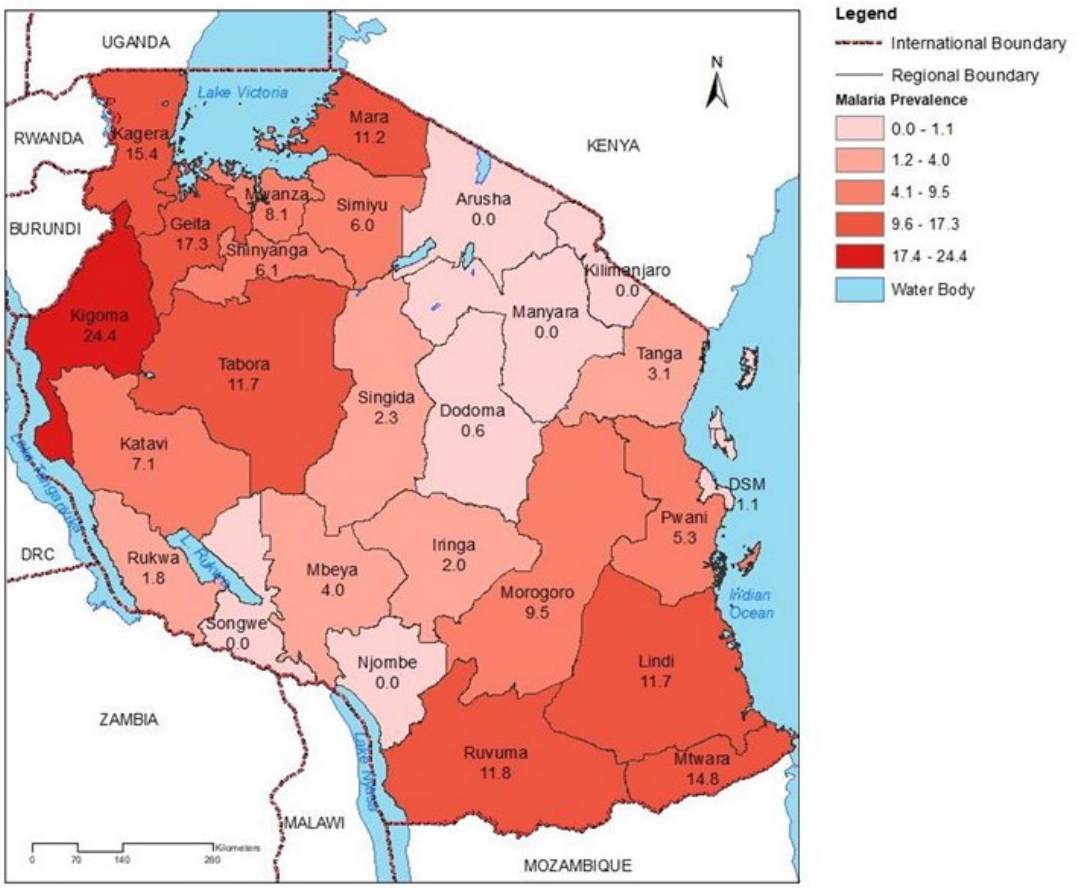


Figure 3.2. Malaria Prevalence by Region in Tanzania, 2017. Malaria prevalence is measured as the percentage of children age 6-59 months with a positive rapid diagnostic test result. Data is extracted from the Tanzania Malaria Indicator Survey, 2017 (MoHCDGEC et al, 2017).

3.4.3 Study Design

A review of existing reports and published literature was conducted followed by secondary analyses of data obtained from sources described in detail below. Case studies were developed based on these analyses.

3.4.4 Data Sources

Programmatic reports of LF activities implemented in Tanzania since the start of the LF Programme in 2000 were obtained from public sources including the Tanzania National NTD Programme, WHO NTD Programme, the WHO Preventive Chemotherapy Databank, and WHO's Expanded Special Project for the Elimination of Neglected Tropical Diseases (ESPEN). Historical information on LF prior to this period was obtained from published literature available between 1900-1999 using the search terms filariasis, Tanzania, Tanganyika, and microfilariae. Data on the distribution of LF across Tanzania was obtained from the Global Atlas of Helminth Infections (GAHI), an online resource developed using geostatistical and

mathematical modelling based on historical and contemporary cross-sectional prevalence surveys (Moraga et al., 2015).

Programmatic reports of vector control activities conducted since 2004, when more intensified vector control activities began in Tanzania, were obtained from public sources including the NMCP, WHO Global Malaria Program, U.S. President's Malaria Initiative (PMI), and World Malaria Reports. Additional information on vector control in Tanzania was obtained from published literature using the search terms Tanzania, vector control, ITNs, LLINs, IRS, bed nets, and malaria.

Data on vector control were obtained from the Tanzania HIV/AIDs and Malaria Indicator Surveys (AIS/MIS) conducted in 2007-08 and 2011-12 and from the Tanzania Demographic and Health Survey and Malaria Indicator Survey (DHS/MIS) conducted in 2015-16. These three surveys are hereafter referred to as the '2007-08', '2011-12', and '2015-16' surveys, respectively. Each survey used probability sampling consisting of a two-stage cluster sample, probability proportional to estimated cluster size, to obtain nationally representative, population-based data. In the present study, DHS/MIS "clusters" are referred to as "sites" to avoid confusion with the term "cluster" used in spatial analysis.

Tanzania administrative boundaries used for mapping were based on the 2012 national census and were obtained from the National Bureau of Statistics (www.nbs.go.tz). Data files used with geographic information system (GIS) software, also known as shapefiles, included secondary administrative boundaries (regions) and tertiary administrative boundaries (districts and wards).

Modelled data on vector species distribution were obtained from a recent study that aimed to define the geographical distributions of dominant malaria vector sibling species in Africa (Wiebe et al., 2017). In addition, data on sites of confirmed insecticide resistance reported since 2004 were obtained from IR mapper (www.IRmapper.com), an online geospatial mapping platform that collates data on insecticide resistance extracted monthly from published, peer-reviewed publications and reports, including PMI Country Insecticide Susceptibility Summaries.

3.4.4.1 LF Prevalence

Source reports and published literature provided background and context on the history and activities of the National LF Programme. Interventions undertaken since the LF Programme began, particularly prevalence studies and disease mapping, were of primary interest.

3.4.4.2 LF Risk

The distribution map of predicted filarial antigenemia prevalence was imported into the geographical information system software ArcGIS 10 (ESRI, Redlands, CA) and aligned with administrative boundaries. To determine LF risk across different areas of the country, the range of predicted antigenemia prevalence was summarized for each of the 25 regions.

3.4.4.3 Vector Control Scale-up

Source reports provided background and context and were used to describe the scale-up of vector control interventions. The indicators of interest were ITN and IRS coverage. For the purposes of this study ITN coverage was assessed as 'household ownership of at least one ITN'. IRS coverage was assessed as 'households reporting spraying of interior walls against mosquitoes in the past 12 months by a government or non-governmental programme'.

3.4.4.4 Geographical Patterns of Vector Control

To identify general geographical trends in vector control across the country during the study period, ITN ownership and IRS coverage were summarized by region for each survey. The percentage change in coverage for each indicator was calculated between each survey year.

Next, household-level data obtained from each survey was imported in IBM SPSS version 24 (Armonk, NY) and used to calculate ITN ownership and IRS coverage by survey site. Site-level data, which included global positioning system (GPS) coordinates of each site (i.e. geo-referenced), were imported into ArcGIS and used to examine the finer spatial distribution of household ITN ownership and IRS coverage. Since the focus of this study is on Mainland Tanzania, survey sites in Zanzibar within the DHS datasets were excluded. Additionally, sites without GPS coordinates were removed since they could not be geo-referenced. The 2007-08 and 2011-12 surveys lacked GPS coordinates for 9 and 10 sites, respectively. All sites in the 2015-16 survey contained GPS coordinates and were used in the analyses.

DHS randomly displaces the GPS coordinates of survey sites to protect the confidentiality of respondents. The displacement is carried out such that urban sites are displaced a distance of 0-2 km and rural sites are displaced a distance of 0-5 km. Additionally, 1% of rural sites are randomly selected and displaced a distance of 0-10 km (Burgert, Colston, Roy, & Zachary, 2013). Displacement is restricted such that georeferenced survey sites remain within the survey region and district. Since the present analysis of DHS/MIS data did not consider local distances, displacement should not have influenced the results.

3.4.4.5 Spatial Clustering of Vector Control

Spatial clustering analysis was conducted in ArcGIS using the spatial analyst extension to identify significant spatial patterns in vector control coverage on a national level. The Moran's I statistic, an inferential statistic, is commonly used to measure spatial autocorrelation patterns, including for LF and malaria (Dolo et al., 2018; Mwakalinga et al., 2016). In the present study, it was used to determine the probability of (as indicated by the p-value) and to what degree (as indicated by the z-score) coverage patterns were clustered, random, or dispersed (Getis & Ord, 1992). In this case the analysis was used to test the null hypotheses that ITN coverage and IRS coverage are randomly distributed throughout the study area. The analysis for each indicator simultaneously considers feature locations (survey sites) and their associated values (site specific ITN or IRS coverage) to calculate the Moran's I Index. The resultant z-score and p-value are used to evaluate the significance of the Moran's I Index. The Global Moran's I was used rather than the alternative local Moran's I since the overall degree of spatial autocorrelation for each DHS/MIS survey was of primary interest (Jacquez, 2008).

3.4.4.6 Identification of ITN and IRS Hotspots

To investigate significant 'hotspots' in ITN and IRS coverage, spatial clustering analysis was conducted in ArcGIS using the spatial analyst extension to calculate Gi* statistics (Ord & Getis, 1995). The Getis-Ord Gi* enables the identification of statistically significant clusters of high values and low values and is commonly used to explore spatial clustering in LF and malaria studies (Barroso et al., 2017; Kim et al., 2018). For the present study, it was used to test the null hypotheses that the observed spatial clustering of high and low ITN coverage and IRS coverage are more pronounced than would be expected in a random distribution of the same values. The analysis considers the location and value of a feature (location of study site and its ITN or IRS coverage) and its relation to its neighbours and their respective features. The resultant z-score and p-value are used to evaluate the significance of clustering of low and high coverage for each indicator. Clusters of high or low values that were significant at the 99% and 95% confidence intervals were included in the subsequent maps (Malvisi, Troisi, & Selwyn, 2018). The Gi* statistic rather than the G statistic was used since it considers all the values in the study area (Ord & Getis, 1995).

3.4.4.7 Case Studies

Survey sites with significant overlapping hotspots for both ITNs and IRS in the 2015-16 survey were identified and mapped in ArcGIS. Case studies were developed to examine factors that may impact LF transmission in these hotspot areas. First, hotspot data were overlaid with the

LF risk map. Next, modelled species data were imported into ArcGIS and the 'zonal statistics tool' in the spatial analyst extension was used to extract zonal statistics indicating the probability of occurrence of *An. gambiae*, *An. funestus*, *and An. arabiensis* in each survey site within the hotspot areas. Finally, data obtained from IRmapper were used to examine evidence of insecticide resistance in the hotspot areas. Resistance data were restricted to confirmed sites of resistance in *Anopheles sp*. reported since 2004 (sites of possible resistance were excluded). Zonal data on household net ownership and percentage of children under five who slept under a net the previous night were obtained from the 2015-16 DHS/MIS report.

3.4.5 Ethical Approval

Access to DHS survey data was authorized by the DHS Program following review of a written request. Data obtained were used only for the purpose of this study and were treated as private and confidential. Per DHS guidelines, GPS data were kept on a secure computer and their use/analysis complied with the Declaration of Helsinki.

3.5 Results

3.5.1 LF Prevalence

Historical studies in Tanzania revealed three main foci of LF transmission – along the coast of the Mainland, offshore on the islands of Zanzibar, Pemba, and Mafia, and in the area surrounding Lake Victoria – and two minor foci in southern Morogoro Region and in Mbeya Region around Lake Nyasa (Malecela et al., 2008). Rapid epidemiological assessments conducted between 1998-2004 using the ICT to detect circulating filarial antigen concluded that every region required MDA for LF, as defined by the WHO threshold of ≥1% antigenemia (Malecela et al., 2008; WHO, 2011b). The results of these community-based mapping surveys are shown in Figure 3.3.

3.5.2 LF Risk

The map of predicted LF antigenemia in Tanzania (LF risk map) reveals a broad high- to low-risk spatial gradient moving from the east coast toward the western inland region (Figure 3.4). LF risk by region is summarized in Table 3.1.

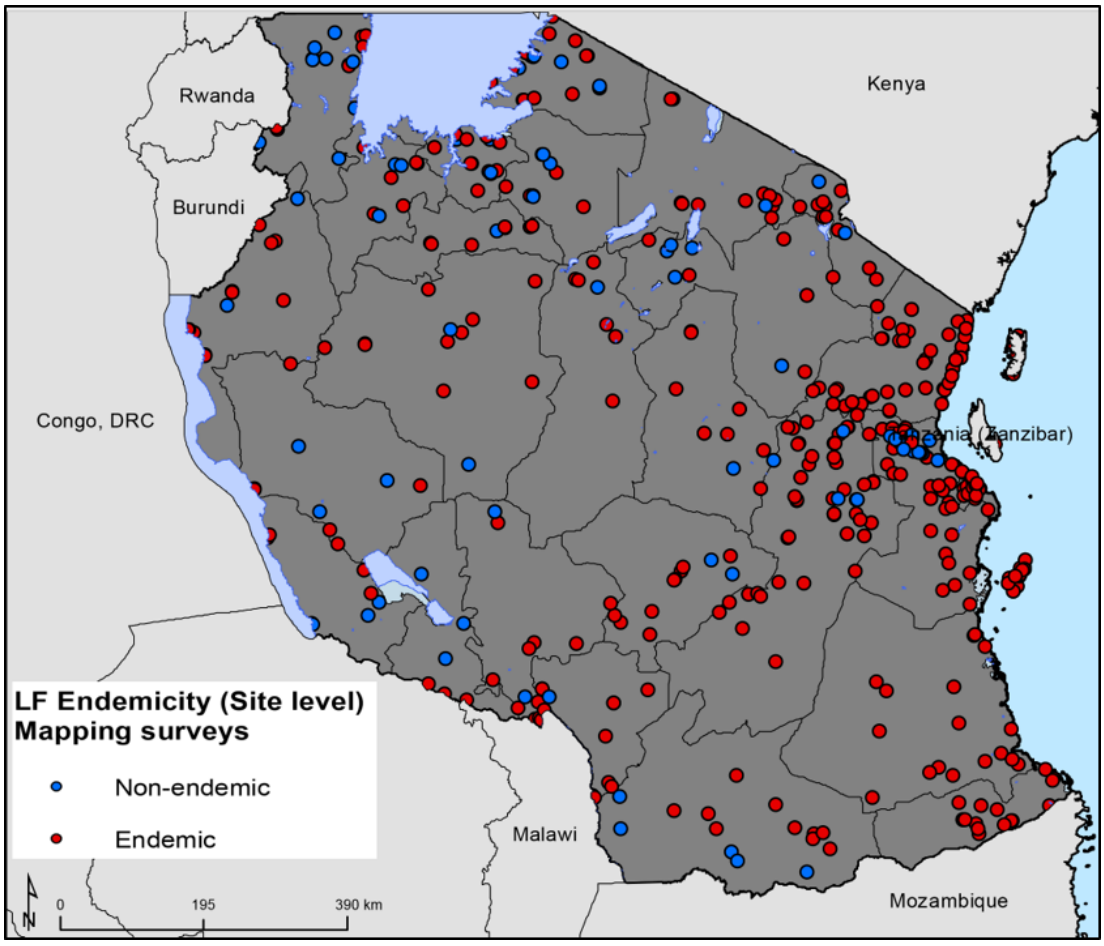


Figure 3.3. LF Endemicity at Community Level in Tanzania prior to MDA Interventions. Data is extracted from ESPEN, 2018 and is based on LF endemicity mapping using ICTs conducted prior to 2004. Survey sites are classified as either endemic (≥1% antigenemia) or non-endemic (≤1% antigenemia) based on WHO criteria for LF MDA.

Regions of highest risk are located along the coast, including Tanga (11-75%) in the Northern Zone, Pwani (31-75%) and Dar es Salaam (31-75%) in the Eastern Zone, and Lindi (21-75%) and Mtwara (31-75%) in the Southern Zone. Further inland, higher risk regions include Iringa (11-40%), Njombe (6-75%) and Ruvuma (6-75%) in the Southern Highlands Zone. A focalized area of higher LF risk is located in Morogoro region (11-75%) and a smaller one is located in Mbeya region (6-75%).

Regions with lowest LF risk are located in the Lake Zone, with Kagera, Geita, Mwanza, and Mara Regions each having a range of predicted antigenemia prevalence of 0-5%. Shinyanga and Simiyu Regions (2-10%) in the Lake Zone and Kigoma Region in Western Zone (0-10%) are also lower risk.

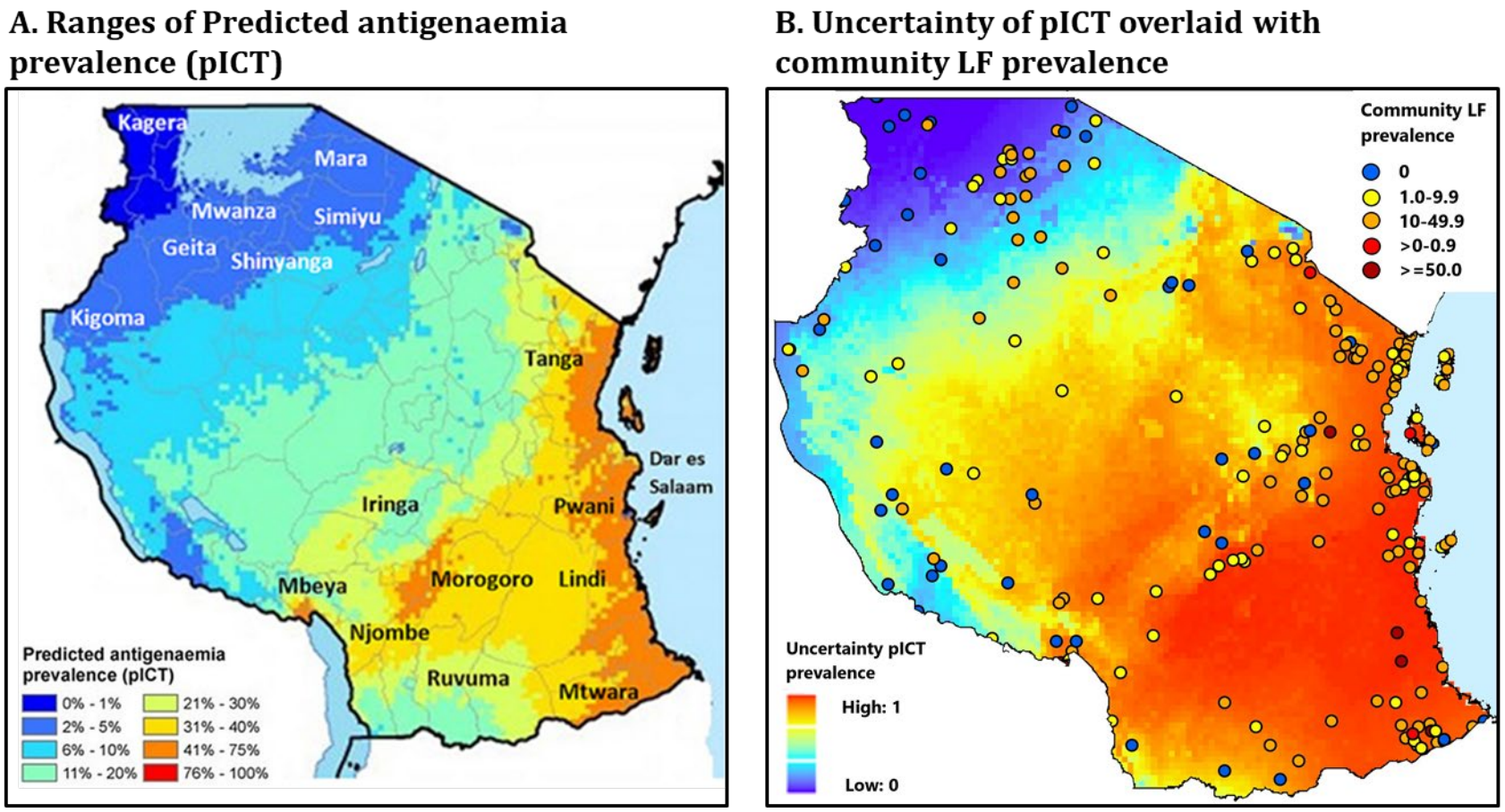


Figure 3.4. Predicted LF Risk, LF Risk Uncertainty, and Community LF Prevalence in Tanzania. Figure A shows predicted antigenaemia prevalence (risk) prior to large-scale MDA from 1990-onwards. Figure B shows the uncertainty of the predicted antigenaemia prevalence overlaid with community LF prevalence as reported by GAHI. All data was extracted from the Global Atlas of Helminths Infections (GAHI, 2017; Moraga et al., 2015).

Table 3.1. Regional Summaries of LF Risk and Vector Control Coverage

Zone	Region	Range of Predicted Antigenemia Prevalence (%)	2007-08 HH with ≥1 ITN (%)	2011-12 HH with ≥1 ITN (%)	2015-16 HH with ≥1 ITN (%)	Percent Change HH with ≥1 ITN between 2007-08 & 2011-12^	Percent Change HH with ≥1 ITN between 2011-12 & 2015-16^
Lake	Kagera*	0-5%	29.5	91.6	89.5	n/a	-2%
Lake	Shinyanga*	2-10%	37.8	94.1	78.7	n/a	-16%
Lake	Simiyu†	2-10%	n/a	94.9	97.6	n/a	+3%
Lake	Geita†	0-5%	n/a	90.8	96.4	n/a	+6%
Lake	Mara	0-5%	56.5	95.8	91.4	+70%	-5%
Lake	Mwanza*	0-5%	48.4	95.9	90.3	n/a	-6%
Western	Kigoma	0-10%	31.1	94.5	93.7	+204%	-1%
Western	Tabora	2-20%	39.8	94.5	90.8	+137%	-4%
South West Highlands	Katavi†	2-20%	n/a	87.7	94.7	n/a	+8%
South West Highlands	Rukwa*	2-20%	29.4	86.2	29.4	n/a	-66%
South West Highlands	Mbeya	6-75%	29.9	91.4	50.4	+206%	-45%
Northern	Kilimanjaro	2-40%	29.9	94.8	63.8	+217%	-33%
Northern	Arusha	2-20%	32.4	84.7	43.1	+161%	-49%
Northern	Tanga	11-75%	38.6	90.5	52.5	+134%	-42%
Central	Manyara	6-40%	22.1	88.6	22.3	+301%	-75%
Central	Singida	6-20%	26.4	94.8	43.9	+259%	-54%
Central	Dodoma	2-20%	28.2	92.8	38.8	+229%	-58%
Southern Highlands	Iringa*	11-40%	17.6	92.1	45.7	n/a	-50%
Southern Highlands	Ruvuma	6-75%	39.4	94.6	66.1	+140%	-30%
Southern Highlands	Njombe†	6-75%	n/a	95.5	48.6	n/a	-49%
Eastern	Pwani	31-75%	47.8	95.4	64.6	+100%	-32%
Eastern	Morogoro	11-75%	44.1	91.2	55.2	+107%	-39%
Eastern	Dar es Salaam	31-75%	70.7	78.5	65.9	+11%	-16%
Southern	Mtwara	31-75%	42.9	93.1	61.3	+117%	-34%
Southern	Lindi	21-75%	40	96.4	69.9	+141%	-27%

*Regional boundaries shifted in 2012, therefore, 2007-08 survey indicators cannot be directly compared to 2011-12 or 2015-16 survey indicators.

†Regions created in 2012. ^Cells shaded green highlight positive percent changes and cells shaded orange highlight negative percent changes.

3.5.3 Vector Control Scale-up

3.5.3.1 Vector Control Interventions

ITNs

Routine distribution of ITNs began in 2004 through the Tanzania National Voucher Scheme (TNVS). Initially, pregnant women were targeted with subsidized nets through antenatal clinics. Infants, targeted through immunization sessions, were added to the programme in 2006. Under the scheme, distributed vouchers could be redeemed for a net at a retail shop after payment of a top-up fee. This subsidized net distribution was accompanied by the commercial sale of nets which was encouraged through social marketing. Despite these efforts, it was evident by 2007 that ownership of nets and usage, particularly among the most vulnerable groups, was well below targeted levels (Marchant et al., 2008). Tanzania was not on track to achieve coverage of malaria interventions of 80% by 2010, the target date established by the Roll Back Malaria Partnership (RBM, 2005). In response, the 2008-2013 National Malaria Strategy included a shift in policy from targeted ITN distribution to achievement of universal coverage, defined as coverage of all sleeping spaces with an LLIN, through no-cost mass campaigns aimed at the entire population (Ministry of Health and Social Welfare, 2008). In addition, the distribution of nets that required re-treatment was to be replaced with distribution of LLINs. The TNVS was continued, but the voucher subsidy was increased to reduce the top-up fee to make LLINs more affordable. In 2009-2010 an under-five LLIN catch-up campaign was implemented to distribute a free LLIN to all children up to five years of age, including those that did not have access to the TNVS. This was followed by universal coverage campaigns (UCCs) in 2010-2011 and again in 2015-16, which aimed at covering all sleeping spaces with an LLIN.

IRS

IRS application on the Mainland of Tanzania began in 2007 in Muleba and Karagwe Districts in Kagera Region in an effort to address epidemic malaria occurring toward the end of the long rainy season. The 2008-2013 National Malaria Strategy included a renewed focus on the expansion of IRS, using Dichloro-Diphenyl-Trichloroethane (DDT) and the long acting lambda-cyhalothrin, in areas of high malaria prevalence and unstable transmission (Ministry of Health and Social Welfare, 2008). The strategy originally included plans to scale-up IRS to half of the Mainland's districts; however, resources were inadequate to achieve this goal and the programme subsequently maintained a focus on the higher prevalence Lake Zone with support

from the PMI. IRS was expanded to cover all districts of Kagera Region in 2009, and all districts in Mwanza and Mara Regions were added to the programme in 2010-2011[1]. In 2012, evidence emerged of increasing insecticide resistance to pyrethroids, and as a result, the IRS strategy in the Lake Zone was changed to include the use of carbamate insecticide (bendiocarb) in Kagera and select areas of Mwanza and Mara Regions in 2013 (PMI, 2013). A pyrethroid was used in the remaining targeted districts. However, bendiocarb resistance led to another insecticide change (to pirimiphos-methyl CS) in 2014 (PMI, 2018). With limited options for alternative insecticides available in Tanzania, as well as the high cost (carbamates are about three times more expensive than pyrethroids and have higher operational costs), plans were made to scale down IRS in the Lake Zone in 2014 (PMI, 2013). A summary table of the IRS activities undertaken in the Lake Zone from 2006-2015 is included in Appendix 1.

3.5.4 Geographical Patterns of Vector Control

3.5.4.1 National and Regional ITN Coverage

Nationally, there was an increase in ITN coverage between the 2007-08 and 2011-12 surveys, from 38.3% to 91.5%. The 2015-16 survey showed a marked decrease in ITN coverage to 65.4%.

Table 3.2. National-level Household ITN Ownership

DHS Survey	No. of Households	Households Owning ≥1 ITN (%)	95% Confidence Interval (%)
2007-08	8,269	38.3	36.3-40.3
2011-12	9,732	91.5	90.6-92.3
2015-16	12,247	65.4	63.6-67.1

ITN coverage by region for each survey is summarized in Table 3.1 and shown in Figure 3.5. Regional trends in ITN coverage reflect the national trend, with coverage increasing in all regions between 2007-08 and 2011-12 (except the five regions for which coverage cannot be directly compared due to changes in administrative boundaries) and decreasing in most regions between 2011-12 and 2015-16. Greater variations in regional coverage are evident in the 2007-08 and 2015-16 surveys compared to 2011-12 survey. The average regional percent change between the 2007-08 and 2011-12 surveys was 158% (ranging from 11% to 301%). Between the 2011-12

[1]Several districts in these regions became part of the new regions of Geita and Simiyu as part of the administrative border changes in 2012.

and 2015-16 surveys, for which all regions can be directly compared, only 3 of 25 regions had an increase in ITN coverage (shaded green in Table 3.1). The remaining 22 regions had a decrease in coverage with a mean percent change of -33% (ranging from -1% to -75%). Notably, 15 of the regions experienced a drop in ITN coverage greater than 20% between the two surveys, with Rukwa and Manyara Regions having the greatest percent changes of -66% and -75%, respectively.

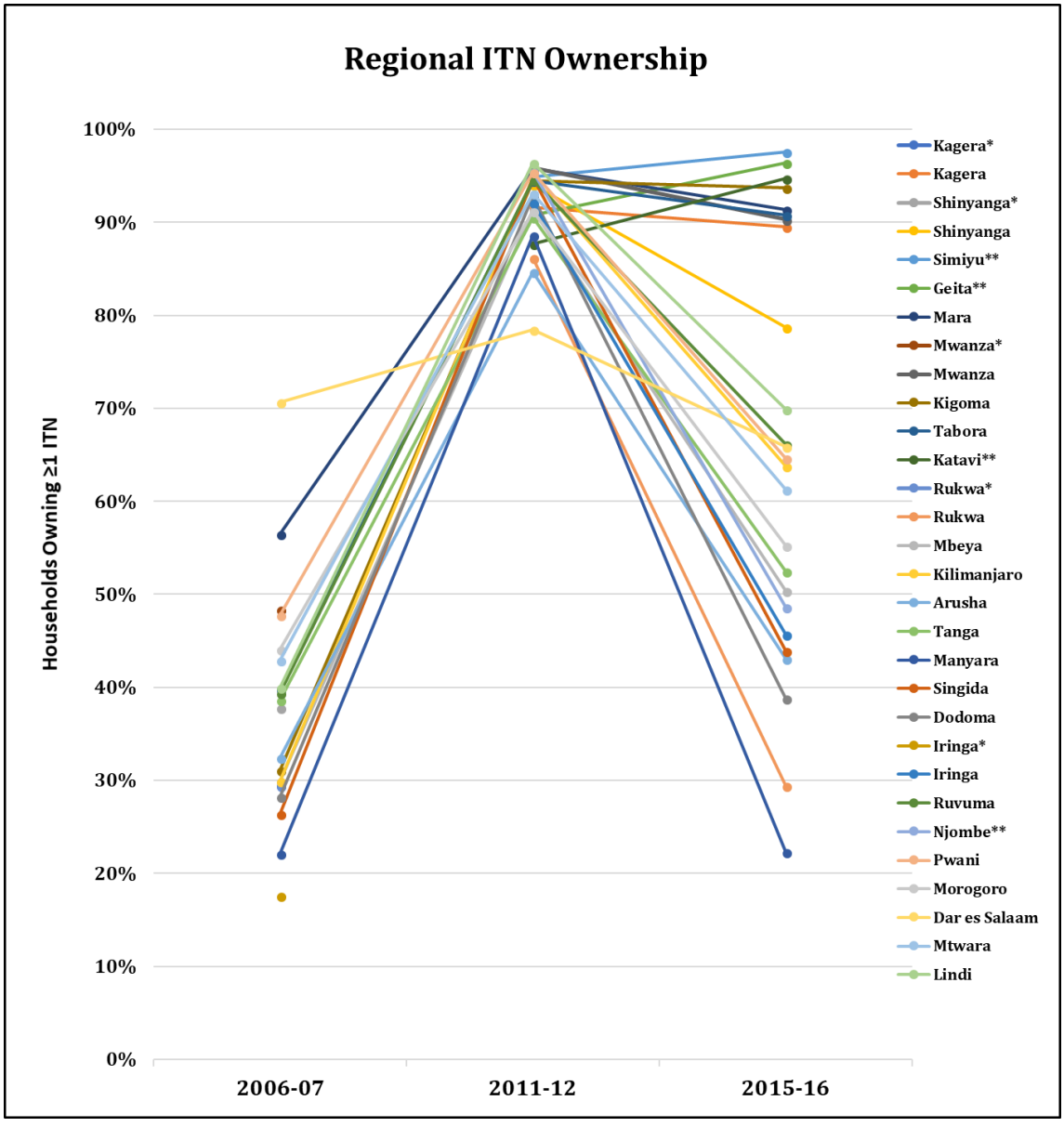


Figure 3.5. Household ITN Ownership by Region and Survey. *Regions that cannot be directly compared due to administrative border changes between the 2007-08 and 2011-12 surveys are shown separately for these survey years. **Four regions were created in 2012 and therefore are not shown in 2007-08.

3.5.4.2 Site-Level ITN Coverage

ITN coverage in each site surveyed for each of the three surveys is shown in Figure 3.6. In 2007-08, a total of 376 sites were assessed. As shown in Figure 3.6A, ITN coverage in survey sites in 2007-08 was highly variable across the country, ranging from 0-100%.

In contrast, the majority of the 498 sites assessed in 2011-12 had ITN coverage ranging from 76 - 100% (Figure 3.6B). Several sites had coverage between 51-75%, however, no sites were below 50%. One site in Dar es Salaam had coverage of 50%.

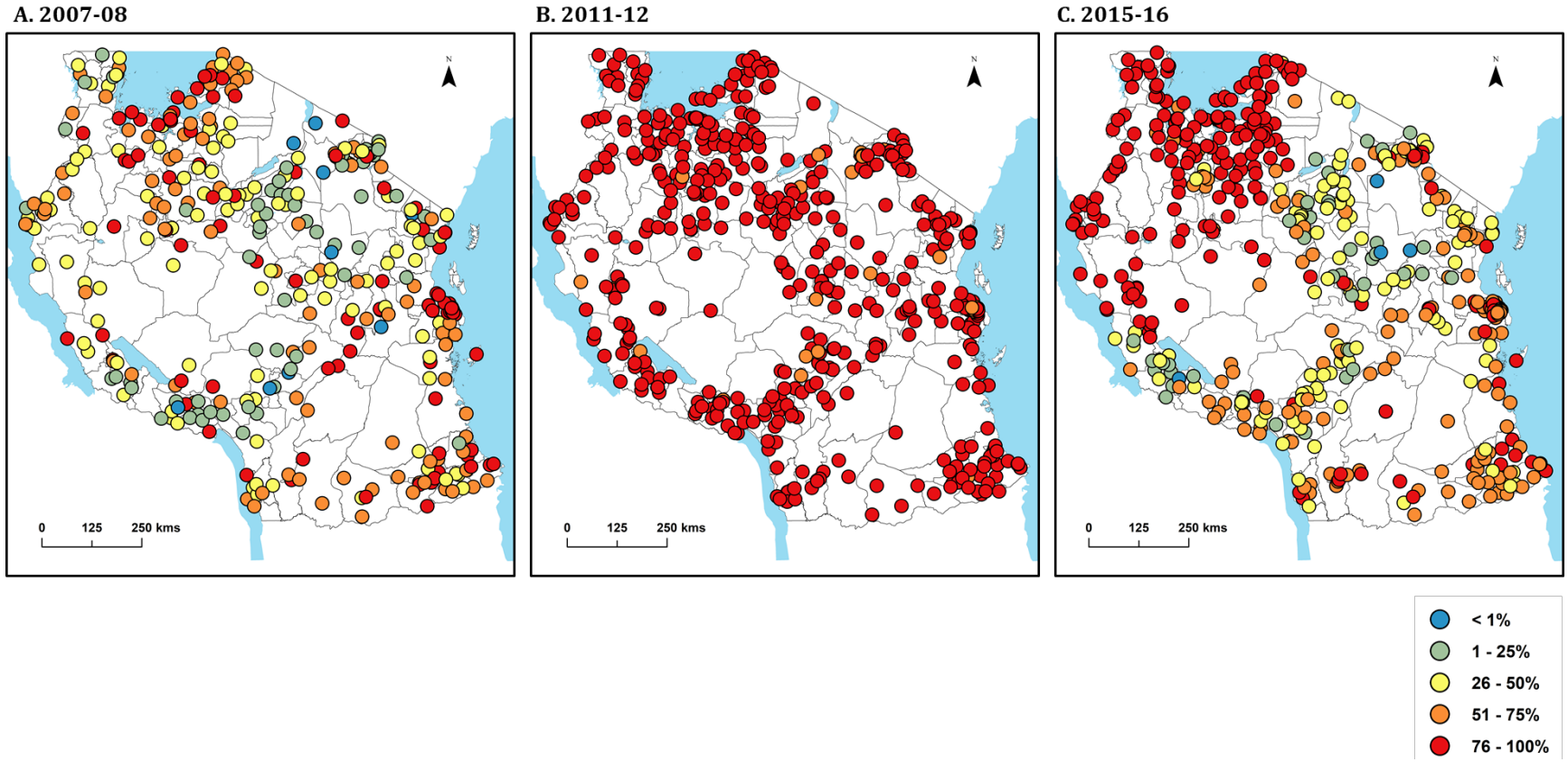


Figure 3.6. Household ITN Ownership in Survey Sites from the (A) 2007-08, (B) 2011-12, and (C) 2015-16 DHS/MIS surveys.

In 2015-16, 527 sites were assessed. Most sites in the north-western part of the country, including the Lake Zone, had ITN coverage above 75% (Figure 3.6C). Coverage in the remaining areas of the country was variable. The majority of sites with coverage below 50% were found in the central part of the country, including four sites with coverage less than 1%. Most sites in the coastal areas had coverage between 51-75%.

3.5.4.3 National and Regional Level IRS Coverage

In 2007-08, only 1.0% of households in Mainland Tanzania reported IRS in the past 12 months. In 2011-12, this increased to 11.6% of households reporting IRS, whilst in 2015-16 it decreased to 4.8% of households (Table 3.3). This is consistent with the limited and focal nature of IRS interventions. Trends in IRS coverage in the Lake Zone better reflect the scale-up of the intervention, with IRS coverage in the 2007-08, 2011-12, and 2015-16 surveys reported to be 3.7%, 42.3%, and 14.9%, respectively. The decrease in 2015-16 shows the scale-down of IRS activities described in section 3.5.3.1.

Regional IRS coverage in the Lake Zone regions targeted with IRS is summarized in Table 3.4. Regions outside the Lake Zone are not included since they were not targeted with IRS.

Table 3.3. National-level Household IRS Coverage

DHS Survey	No. of Households	Households Reporting IRS (%)	95% Confidence Interval (%)
2007-08	8,269	1.0	0.5-2.2
2011-12	9,732	11.6	0.6-10.4
2015-16	12,247	4.8	4.0-5.7

Table 3.4. Regional-level Household IRS Coverage in the Lake Zone

Region	2007-08 HH with IRS in past 12 months (%)	2011-12 HH with IRS in past 12 months (%)	2015-16 HH with IRS in past 12 months (%)
Kagera*	9.6	91.5	24.9
Simiyu†	n/a	9.1	2.9
Geita†	n/a	50.4	14.9
Mara	0.3	61	19.3
Mwanza*	0	40.1	17.6

*Regional boundaries shifted in 2012; therefore, 2007-08 survey indicators cannot be directly compared to 2011-12 or 2015-16 survey indicators. †Regions created in 2012.

3.5.4.4 Cluster-Level IRS Coverage

Figure 3.7 shows coverage of IRS in survey sites for each survey. These maps reflect the highly focal scale-up of IRS on Mainland Tanzania during this period, with very little spraying in 2007-08 (in Kagera Region only) and scale-up in the regions of the Lake Zone in 2011-12, including in Kagera, Geita, Mwanza, and Mara Regions. Many sites in these regions have IRS coverage greater than 75% in 2011-12. There is a decline in coverage in the regions of the Lake Zone in 2015-16, with no sites having IRS coverage greater than 75%.

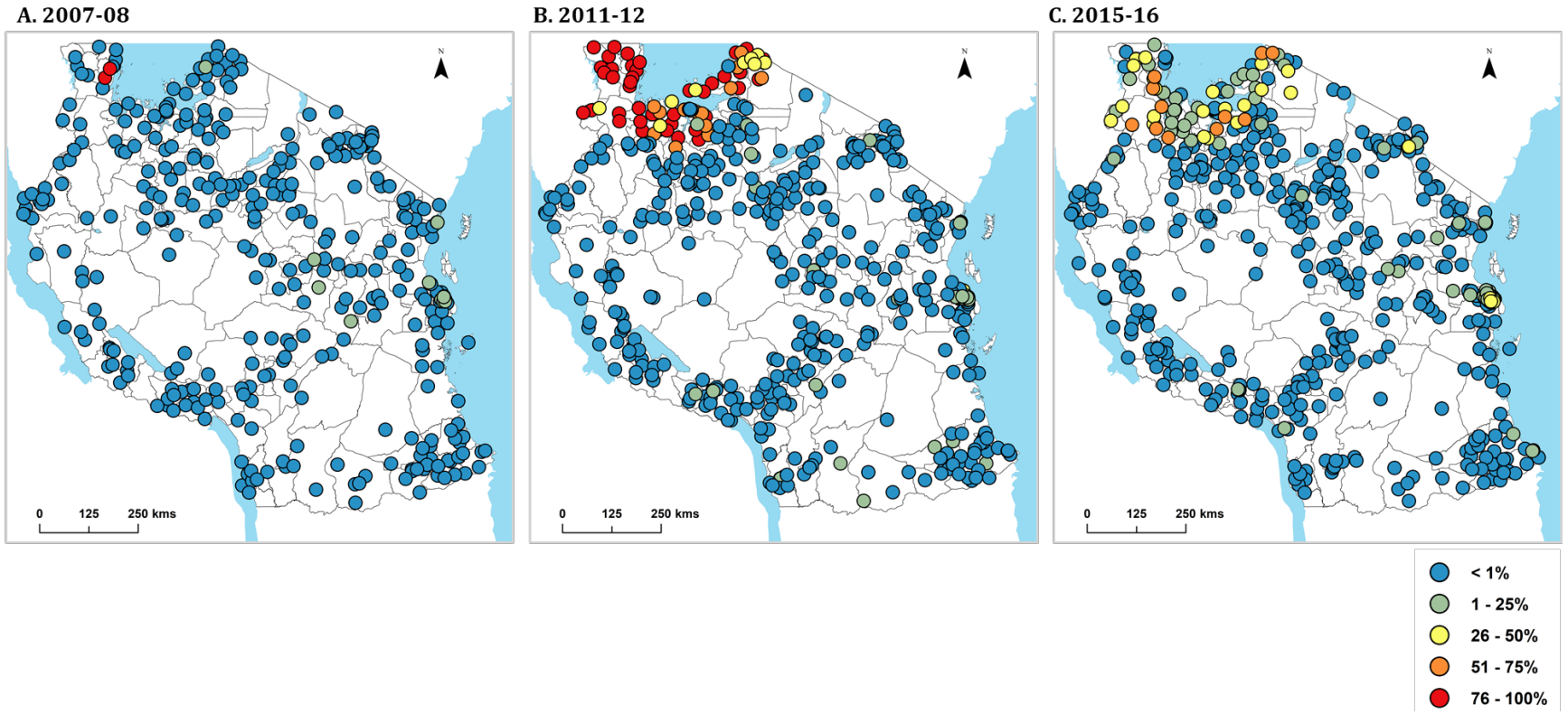


Figure 3.7. Household IRS Coverage in Survey Sites from the (A) 2007-08, (B) 2011-12, and (C) 2015-16 DHS/MIS surveys.

3.5.5 Spatial Clustering of Vector Control

Spatial analysis for ITNs and IRS indicated positive autocorrelation (i.e., clustering) for each indicator in each survey. As shown in Table 3.5, statistically significant p-values ($p<0.001$) were found for each Moran's I Index. Given the resultant z-scores, the null hypothesis can be rejected, and it can be concluded that ITN and IRS coverage in each survey are not randomly distributed throughout the study area. In each analysis, the Moran's I Index was found to be positive, indicating that the spatial distribution of high and low coverage in the study area is clustered (rather than dispersed). Thus, it can be concluded that there is less than 1% likelihood that the clustered pattern for each indicator in each survey could be the result of random chance. Based on the differences in the z-scores for ITN coverage in each survey, it can be concluded that spatial clustering is more intense in 2011-12 than in the other two surveys. The same pattern is observed for spatial clustering of IRS coverage. Detailed spatial autocorrelation reports (ArcGIS output) are included in Appendix 2.

Table 3.5. Autocorrelation Results for ITNs and IRS, by Survey

Survey	Moran's I Index	z-score	p-value
ITNs			
2007-08	1.071	14.25	<0.001
2011-12	0.690	24.45	<0.001
2015-16	0.374	12.30	<0.001
IRS			
2007-08	0.207	3.45	<0.001
2011-12	0.397	14.12	<0.001
2015-16	0.258	8.58	<0.001

3.5.6 Identification of ITN and IRS Hotspots

Getis Ord hotspot analysis for both ITN and IRS coverage identified statistically significant clusters of low and high coverage in each survey (z-scores, 95% CI, -1.96 and +1.96 SD). High positive critical values (z-scores) indicate spatial clustering of high ITN and IRS coverage sites and high negative critical values indicate spatial clustering of low ITN and IRS coverage sites. For each indicator and year, statistically significant high coverage hotspots include more relatively intense clustering shown in red (99% CI, >2.58 SD) and relatively less intense clustering shown in orange (95% CI, 1.96 – 2.58 SD). Significant low coverage hotspots include more relatively intense

clustering shown in dark blue (99% CI, <-2.58 standard deviations) and relatively less intense clustering shown in light blue (95% CI, -2.58 - -1.96 standard deviations).

ITNs

As shown in Figure 3.8, hotspot analysis also showed significant spatial clustering trends for ITNs. In 2007-08, high coverage hotspots are concentrated in the Lake Zone Regions of Mwanza and Mara, as well as in Pwani and Dar es Salaam (Figure 3.8A). These statistically significant high coverage hotspots include a mix of more intense clustering (shown in red) and less intense clustering (shown in orange). Low coverage hotspots are found throughout the central portion of the country with a mix of more and less intense clustering (shown in dark blue and light blue, respectively).

In 2011-12 (Figure 3.8B), high coverage hotspots are found in a broader area south of the Lake Zone, including Mwanza, Mara, Geita, Simiyu, Shinyanga, and Tabora Regions. High coverage hotspots also appear in Njombe, Ruvuma, Lindi, Kilimanjaro, and Kigoma. Pwani Region and Dar es Salaam, which had high coverage hotspots in 2007-08, have only low coverage hotspots in 2011-12. Low coverage hotspots appear in fewer regions in the central portion of the country in 2011-12, but persist in Manyara, Arusha, and Kilimanjaro Regions, and appear in Katavi and Rukwa Regions.

In 2015-16 (Figure 3.8C), high coverage hotspots are found only in the western part of the country, emanating out from the Lake Zone. The majority of these high coverage hotspots show intense clustering (indicated in red). Low coverage hotspots appear throughout a wide portion of the central and southwestern regions of the country and indicate more intense spatial clustering than the low coverage hotspots in the 2007-08 and 2011-12 surveys.

IRS

As shown in Figure 3.9, hotspot analysis also showed significant spatial clustering trends for IRS. As expected, hotspots for IRS are concentrated where the intervention was focused – in the Lake Zone Regions. In 2007-08, high coverage hotspots are found in Kagera Region in the Lake Zone (Figure 3.9A). In 2011-12 (Figure 3.9B) and 2015-16 (Figure 3.9C), high coverage hotspots are found throughout the regions of the Lake Zone. Almost all these high coverage hotspots show intense clustering (as shown in red). Although low coverage hotspots are shown in 2011-12 and

2015-16, there was no IRS implemented through the NMCP in areas outside the Lake Zone in these years.

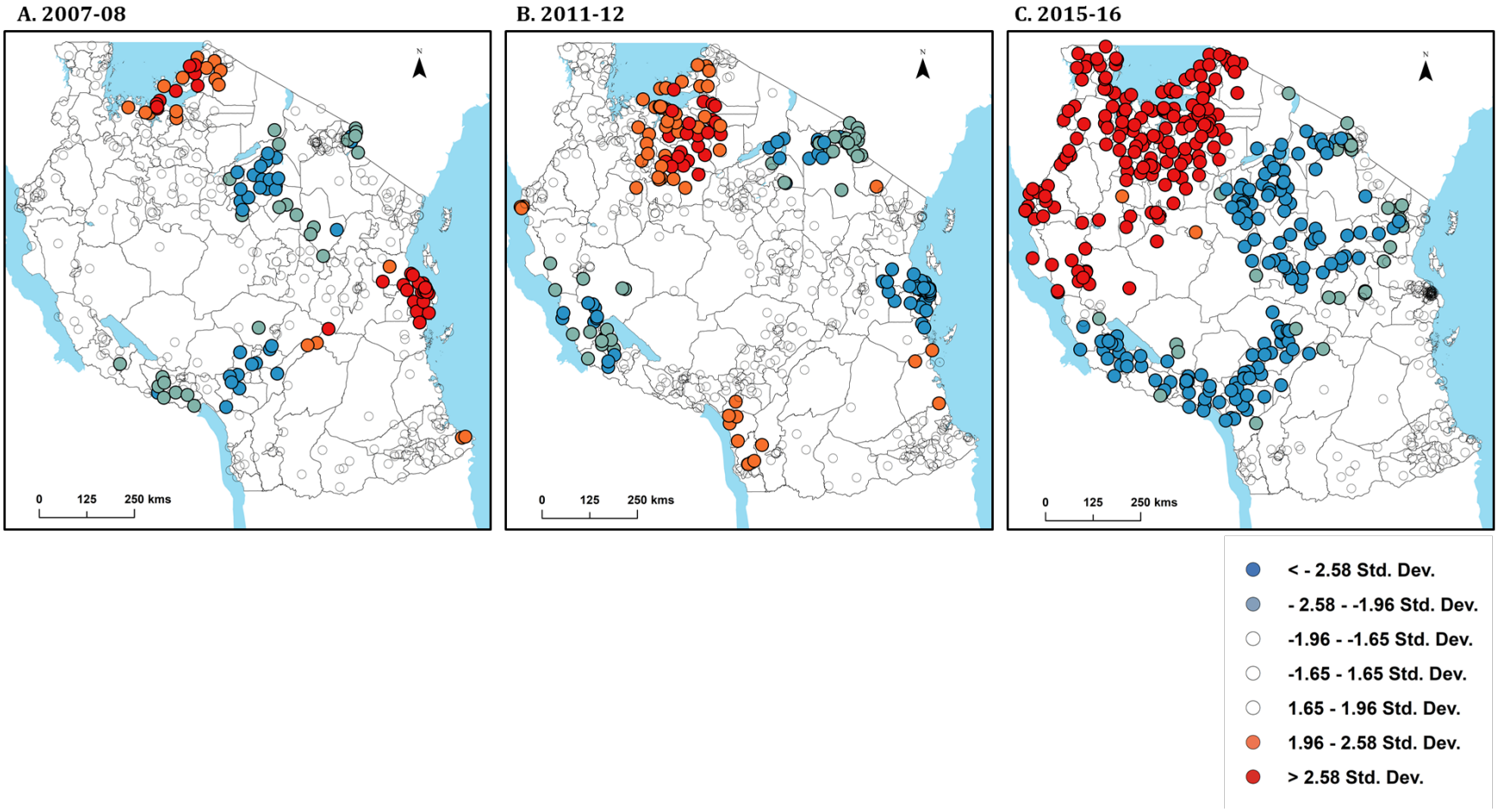


Figure 3.8. ITN Hotspots in Survey Sites from the (A) 2007-08, (B) 2011-12, and (C) 2015-16 DHS/MIS surveys.

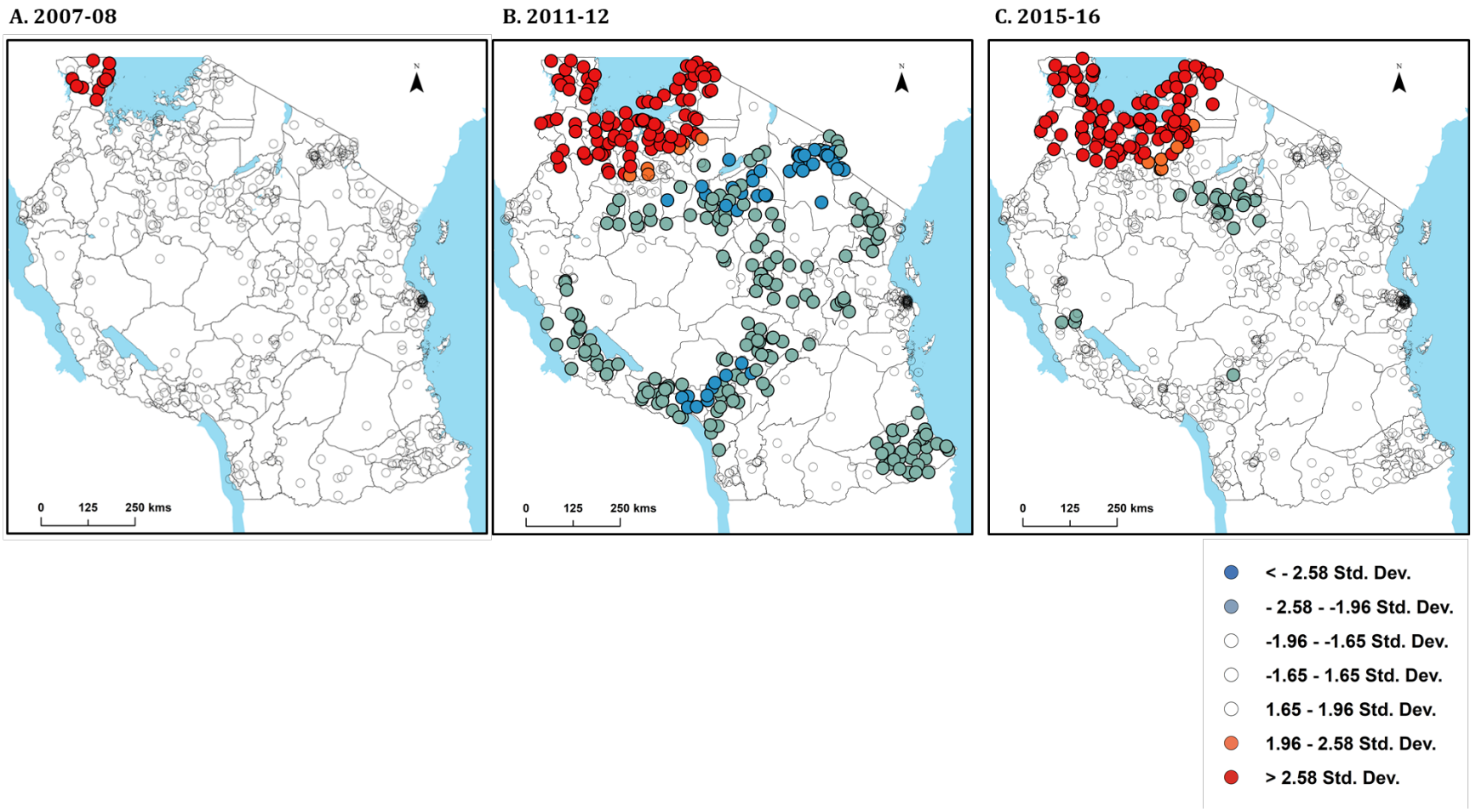


Figure 3.9. IRS Hotspots in Survey Sites from the (A) 2007-08, (B) 2011-12, and (C) 2015-16 DHS/MIS surveys.

3.5.7 Case Studies

The 2015-16 hotspot results for ITNs and IRS were examined further to identify survey sites that had significant hotspots for both ITNs and IRS (both low or both high). When survey sites with significant clustering for both indicators are isolated, the resulting map reveals high vector control coverage hotspots in the Lake Zone and low vector control coverage hotspots in the Central Zone (Figure 3.10). These hotspots are overlaid with the national LF risk map in Figure 3.11 and considered further in the two case studies below. Regional maps of the predicted probability of *An. gambiae*, *An. funestus*, and *An. arabiensis*, which were used to produce the species occurrence maps presented in each case study, are attached in Appendix 3.

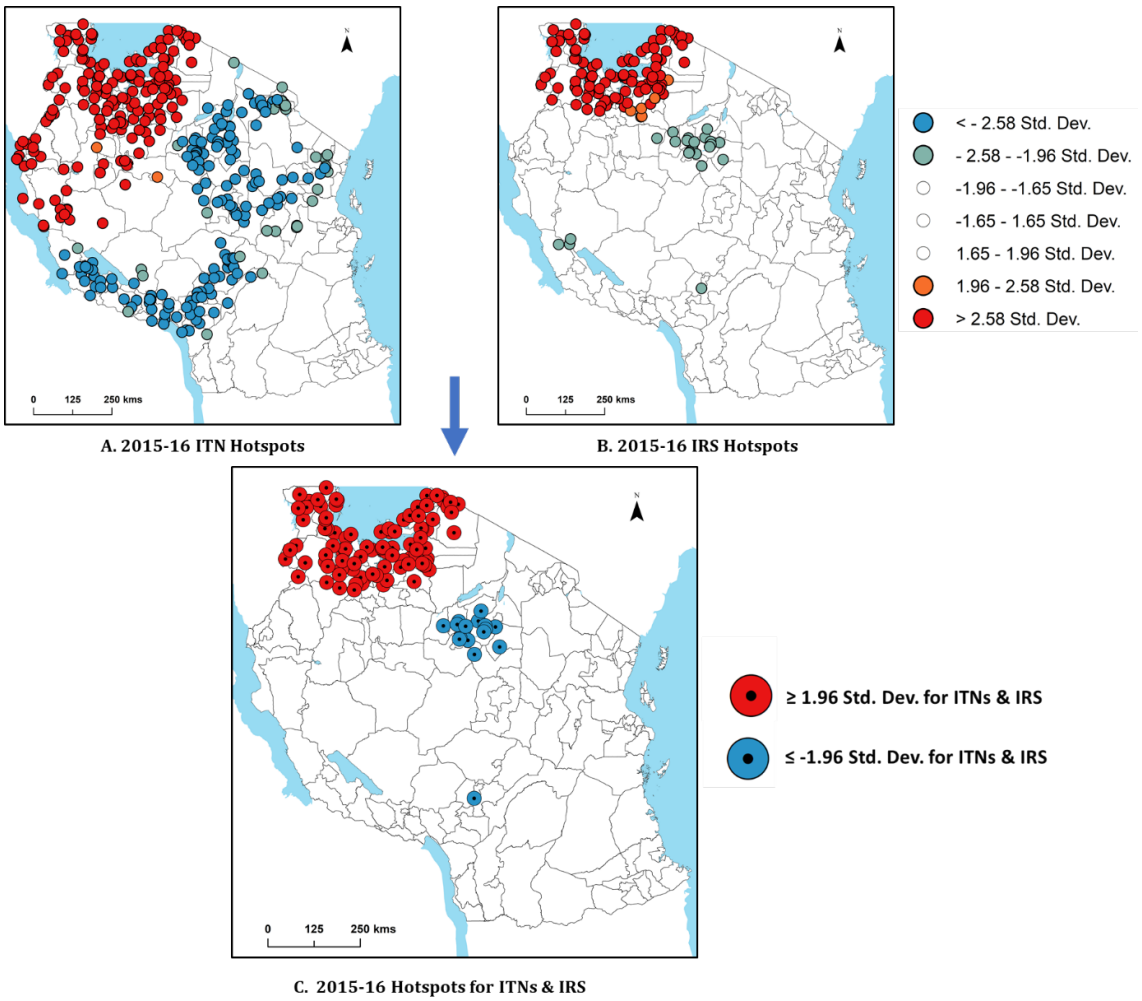


Figure 3.10. Spatial Overlap of ITN & IRS Hotspots, DHS Survey Sites 2015-16

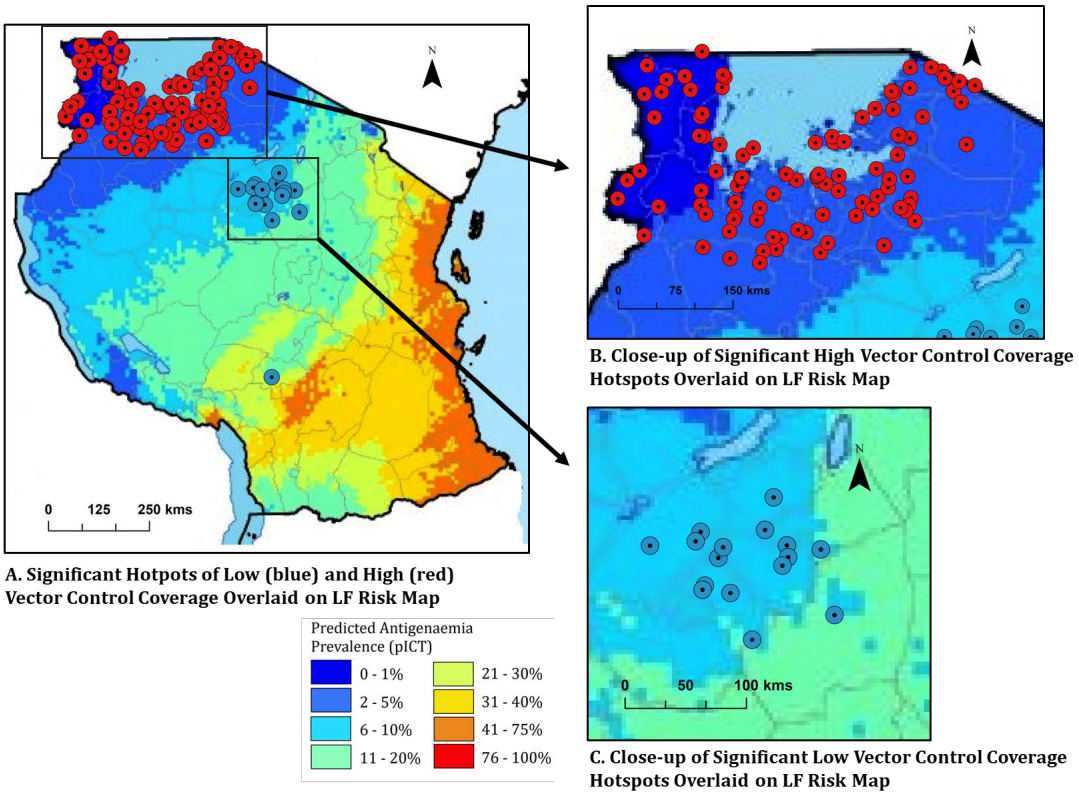


Figure 3.11. Significant Hotspots of Vector Control Overlaid with LF Risk. Figure A shows predicted antigenaemia prevalence (risk) prior to large-scale MDA from 1990-onwards (LF risk) overlaid with significant hotspots of low and high vector control coverage from the 2015-16 DHS. Figures B and C show close-ups of the Lake Zone (B) and Central Zone (C).

3.5.7.1 Case Study One: The Lake Zone

LF Scenario: The Lake Zone of Tanzania, which includes the six regions of Kagera, Geita, Mwanza, Shinyanga, Simiyu, and Mara, falls within the lowest and second lowest bands of predicted LF risk in the country. Kagera region has a predicted antigenemia prevalence of 2-5%, while the remaining regions fall primarily within the range of 6-10% pICT. Historical evidence suggests that LF was prevalent in the Lake Zone, with reported rates of microfilaremia as high as 30-40% in some areas (Hawking, 1957; Jordan, 1956). LF mapping conducted by the MOHSW in 2004 resulted in 24 of 27 districts being classified as LF endemic based on levels of antigenemia by ICT of ≥1% (unpublished data not shown). However, none of the districts in the Lake Zone have ever received MDA for LF.

Vector Control Scenario: As shown in this chapter, the Lake Zone has been an area of intensive focus for vector control activities since 2004, including distribution of ITNs and later LLINs through routine distribution channels and more recently through mass LLIN campaigns in 2009-10, 2010-11, and 2015-16. It has also been the major focus of PMI-funded IRS activities since 2006-07. Household ownership of at least one net in the Lake Zone was reported to be 66.9% in the 2007-08 AIS/MIS. In the 2011-12, net ownership was reported to be 96.5%, however due to administrative boundary changes between the two surveys, these figures cannot be directly compared. In the 2015-16 DHS/MIS net ownership in the Lake Zone was reported to be 93.1%, a slight decrease from the previous survey. For these same surveys, the percentage of children under five years of age who slept under a net the previous night was found to be 44.1%, 77.3%, and 76.4%, respectively. These overall increases, along with the scale-up of IRS, are reflected by the high coverage vector control hotspots identified in the zone (Figure 3.10C), which overlaps with the lowest LF risk areas in the country (Figure 3.11B).

Potential Positive Implications for LF: Even in the absence of MDA, it is possible that the significant scale-up of both ITNs and IRS has contributed to suppression of LF transmission, particularly given that LF risk was relatively low to begin with in the Lake Zone. If this is indeed the case, it is a tremendous contribution of the malaria control programme to have eliminated the need for initiating a large-scale mass treatment programme for LF in this area. It is also possible that ongoing vector control interventions may help to minimize the risk of LF resurgence in this area in the future (Burkot, Durrheim, Melrose, Speare, & Ichimori, 2006).

Potential Risks for LF: Studies have shown that ITNs and IRS can alter the composition of the *An. gambiae s.l.* complex (Bayoh et al., 2010; Lindblade et al., 2006; Magesa et al., 1991). *An.*

gambiae s.l and *An. funestus* have historically been reported as the dominant vectors of LF in the Lake Zone (Rwegoshora et al., 2005). However recent data, as shown in Figure 3.12, indicates *An. arabiensis* has a high probability of occurrence in the survey sites in the central and eastern areas of the Lake Zone. Changes in vector composition could affect the efficiency of LF transmission. For example, *An. arabiensis* tends to be more exophilic and exophagic than *An. gambiae* (Mahande, Mosha, Mahande, & Kweka, 2007; Tirados, Costantini, Gibson, & Toor, 2006). Additionally, if vector control has indeed reduced transmission of LF in the Lake Zone, emerging insecticide resistance could be a concern. As shown in Figures 3.14 and 3.14, insecticide resistance has been reported throughout the Lake Zone, which has been under high insecticidal pressure as shown by the hotspot analysis.

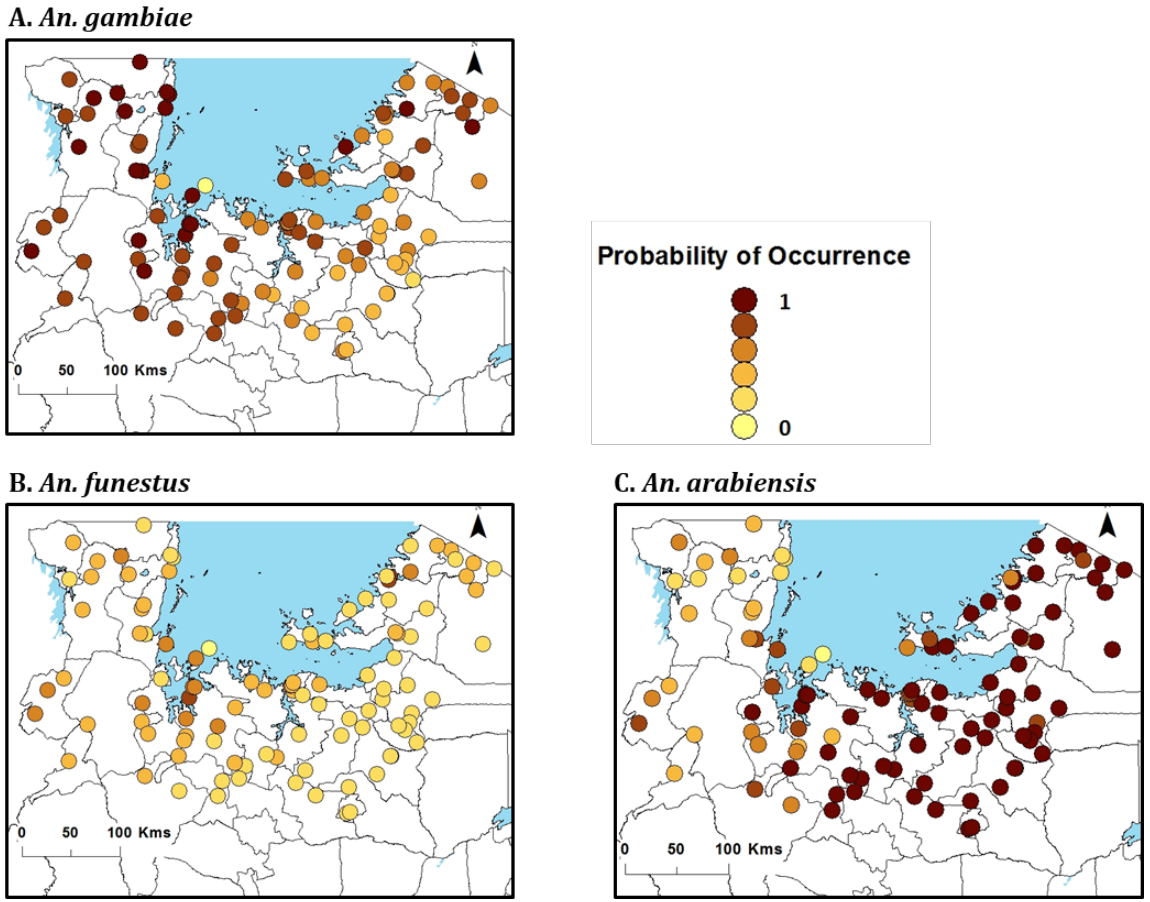


Figure 3.12. Probability of Occurrence of Mosquito Species in the Lake Zone DHS sites with Significant High Clustering of Both ITNs and IRS in 2015-16. Data on mosquito species is extracted from Wiebe et al., 2017.

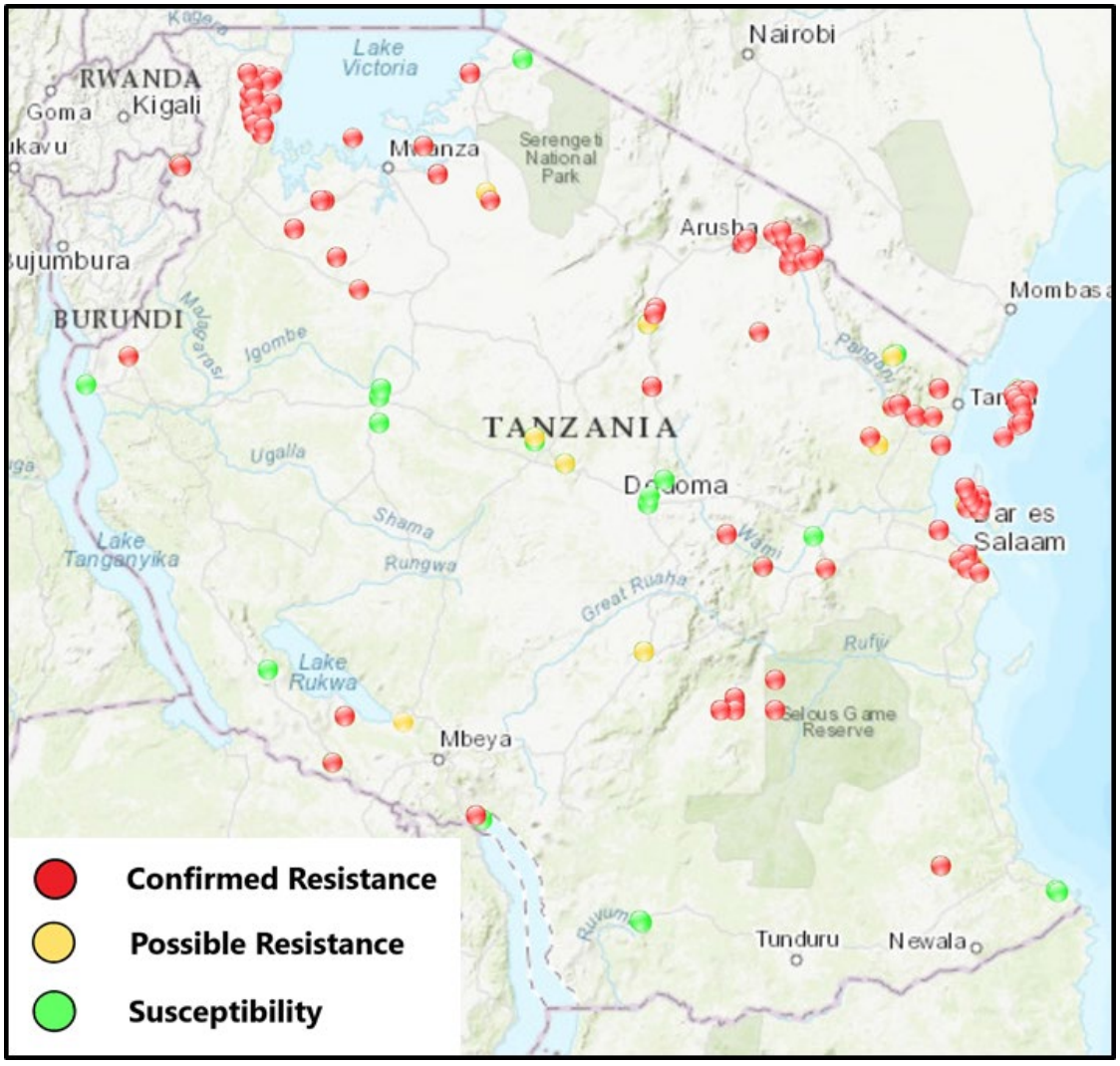


Figure 3.13. Insecticide Resistance and Susceptibility in Tanzania, 2005-2018. Data is extracted from IR Mapper (IRmapper.com) and includes sites of confirmed and possible insecticide resistance and susceptibility for the vector species An. arabiensis, An. funestus, and An. gambiae as reported between 2005 and 2018.

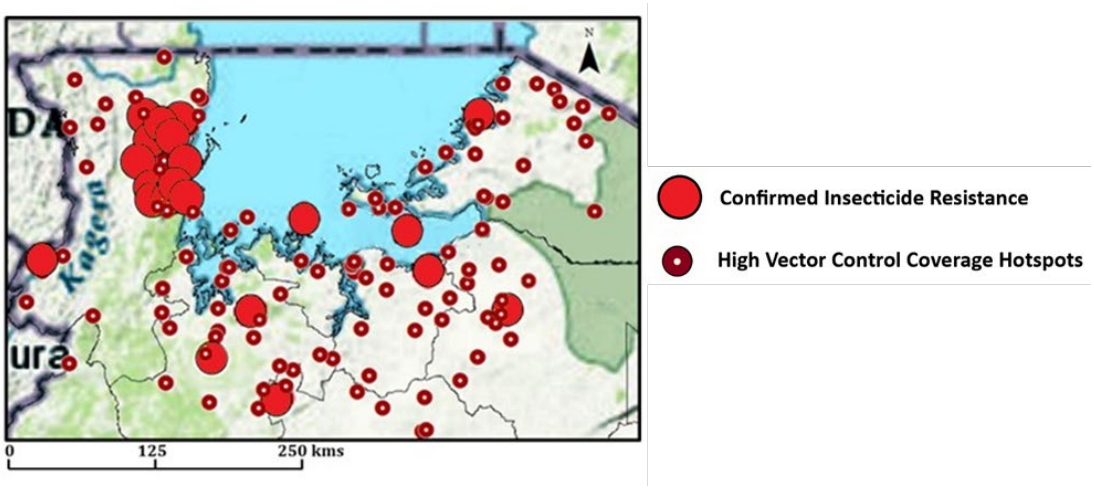


Figure 3.14. Sites of Confirmed Insecticide Resistance Overlaid with High Vector Control Hotspots in the Lake Zone. Insecticide resistance data is extracted from IR Mapper (IRmapper.com) and includes sites of confirmed insecticide resistance for the vector species *An. arabiensis, An. funestus,* and *An. gambiae* as reported between 2005 and 2018. Vector control hotspot data is a close-up of the data presented in section 3.5.7.

3.5.7.2 Case Study Two: The Central Zone

LF Scenario: The Central Zone of Tanzania, which includes the three regions of Singida, Dodoma, and Manyara, includes a band of predicted LF risk that ranges from 6-20% pICT. Mapping conducted by the MOHSW in 2004 concluded that 11 of the 14 districts surveyed in the Central Zone had levels of antigenemia measured with ICT of ≥1% (unpublished data not shown). The Central Zone was prioritized for LF MDA, which has taken place in each of its regions (Singida, Dodoma, and Manyara).

Vector Control Scenario: The Central Zone has benefited from the ITN/LLIN distribution mechanisms that have been scaled-up throughout the Mainland since 2004, including routine distribution of nets and more recently through mass LLIN campaigns. It has not been included in the IRS programme because areas of higher malaria risk were prioritized. Household ownership of at least one net in the Central Zone was reported to be 43.4% in the 2007-08 AIS/MIS. This increased to 93.9% in the 2011-12, then decreased substantially to 41.0% in 2015-16. For these same surveys, the percentage of children under five years of age who slept under a net the previous night was found to be 19.8%, 74.5%, and 28.6%, respectively. These decreases in 2015-16, along with the lack of IRS, are reflected in the low coverage vector control hotspots found in the zone (Figure 3.10C), which overlaps with the lowest LF risk areas in the country (Figure 3.11C).

Potential Negative Implications for LF: Following five annual rounds of MDA, 13 of the districts in Singida and Dodoma underwent TAS for LF in 2016. All but two of the districts were determined to have interrupted LF transmission. The two districts with ongoing

transmission were Kondoa and Chemba in Dodoma region. Interestingly, these districts include two of the DHS/MIS 2015-16 survey sites with low vector control coverage hotspots. Kondoa had an ICT prevalence of 22% in the 2004 LF rapid mapping survey (unpublished data). Chemba was not yet a district in 2004 but was in an area determined to require MDA. In these districts, it can be speculated whether vector control could have hastened the interruption of LF transmission if coverage had been higher.

Potential Risks for LF: Similar to the data presented in the Lake Zone case study, recent data indicates that *An. arabiensis* has a high probability of occurrence in the survey sites in the Central Zone (Figure 3.16). This is coupled with a low probability of occurrence of *An. gambiae* and *An. funestus* in these survey sites. Again, since changes in vector composition could affect the efficiency of LF transmission, changes in species distribution also need to be monitored, including in the districts that have successfully passed LF TAS and have stopped MDA. In these districts, changes in vector composition have the potential to influence conditions leading to the re-establishment of LF transmission. Although insecticidal pressure may be lower in the Central Zone than in the Lake Zone because vector control coverage has been lower, there are reports of confirmed insecticide resistance (Figure 3.17). Insecticide resistance should be routinely monitored in the area, as it could impact the efficacy of ITNs in the future, which could in turn have an impact on LF transmission.

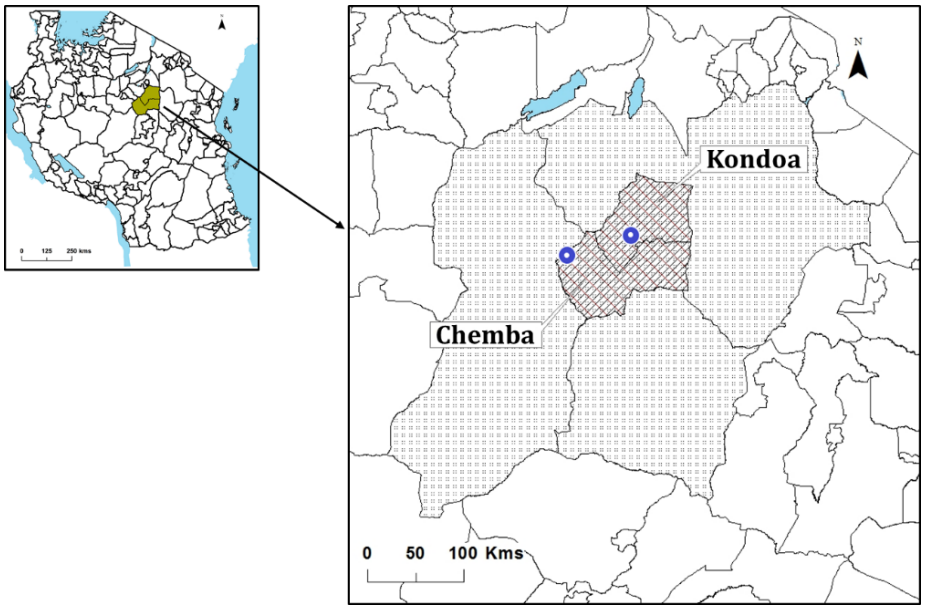


Figure 3.15. Districts that Failed LF Transmission Assessment Surveys in 2016 in the Central Zone. Sites in blue are survey sites with low vector control coverage hotspots from the 2015-16 DHS

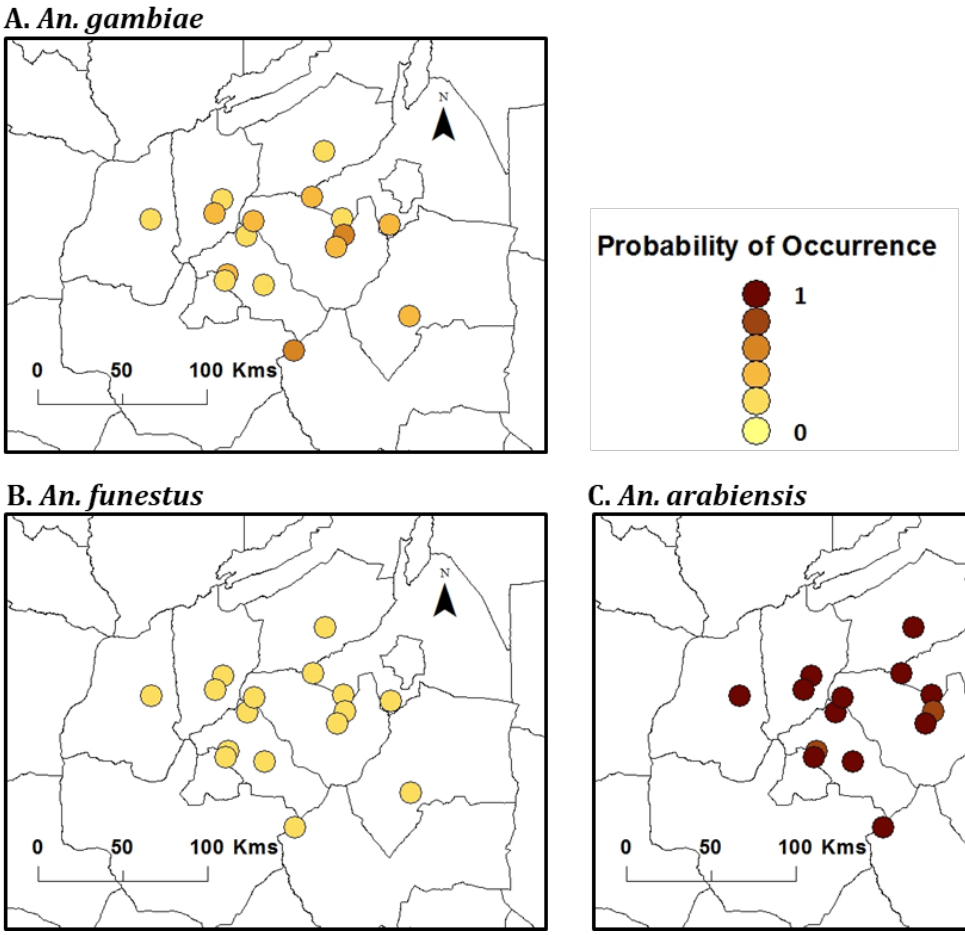


Figure 3.16. Probability of Occurrence of Mosquito Species in the Central Zone DHS sites with Significant Low Clustering of Both ITNs and IRS in 2015-16. Data on mosquito species is extracted from Wiebe et al., 2017.

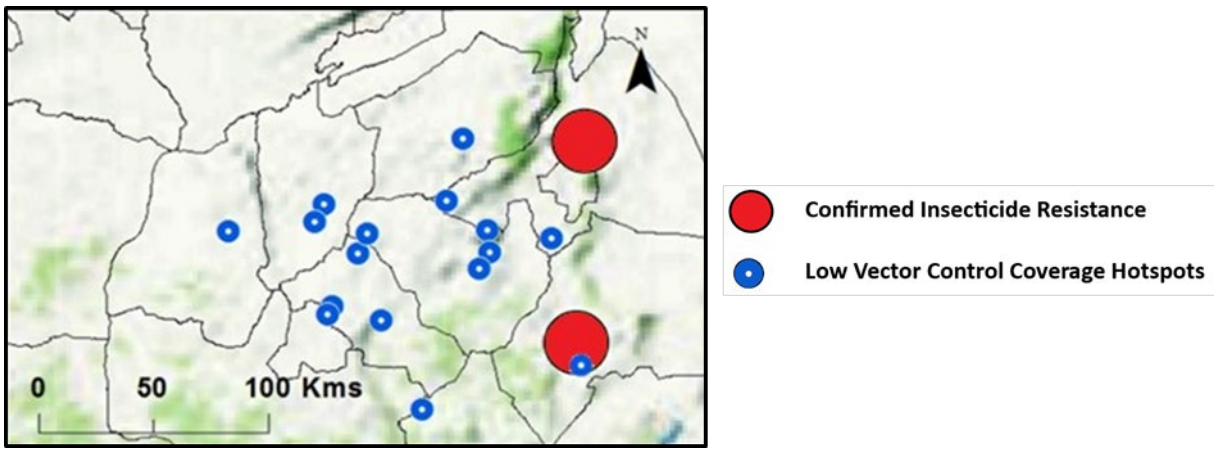


Figure 3.17. Sites of Confirmed Insecticide Resistance Overlaid with Low Vector Control Hotspots in the Central Zone. Insecticide resistance data is extracted from IR Mapper (IRmapper.com) and includes sites of confirmed insecticide resistance for the vector species An. arabiensis, An. funestus, and An. gambiae as reported between 2005 and 2018. Vector control hotspot data is a close-up of the data presented in section 3.5.7.

3.6 Discussion

This chapter highlights that although LF is prevalent throughout Mainland Tanzania, LF risk is highly variable throughout the country. Major national efforts to distribute ITNs/LLINs over the past decade have been largely successful. Coverage maps confirm that ITN ownership was highly variable across Mainland Tanzania prior to the nationwide ITN/LLIN campaigns that began in 2009. It is evident that by 2011-12, these campaigns had significantly increased ITN ownership throughout the country. IRS has been more focalized but scaled-up progressively in areas of greatest malaria risk, primarily around Lake Victoria.

However, despite the gains shown in 2011-12, reported ITN ownership in 2015-16 decreased substantially. It should be noted that only nine regions had been covered by the 2015-16 UCC when the 2015-16 DHS was administered. ITN ownership was relatively high in those 9 regions (above 70%); however, in those regions not yet reached by the UCC, ITN ownership ranged from 20-61%. Although the DHS did not fully reflect the impact of the UCC on ITN coverage, it did highlight a worrying trend - that between implementation of large-scale UCCs, ITN coverage waned rather significantly in a short amount of time.

Spatial analysis of ITN ownership and IRS coverage revealed significant hotspots of low and high coverage from the most recent DHS survey (2015-16). Case studies examined these patterns in two scenarios: one with low LF risk and high vector control coverage hotspots and one with moderate LF risk and low vector control coverage hotspots. In the Lake Zone, intensive vector control may have contributed to reduced transmission of LF such that MDA may no longer be warranted. However, further studies on the status of LF transmission in the Lake Zone are required. In the Central Zone, two districts failed an LF TAS after five successful rounds of MDA. This case study revealed that these districts were in low vector control hotspots. Given the assumption that vector control can reduce LF transmission, it can be speculated that higher vector control coverage in these districts could have potentially facilitated elimination of LF transmission. The case studies also emphasised that both insecticide resistance and changes in species distribution should be monitored since they have the potential to influence conditions that may affect LF transmission.

In addition to the case studies presented, other scenarios in Tanzania revealed in this study warrant further consideration. First, the pattern of low ITN hotspots in a rather large area through the central part of the county is of interest. Malaria prevalence is low in many of these regions (e.g., Manyara <1%) and although the UCCs have included these regions, it cannot be assumed that they will be prioritized for increased focus or investment given

limited resources. This could have implications for the LF programme since LF risk is moderate to high in all these regions.

Second, the regions with relatively high vector control coverage and high LF risk may be vulnerable if vector control interventions begin to have reduced efficacy due to the emergence of insecticide resistance (Hemingway et al., 2016). Reports of insecticide resistant mosquitoes (Kisinza et al., 2017; Ojuka et al., 2015; Riveron et al., 2015) are of great concern for malaria programmes, yet insecticide resistance is not often discussed in the context of LF programs. This is mainly because the global strategy to eliminate LF relies on MDA. However, it has been argued that vector control be considered as a supplemental strategy to expedite and sustain interruption of LF transmission (Bockarie et al., 2009).

Lastly, the maps of estimated relative probability of occurrence for *An. gambiae, An. funestus,* and *An. arabiensis* by region (Appendix 3) show *An. arabiensis* has a relatively wide modelled geographical distribution. This may reflect a shift in sibling species composition taking place over time in Tanzania (Russell et al., 2011), which could be impacting the transmission dynamics of LF. Derua and colleagues reported a change in *Anopheles gambiae s.l*. sibling species composition in north-eastern Tanzania with *An. arabiensis* becoming the most common sibling species after having been the rarest in earlier studies (Derua et al., 2012). *An. arabiensis* has been shown to be an LF vector in Tanzania, and an increase in its relative abundance in areas with ongoing LF transmission is of concern since its exophilic behaviour means vector control measures such as ITNs and IRS will have reduced impact (Lindblade et al., 2006).

The significant scale up of vector control interventions for malaria in Tanzania in the past decade has likely had an influence on LF transmission. This study highlights the need for vector control interventions for malaria to be coordinated with the LF programme so that low ITN/LLIN coverage areas that may have an impact on both diseases can be addressed. These interventions should continue to be monitored and their implications for influencing LF transmission considered as Tanzania progresses toward achieving national elimination of LF.

Chapter Four

Vector Control Interventions in the Lake Zone of Tanzania: Potential Negative Impact of Indoor Residual Spraying on Net Ownership?

4.1 Introduction

Major efforts were undertaken in Tanzania to reduce malaria prevalence by increasing vector control coverage between 2004-2015, including nationwide distribution of ITNs/LLINs through routine channels and campaigns, and focalized implementation of IRS in the Lake Zone. Overall these efforts have been largely successful. Nationally, household ITN ownership increased from 38.3% to 91.5% between the 2007-08 and 2011-12 DHS/MIS. During this same period, IRS coverage was scaled-up significantly in areas of greatest malaria risk, primarily around Lake Victoria.

Unfortunately, the 2015-16 DHS revealed that household ITN ownership had decreased from 91.5% to 65.4% on Mainland Tanzania (MoHCDGEC et al, 2016). Between the 2011-12 MIS and the 2015-16 DHS, 22 regions had a decrease in ITN ownership. Fifteen of these regions had a decrease greater than 20% between the two surveys. In addition to an overall decline in ITN coverage, the results of the 2015-16 DHS highlighted significant variation in net coverage between regions, ranging from 22.3% to 97.6% (MoHCDGEC et al, 2016). Furthermore, the 2015-16 DHS was implemented before the UCC in most of the regions, indicating that ITN ownership was waning in many regions prior to the 2015-16 UCC.

Studies assessing the performance of mass campaigns have shown dramatic short-term gains in net coverage. Indeed, assessments in countries up to six months after a campaign have documented increases in net coverage up to 40% to 60% above pre-campaign levels (Bennett et al., 2012; Centers for Disease Control and Prevention, 2005; Kulkarni et al., 2010; Thwing et al., 2008; West et al., 2012; Zollner et al., 2015). Studies demonstrating the maintenance of high coverage in the longer-term are mixed, however, with coverage several years post-campaign often depending on whether or not continuous net delivery strategies were also utilized (Kilian, Wijayanandana, Ssekitoleeko, Killian, & Org, 2009).

National and regional data from large population-based surveys such as the DHS may mask local variations that may be critical to address local barriers to sustaining high coverage (Kazembe, Appleton, & Kleinschmidt, 2007). When feasible, local factors that may be associated with household net coverage should be considered (Kazembe et al., 2007). Since poorer households tend to have lowest ITN coverage, univariate measures of household building materials, size, and ownership of commodities, among other factors, can be useful to assess as determinants of net coverage (Bernard et al., 2009; Hailu et al., 2016; C. Taylor, Florey, & Ye, 2017; Ye, Patton, Kilian, Dovey, & Eckert, 2012). Such data is relatively feasible to collect even during small-scale household surveys that do not have the resources to

develop more extensive consumption-based measures of socioeconomic status (SES) (Somi et al., 2008).

In the present study of LF, coverage of vector control measures for malaria are important to consider due to their potential impact on LF transmission where the diseases are co-endemic and transmitted by the same mosquito vectors, as they are in Tanzania (Bockarie et al., 2009; Kelly-Hope et al., 2013; van den Berg, Kelly-Hope, & Lindsay, 2013).

Following on Chapter 3, which examined predicted LF risk and national trends in vector control coverage, this chapter examines vector control coverage on a local scale in the Lake Zone of Tanzania.

4.1.1 Aims

The overall aims of this chapter are to 1) determine household ownership of mosquito nets and household IRS coverage in study sites in the Lake Zone of Tanzania in the context of intensified national vector control programmes for malaria, and 2) to assess factors driving household net ownership in the study population.

4.1.2 Objectives

- To determine household net ownership and IRS coverage in the six study sites pre- and post- UCC and IRS campaigns
- To evaluate the relationship between household IRS and net ownership
- To evaluate the relationship between socioeconomic proxy indicators and household net ownership
- To assess annual predictors of household net ownership
- To examine the spatial relationship between household IRS and net ownership

4.2 Methods

4.2.1 Study Sites

The Lake Zone of Tanzania was chosen as the focus of the study due to the NMCP's planned scale-up of IRS in the area. The Lake Zone is divided into six regions comprised of 37 districts. The Lake Victoria Basin experiences long rains (masika) from March to May and short rains (mvuli) from October to December and often into January (Rowhani et al., 2011). Malaria transmission takes place throughout the year with peaks occurring in December to January following the short rains and from June to July following the long rains (West et al., 2012).

4.2.2 Study Population

The Lake Zone has an estimated population of 11.8 million people (National Bureau of Statistics, 2016). Life expectancy at birth in Tanzania is 64.9 years and the fertility rate (average births per woman) is 5.1 (World Development Indicators database, 2018).

Most households in the study districts are located in rural areas. The average household size ranges from 4.7 to 6.5 persons per household (Table 4.1). The most common occupation among the working population in every district is farming and the main industries are commercial agriculture, food crops, and forestry (NBS, 2016).

Table 4.1. Demographics of Study Districts

Site Type	Region	Study Site	District	District-Level Demographics*		
				No. of Households	Rural Households (%)	Average Household Size
Intervention	Mara	Nyambori	Rorya	52,492	94.9	4.7
	Mwanza	Bwisya	Ukerewe	59,000	85.8	5.7
	Mwanza	Mwaliga	Sengerema	109,334	87.4	6.0
	Geita	Bunegezi	Geita	134,608	75.5	5.9
Control (no IRS)	Geita	Igulwa	Bukombe	37,660	75.0	5.9
	Simiyu	Zanzui	Maswa	52,140	89.6	6.5

*National Bureau of Statistics, 2013

To identify specific study sites, first, districts that were classified as endemic for LF by the MOHSW were identified (unpublished data, 2004). To determine potential intervention sites, villages within LF-endemic districts that were targeted to receive IRS but had not yet been sprayed were identified. This narrowed potential intervention sites considerably because the IRS programme had already begun a rapid expansion at the time. From among the list of villages not yet sprayed, villages located in districts with the highest LF endemicity were selected. To identify potential 'control sites', districts in the Lake Zone that were *not* targeted to receive IRS during the three-year study period were identified and categorized by LF endemicity. Villages to be used as control sites were then selected from within these districts following consultation with the National NTD Program to determine which had the greatest likelihood of ongoing LF transmission based on programmatic and historical data. Four intervention study sites that would be receiving IRS and two control study sites that would not receive IRS were ultimately selected. The locations of the Lake Zone and the selected study sites are shown in Figure 4.1 and Figure 4.2, respectively.

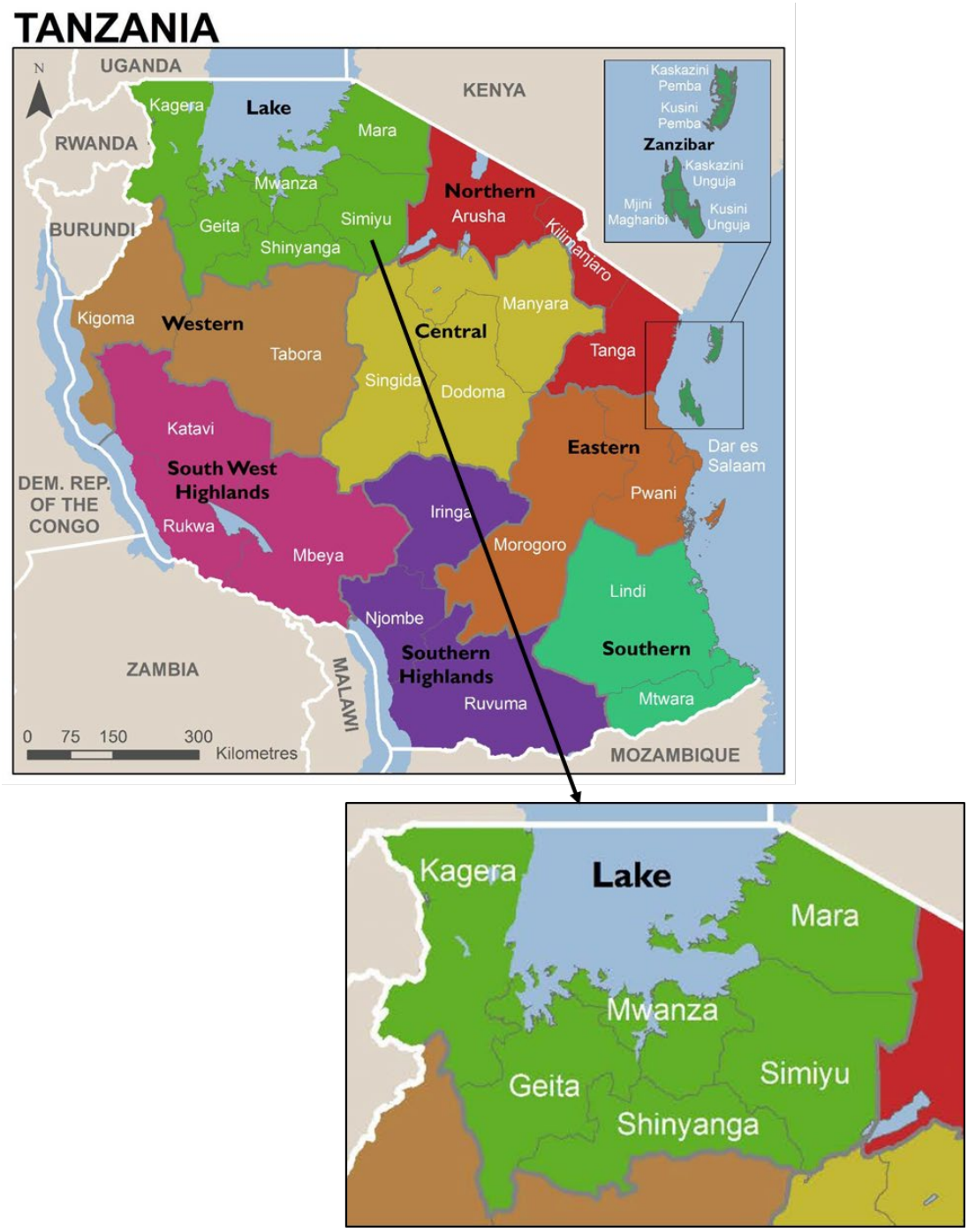


Figure 4.1. Map of the Lake Zone with Regions (white text) and Zones (black text) labelled.

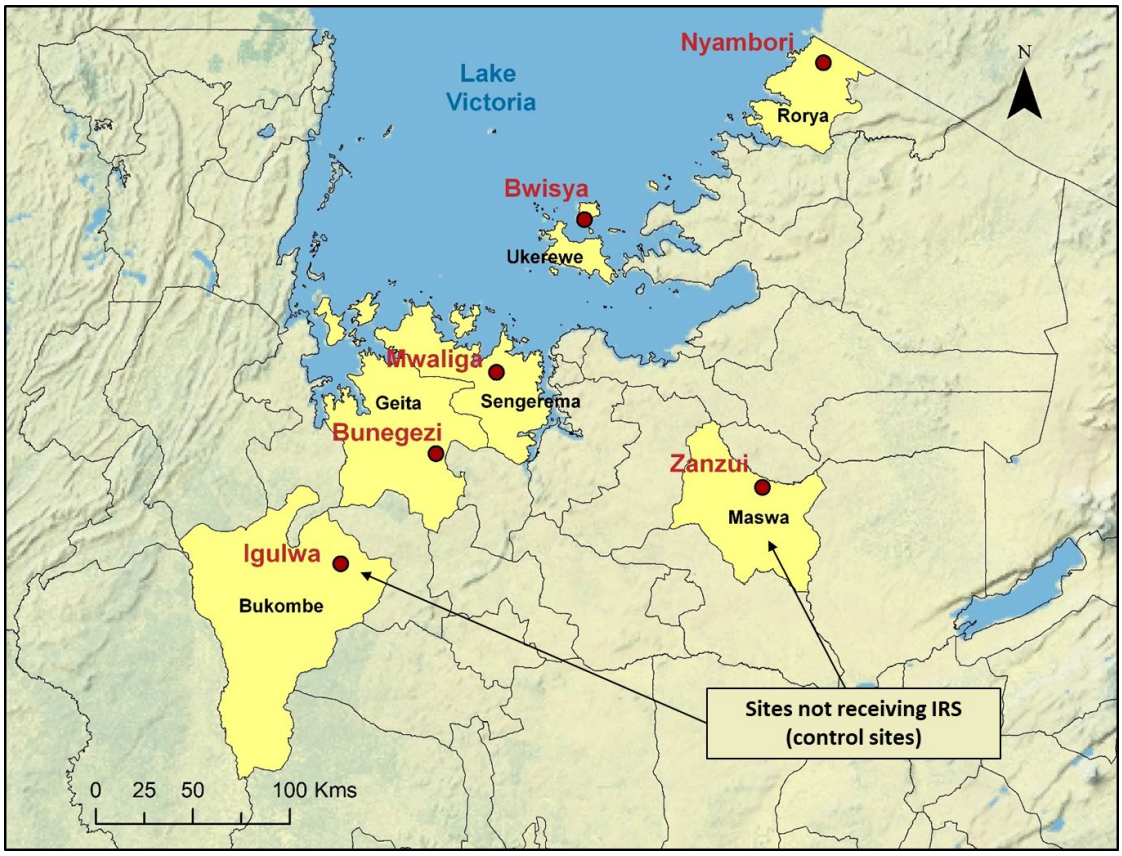


Figure 4.2. Location of the Study Sites included in this study (red text) and the districts in which they are located (yellow shading/black text). The two study sites not receiving IRS are indicated. The remaining four sites received IRS during the study period.

4.2.3 Study Design

The planned UCC and scale-up of IRS in the Lake Zone provided an opportunity to undertake three annual cross-sectional surveys to examine household net ownership and coverage of IRS in the study sites before and after implementation of the campaigns. The campaigns were undertaken by the NMCP; however, this study was able to take advantage of their timing to assess vector control coverage before and after the campaigns. Together with the LF component of this study, this design enabled assessment and comparison of vector control coverage over time in the study sites as well as analysis of its potential association with LF transmission (measured as exposure).

A structured household questionnaire was developed to assess local factors that may be associated with vector control coverage (Kazembe et al., 2007). The questionnaire was based on DHS and MIS survey instruments to enable comparison of local results to nationally representative DHS/MIS results in Tanzania. In addition to collection of basic demographic information on household occupants, such as age and sex, and coverage of vector control in the household, several questions were adapted from the DHS/MIS surveys, including those related to household commodities, household building materials and size, and household

size. Such indicators have been useful in other settings to assess determinants of vector control coverage (Bernard et al., 2009; Hailu et al., 2016; C. Taylor et al., 2017; Ye et al., 2012).

Household questionnaires were administered in the six study sites in 2011, 2012, and 2013. A timeline of government interventions and study activities is shown in Figure 4.3.

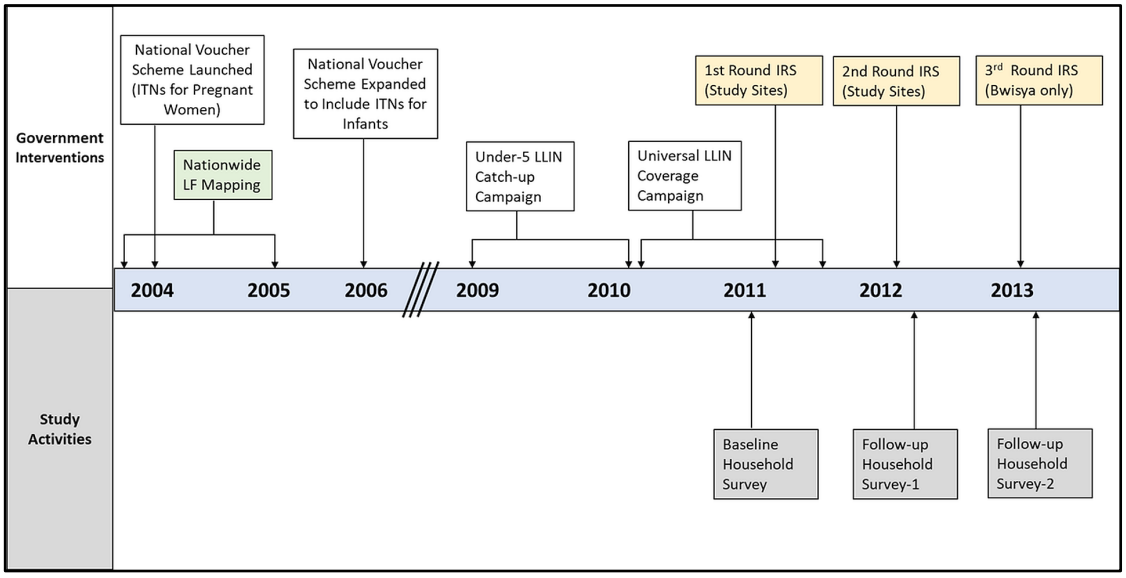


Figure 4.3. Timeline of interventions conducted by the MOHSW and NMCP and study activities preceding and during the 2011-2013 study period.

4.2.4 Administration of Household Survey

Questionnaire: The questionnaire was divided into four sections. The first section collected information to identify the household, including its location. GPS coordinates were recorded at each household using handheld GPS devices. The second section collected demographic information on household members, such as age and sex. The third section collected information on commodities owned by the household (*e.g.* electricity, paraffin lamp, radio, *etc.*), the primary building materials of the floor, walls, and roof of the main dwelling unit, as well as the number of rooms used for sleeping. The fourth section collected information on mosquito control measures used by the household. The household questionnaire is attached in Appendix 4.

Primary focus: The variables of primary interest in this study were whether the house had been sprayed against mosquitoes in the past 12 months and by whom, and whether the household owned at least one net. Due to the nature of the IRS intervention, including the unique uniforms and equipment of sprayers as well as the need for occupants to remove household effects prior to spraying, respondent recall was expected to be high for the response to whether the house had been sprayed or not. False reporting of IRS in areas not

under the IRS programme was also expected to be low (Roll Back Malaria Partnership, 2011). The principal investigator coordinated closely with the IRS team during the study to keep apprised of actual spray dates for each intervention study site.

Data collection teams: Three data collection teams were utilized to administer the survey. Each team, consisting of a supervisor, an assistant, and three technicians, was assigned to administer the survey in two study sites. Prior to deployment to study sites, a two-day protocol training was held in Mwanza, Tanzania for all team members. The training was facilitated by the principal investigator of the study, who was assisted by members of the National NTD Programme.

Village preparation: Upon arrival at each study site, the team met with village leaders to explain the purpose and methods of the study and to obtain informed consent. A local guide with knowledge of the village demography was recruited, and if available, a map of the village was obtained to facilitate household selection and movement of the team. If a map was not available, a simple map was drawn by the guide with houses mapped and numbered. All surveys were administered at the location of the household. The local guide accompanied the team during data collection. Survey teams began data collection in the morning and worked through the afternoon. On average, it took teams approximately one week to complete the survey in each study site. It was not possible to blind data collection teams to the spraying status of the village due to the visibility of community preparations for IRS.

Household selection:

Targeted sample sizes were determined based on the number of children that would be sampled for LF antibodies in each village (for the LF component of the study). The number of children sampled was limited by the number of filter papers available for blood collection. Filter papers were assigned to villages proportional to population based on available knowledge and discussions with local field teams, and teams were instructed to sample as many houses as required to utilize all the filter papers. In each village, convenience sampling was done to maximize the use of limited funding resources and time in the field. All known houses in the village were numbered and simple random number generation was used to select households for inclusion. If a randomly selected household refused to participate or was not available, then the next house on the right was sampled. At each household, signed informed consent was obtained from the head of the household or another adult that lived in the house prior to administration of the survey.

The protocol above was followed for each year of data collection, including the simple random selection of households. Households were not intentionally targeted for repeat sampling and were not excluded if they were selected more than once. In 2011 and 2012 data were collected using paper-based forms, while in 2013 handheld tablets were utilized. In 2011 the survey was administered in January-February to collect baseline data before the IRS program began spraying in the intervention study sites. In 2012 and 2013, the survey was administered in July-August.

4.2.5 Analysis

For the 2011 and 2012 surveys, data from paper-based questionnaires were entered into Microsoft Excel (Redmond, WA). Data from the 2013 survey was uploaded from the field using the open-source OpenDataKit (OpenDataKit, 2011) and subsequently exported into Microsoft Excel (Redmond, WA). Statistical analysis was conducted in IBM SPSS version 24 (Armonk, NY).

Results are presented under four areas: univariate, bivariate, multivariate and spatial analysis.

4.2.5.1 Main Variables and Univariate Analysis

Net Ownership: Household net ownership was measured and analysed using a dichotomous variable measured as 'ownership of one or more mosquito nets per household'. First, data on household net ownership in all study sites were aggregated and analysed to examine overall trends and allow for general comparison to the trends observed in the DHS data presented in Chapter 3. Second, net ownership by year in each study site was calculated and plotted with 95% confidence intervals to examine trends and differences between study sites. A chi-square test was used to determine if there was a significant difference in household net ownership between study sites. Post hoc analysis involved pairwise comparisons using the z-test of two proportions with a Bonferroni correction. Households with no data on net ownership were excluded from analysis related to net ownership (1.2% of households surveyed). This occurred in some cases due to no response recorded for the question, or a response of 'do not know' and may have been a result of respondents not wanting their house to be entered by survey teams to view nets.

IRS Coverage: IRS coverage was measured and analysed using a dichotomous variable measured as 'household sprayed in past twelve months by a government programme'. First, data on IRS coverage in all study sites were aggregated and analysed to examine overall trends and allow for general comparison to the trends observed in the DHS data presented

in Chapter 3. Second, IRS coverage by year in each study site was calculated and plotted with 95% confidence intervals to examine crude differences between study sites. A chi-square test was used to determine if there was a significant difference in household IRS between intervention study sites. Households with no data on IRS were excluded from analysis related to IRS coverage (0.9% of households surveyed). This occurred due to a response of 'do not know' to the survey question asking if the house had been sprayed.

Socioeconomic Status: Proxy indicators were used to assess SES, which included housing infrastructure (building materials and house size) and ownership of specific commodities (Galobardes, Shaw, Lawlor, Lynch, & Smith, 2006; McKenzie, 2005). Building materials of the main dwelling were measured and analysed using categorical variables for flooring, walls, and roofing. Additionally, using an approach described by Wanzirah et al., a dichotomous housing quality variable was created to define a 'modern' and a 'traditional' house from the categorical variables used for the building materials of the dwelling. If a house used finished building materials for flooring, walls, and roofing, it was considered 'modern'. The remaining houses using rudimentary materials for any of these components were considered 'traditional' (Wanzirah et al., 2015). House size was determined based on the number of rooms in the house used for sleeping and was measured and analysed as a dichotomous variable (≤3 rooms versus > 3 rooms). Ownership of individual household commodities were measured and analysed as dichotomous variables.

The aggregate results for net ownership, IRS Coverage, and select SES proxy indicators in the study population are then compared to results from the 2011-12 MIS, which corresponds most closely in time with the present study.

4.2.5.2 Bivariate Analysis

Relationship Between IRS Coverage and Household Net Ownership

The variables for household IRS coverage and household net ownership were dichotomous with independent groups (yes/no). Therefore, odds ratios were calculated to investigate the association between household IRS coverage and household net ownership (Agresti, 2007). Chi-square tests were used to determine if there was a significant difference ($p<0.05$) in household net ownership based on type of study site (control versus intervention) and household IRS coverage.

Relationship Between Housing Infrastructure, Quality, and Commodity Ownership and Household Net Ownership

The variables for housing infrastructure, quality, and commodity ownership and the dependent variable household net ownership were dichotomous with independent groups. Therefore, odds ratios were calculated to investigate the association between each of the independent variables and household net ownership (Agresti, 2007). Chi-square tests were used to determine if there was a significant difference ($p<0.05$) in household net ownership based on housing infrastructure, quality, and ownership of commodities.

4.2.5.3 Multivariate Analysis

Given that the dependent variable 'household net ownership' was dichotomous and there were two or more independent dichotomous variables, binomial logistic regression was selected to assess the predictors of household net ownership in each year. The data met the required assumptions for the use of binomial logistic regression, including: presence of two or more independent variables, which in this case were all dichotomous, and independence of observations. In addition, the categories of the dependent variable and each independent variable were mutually exclusive with a minimum of 50 cases per independent variable. Initially, all variables that were statistically significant ($p<0.05$) from bivariate analysis were included in the regression model for each year. Variables that were not significant ($p>0.05$) and did not improve the model's fit based on chi-square analysis were subsequently removed (Hosmer, Lemeshow, & Sturdivant, 2013).

An alternative approach would have been to use stepwise reduction of the maximum model to a minimum model through selection of variables based on their significance level and comparison of models using chi square tests (Crawley, 2007). However, variable selection based on the more purposeful and non-automated approach was ultimately deemed more appropriate (Hosmer, Lemeshow, & Sturdivant, 2013).

4.2.5.4 Spatial Analysis

Household-level data, which included the geographical coordinates of the household, were imported into ArcGIS 10 (ESRI, Redlands CA) and used to examine the finer spatial distribution of household net ownership and IRS coverage in each study site.

4.2.6 Ethical Approval and Informed Consent

The study protocol was approved the National Institute of Medical Research (NIMR), Tanzania, and the LSTM Research Ethics Committee. The study was conducted in collaboration with the National NTD Program of the MOHSW, Tanzania. Community leaders

in each study site and all participants were informed of the objectives of the study, risks and benefits, and that participation was entirely voluntary. Local community leaders provided permission for teams to conduct the study. Households were only surveyed if written informed consent was provided by the head of the household or another adult residing in the house. Consent forms were translated from English into Kiswahili for use in the field.

4.3 Results

4.3.1 Study Population

The survey was administered in 2011, 2012, and 2013 in each of the six study sites, with a total of 2,432 questionnaires completed during the study period. The number of questionnaires completed by study site and year is summarized in Table 4.2.

Table 4.2. Number of Household Questionnaires Administered by Year and Study Site

Study type	Study Site	2011	2012	2013	Total
Intervention	Nyambori	211	100	144	455
	Bwisya	242	73	78	393
	Mwaliga	111	132	117	360
	Bunegezi	164	126	92	382
Control	Igulwa	224	159	93	476
	Zanzui	129	153	84	366
Total	Total	1,081	743	608	2,432

4.3.2 Univariate Results

Household net ownership and IRS coverage in the six study sites pre- and post- UCC and IRS campaigns is presented below. Aggregate results for these indicators are then compared to results from the 2011-12 MIS for the Lake Zone.

4.3.2.1 Net Ownership

The total proportion of households in all study sites reporting ownership of ≥1 net in the 2011, 2012, and 2013 surveys is shown in

Figure 4.4. Overall, household ownership of mosquito nets decreased significantly ($p<0.05$) from 72.6% (95% CI 69.8-75.2%) in 2011 to 50.3% in 2013 (95% CI 46.4-54.3%). The difference between ownership in 2011 and 2012 was not statistically significant ($p>0.05$), the latter being 72.0% (68.7-75.2%).

The proportion of households in each study site reporting ownership of ≥1 net in 2011, 2012, and 2013 is detailed in Table 4.3. In each year, net ownership varied considerably between study sites, with a range of 19.5-98.2% in 2011, 53.5-89.4% in 2012, and 28.3-66.7% in 2013.

There was a statistically significant difference in proportions of households owning ≥1 net within each year ($p<0.0005$).

In 2011, the proportion of households owning ≥1 net in Mwaliga, Bunegezi, and Igulwa was significantly higher than the other study sites ($p<0.05$) and the proportion of households owning ≥1 net in Zanzui was significantly lower than the other study sites ($p<0.05$). In 2012, the proportion of households owning ≥1 net in the intervention sites of Nyambori, Bwisya, Mwaliga, and Bunegezi was not significantly different ($p>0.05$); however, they each had significantly higher net ownership than the control sites Igulwa and Zanzui ($p<0.05$). In 2013, the proportion of households owning ≥1 net in Nyambori, Bwisya, Igulwa, and Zanzui was not significantly different ($p>0.05$) but they each had significantly higher net ownership than Mwaliga and Bunegezi ($p<0.05$).

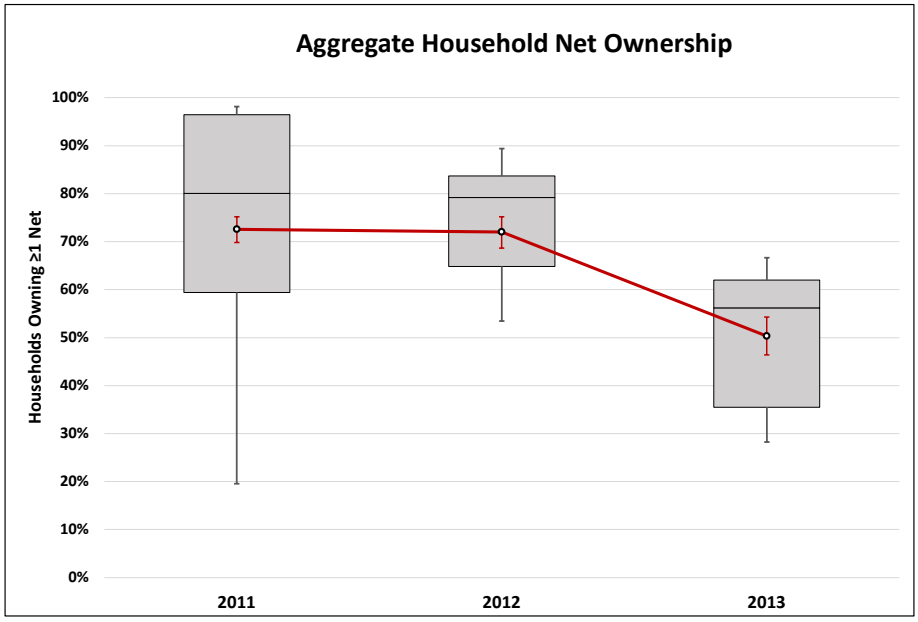


Figure 4.4. Household Net Ownership, by Year. Box plot (grey) includes range of reported net ownership aggregated by village; point estimates for the overall study population (white), show bars representing 95% confidence intervals (red).

Table 4.3. Household Net Ownership by Year and Study Site

Study Site	% of Households Owning ≥1 Nets (95% CI)		
	2011	2012	2013
Intervention Sites			
Nyambori	67.5 (60.8-73.7)	80.2 (71.2-87.0)	66.7 (58.6-73.9)
Bwisya	56.7 (50.4-62.9)	84.8 (74.3-91.6)	57.7 (46.6-68.0)
Mwaliga	98.2 (93.6-99.5)	89.4 (83.0-93.6)	29.1 (21.6-37.9)
Bunegezi	92.6 (87.5-95.7)	78.2 (70.2-84.6)	28.3 (20.1-38.2)
All Intervention Sites	74.2 (70.9-77.3)	83.3 (79.4-86.5)	46.6 (42.0-51.4)
Control Sites			
Igulwa	97.8 (94.9-99.0)	53.5 (45.7-61.0)	63.4 (53.3-72.5)
Zanzui	19.5 (13.6-27.2)	60.4 (52.4-67.9)	54.8 (44.1-65.0)
All Control Sites	69.2 (64.2-73.8)	56.8 (51.2-62.2)	59.3 (52.0-66.3)

Trends in net ownership over the study period also varied by study site. As shown in Figure 4.5, three of the study sites (Nyambori, Bwisya, and Zanzui) had increases in ownership between the 2011 and 2012 surveys, while three (Mwaliga, Bunegezi, and Igulwa) had decreases in ownership. Ownership in all study sites except Igulwa decreased between the 2012 and 2013 surveys.

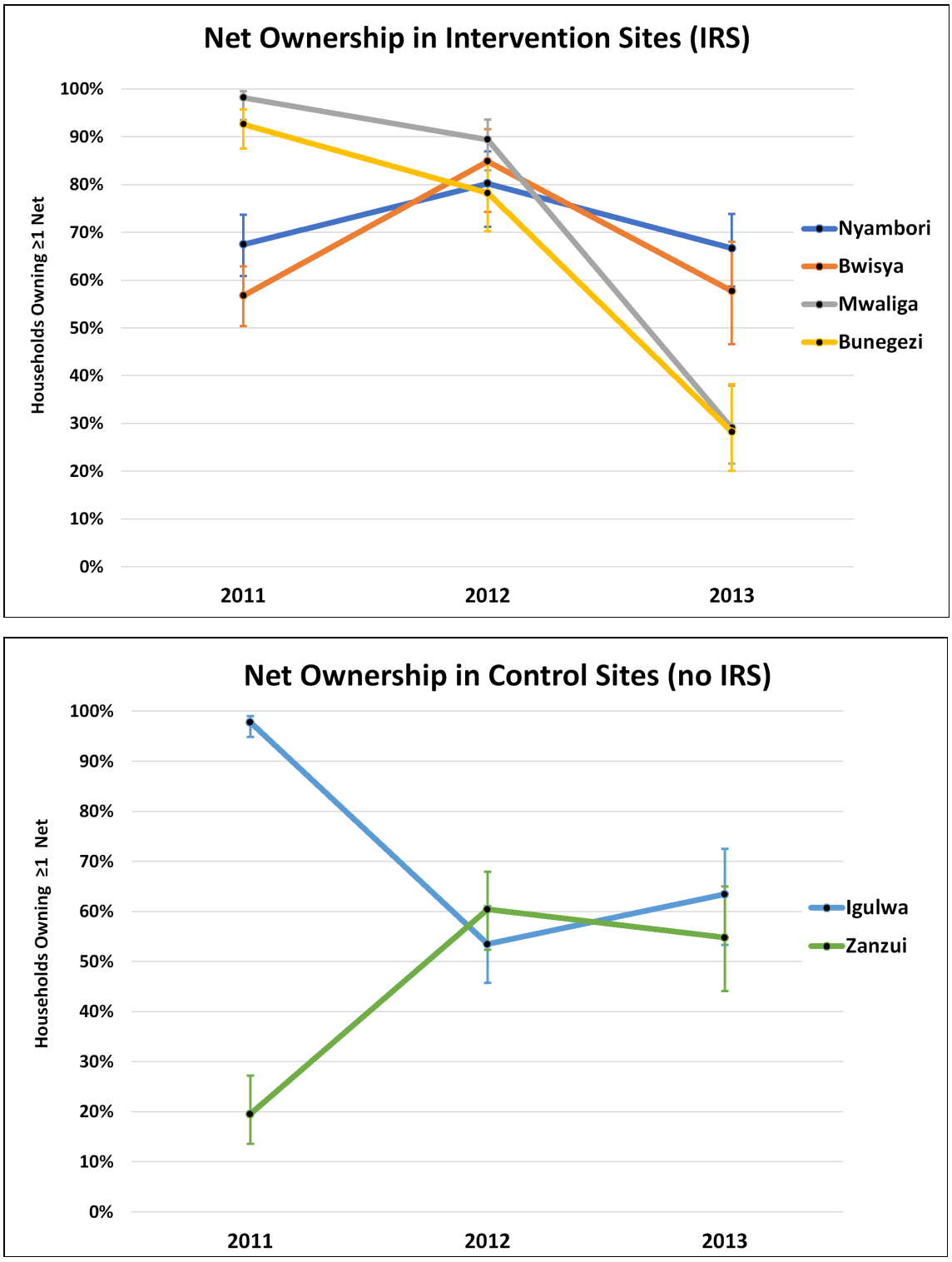


Figure 4.5. Household Net Ownership in Control and Intervention Sites, by Year (bars represent 95% confidence intervals).

4.3.2.2 IRS Coverage

The total proportion of households in the intervention sites reporting IRS in the 2011, 2012, and 2013 surveys is shown in Figure 4.6. IRS coverage in the intervention sites increased from 0.7% in 2011 (95% CI 0.2-2.1%) to 51.7% in 2012 (95%CI 47.0-56.4%) to 94.0% in 2013 (95% CI 91.3-95.9%). The difference between IRS coverage in the intervention sites in each year was statistically significant ($p<0.05$).

The proportion of households in each study site reporting IRS in 2011, 2012, and 2013 is shown in Figure 4.7. IRS coverage increased progressively in all intervention sites over the study period. There was not a statistically significant difference in proportions of households receiving IRS in the intervention sites in 2011 ($p=0.471$) or 2013 ($p=0.064$); however, there was a significant difference in 2012 ($p<0.0005$) with coverage ranging from 42.4% to 76.1%. In 2012, the proportion of households reporting IRS in Nyambori and Bwisya, was not significantly different ($p>0.05$); however, they each had significantly higher IRS coverage than Mwaliga and Bunegezi ($p<0.05$).

Trends in IRS coverage over the study period were similar for all intervention sites, with coverage increasing between 2011 and 2012, and again between 2012 and 2013 in each site. IRS coverage in control sites was low in all years (less than 5%).

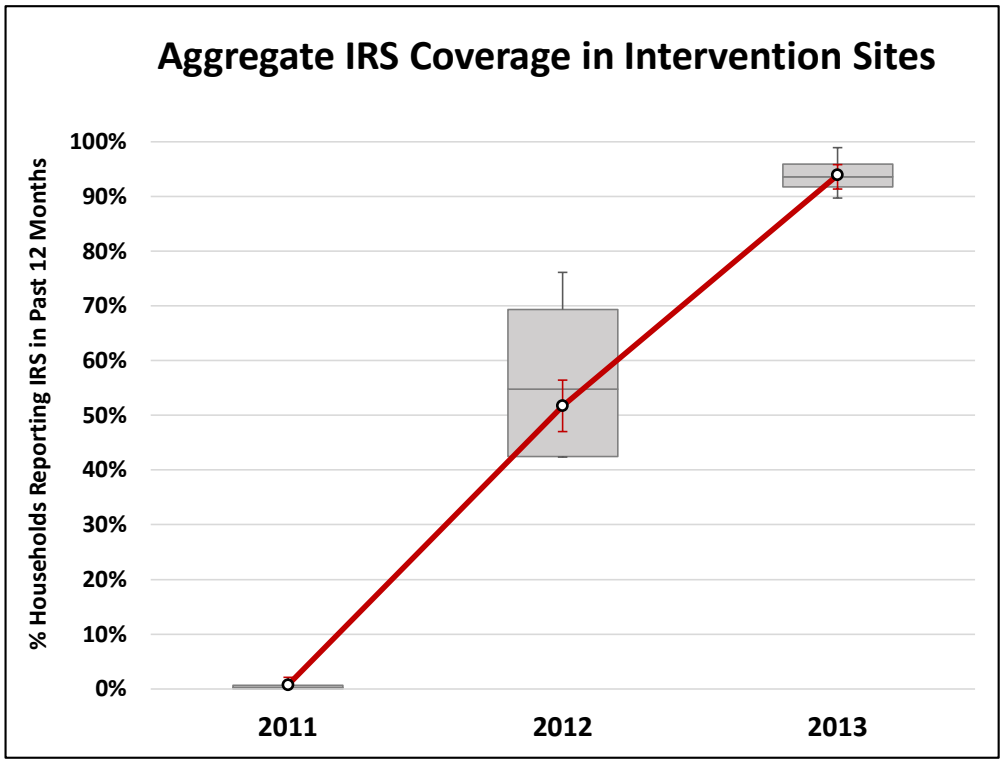


Figure 4.6. Household IRS Coverage, by Year. Box plot (grey) includes aggregate household IRS coverage by village; point estimates for overall IRS coverage (white) show bars representing 95% confidence intervals.

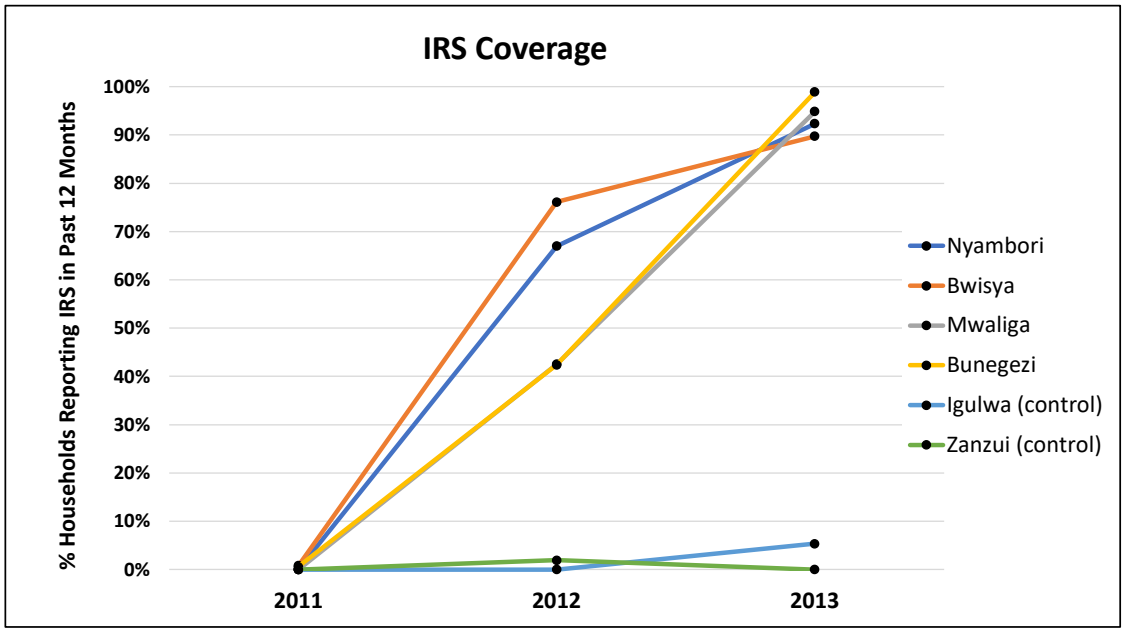


Figure 4.7. Household IRS Coverage by Year and Study Site

4.3.2.3 Housing Infrastructure (building materials, quality, and house size) and Commodity Ownership

Figure 4.8 includes summary statistics for the variables described below.

Building Materials

Over half (62.2%) of surveyed households used iron or metal sheeting as the main roofing material, while 36.9% used grass, thatch, or mud. Less than 1% used tiles or concrete.

Materials used for wall included poles and/or mud (30.9%), sun-dried bricks (31.1%), grass (8.1%), and cement blocks (3.1%). Less than 0.5% used wood or stone.

The majority of households (70.7%) used earth, sand, or dung as the main floor material. Cement was used for flooring in 23.9%, while wood plants, bamboo, or palm was used in 4.8% of households. Less than 0.5% of households used parquet, polished wood, ceramic tiles, terrazzo, or carpet.

Quality

Based on the variable developed for housing quality, 76.7% of households were classified as 'traditional', while 23.3% were classified as 'modern'.

Size

Houses with three or fewer rooms used for sleeping (79.9%) were more common than larger houses with more than three rooms used for sleeping (20.3%).

Ownership of Commodities

Few houses reported having electricity (2.1%). However, over half of all households reported owning a radio (55.3%), while just under half reported owning a mobile phone (45.5%). One percent or fewer households reported ownership of a television, refrigerator, or landline telephone. Household ownership of both an iron and lamp varied more than expected across survey years. Further inquiry revealed there was confusion among field teams regarding the definition of these commodities; therefore, they were excluded from further analysis.

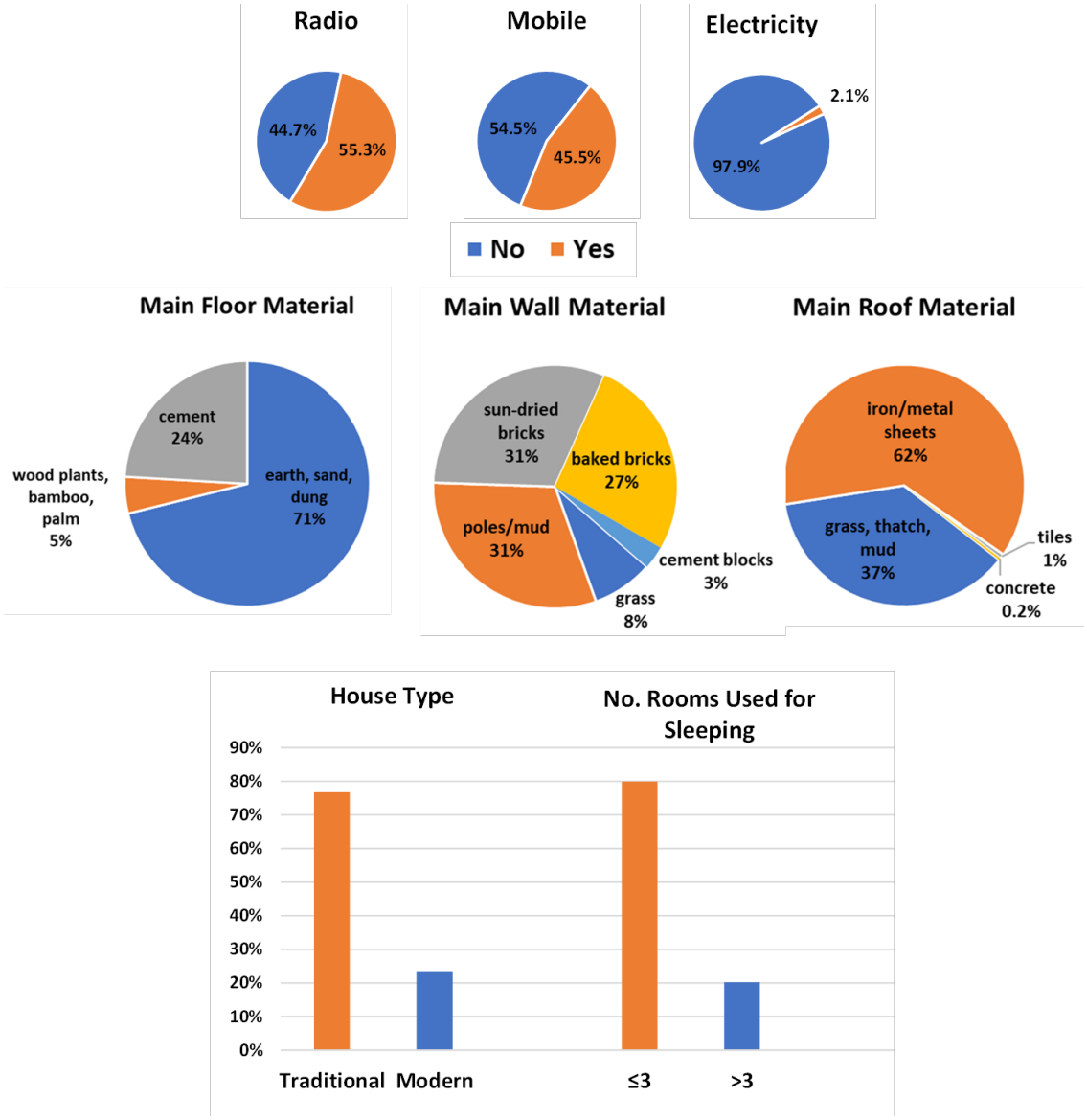


Figure 4.8. Characteristics of Households Surveyed. Charts include commodity ownership, building materials of house, type of house (traditional versus modern), and number of rooms used for sleeping.

4.3.2.4 Comparison of Univariate Results with 2011-12 MIS

Aggregate results for household ITN ownership and IRS coverage from the six study sites in the present study were compared to results for these indicators reported in the 2011-12 MIS for rural Mainland Tanzania and the Lake Zone (Table 4.4). The first cross-sectional survey in the present study was administered from January – February 2011, before implementation of the UCC or IRS campaigns. Aggregate household ITN ownership in the 2011 survey was 72.6% and aggregate IRS coverage was 0.7%. The 2011-12 MIS was administered between December – May 2011 and may reflect post- campaign data depending on the timing of the field work and

campaigns in each zone. For the Lake Zone, household ITN ownership was 94.0% in the 2011-12 MIS, and IRS coverage was 42.3%; thus, it is likely that the MIS fieldwork took place after the UCC and IRS campaigns had been administered in the Lake Zone. The second and third cross-sectional surveys were completed in July-August of 2012 and 2013, respectively. Although these data cannot be directly compared to MIS results, they reflect a downward trend in ITN ownership. By the time of the 2015-16 DHS in Tanzania, which was conducted after the present study concluded, ITN ownership in rural Mainland Tanzania had declined to 64.8% (MoHCDGEC, 2016).

Table 4.4. Comparison of Household ITN Ownership and IRS Coverage to 2011-12 MIS Results for Rural Mainland and Lake Zone, Tanzania

	Present Study			2011-12 MIS Results	
	2011	2012	2013	Rural Mainland	Lake Zone
Household ITN Ownership (%)	72.6	72.0	50.3	92.4	94.0
Household IRS Coverage (%)	0.7	51.7	94.0	14.4	42.3

Aggregate results for select household commodities and the primary household flooring material from the six study sites in the present study were compared to results for these indicators reported in the 2011-12 MIS for rural Mainland Tanzania (Table 4.5). The MIS report does not provide zonal statistics: therefore, results for rural Mainland were included. Although these indicators cannot be directly compared, overall the results of the present study are consistent with the results from the 2011-12 MIS.

Table 4.5. Comparison of Select Socioeconomic Proxy Indicators to 2011-12 MIS Results for Rural Mainland Tanzania

	Present Study	2011-12 MIS
	Aggregate	Rural Mainland
Electricity	2.1	3.6
Radio	55.3	57.1
Mobile Phone	45.5	51.3
Primary Flooring Material		
Earth, sand, or dung	70.7	81.2

4.3.3 Bivariate Results

The relationship between household IRS and net ownership and between socioeconomic proxy indicators and household net ownership was assessed using bivariate analysis.

4.3.3.1 Relationship Between Household IRS and Net Ownership

Household net ownership by type of study site (control vs intervention) and status of household IRS in the 2011, 2012, and 2013 surveys is summarized in Table 4.6.

In 2011, prior to the introduction of IRS, households in intervention sites were 1.3 times more likely to own ≥1 net than households in control sites, however this was not significant (OR=1.3, 95% CI .97 – 1.7, p=0.085). In 2012, after the introduction of IRS, households in intervention sites were 3.8 times more likely to own ≥1 net than households in control sites (OR=3.8, 95% CI 2.7-5.2, p<0.0005). This reverses in 2013, such that households in intervention sites were .60 times less likely to own ≥1 net than households in control sites (OR=.60, 95% CI .42-.85, p=0.004).

A similar trend is observed when household net ownership is compared in households that reported receiving IRS versus those that did not. In 2012, households reporting IRS were 11.3 times more likely to own ≥1 net than households that did not report IRS (OR=11.3, 95% CI 6.1-20.7, p<0.0005). In 2013, this reverses such that households reporting IRS were .63 times less likely to own ≥1 net than households that did not report IRS (OR= .63, 95% CI .45-.89, p=0.008).

Comparing net ownership in control sites across years reveals that households in 2013 were .65 times less likely to own ≥1 net than households in 2011 (OR=.65, 95% CI .45-.94, p=0.023). The same comparison in intervention sites in 2013 versus 2011 shows that households in 2013 were .30 times less likely to own ≥1 net than households in 2011 (OR=.30, 95% CI .24-.39, p<0.0005). This is consistent with and reflects the overall decrease in net ownership during the study period in both intervention and control sites pre- and post- UCC and IRS campaigns.

However, when household net ownership in 2012 is compared to net ownership in 2013, control sites and intervention sites reveal different trends (Table 4.7). In control sites, there was no significant difference in the likelihood of households owning ≥1 net in 2013 versus 2012 (OR=1.1, 95%CI .76-1.6, p=0.591). In contrast, in intervention sites, households in 2013 were significantly less likely than households in 2012 to own ≥1 (OR=0.18, 95% CI .13-.25, p<0.0005).

Table 4.6. Household Net Ownership by Site Type and Household IRS

	2011				2012				2013			
	N	n HHs ≥1 Net (%)	OR (95% CI)	p-value	N	n HHs ≥1 Net (%)	OR (95% CI)	p-value	N	% HHs ≥1 Net (%)	OR (95% CI)	p-value
Site Type												
Control	351	243 (69.2%)			308	175 (56.8%)			177	105 (59.3%)		
Intervention	718	533 (74.2%)	1.3 (.97-1.7)	0.085	419	348 (83.1%)	3.7 (2.7-5.2)	<0.0005*	431	201 (46.6%)	0.60 (.42 – .854)	0.004*
Household IRS												
No	1065	772 (72.5%)			496	304 (61.3%)			198	115 (58.1%)		
Yes	3	3 (100%)	-	-	226	214 (94.7%)	11.3 (6.1-20.7)	<0.0005*	410	191 (46.6%)	.63 (.45-.89)	0.008*

*p-value <0.05 indicating significance

Table 4.7. Household Net Ownership in 2013 versus 2012 by Site Type

	N	n HHs ≥1 Net (%)	OR (95% CI)	p-value
Intervention Sites				
2012	419	348 (83.1%)	-	-
2013	431	201 (46.6%)	0.18 (.13-.25)	<0.0005*
Control Sites				
2012	308	175 (56.8%)	-	-
2013	177	105 (59.3%)	1.1 (.76-1.6)	0.591

4.3.3.2 Relationship Between Socioeconomic Proxy Indicators and Net Ownership

Household net ownership by household building materials, quality, and size, as well as household ownership of commodities is summarized in Table 4.8 for each survey year.

4.3.3.3 Building Materials and Housing Quality

In 2011, houses with finished floor materials were 5.3 times more likely than houses with natural floor materials to own ≥1 net (OR=5.3, 95%CI 3.3-8.5, p<0.0005). Similarly, houses using bricks or cement blocks as wall materials were 12 times more likely than houses with natural wall materials to own ≥1 net (OR=12.3, 95% CI 8.8-17.0, p<0.0005), and houses with finished roof

materials were four times more likely than houses with natural roof materials to own ≥1 net (OR=4.0, 95% CI 3.0-5.4, p<0.0005). Houses defined as 'modern' based on these building components were 4.8 times more likely than 'traditional' houses to own ≥1 net in 2011 (OR=4.8, 95% CI 3.0-7.8, p<0.0005).

In 2012, after the introduction of IRS in intervention sites, most of these relationships reverse. Houses with finished floor materials were .61 times less likely than houses with natural floor materials to own ≥1 net (OR=.61, 95% CI .43-.87, p=0.006). Similarly, houses with finished roof materials were .89 times less likely than houses with natural roof materials to own ≥1 net (OR=.89, 95% CI .63-1.3, p=0.520), although this was not significant. However, houses using bricks or cement blocks as wall materials were 1.7 times more likely than houses using natural wall materials to own ≥1 net (OR=1.7, 1.3-2.4, p=0.001). Houses defined as 'modern' were .63 times less likely than 'traditional' houses to own ≥1 net in 2012 (OR=.63, 95% CI .44-.91, p=0.013).

In 2013, most of these relationships reverse again. Houses with finished floor materials were 1.7 times more likely than houses with natural floor materials to own ≥1 net (OR=1.7, 95% CI 1.2-2.5, p=0.003). Similarly, houses using bricks or cement blocks as wall materials were 1.1 times more likely than houses with natural roof materials to own ≥1 net (OR=1.1, 95% CI .80-1.5, p=0.530), and houses with finished roof materials were 1.2 times more likely than houses using natural wall materials to own ≥1 net (OR=1.2, 95% CI .85-1.6, p=0.334), although neither of these was significant. Houses defined as 'modern' were 1.7 times more likely than 'traditional' houses to own ≥1 net in 2013 (OR=1.7, 95% CI 1.2-2.4, p=0.004).

4.3.3.4 Size of House

In 2011, houses with more than three rooms used for sleeping were 2.2 times more likely than houses with three or fewer rooms used for sleeping to own ≥1 net (OR=2.2, 95% CI 1.4-3.5, p=0.001). There was no significant relationship between the size of the house and net ownership in 2012 (OR=.99, 95% CI .66-1.5, p=.975) or in 2013 (OR=1.2, 95% CI .82-1.6, p=.406).

4.3.3.5 Ownership of Commodities

In 2011, households that owned a mobile phone were 3.7 times more likely than households that did not own a mobile phone to own ≥1 net (OR=3.7, 95% CI 2.7-5.0, p<0.0005). Similarly, households that owned a radio were 2.3 times more likely than households that did not own a radio to own ≥1 net (OR=2.3, 95% CI 1.7-3.0, p<0.0005). In 2012, there was no significant relationship between net ownership and mobile phone (OR=1.1, 95% CI .80-1.5, p=0.559) or

radio ownership (OR=.87, 95% CI .63-1.2, p=0.400). However, in 2013, households that owned a mobile phone were 3.0 times more likely than households that did not own a mobile phone to own ≥1 net (OR=3.0, 95% CI 2.2-4.2, p<0.0005), while households that owned a radio were 1.7 times more likely than households that did not own a radio to own ≥1 net (OR=1.7, 95% CI 1.2-2.3, p=0.003).

Household ownership of a television, refrigerator, landline telephone, and electricity were rare in this study population, resulting in low sample sizes that did not allow for comparison across survey years. As a result, they were not analysed further. As discussed in section 4.3.2, ownership of an iron and lamp were excluded from analysis.

Table 4.8. Relationship Between Household Building Materials, Quality, Size, and Commodities and Household Net Ownership

	2011				2012				2013			
	N	n (%) Owning ≥1 Net	Odds Ratio (95% CI)	p-value	N	n (%) Owning ≥1 Net	Odds Ratio (95% CI)	p-value	N	n (%) Owning ≥1 Net	Odds Ratio (95% CI)	p-value
Floor Material												
Natural (earth, sand, dung, wood plants, bamboo, or palm)	831	559 (67.3%)			540	403 (74.6%)			436	203 (46.6%)		
Finished (cement, parquet, polished wood, ceramic tiles, or terrazzo)	237	217 (91.6%)	5.3 (3.3-8.5)	<.0005*	184	118 (64.1%)	.61 (.43-.87)	.006*	172	103 (59.9%)	1.7 (1.2-2.5)	.003*
Wall Material												
Natural (grass, poles, or mud)	410	180 (43.9%)			296	193 (65.2%)			226	110 (48.7%)		
Bricks (sun-dried or baked) or Cement blocks	657	595 (90.6%)	12.3 (8.8-17.0)	<.0005*	431	330 (76.6%)	1.7 (1.3-2.4)	.001*	382	196 (51.3%)	1.1 (.80-1.5)	.530
Roof Material												
Natural (grass, thatch, or mud)	434	244 (56.2%)			230	169 (73.5%)			218	104 (47.7%)		
Finished (iron/metal sheets, tiles, or concrete)	632	530 (83.9%)	4.0 (3.0-5.4)	<.0005*	496	353 (71.2%)	.89 (.63-1.3)	0.520	390	202 (51.8%)	1.2 (.85-1.6)	.334
House Type (quality)												
traditional	845	573 (67.8%)			552	410 (74.3%)			439	205 (46.7%)		
modern	222	202 (91.0%)	4.8 (3.0-7.8)	<.0005*	172	111 (64.5%)	.63 (.44-.91)	.013*	169	101 (59.8%)	1.7 (1.2-2.4)	.004*
No. Rooms Used for Sleeping (size)												
≤ 3	918	650 (70.8%)			589	424 (72.0%)			405	199 (49.1%)		
> 3	144	121 (84.0%)	2.2 (1.4-3.5)	.001*	135	97 (71.9%)	.99 (.66-1.5)	.975	203	107 (52.7%)	1.2 (.82-1.6)	.406
Mobile Phone												
no	596	371 (62.2%)			408	290 (71.1%)			302	111 (36.8%)		
yes	472	405 (85.8%)	3.7 (2.7-5.0)	<.0005*	319	233 (73.0%)	1.1 (.80-1.5)	0.559	306	195 (63.7%)	3.0 (2.2-4.2)	<.0005*
Radio												
no	477	303 (63.5%)			346	254 (73.4%)			249	107 (43.0%)		
yes	591	473 (80.0%)	2.3 (1.7-3.0)	<.0005*	381	269 (70.6%)	.87 (.63-1.2)	0.400	359	199 (55.4%)	1.7 (1.2-2.3)	.003*

*p-value <0.05 indicating significance

4.3.4 Multivariate Results

Binomial logistic regression models constructed to ascertain the predictors of household net ownership for each year are summarized in Table 4.9.

4.3.4.1 Predictors of Household Net Ownership

2011

In 2011, the most significant predictors of household net ownership were study site, wall material of the house, and ownership of a mobile phone. The logistic regression model based on these predictors is statistically significant, $\chi^2(7) = 450.4$, $p<0.0005$. The model explained 49.8% (Nagelkerke R^2) of the variance in household net ownership and the training data set correctly classified 81.8% of cases. Each of the predictors were statistically significant ($p<0.05$). Households using bricks or cement blocks for wall materials were 3.4 times more likely to own ≥1 net than households using natural wall materials (OR=3.4, 95% CI 2.3-5.1, p<0.0005). Households owning a mobile phone were 2.0 times more likely to own ≥1 net than households not owning a mobile phone (OR=2.0, 95% CI 1.4-3.1, p=0.001). Household IRS was not included in this model since the intervention had not yet been initiated.

2012

In 2012, the most significant predictors of household net ownership were study site, household IRS, wall material of the house, and ownership of a mobile phone. The logistic regression model based on these predictors is statistically significant, $\chi^2(8) = 149.9$, $p<0.0005$. The model explained 26.9% (Nagelkerke R^2) of the variance in household net ownership and the training data set correctly classified 73.5% of cases. Each of the predictors were statistically significant ($p<0.05$). Households using bricks or cement blocks for wall materials were 2.3 times more likely to own ≥1 net than households using natural wall materials (OR=2.3, 95% CI 1.5-3.7, p<0.0005). Households owning a mobile phone were 2.0 times more likely to own ≥1 net than households not owning a mobile phone (OR=2.0, 95% CI 1.3-3.3, p=0.004). Households that received IRS were 8.7 times more likely to own ≥1 net than households that did not receive IRS (OR=8.7, 95% CI 4.2-17.9, p<0.0005).

2013

In 2013, the most significant predictors of household net ownership were study site, wall material of the house, and ownership of a mobile phone. The logistic regression model based on

these predictors is statistically significant, $\chi^2(8) = 99.1$, $p < 0.0005$ (2013 Model A in Table 4.9). The model explained 20.1% (Nagelkerke R^2) of the variance in household net ownership and the training data set correctly classified 67.3% of cases. Study site, wall material, and mobile phone ownership were statistically significant (p<0.05). Households using bricks or cement blocks for wall materials were 2.5 times more likely to own ≥1 net than households using natural wall materials (OR=2.5, 95% CI 1.5-4.2, p<0.0005). Households owning a mobile phone were 2.1 times more likely to own ≥1 net than households not owning a mobile phone (OR=2.1, 95% CI 1.4-3.1, p=0.001). Household IRS was not a significant predictor of net ownership (OR= .99, 95% CI .44-2.2, p=0.972).

When the interaction effect of IRS by study site is examined (2013 Model B in Table 4.9), household IRS becomes a significant predictor of net ownership, along with wall material and mobile phone ownership. 2013 Model B is statistically significant, $\chi^2(7) = 87.9$, $p<0.0005$. The model explained 18.0% (Nagelkerke R^2) of the variance in household net ownership and the training data set correctly classified 66.6% of cases. Households using bricks or cement blocks for wall materials were 2.0 times more likely to own ≥1 net than households using natural wall materials (OR=2.0, 95% CI 1.3-3.2, p=0.002). Households owning a mobile phone were 2.1 times more likely to own ≥1 net than households not owning a mobile phone (OR=2.1, 95% CI 1.4-3.1, p<0.0005). IRS was significantly associated with a decreased likelihood of household net ownership in two of the intervention sites and an increased likelihood of household net ownership in one of the intervention sites. Households that received IRS in Mwaliga were .32 times less likely to own ≥1 net than households that did not receive IRS (OR=.32, 95% CI .19-.55, p<0.0005). Households that received IRS in Bunegezi were .43 times less likely to own ≥1 net than households that did not receive IRS (OR=.43, 95% CI .23-.79, p=0.006). Households that received IRS in Nyambori were 2.2 times more likely to own ≥1 net than households that did not receive IRS (OR=2.2, 95% CI 1.3-3.8, p=0.002).

Table 4.9. Predictors of Household Net Ownership by Survey Year

Predictor	B	SE	Wald χ^2	*df*	*p*	Odds Ratio	95% CI for Odds Ratio	
							Lower	Upper
2011								
Study Site			118.323	5	.000*			
Nyambori	2.143	.283	57.295	1	.000*	8.524	4.894	14.847
Bwisya	1.585	.279	32.238	1	.000*	4.881	2.824	8.438
Mwaliga	4.626	.763	36.780	1	.000*	102.102	22.896	455.318
Bunegezi	3.224	.408	62.352	1	.000*	25.135	11.290	55.955
Igulwa (control)	4.047	.528	58.694	1	.000*	57.211	20.317	161.098
Wall Material	1.221	.209	34.241	1	.000*	3.389	2.252	5.101
Mobile	.713	.206	12.015	1	.001*	2.039	1.363	3.051
Constant	-1.968	.254	59.827	1	.000	.140		
2012								
Study Site			28.968	5	.000*			
Nyambori	.150	.384	.153	1	.696	1.162	.548	2.465
Bwisya	.170	.457	.139	1	.709	1.185	.484	2.902
Mwaliga	.955	.376	6.463	1	.011*	2.599	1.245	5.427
Bunegezi	.081	.335	.058	1	.809	1.084	.562	2.090
Igulwa (control)	-1.070	.302	12.584	1	.000*	.343	.190	.619
IRS	2.162	.368	34.504	1	.000*	8.685	4.222	17.865
Wall Material	.843	.236	12.758	1	.000*	2.324	1.463	3.693
Mobile	.712	.249	8.190	1	.004*	2.038	1.251	3.317
Constant	-.132	.212	.389	1	.533	.876		
2013 (Model A)								
Study Site			46.718	5	.000*			
Nyambori	.814	.486	2.809	1	.094	2.257	.871	5.849
Bwisya	.302	.499	.367	1	.545	1.353	.509	3.594
Mwaliga	-1.404	.517	7.367	1	.007*	.246	.089	.677
Bunegezi	-1.043	.556	3.513	1	.061	.352	.118	1.049
Igulwa (control)	-.363	.346	1.098	1	.295	.696	.353	1.371
IRS	-.014	.409	.001	1	.972	.986	.442	2.199
Wall Material	.930	.255	13.314	1	.000*	2.536	1.538	4.180
Mobile	.718	.208	11.907	1	.001*	2.050	1.363	3.081
Constant	-.674	.277	5.912	1	.015	.510		
2013 (Model B)								
IRS: Study Site			39.647	5	.000*			
IRS: Nyambori	.811	.264	9.396	1	.002*	2.249	1.339	3.777
IRS: Bwisya	.296	.305	.943	1	.332	1.344	.740	2.443
IRS: Mwaliga	-1.134	.269	17.720	1	.000*	.322	.190	.545
IRS: Bunegezi	-.855	.313	7.469	1	.006*	.425	.230	.785
IRS: Igulwa (control)	-.351	.928	.143	1	.705	.704	.114	4.341
Wall Material	.699	.229	9.361	1	.002*	2.013	1.286	3.150
Mobile	.726	.200	13.124	1	.000*	2.066	1.395	3.059
Constant	-.668	.235	8.064	1	.005	.513		

*p-value <0.05 indicating significance

4.3.5 Spatial Results

Spatial patterns of household IRS and net ownership were examined in each study site. Of interest were the study sites in which IRS was found to be a predictor of net ownership in 2013. These included Nyambori, Bunegezi, and Mwaliga. Figures 4.9, 4.10, and 4.11 show the distribution of households that reported IRS (yes/no) and ownership of at least one net (yes/no) in each year in these three sites, respectively.

4.3.5.1 IRS

As highlighted in section 4.3.2, IRS coverage was very low in 2011 in Nyambori, Bunegezi, and Mwaliga because IRS had not yet been initiated by the NMCP. In 2012, the expansion of IRS is evident in each site (as shown in green), and the *decrease* in houses *not* owning at least one net (indicated by a black diamond) compared to 2011 is evident (Figures 4.9, 4.10, and 4.11). In all three sites, the distribution of households receiving IRS in 2013 appears to be dispersed throughout the site.

4.3.5.2 IRS and Lack of Net Ownership

Spatial patterns or clustering of households receiving IRS and not owning at least one net in 2013 were examined.

In Nyambori (Figure 4.9), where IRS was found to have a positive effect on net ownership in 2013, there may be some clustering of households receiving IRS but not owning nets (areas highlighted in yellow).

In Bunegezi, where IRS was found to have a negative effect on net ownership in 2013, the second round of IRS reached the majority of houses and was coupled with an *increase* in houses *not* owning at least one net (Figure 4.10). However, upon examination of the 2013 map for Bunegezi, there doesn't appear to be clustering of households not receiving IRS given that houses falling into this category were highly prevalent.

In Mwaliga, where IRS was also found to have a negative effect on net ownership in 2013, there is a similar pattern in 2013 as was found in Bunegezi (Figure 4.11). Examination of the 2013 map of Mwaliga does not reveal apparent clustering of households not owning nets, again due mostly to the fact that most households fall into this category. However, when the 2013 map of Mwaliga is compared to the 2012 map, it appears houses in the area that reported IRS in 2012 (highlighted in grey) may have been more likely to not own a net in 2013.

No formal spatial statistics were performed to further investigate these relationships since the outcome measure was binary and the detailed geographical data required was beyond the scope of this study.

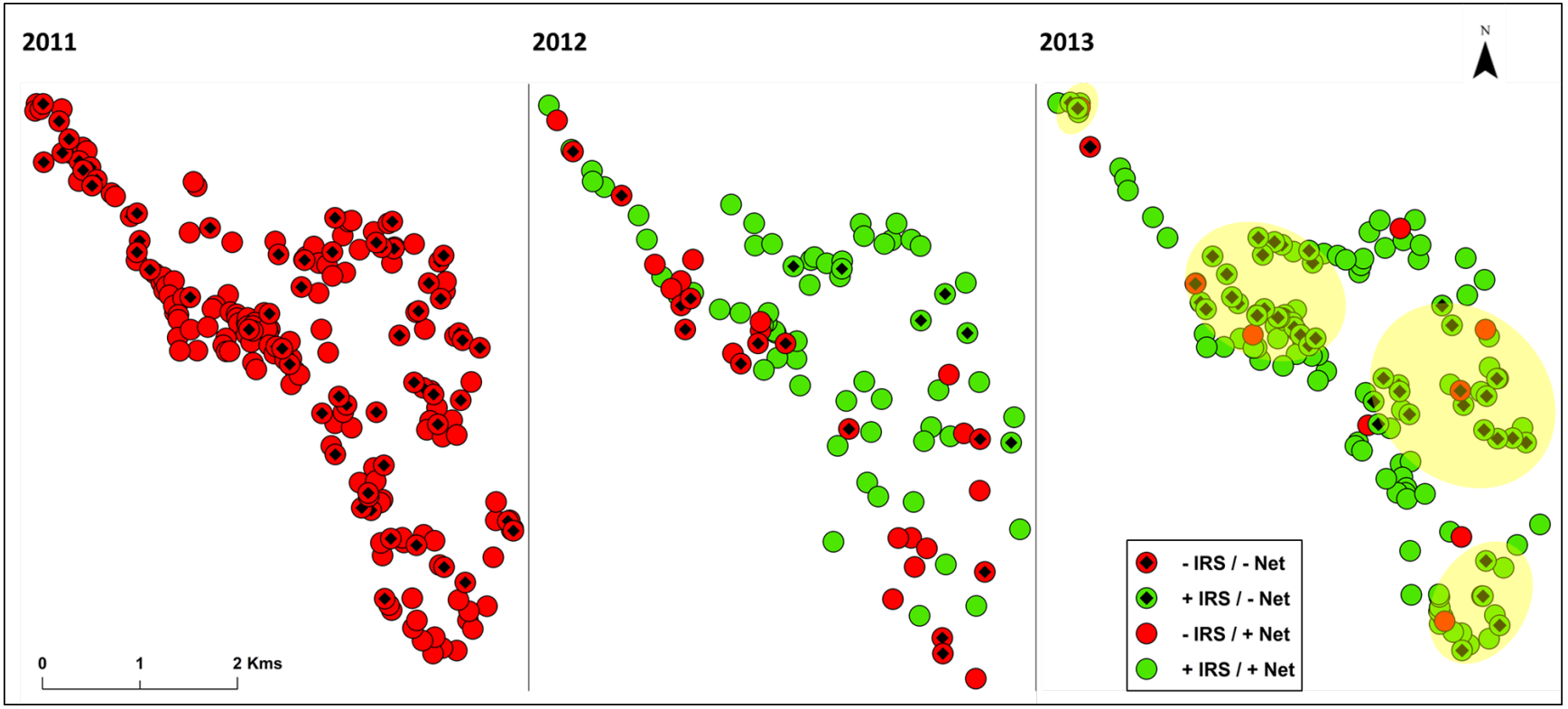


Figure 4.9. Household Net Ownership and IRS in Nyambori, 2011-2013. Areas of potential clustering of +IRS/-Net in 2013 are highlighted in yellow.

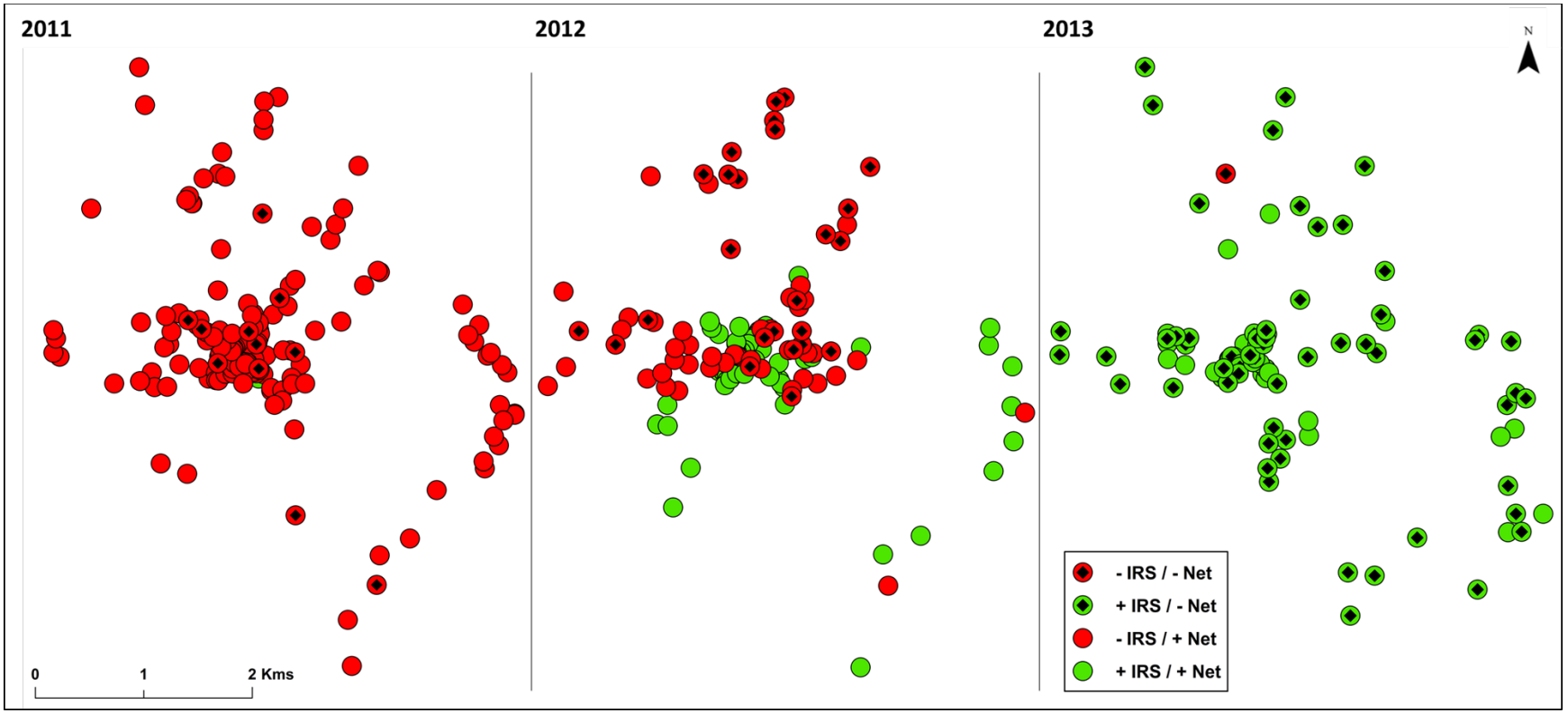


Figure 4.10. Household Net Ownership and IRS in Bunegezi, 2011-2013

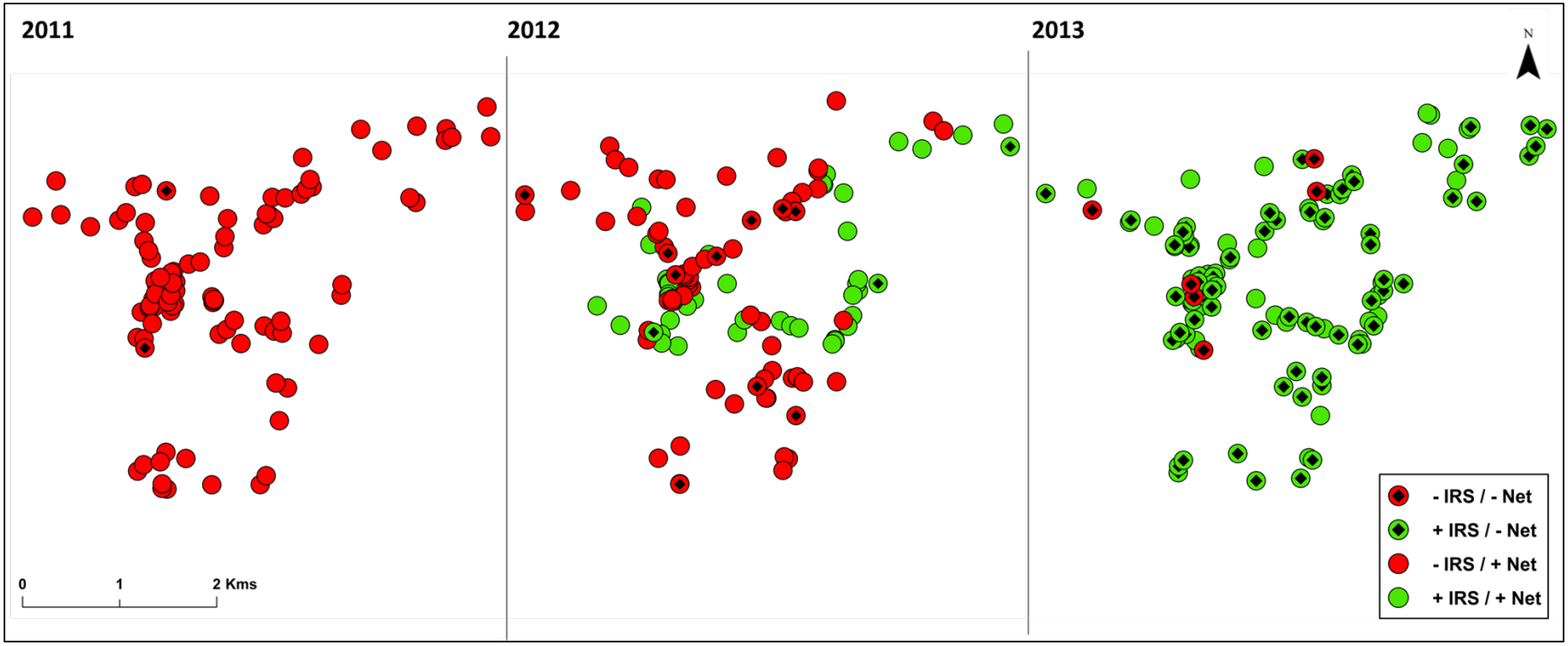


Figure 4.11. Household Net Ownership and IRS in Mwaliga, 2011-2013

4.4 Discussion

This chapter highlights a significant overall decrease in household net ownership in the Lake Zone of Tanzania despite implementation of a nationwide UCC during the study period. At the same time, scale-up of IRS was achieved with coverage reaching 94% of the households in targeted villages. Proxy indicators of SES were found to be positively associated with net ownership, a finding that is consistent with previous country-level studies showing that households with higher SES are more likely to own and/or use nets (Baume & Franca-Koh, 2011; Goesch et al., 2008; Kanyangarara et al., 2018; Sena, Deressa, & Ali, 2013).

In 2013 IRS was found to be a negative predictor of household net ownership in half of the study sites that received IRS. This suggests that IRS scale-up may have precipitated declining net ownership. It is possible that reduction in mosquito populations following IRS led households to dispose of their nets (Rek et al., 2018). However, there is an absence of published data on the potential negative impact of IRS on household net coverage. Why IRS was a predictor of net ownership in some study sites and not in others is not clear. It is important that this relationship be studied further given the potential for IRS programmes to have an unintended negative impact on longer-term net ownership/usage, which could in turn impact LF transmission (Richards et al., 2013).

The decline in net ownership in the majority of study sites in 2013 indicates that increases in net ownership were transient in this study population. Similar short-lived gains following UCCs have been reported elsewhere. In Malawi, net use declined one year after a UCC despite ongoing routine distribution of nets (Buchwald et al., 2016). Surveys administered two years after the 2011 UCC in Tanzania found marked variations in net coverage, ranging from 62.3% to 83.3% across districts (Mboma et al., 2018). One of the districts in the Mboma study had LLIN coverage that was 28.8% lower than that reported in the region in the 2011-12 MIS. Studies in other settings have found more sustained effects of net campaigns on ownership and usage following campaigns (Hetzel et al., 2012; Lindblade et al., 2004). The results of the present study confirm that significant local variations in net coverage exist and that the sustainability of high coverage achieved following a national campaign may be inconsistent across geographic areas.

The timing of household surveys in this study was constrained by the IRS programme, which kept to a rigid schedule of spraying. This necessitated administering 2011 (pre-IRS baseline surveys) in January-February at the end of the short rains (Rowhani et al., 2011). In contrast, 2012 and 2013 surveys were administered in July-August, between rainy seasons, as dictated

by the availability of the NTD Programme staff in Tanzania who were involved in the fieldwork. Since seasonal changes in rainfall and prevalence of biting mosquitoes can influence net ownership, the timing of the surveys between rainy seasons in 2012 and 2013 may have resulted in lower net ownership than if it had been assessed during peak transmission times (Baume & Marin, 2007; Korenromp, E.L., Miller, J., Cibulskis, R.E., Kabir, C.M., Alnwick, D. & Dye, 2003; Pulford, Hetzel, Bryant, Siba, & Mueller, 2011; Thwing et al., 2008). As a result, the decline in net ownership may be overestimated. However, to account for this, net ownership rather than usage was assessed since usage is likely to vary by season based on the presence/absence of biting mosquitoes (Nathan & Sedekia, 2011). Nevertheless, the negative impact of IRS on net ownership (in two villages), is not complicated by this methodological limitation.

Despite Tanzania's ongoing efforts to scale-up ITNs over the past decade, this study revealed villages with low net ownership, despite intensive vector control campaigns. Even more concerning, it revealed an overall decline in net ownership post-UCC and IRS campaigns. These results could have implications for any communities in the Lake Zone where LF transmission is ongoing. It is important that LF transmission be further assessed in the Lake Zone so that if necessary, measures can be taken to mitigate the potential effect of declining net ownership on LF transmission in the area.

Chapter Five

Potential Ongoing Transmission of Lymphatic Filariasis in the Lake Zone of Tanzania in the Absence of Mass Drug Administration and the Potential Impact of Vector Control for Malaria

5.1 Introduction

LF is widespread in Tanzania with an estimated 15.6 million people requiring annual preventive chemotherapy (WHO, 2017c). Major clinical manifestations, such as hydrocele and lymphoedema, are common in afflicted areas and contribute to permanent disability (Mshana, Baraka, Misinzo, & Makunde, 2016; WHO, 2013b). In Tanzania, LF is caused by the filarial worm *W. bancrofti* and is targeted with a strategy of annual MDA to deliver the antifilarial drugs albendazole and ivermectin in endemic districts (ref NTD master plan). The MOHSW has committed to the national elimination of LF and has included a target of interrupting transmission in over 90% of endemic districts by 2020 in its Health Sector Strategic Plan for 2015-2020 (United Republic of Tanzania Ministry of Health and Social Welfare, 2015).

To document the burden of LF in Tanzania, every district was mapped for LF between 1998-2004 by the National LF Programme using the ICT. Based on WHO guidelines at the time, the methodology included testing 50-100 people over the age of 5 in 1-2 villages in each district. Districts with an antigenemia prevalence of at least 1% in at least one of the sampled villages were classified as endemic. The results indicated that almost every district in the country was LF-endemic and therefore required MDA, including the districts of the Lake Zone. Due to limited resources at the time, the LF Programme initially prioritized districts with highest endemicity to be targeted with MDA. In 2009, donor resources for NTDs increased and an integrated NTD Programme was launched. At that time, many of the LF-endemic districts in the country had not yet started MDA, including those in the Lake Zone, and as the programme began to gradually scale-up, there was uncertainty regarding whether MDA was still required in untreated areas. For example, one study in three districts in the western part of the country that had previously identified up to 30% antigenemia, found 0% antigenemia and microfilaraemia upon reassessment in 2010 (WHO, 2016c).

If LF transmission did cease in some areas sometime after initial LF mapping in Tanzania, it is unclear why. NTDs such as LF are associated with poverty and most commonly afflict those living in rural and remote areas such as the Lake Zone (Hotez et al., 2009). There were general improvements in living conditions between the LF surveys in this area; however, proxy measures of SES among rural households did not change drastically during this time period. For example, between the 2004-05 DHS and 2010 DHS, coverage of electricity in rural households increased only modestly from 1.3% to 3.4%. Similarly, access to clean water sources among rural households increased from 36.9% to 47.9%, whilst access to improved

sanitation facilities increased from 1.3% to 8.5% (National bureau of Statistics (NBS) and ICF Macro, 2011; National Bureau of Statistics (NBS) and ORC Macro, 2005). Furthermore, it is likely that these minor increases in SES indicators are occurring disproportionately in the LF-at-risk population living in these areas (Hotez, Ottesen, Fenwick, & Molyneux, 2006).

LF and malaria are co-endemic in Tanzania and share a common vector - the *Anopheles* mosquito (Muturi, 2008). Given that malaria transmission continued in the Lake Zone during this period (TACAIDS et al., 2008), it does not seem likely that modest socioeconomic improvements alone would have resulted in LF elimination. Indeed, other NTDs that are often co-endemic with LF, such as soil-transmitted helminths and schistosomiasis, persist in the Lake Zone (Bukindu, Morona, & Mazigo, 2016; Siza et al., 2015). However, one major change during this period were large-scale efforts to increase vector control coverage, particularly of ITNs and later LLINs, as described in Chapters 3 and 4.

It has been suggested that vector control interventions for malaria may impact LF transmission since they can serve as a protective barrier between mosquitoes and humans and reduce mosquito populations (Bockarie et al., 2009; Kelly-Hope et al., 2013; Lengeler, 2004). Several studies have demonstrated an impact of nets on LF transmission; however, studies on the impact of IRS on LF transmission are limited (Ashton et al., 2011; Bockarie et al., 2002; Bøgh et al., 1998; Burkot et al., 1990; Nsakashalo-Senkwe et al., 2017; Pedersen & Mukoko, 2002; Rebollo et al., 2015; Reimer et al., 2013a; Richards et al., 2013; Webber, 1979). Most of these studies were conducted in areas with *high* prevalence of LF and in the context of *increasing* net coverage. Importantly, there is a lack of research on the impact of nets on LF transmission in areas with a *low* prevalence of LF, and further in the context of *decreasing* net coverage, as was shown in Chapter 3 to have occurred in Tanzania between 2011-12 and 2015-16. Areas of low LF prevalence will become increasingly common in the post-MDA settings as countries reach their MDA targets and therefore should be considered.

As shown in the Lake Zone Case Study in Chapter 3, the Lake Zone of Tanzania falls within the lowest and second lowest bands of predicted LF risk in the country, with regional predicted antigenemia prevalence ranging from 2-10%. This area was also found to have significant hotspots of high vector control coverage, indicating intensive insecticidal pressure in the area. This, coupled with the demonstrated changes in dominant vector species and emerging insecticide resistance, warrant further examination of LF transmission in this area.

The detection of antifilarial antibodies is becoming increasingly recognized as a potentially meaningful indicator for LF programmes (Dewi et al., 2015; Hamlin et al., 2012; Lau et al.,

2014; Mladonicky et al., 2009; Plucinski et al., 2018; Sullivan et al., 2016; Won, Robinson, et al., 2018; Won, Sambou, et al., 2018). Measures of antibody responses to *W. bancrofti* are more sensitive than antigen detection and usually precede detection of antigen, making them early indicators of exposure and infection (Kubofcik, Fink, & Nutman, 2012; Washington et al., 2004). Although antibody tests do not distinguish between current and past infection, detection of antifilarial antibodies in young children may provide the earliest indicator of LF exposure, and therefore ongoing transmission (Steel, Kubofcik, Ottesen, & Nutman, 2012; Weil & Ramzy, 2007). A recently developed serological assay based on the *W. bancrofti* infective larval (L3) antigen Wb123 has been shown to be highly sensitive, and importantly, demonstrates minimal to no cross reactivity with other filarial species, which was a major limitation of previous assays (Kubofcik et al., 2012). Relevant to the current study, it has been suggested that the Wb123 ELISA could be used to map LF in areas where *W. bancrofti* status is unknown (Steel et al., 2013). However, the use of more sensitive serological tools, such as the Wb123 ELISA, to map LF or rule out its presence warrants further research to inform its potential use in the GPELF.

This chapter therefore assesses LF exposure, and thereby presumed ongoing transmission, in six villages within districts of the Lake Zone that were classified as LF-endemic following the national mapping efforts completed in 2004. Exposure in young children is assessed using the Wb123 ELISA prior to and following implementation of a UCC in all six villages and IRS campaigns in four of the villages.

5.1.1 Aims

The aims of this chapter are to 1) investigate evidence of LF transmission in study sites in the Lake Zone of Tanzania, and 2) assess factors influencing changes in LF exposure over time.

5.1.2 Objectives

- To investigate evidence of ongoing transmission of LF in six study sites by measuring LF exposure (seroprevalence) in children at baseline
- To assess changes in exposure to LF in children pre- and post- UCC and IRS campaigns
- To evaluate the relationship between LF seroprevalence and household net ownership, household IRS coverage, and socioeconomic proxy indicators
- To examine site-specific trends in seroprevalence in relation to changes in vector control coverage over time
- To assess predictors of LF seroprevalence in the study population

5.2 Methods

5.2.1 Study Sites

The study included the six study sites described in detail in Chapter 4 and shown in Figure 4.2. Site selection was based on the criteria previously defined.

5.2.2 Study Population

The general population of the study areas was described in Chapter 4. The target study population for this serological component of the study was 2-7-year-old children living in the households surveyed. The results of the rapid LF mapping conducted by the MOHSW in 2004 are shown in Table 5.1.

Table 5.1. 2004 District LF Rapid Mapping Results (antigenemia tested using ICT)

District	2004 District-Level LF Mapping Results
Rorya	13.5
Ukerewe	11.6
Sengerema	5.3
Geita	5.4
Maswa	5.6
Bukombe	14.8

5.2.3 Study Design

Cross-sectional surveys were conducted over three years to assess Wb123 seroprevalence among children 2-7 years of age in six study sites. Baseline seroprevalence surveys were administered in 2011 prior to implementation of a UCC, which was implemented by the NMCP in all study sites, and prior to implementation of an IRS campaign, which was implemented by the NMCP in four of the study sites (designated in this study as 'intervention sites'). Follow-up seroprevalence surveys were administered in 2012 and 2013 in all study sites. The seroprevalence surveys were conducted simultaneously with the household questionnaires described previously.

5.2.4 Data Collection

Blood samples were collected from children 2-7 years of age living in the households selected for inclusion in the household survey. The data collection teams, preparation of villages, and household selection were previously described.

Blood Samples: After obtaining written consent from a parent, finger-prick blood samples were obtained from each child. The finger to be pricked was first cleaned with an alcohol swab and allowed to dry. The ventral side of the finger was then pricked using a sterile lancet, which was immediately discarded into a sharp's container. A droplet of whole blood from the finger prick was placed on each of the protrusions of a filter paper disk (Tropbio, Cellabs, Sydney, Australia) labelled with the subject's identification number, ensuring the protrusions were completely covered with blood on both sides (no white showing). The protrusions are calibrated to hold the correct amount of blood when fully covered (10 µl). The disks were air dried at room temperature for a minimum of two hours.

Handling and Storage of Dried Blood Spots (DBS): Once the disk was completely dried, it was placed in a small plastic bag. Groups of disks in individual bags were placed into larger plastic bags with a silica gel desiccant. The disks were returned to the MOHSW in Dar es Salaam, where they were stored at -20°C before shipment to the Centres for Disease Control and Prevention (CDC), Atlanta, USA, where they were stored at -20°C until being shipped to Smith College for laboratory analysis.

Laboratory Forms: For each child sampled, a laboratory form (Appendix 5) was used to record demographic data including sex, age, and household location. The form was cross-linked to the household questionnaire using a unique identification number for each household. This enabled household level indicators such as household commodity ownership, building materials of the house, household ownership of nets, and household receipt of IRS to be linked to each child sampled.

5.2.5 Laboratory Analysis

Serological analysis was performed at the Williams Laboratory at Smith College, Massachusetts, USA using the Filaria Detect IgG4 ELISA kit (InBios, Seattle, USA) to examine DBS samples to determine IgG4 antibody response to *W. bancrofti* antigen. The test is used for qualitative detection of antibody to the highly specific Wb123 antigen expressed primarily in infective stage larvae (L3) of *W. bancrofti* (Kubofcik et al., 2012).

Wb123 ELISA Protocol: Plates containing microtiter wells pre-coated with Wb123 antigen were used. DBS were eluted in 250 µl of Tris-HCL buffered solution with Tween 20 (0.05%) yielding a 1:50 serum dilution. Kit positive, low positive, and negative controls were diluted 1:50 in sample dilution buffer. In-house controls were diluted 1:1500 H3 and 1:900 H19 in sample dilution buffer. DBS samples and diluted controls were incubated overnight at 4°C on a slow rocking platform. Following

overnight elution, all kit reagents and incubated samples were brought to room temperature (~25°C) for 30 minutes. Controls were thoroughly mixed by vortexing at half-speed using short pulses. Extracted samples and controls were added at 100 µl per well to the ELISA plate, in duplicate. The plate was sealed and incubated at 37°C for 30 ± 2 minutes. After incubation, the plate was washed 6 times in washing buffer using a Wellwash Versa plate washer (Fisher Scientific, Waltham, USA). Mouse monoclonal anti-human IgG4 conjugated with horseradish peroxidase (HRP) in Tris buffered solution diluted to 1:100 in PBS was added at 100 µl per well. The plate was sealed and incubated at 37°C for 30 ± 2 minutes. Following incubation, the plate was washed 6 times. TMB substrate was added at 100 µl per well and incubated at room temperature in the dark for the number of minutes determined by the TMB optimization procedures outlined below. Following incubation, 50 µl of stop solution (1N sulfuric acid) was added to each well to stop the reaction. The plate was incubated uncovered for a further 1 minute at room temperature. Plates were then read at 450 nm with a SpectraMax 5 ELISA reader using Softmax® Pro 7.0 software (Molecular Devices LLC, Sunnyvale, USA).

All samples were tested in duplicate and mean optical density (OD) values were calculated for each sample. H19 ratios were calculated by dividing the mean OD for each sample by the mean OD for the H19 standard run on the same plate. To determining which samples required retesting, samples with an H19 ratio >0.87 and for which the mean OD value for the H19 control was >0.396 (the lower limit for a "valid" H19 control OD) were considered 'positive'.

Samples were retested if they met any of the following criteria:

1. For 'negative' samples, if the mean OD value for the H19 standard was above the acceptable range (0.396–0.542), another H19 ratio was calculated using an H19 value of 0.396 (the lower limit of the acceptable range). If re-analysis produced a "positive" result (H19 ratio > 0.87), then the sample was retested.
2. For 'positive' samples, if the mean OD value for the H19 standard was below 0.396, the sample was retested.
3. For samples with discordant H19 ratio results (i.e. resulting in differing classifications of positivity), the sample was retested if the difference between replicate OD values was >0.05.

TMB Optimization: A TMB optimization step was incorporated prior to sample testing to compensate for temperature and environmental variability between labs. TMB optimization was performed each time a new lot of kits were opened and prior to each round of testing based on the year the samples were collected. To determine the optimal TMB incubation time, positive, low positive, and negative controls were diluted 1:50, and in-house controls for H3 and H19 were diluted to final concentrations of 1:1500 and 1:900, respectively, in Tris-HCL buffered solution with Tween 20 (0.05%). The ELISA procedure was completed per the above methods, except stop solution was added at 2-minute intervals starting at 5 minutes, until the time interval that met all the pass/fail kit control requirements and had an H3 OD value closest to 1.0 was determined. This time became the TMB incubation time for all the assays in the same lot and year of samples.

5.2.6 Determination of Cut-offs for Wb123 ELISA

The Filaria Detect IgG4 ELISA yields a quantitative value that is related to the level of antibody response. However, in a low prevalence setting, there is no gold standard that can be used to distinguish a positive response from a negative response (Gass et al., 2012). Therefore, a mixture modelling approach recently developed by Sullivan et al. was used to establish positive and negative serologic cut-offs. The approach employed builds on conventional mixture modelling methods for determination of serological cut-offs, but offers several modifications that increase the certainty with which cut-offs are set in low prevalence settings (Sullivan et al., 2016). Notably, it creates an indeterminate range that ultimately results in a higher degree of certainty in positive and negative classifications. After applying the mixture modelling approach, results falling within the indeterminate range were excluded from further analysis.

5.2.7 Statistical Analysis

ELISA results were entered into Microsoft Excel (Redmond, WA). Statistical analyses were conducted in IBM SPSS version 24 (Armonk, NY) and the R statistical environment (R Core Team, 2014).

Results will be presented under four areas: univariate, bivariate, multivariate and site-specific trends.

5.2.7.1 Main Variables and Univariate Analysis

LF Seroprevalence: LF seropositivity was analysed as a dichotomous variable. First, data on LF seroprevalence in all study sites were aggregated and analysed to examine overall trends.

Second, LF prevalence by year in each study site was calculated and plotted with 95% confidence intervals to examine trends and differences between study sites. A chi-square test was used to determine if there was a significant difference in LF prevalence between study sites. Post hoc analysis involved pairwise comparisons using the z-test of two proportions with a Bonferroni correction.

Vector Control Coverage: Data on household vector control from the household questionnaire were presented in Chapter 4. Household mosquito net ownership and IRS were each measured and analysed using a dichotomous variable measured as 'ownership of one or more mosquito nets per household', and 'household sprayed in past twelve months by a government program', respectively. Odds ratios were calculated, and chi-square tests were used to determine if there was a significant difference in household net ownership based on LF serology and to determine if there was a significant difference in LF serology between study sites receiving IRS and those not receiving IRS. Subjects with no household data on net ownership were excluded from analysis related to net ownership (1.2% of households surveyed). This occurred in some cases due to no response recorded for the question, or a response of 'do not know', and may have been a result of respondents not wanting their house to be entered by survey teams to view nets. Subjects with no household data on IRS were excluded from analysis related to IRS coverage (0.9% of households surveyed). This occurred due to a response of 'do not know' to the survey question asking if the house had been sprayed.

Socioeconomic Status: The proxy indicators described in Chapter 4 were used to assess SES, which included housing infrastructure (building materials, quality, and house size) and ownership of specific commodities. Building materials of the main dwelling were measured and analysed using categorical variables for flooring, walls, and roofing. The dichotomous housing quality variable described previously was used to classify each house as 'modern' or 'traditional'. House size was determined based on the number of rooms in the house used for sleeping and was measured and analysed as a dichotomous variable (≤3 rooms versus > 3 rooms). Ownership of individual household commodities were measured and analysed as dichotomous variables.

5.2.7.2 Bivariate Analysis

Relationship Between LF Seropositivity and Key Individual, Household, and Community Indicators

Odds ratios were calculated, and chi-square tests were used to determine if there was a significant difference in LF seropositivity based on: gender, age, site type (intervention versus control), net ownership, IRS coverage, housing infrastructure, quality, and commodity ownership in each year.

Site-specific Trends in Wb123 Seroprevalence in Relation to Vector Control Coverage

Annual Wb123 seroprevalence, household net ownership, and IRS coverage from 2011-2013 were graphed to visually compare trends over time in: all study sites combined (aggregate), control sites, intervention sites, and within each individual study site.

5.2.7.3 Multivariate Analysis

Binomial logistic regression models were constructed to ascertain the predictors of LF seroprevalence for each year. Initially, all variables that were statistically significant ($p<0.05$) from bivariate analysis were included in the regression model for each year. Variables that were not significant ($p<0.05$) and did not improve the model's fit were subsequently removed.

5.2.7.4 Ethical Approval and Informed Consent

The study protocol was approved by NIMR, Tanzania and LSTM Research Ethics Committee. The study was conducted in collaboration with the National NTD Program of the MOHSW, Tanzania. Community leaders in each study site and all participants were informed of the objectives of the study, risks and benefits, and that participation was entirely voluntary. Local community leaders provided permission for teams to conduct the study. Blood samples were only taken if written informed parental consent was obtained. Consent forms were translated from English into Kiswahili for use in the field.

5.3 Results

5.3.1 Study Population

ELISA results were obtained for 6,854 DBS samples collected from children 2-7 years of age in the six study sites over the three-year study period. Table 5.2 summarizes the number of samples tested by study site and year.

5.3.2 Wb123 ELISA Cut-off Determination

Using the mixture model described above, the raw cut-off value for the Wb123 ELISA was determined to be 0.38 standardized OD units, with an indeterminate range of 0.32-0.44 defined observations with <80% certainty of classification. Using these cut-offs, the observed data are classified as 20.5% positive (≥0.44 standardized OD units), 7.8% indeterminate (0.32–0.44), and 71.6% negative (≤0.32 standardized OD units). Using the raw cut-off without the indeterminate range results in a positive prevalence of 23.6 % and a negative prevalence of 76.4%. The mixture model definitions of positive and negative are used for all further analyses, with samples classified as indeterminate excluded.

Table 5.2. Number of Children Sampled by Year and Study Site

Study Site	2011	2012	2013	Total
Nyambori	381	401	353	1135
Bwisya	455	529	520	1504
Mwaliga	253	270	267	790
Bunegezi	294	334	285	913
Igulwa	425	493	468	1386
Zanzui	378	396	352	1126
Total	2186	2423	2245	6854

Table 5.3. Positive, Negative and Indeterminate Wb123 ELISA Results

	Negative N (%)	Indeterminate N (%)	Positive N (%)	Total (N)
Raw Cut-off	5234 (76.4)	0 (0)	1620 (23.6)	6854
Cut-off with 80% Certainty	4910 (71.6)	537 (7.8)	1407 (20.5)	6854

5.3.3 Univariate Results

5.3.3.1 Overall seroprevalence of Wb123

As shown in Figure 5.1, the baseline survey conducted in 2011 found an overall LF seroprevalence in the study population of 27.9%. Seroprevalence decreased significantly over the study period to 18.3% in 2013 ($p<0.0005$).

The decrease in seroprevalence between 2011 and 2012 was significant ($p<0.0005$), the latter being 21.0%. The decrease between 2012 and 2013 was also significant ($p=0.025$).

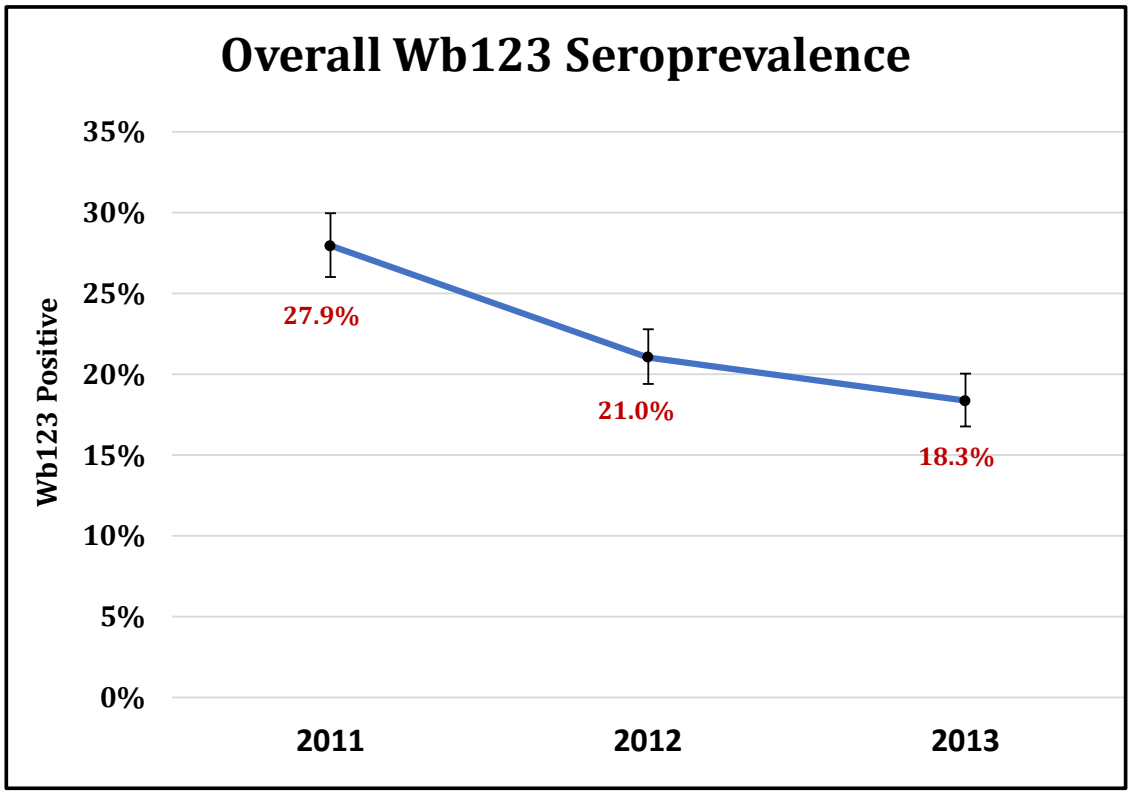


Figure 5.1. Aggregate Wb123 Seroprevalence by Survey Year (all study sites combined)

Overall, the proportion of children positive for Wb123 antibodies was found to increase progressively with age (Figure 5.2). Wb123 seropositivity was significantly associated with age in each survey year ($p<0.0005$ each year). The proportion of children sampled by age was not statistically different across years ($p>0.05$), with the exception that more seven-year-olds were sampled in 2013 in the control sites than in 2011 and 2012 (Appendix 6).

In total, 3,240 females (47.2%) and 3,614 males (52.8%) were tested. The difference in proportions of females tested versus males was not statistically significant in any of the survey years ($p>0.05$ each year). Wb123 seropositivity was not associated with gender in any of the survey years ($p>0.05$ each year).

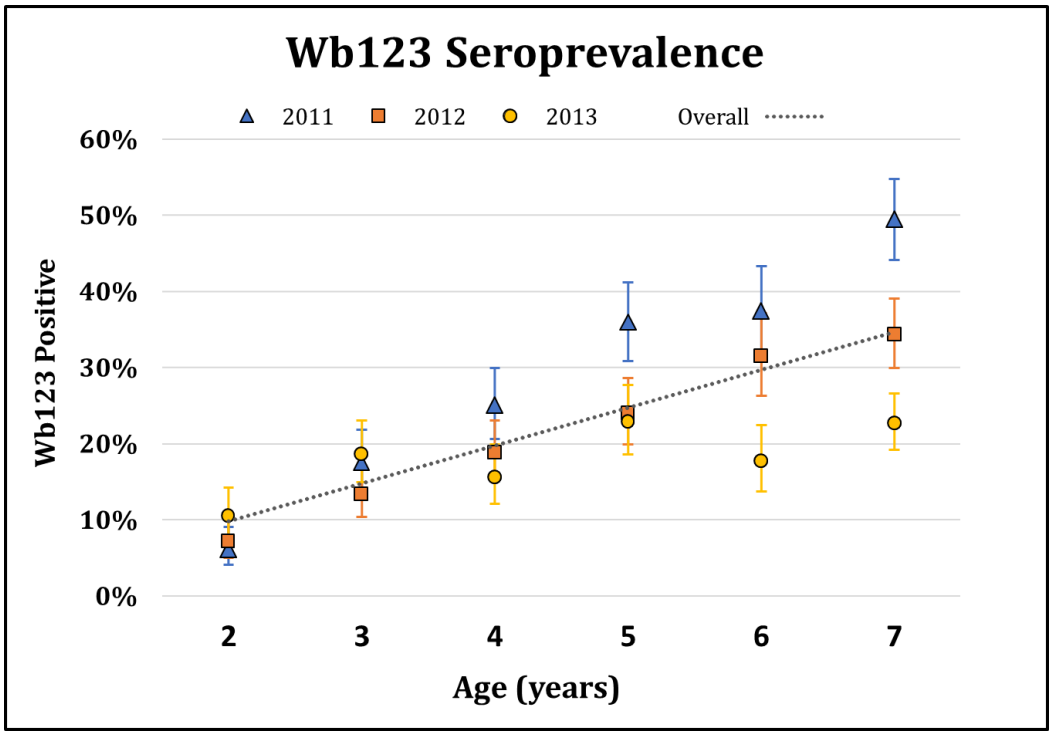


Figure 5.2. Wb123 Seropositivity by Age. Data are aggregated for study population across the study period (excluding results classified as indeterminate). Error bars represent 95% confidence intervals.

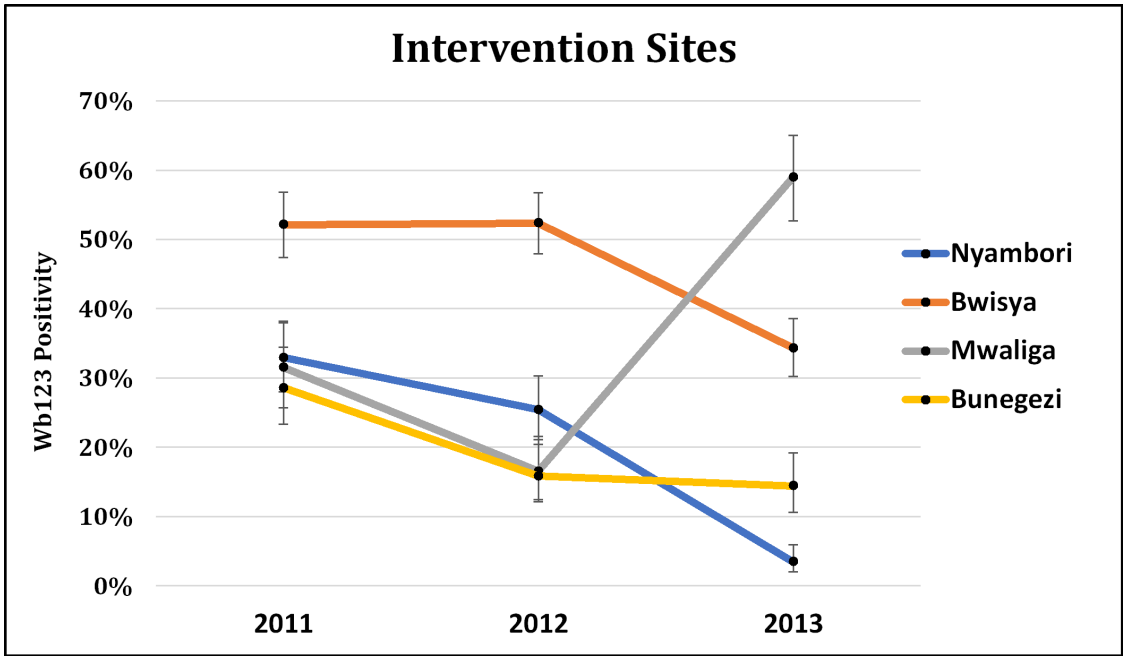
The proportion of children found to be seropositive in each study site in 2011, 2012, and 2013 is detailed in Table 5.4. Seroprevalence varied considerably between study sites in each year, with a range of 7.1-52.1% in 2011, 3.1-52.4% in 2012, and 3.4-59.0% in 2013. In all study sites, except for Mwaliga, seroprevalence decreased between 2011 and 2013, however the decrease in Igulwa was not significant. Seroprevalence in Mwaliga increased by 87% from 2011 to 2013 (p<0.0005).

Table 5.4. Wb123 Seroprevalence by Year and Study Site

Study Site	Wb123 Seroprevalence (95% CI)			2011 vs. 2013	
	2011	2012	2013	% change	p-value
Intervention Sites	38.5 (35.8-41.2)	31.2 (28.8-33.7)	26.8 (24.5-29.3)	-35%	<.0005*
Nyambori	32.9 (28.0-38.2)	25.4 (21.1-30.3)	3.4 (2-5.9.0)	-90%	<.0005*
Bwisya	52.1 (47.4-56.8)	52.4 (47.9-56.7)	34.3 (30.2-38.6)	-34%	<.0005*
Mwaliga	31.5 (25.7-37.9)	16.5 (12.5-21.6)	59.0 (52.3-65.1)	+87%	<.0005*
Bunegezi	28.6 (23.4-34.4)	15.8 (12.2-20.4)	14.4 (10.6-19.2)	-50%	<.0005*
Control Sites	10.4 (8.4-12.8)	4.5 (3.3-6.1)	4.1 (2.9-5.7)	-63%	<.0005*
Igulwa	7.1 (5.0-10.1)	5.6 (3.9-8.1)	4.2 (2.7-6.5)	-41%	0.072
Zanzui	14.2 (10.9-18.4)	3.1 (1.8-5.3)	3.8 (2.2-6.4)	-73%	<.0005*
All Sites	27.9 (26.0-30.0)	21.0 (19.4-22.8)	18.3 (15.8-19.0)	-34%	<.0005*

*p-value <0.05 indicating significance

In aggregate, intervention sites had a 35% decrease in seroprevalence between 2011 and 2013 ($p<0.0005$), whilst control sites had a 63% decrease ($p<0.0005$). As shown in Figure 5.3, the intervention and control sites show a similar trend downward trend in seroprevalence over the study period, except for Mwaliga, which shows an increase.



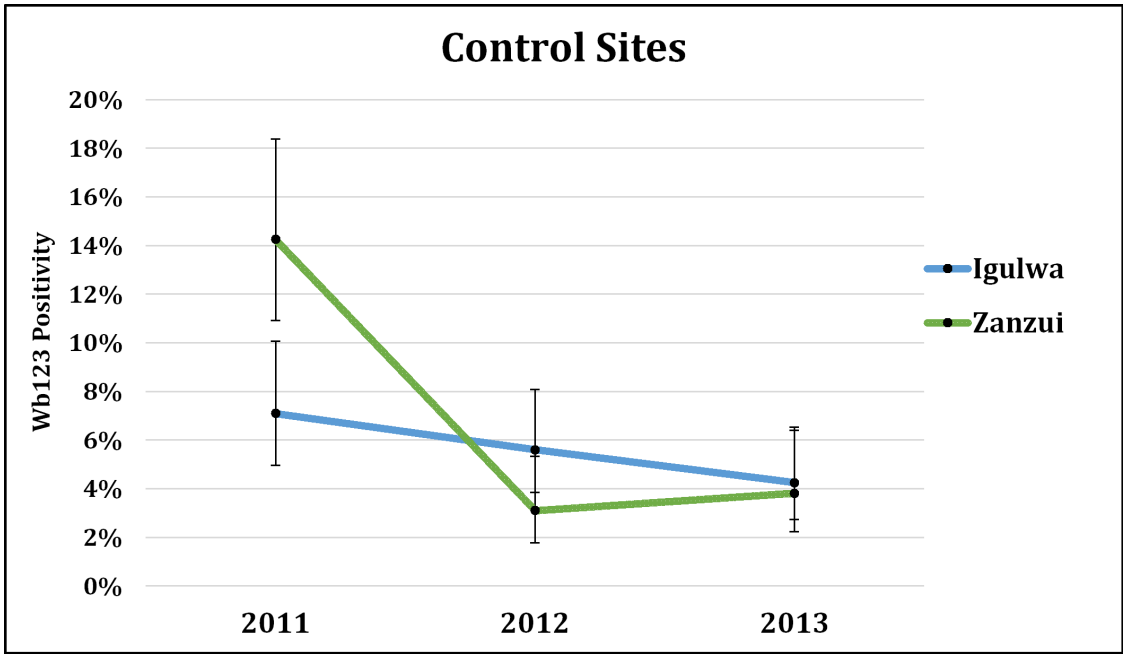


Figure 5.3. Wb123 Seroprevalence in Intervention and Control Sites by Year. Bars represent 95% confidence intervals. Note, graphs are drawn at different scales.

5.3.3.2 Vector Control Coverage and Socioeconomic Status

Household data on net ownership, IRS coverage, housing infrastructure (building materials, quality, and size), and ownership of specific commodities in each study site were presented in Chapter 4.

5.3.4 Bivariate Results

5.3.4.1 Relationship Between LF Seropositivity and Key Individual, Household, and Community Indicators

Odds ratios were calculated, and chi-square tests were used to determine if there was a significant difference in LF seropositivity based on: gender, age, household net ownership, community net ownership, household IRS coverage, community IRS coverage, housing infrastructure and quality, and household commodity ownership in each year.

Gender and Age

There was no significant difference in LF seropositivity by gender in any of the survey years (Table 5.5). In 2011 and 2012, each year increase in age was associated with a significantly greater likelihood of LF seropositivity compared to the two-year-old reference category. In 2013, the relationship between each age compared to the two-year-old reference category varied (Table 5.5).

Table 5.5. Association Between Demographic Variables and Wb123 Seropositivity

	2011				2012				2013			
	N	**n Wb123 positive (%)**	**OR (95% CI)**	**p-value**	**N**	**n Wb123 positive (%)**	**OR (95% CI)**	**p-value**	**N**	**n Wb123 positive (%)**	**OR (95% CI)**	**p-value**
Gender												
Female	948	255 (26.9)	-	-	1056	204 (19.3)	-	-	1002	176 (17.6)	-	-
Male	1006	291 (28.9)	1.1 (.91-1.3)	.318	1187	268 (22.6)	1.2 (.99-1.5)	.059	1118	213 (19.1)	1.1 (.89-1.4)	.377
Age (Years)												
2	361	22 (6.1)	-	-	393	28 (7.1)	-	-	325	34 (10.5)	-	-
3	333	58 (17.4)	3.3 (1.9-5.4)	<.0005*	411	55 (13.4)	2.014 (1.2-3.2)	.004*	354	66 (18.6)	2.0 (1.3-3.1)	.003*
4	328	82 (25.0)	5.1 (3.1-8.5)	<.0005*	378	71 (18.8)	3.0 (1.9-4.8)	<.0005*	333	52 (15.6)	1.6 (1.0-2.5)	.050
5	329	118 (35.9)	8.6 (5.3-14.0)	<.0005*	367	88 (24.0)	4.1 (2.6-6.5)	<.0005*	324	74 (22.8)	2.5 (1.6-3.9)	<.0005*
6	265	99 (37.4)	9.2 (5.6-15.1)	<.0005*	283	89 (31.4)	6.0 (3.8-9.5)	<.0005*	294	52 (17.7)	1.8 (1.2-2.9)	.009*
7	338	167 (49.4)	15.0 (9.3-24.3)	<.0005*	411	141 (34.3)	6.8 (4.4-10.5)	<.0005*	490	111 (22.7)	2.5 (1.7-3.8)	<.0005*

*p-value <0.05 indicating significance

Net Ownership and IRS Coverage

LF seroprevalence by household and community net ownership and IRS coverage in the 2011, 2012, and 2013 surveys is summarized in Table 5.6.

In 2011, children living in households that owned ≥1 net were .73 times less likely to be Wb123 seropositive than children living in households that owned no nets (OR=.73, 95% CI .60-.90, p=0.003). A similar association is found in 2013; children living in households that owned ≥1 net were .78 times less likely to be seropositive than children living in households that owned no nets (OR=.78, 95% CI .63-.98, p=0.029). Conversely, in 2012, children living in households that owned ≥1 net were 1.4 times more likely to be seropositive than children living in households that owned no nets (OR=1.4, 95% CI 1.1-1.8, p=0.008).

In 2011, children living in study sites in which at least 60% of the surveyed households owned ≥1 net were .55 times less likely to be seropositive than children living in study sites in which less than 60% of the surveyed households owned ≥1 net (OR=.55, 95% CI .45-.67, p<0.0005). In 2013, children living in study sites in which at least 60% of the surveyed households owned ≥1 net were .11 times less likely to be seropositive than children living in study sites in which less than 60% of the surveyed households owned ≥1 net (OR=.11, 95% CI .08-.16, p<0.0005). None of the study sites in 2012 had community net ownership below 60%.

In 2012, after initiation of the IRS programme in the intervention sites, children living in households that received IRS were 3.4 times more likely to be seropositive than children living in households that did not receive IRS (OR=3.4, 95% CI 2.7-4.2, p<.0005). In 2013, children living in households that received IRS were 4.8 times more likely to be seropositive than children living in households that did not receive IRS (OR=4.8, 95% CI 3.6-6.5, p<.0005).

In 2012, children living in study sites in which at least 60% of the surveyed households received IRS were 7.0 times more likely to be Wb123 seropositive than children living in study sites in which less than 60% of the surveyed households had received IRS (OR=7.0, 95% CI 5.6-8.8, p<0.0005). In 2013, this odds ratio increases to 8.7 (OR=8.7, 95% CI 6.0-12.6, p<0.0005).

Table 5.6. Association Between Net Ownership and IRS Coverage and Wb123 Seropositivity

	2011				2012				2013			
	N	**n Wb123 positive (%)**	**OR (95% CI)**	**p-value**	**N**	**n Wb123 positive (%)**	**OR (95% CI)**	**p-value**	**N**	**n Wb123 positive (%)**	**OR (95% CI)**	**p-value**
Household Net Ownership												
No	629	203 (32.3)	-	-	636	108 (17.0)	-	-	1035	210 (20.3)	-	-
Yes	1306	338 (25.9)	.73 (.60-.90)	.003*	1528	337 (22.1)	1.4 (1.1-1.8)	.008*	1078	179 (16.6)	.78 (.63-.98)	.029*
Community Net Ownership												
< 60%	763	270 (35.4)	-	-	0	0	-	-	1324	358 (27.0)	-	-
≥ 60%	1191	276 (23.2)	.55 (.45-.67)	<.0005*	2243	472 (21.0)	-	-	796	31 (3.9)	.11 (.08-.16)	<.0005*
Household IRS												
No	1936	540 (27.9)	-	-	1395	182 (13.0)	-	-	847	58 (6.8)	-	-
Yes	5	1 (20.0)	.65 (.07-5.8)	.572^	779	262 (33.6)	3.4 (2.7-4.2)	<.0005*	1257	329 (26.2)	4.8 (3.6-6.5)	<.0005*
Community IRS Coverage												
< 60%	1954	546 (27.9)	-	-	1408	128 (9.1)	-	-	789	32 (4.1)	-	-
≥ 60%	0	0	-	-	835	344 (41.2)	7.0 (5.6-8.8)	<.0005*	1331	357 (26.8)	8.7 (6.0-12.6)	<.0005*

*p-value <0.05 indicating significance, ^Fisher's Exact Test

Housing Infrastructure, Quality, and Commodity Ownership

LF seroprevalence by household building materials, quality, and size, as well as household ownership of commodities is summarized in Table 5.7 for each survey year.

Building Materials and Housing Quality

In all years, children living in houses using finished floor materials were significantly less likely than children living in houses with natural floor materials to be Wb123 seropositive. In 2011, children living in houses with finished floor materials were .25 times less likely to be seropositive than children living in houses with natural floor materials (OR=.25, 95% CI .18-.35, p<0.0005). In 2012, the odds ratio increases to .42 (95% CI .32-.55, p<0.0005) and in 2013 it was found to be .29 (95% CI .21-.39, p<0.0005).

Similarly, children living in houses using bricks or cement blocks as wall materials were less likely than children living in houses using natural wall materials to be seropositive, although this relationship was not significant in 2013. In 2011, children living in houses with brick or cement wall materials were .65 times less likely to be seropositive than children living in houses with natural wall materials (OR=.65, 95% CI .53-.79, p<0.0005). In 2012, the odds ratio decreases to .47 (95% CI .38-.58, p<0.0005). The odds ratio in 2013 was .96 (95% CI .77-1.2) but was not significant (p=.710).

Children living in houses using finished roof materials were less likely to be seropositive than children living in houses using natural roof materials, but this relationship was not significant in 2013. In 2011, children living in houses with finished roof materials were .71 times less likely to be seropositive than those living in houses with natural roof materials (OR=.71, 95% CI .58-.86, p=.001). In 2012, the odds ratio decreases to .66 (95% CI .54-.82, p<0.0005). The odds ratio in 2013 was 1.0 (95% CI .81-1.3, p=.710), indicating no relationship between seropositivity and household roof materials.

In all years, children living in houses defined as ‘modern’ were significantly less likely than those living in ‘traditional’ houses to be seropositive. In 2011, children living in modern houses were .28 times less likely to be seropositive than those living in traditional houses (OR=.28, 95% CI .20-.39, p<0.0005). In 2012, the odds ratio increases to .43 (95% CI .33-.57, p<0.0005). The odds ratio in 2013 was found to be .30 (95% CI .22-.40, p<0.0005).

Size of House

There was no significant relationship between the size of the house and LF seropositivity in 2011 (OR=.82, 95% CI .62-1.1, p=0.153). In 2012, children living in larger houses were 2.1 times more likely to be seropositive than those living in smaller houses (OR=2.1, 95% CI 1.7-2.6, p<0.0005). However, in 2013, this relationship reverses and children living in larger houses are .76 times less likely to be seropositive (OR=.76, 95% CI, .60 -.95, p=0.016).

Ownership of Commodities

In all years, children living in households that owned a mobile phone were significantly less likely to be seropositive than those living in households that did not own a mobile phone. In 2011, children living in households that owned a mobile phone were .53 times less likely to be seropositive than those living in houses without a mobile phone (OR=.53, 95% CI .43-.65, p<0.0005). This odds ratio decreases in 2012 to .46 (95% CI, .37 -.58, p<0.0005) and increases in 2013 to .67 (95% CI .54-.84, p<.0005).

Similarly, children living in households that owned a radio were less likely to be seropositive than those living in households that did not own a radio, however this relationship was only significant in 2011 and 2012. In 2011, children living in households that owned a radio phone were .75 times less likely to be seropositive than those living in houses that did not (OR=.75, 95% CI .61-.91, p=.004). This odds ratio decreases in 2012 to .47 (95% CI .38 -.58, p<0.0005) and increases in 2013, but is not significant (OR=.82, 95% CI, .66-1.0, p<.0005).

As discussed in Chapter 4, household ownership of a television, refrigerator, landline telephone, and electricity were rare in this study population, resulting in low sample sizes that did not allow for comparison across survey years. As a result, they were not analysed further. Also, as discussed previously, ownership of an iron and lamp were excluded from analysis.

Table 5.7. Relationship Between Housing Materials, Type, Size, and Commodity Ownership and Wb123 Seropositivity

	2011				2012				2013			
	N	**n Wb123 positive (%)**	**Odds Ratio (95% CI)**	**p-value**	**N**	**n Wb123 positive (%)**	**Odds Ratio (95% CI)**	**p-value**	**N**	**n Wb123 positive (%)**	**Odds Ratio (95% CI)**	**p-value**
Floor Material												
Natural	1560	503 (32.2)			1651	402 (24.3)			1464	337 (23.0)		
Finished	384	41 (10.7)	.25 (.18-.35)	<.0005*	586	69 (11.8)	.42 (.32-.55)	<.0005*	656	52 (7.9)	.29 (.21-.39)	<.0005*
Wall Material												
Natural	838	277 (33.1)			1076	296 (27.5)			877	164 (18.7)		
Bricks or Cement	1100	266 (24.2)	.65 (.53-.79)	<.0005*	1162	176 (15.1)	.47 (.38-.58)	<.0005*	1240	224 (18.1)	.96 (.77-1.2)	.710
Roof Material												
Natural	865	276 (31.9)			756	195 (25.8)			830	151 (18.2)		
Finished	1074	267 (24.9)	.71 (.58-.86)	.001*	1480	277 (18.7)	.66 (.54-.82)	<.0005*	1290	238 (18.4)	1.0 (.81-1.3)	.881
House Type (quality)												
traditional	1585	503 (31.7)			1678	404 (24.1)			1474	337 (22.9)		
modern	353	40 (11.3)	.28 (.20-.39)	<.0005*	559	67 (12.0)	.43 (.33-.57)	<.0005*	646	52 (8.0)	.30 (.22-.40)	<.0005*
No. Rooms Used for Sleeping (size)												
≤ 3	1630	466 (28.6)			1634	284 (17.4)			1212	244 (20.1)		
> 3	324	80 (24.7)	.82 (.62-1.1)	.153	609	188 (30.9)	2.1 (1.7-2.6)	<.0005*	905	145 (16.0)	.76 (.60-.95)	.016*
Mobile Phone												
no	1128	375 (33.2)			1323	344 (26.0)			925	201 (21.7)		
yes	816	169 (20.7)	.53 (.43-.65)	<.0005*	920	128 (13.9)	.46 (.37-.58)	<.0005*	1192	188 (15.8)	.67 (.54-.84)	<.0005*
Radio												
no	874	273 (31.2)			1096	299 (27.3)			864	174 (20.1)		
yes	1070	271 (25.3)	.75 (.61-.91)	.004*	1147	173 (15.1)	.47 (.38-.58)	<.0005*	1253	215 (17.2)	.82 (.66-1.0)	.082

*p-value <0.05 indicating significance

5.3.4.2 Relationship Between LF Seropositivity and Site Type

As shown in section 5.3.3.1 and Table 5.4, overall LF seroprevalence decreased significantly in both the intervention and control sites.

LF Seropositivity by type of study site (control versus intervention) in the 2011, 2012, and 2013 surveys is summarized in Table 5.8. In 2011, prior to the introduction of IRS and the UCC, children living in intervention sites were 5.4 times more likely to be seropositive than those living in control sites (OR=5.4, 95% CI 4.1-7.0, p<0.0005). In 2012 and 2013, seroprevalence declined in both control and intervention sites, but was still much higher in intervention sites. As a result, in 2012, children living in intervention sites were 9.7 times more likely to be seropositive than children living in control sites (OR=9.7, 95% CI 6.9-13.7, p<0.0005). In 2012, children living in intervention sites were 8.7 times more likely to be seropositive than children living in control sites (OR=8.7, 95% CI 6.0-12.6, p<0.0005).

Table 5.8. Wb123 Seroprevalence in 2011 versus 2013 by Site Type

	2011				2012				2013			
	N	**n Wb123 positive (%)**	**OR (95% CI)**	**p-value**	**N**	**n Wb123 positive (%)**	**OR (95% CI)**	**p-value**	**N**	**n Wb123 positive (%)**	**OR (95% CI)**	**p-value**
Site Type												
Control	732	76 (10.4)	-	-	851	38 (4.5)	-	-	789	32 (4.1)	-	-
Inter-vention	1222	470 (38.5)	5.4 (4.1-7.0)	<.0005*	1392	434 (31.2)	9.7 (6.9-13.7)	<.0005*	1331	357 (26.8)	8.7 (6.0-12.6)	<.0005*

*p-value <0.05 indicating significance

5.3.5 Site-Specific Trends in Seroprevalence in Relation to Vector Control

Figures 5.4 through 5.7. show overlaid trends in LF seroprevalence, household net ownership, and IRS coverage from 2011 to 2013.

5.3.5.1 Aggregate Trends

As shown in Figure 5.4A, within the overall study population (all sites) a significant increase in IRS was coupled with a significant decrease in both household net ownership and Wb123 seroprevalence among children. When study sites are aggregated into control and intervention sites (Figures 5.4A and 5.4B), they each show the same trends as those found in the overall study population.

As shown in Figure 5.5, in the intervention sites in which IRS was positively associated with net ownership in 2013 (Nyambori and Bwisya), net ownership did not change significantly from 2011 to 2013 (i.e. coverage over 60% was maintained) and Wb123 seroprevalence was

reduced by half, from 43.8% to 21.4% ($p<0.05$). Conversely, in the intervention sites in which IRS was negatively associated with net ownership in 2013 (Mwaliga and Bunegezi), net ownership decreased significantly from 94.8% in 2011 to 28.7% in 2013 ($p<0.05$) whilst Wb123 seroprevalence in these sites increased significantly from 29.9% to 35.9% ($p<0.05$).

5.3.5.2 Trends in Individual Study Sites

When examined individually, study sites show varying trends in Wb123 seroprevalence, net ownership, and IRS coverage over the study period.

Intervention Sites

In Nyambori and Bwisya, which each had relatively high Wb123 seroprevalence at baseline in 2011 (both above 50%), household net ownership did not change significantly between 2011 and 2013. Marked increases in IRS coverage and significant decreases in Wb123 seroprevalence occurred in each site (Figures 5.6A and 5.6B).

Whereas in Mwaliga, the only study site with an increase in Wb123 seroprevalence during the study period, there was a dramatic decline in household net ownership between 2011 and 2013 from 98.2% to 29.1% (Figure 5.6C). Wb123 seroprevalence increased significantly from 31.5% to 59.0% in this study site even with a significant increase in IRS coverage.

Conversely, in Bunegezi, there was also a dramatic decline in household net coverage from 92.6% to 28.3% (Figure 5.6D); however, the significant increase in IRS coverage occurred alongside a significant decrease in Wb123 seroprevalence from 28.6% to 14.4%.

Control Sites

In Igulwa, although there was no IRS campaign, by 2013 5.4% of households reported receiving IRS. Net ownership dropped significantly over the study period from 97.8% to 63.4% and there was no significant change in Wb123 seroprevalence (Figure 5.7A).

Conversely, in Zanui, which started with a very low baseline household net ownership of 19.5%, there was a significant increase in net ownership to 54.8% during the study period. This occurred together with a significant decrease in Wb123 seroprevalence from 14.2% to 3.8% even though there was no reported IRS during the study period (Figure 5.7B).

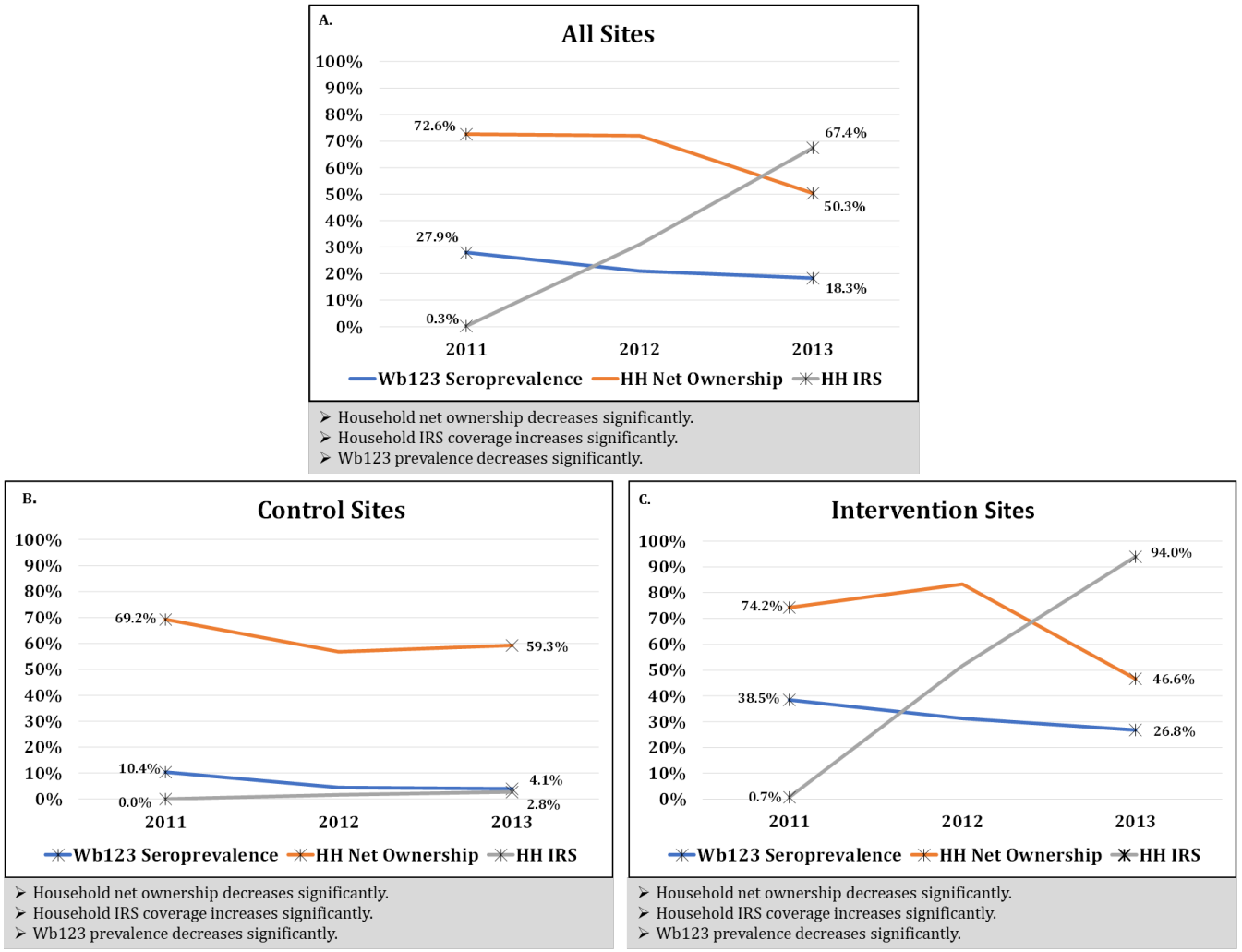
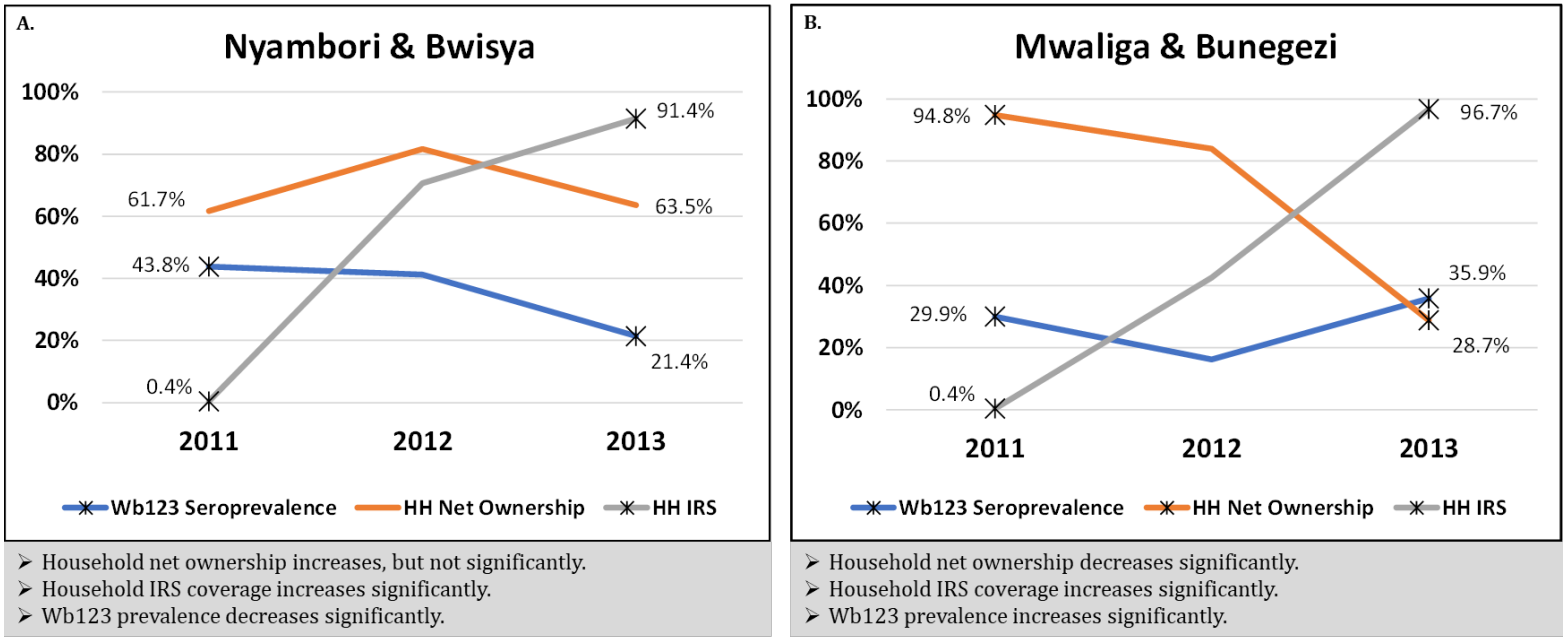


Figure 5.4. Overall Trends in Wb123 Seroprevalence, Net Ownership, and IRS Coverage in All Sites, Control Sites and Intervention Sites. Significant changes ($p<0.05$) in each indicator between 2011 and 2013 are shown with an 'X'.



- Household net ownership increases, but not significantly.
- Household IRS coverage increases significantly.
- Wb123 prevalence decreases significantly.

- Household net ownership decreases significantly.
- Household IRS coverage increases significantly.
- Wb123 prevalence increases significantly.

Figure 5.5. Trends in Wb123 Seroprevalence in Sites that Maintain Higher Net Ownership versus those with a Precipitous Decline in Net Ownership. Significant changes ($p<0.05$) in each indicator between 2011 and 2013 are shown with an 'X'.

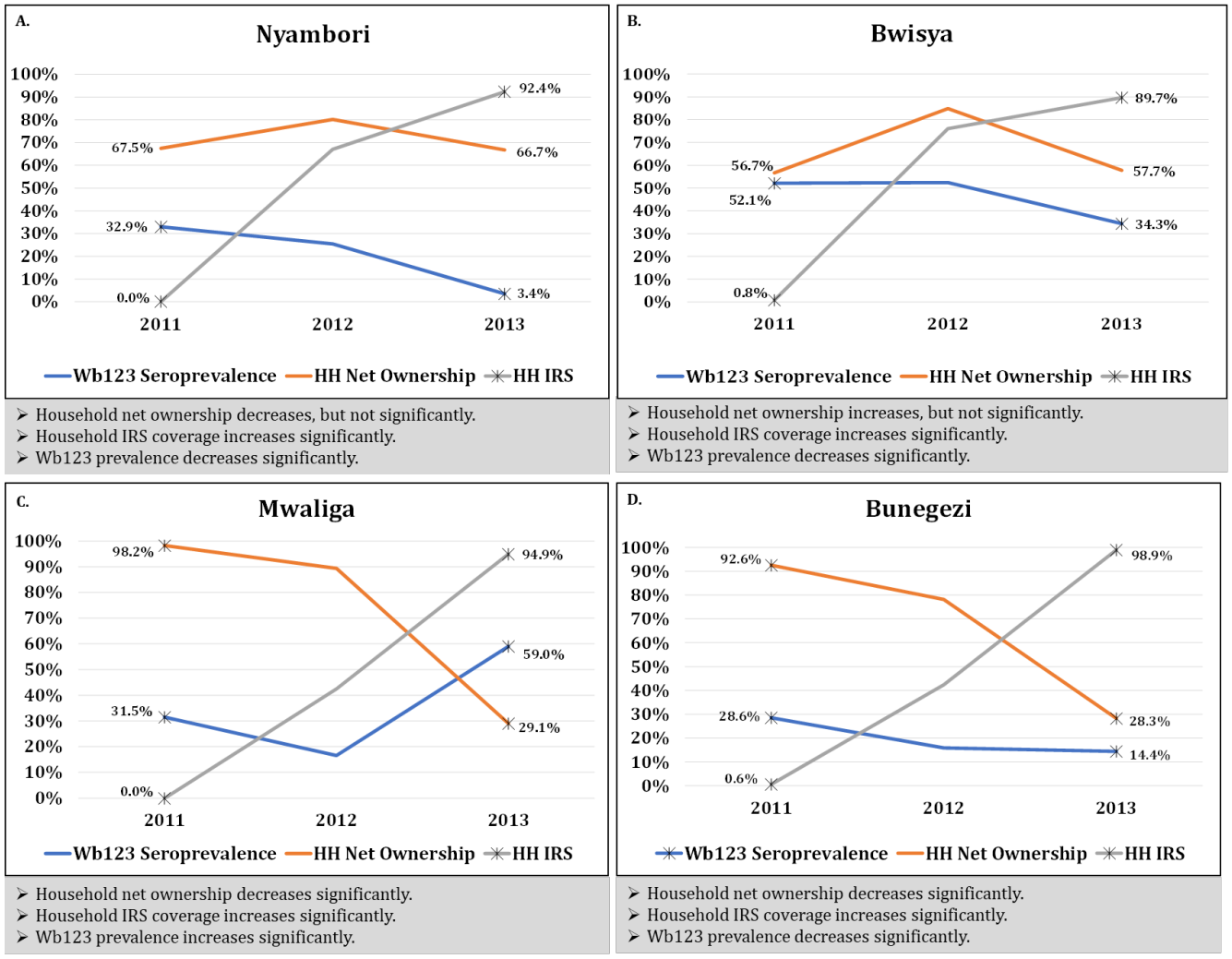
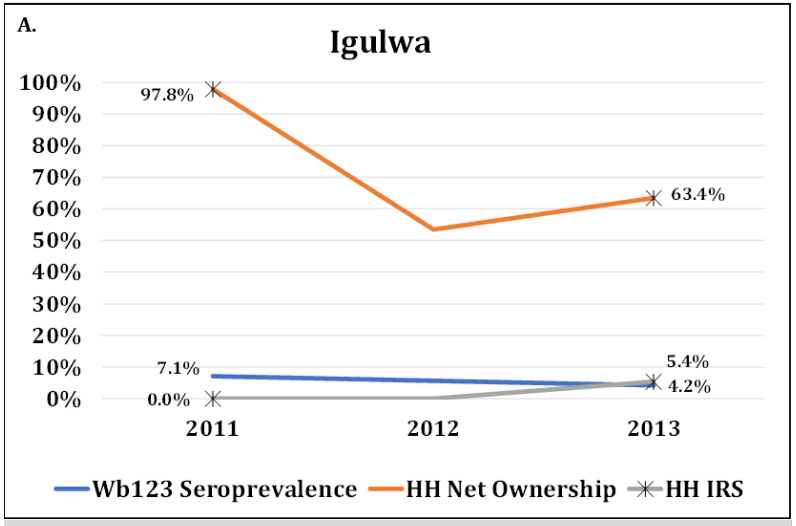
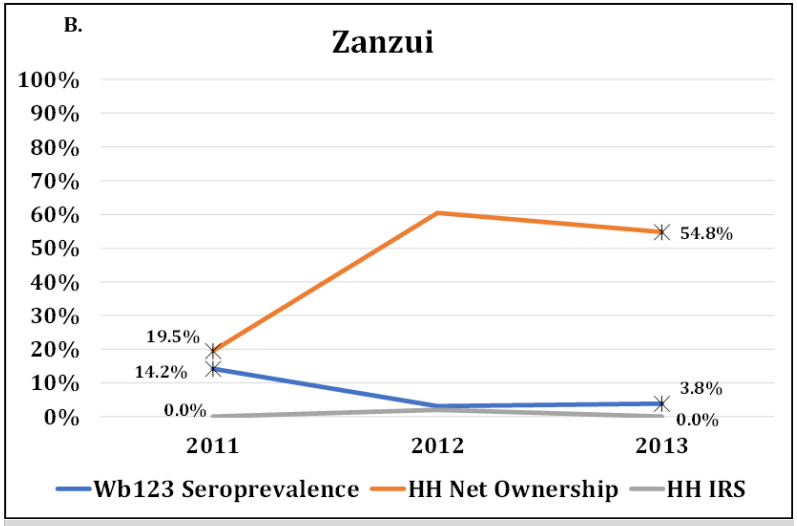


Figure 5.6. Trends in Wb123 Seroprevalence, Net Ownership, and IRS Coverage in Intervention Sites. Significant changes ($p<0.05$) in each indicator between 2011 and 2013 are shown with an 'X'.



- Household net ownership decreases significantly.
- Household IRS coverage increases significantly.
- Wb123 prevalence decreases, but not significantly.



- Household net ownership increases significantly.
- Household IRS coverage remains at 0%.
- Wb123 prevalence decreases significantly.

Figure 5.7. Trends in Wb123 Seroprevalence, Net Ownership, and IRS Coverage in Control Sites. Significant changes ($p<0.05$) in each indicator between 2011 and 2013 are shown with an 'X'.

5.3.6 Multivariate Results

Binomial logistic regression models constructed to ascertain the predictors of Wb123 seropositivity for each year are summarized in Table 5.9.

5.3.6.1 Predictors of LF Seropositivity

2011

In 2011, the most significant predictors of seropositivity were age, house type (traditional versus modern), site type (control versus intervention) and household net ownership. The logistic regression model based on these predictors is statistically significant, $\chi^2(4) = 455.5$, $p<0.0005$. The model explained 30.3% (Nagelkerke R^2) of the variance in seropositivity and the training data set correctly classified 77.0% of cases. Increasing age was positivity associated with seropositivity (OR=1.6, 95% CI 1.5-1.8, p<0.0005). Children living in intervention sites were 6.5 times more likely to be seropositive than those living in control sites (OR=6.5, 95% CI 4.8-8.8, p<0.0005). Children living in a modern house were .60 times less likely to be seropositive than those living in a traditional house (OR=.60, 95% CI .40-.89, p=0.011). Children living in a household with at least one net were .54 times less likely to be seropositive than those living in a house with no nets (OR=.54, 95% CI .42-.69, p<0.0005).

2012

In 2012, the most significant predictors of seropositivity were community Wb123 seroprevalence at baseline in 2011, age, and household net ownership. The logistic regression model based on these predictors is statistically significant, $\chi^2(3) =522.1$, $p<0.0005$. The model explained 33.6% (Nagelkerke R^2) of the variance in seropositivity and the training data set correctly classified 84.3% of cases. Children living in study sites with a higher baseline seroprevalence were 1.1 times more likely to be seropositive in 2012 than those living in study sites with lower baseline seroprevalence (OR=1.08, 95% CI 1.07-1.09, p<0.0005). Increasing age was positivity associated with seropositivity (OR=1.5, 95% CI 1.4-1.6, p<0.0005). Children living in a household with at least one net were .74 times less likely to be seropositive than those living in a house with no nets (OR=.74, 95% CI .55-.98, p=0.038).

2013

In 2013, the most significant predictors of seropositivity were community Wb123 seroprevalence at baseline (in 2011), age, and household net ownership. The logistic regression model based on these predictors is statistically significant, $\chi^2(3) =226.1$, $p<0.0005$. The model explained 16.5% (Nagelkerke R^2) of the variance in seropositivity and the training

data set correctly classified 80.9% of cases. Children living in study sites with a higher baseline seroprevalence were more likely to be seropositive in 2013 than those living in study sites with lower baseline seroprevalence (OR=1.05, 95% CI 1.05-1.06, p<0.0005). Increasing age was positivity associated with seropositivity (OR=1.2, 95% CI 1.1-1.3, p<0.0005). Children living in households owning at least one net were .73 times less likely to be seropositive than those living in a house with no nets (OR=.73, 95% CI .58-.92, p=0.009).

Table 5.9. Predictors of Wb123 Seroprevalence by Survey Year

Predictor	B	SE	Wald χ^2	*df*	*p*	Odds Ratio	95% CI for Odds Ratio	
							Lower	Upper
2011								
Age	0.491	0.035	191.820	1	.000*	1.635	1.525	1.753
House Type[1]	-0.516	0.203	6.475	1	.011*	0.597	0.401	0.888
Site Type[2]	1.878	0.154	148.478	1	.000*	6.539	4.834	8.844
HH Net Ownership	-0.620	0.128	23.491	1	.000*	0.538	0.419	0.691
Constant	-4.115	0.234	309.094	1	.000	0.016		
2012								
Baseline Wb123 Seroprevalence[3]	0.079	0.004	309.631	1	.000*	1.082	1.073	1.092
Age	0.374	0.037	102.795	1	.000*	1.454	1.352	1.563
HH Net Ownership	-0.304	0.146	4.323	1	.038*	0.738	0.554	0.983
Constant	-5.445	0.274	394.003	1	.000	0.004		
2013								
Baseline Wb123 Seroprevalence[3]	.053	.004	178.262	1	.000	1.054	1.046	1.063
Age	.179	.034	27.247	1	.000	1.196	1.118	1.279
HH Net Ownership	-.314	.120	6.873	1	.009	.730	.577	.924
Constant	-3.898	.241	261.279	1	.000	.020		

*p-value <0.05 indicating significance

[1]House Type compares houses defined as modern to the reference category of traditional

[2]Site Type compares intervention sites to the reference category of control sites

[3]Baseline Wb123 Seroprevalence refers to the community Wb123 seroprevalence measured during the baseline survey in 2011, which varied by study site

5.4 Discussion

This study found high Wb123 seropositivity in villages located within districts of the Lake Zone of Tanzania that were suspected to no longer have ongoing transmission at the time the study was initiated. Notably, young children born during the study period showed evidence of LF exposure. In the absence of any history of MDA, household net ownership was found to be significantly associated with a decrease in Wb123 seroprevalence, despite an overall decline in net ownership over the study period. Similar to the inter-village variations in net ownership presented in the previous chapter, Wb123 seroprevalence also varied markedly by study site. Proxy indicators of low SES were found to be positively associated with Wb123 seropositivity, as was increasing age. Multivariate analyses revealed that after implementation of the UCC (in all sites) and IRS (in four sites), Wb123 seropositivity was influenced by age, household net ownership, and community seroprevalence at baseline. However, the models accounted for less than 50% of the observed variance in seropositivity, indicating that other factors contributed significantly to Wb123 seropositivity in this study population.

Although bivariate analyses appear to suggest that IRS contributes positively to Wb123 seropositivity, this is likely because study sites that received IRS had higher seroprevalence before the IRS campaign than control sites. Also, as shown in Chapter 4, IRS was associated with a decrease in net ownership in households included in this study population. Thus, it is possible that IRS may have contributed indirectly to Wb123 seropositivity through its effect on net ownership. To this author's knowledge there are no published studies demonstrating a negative impact of IRS on net ownership or usage. However, it seems plausible that a reduction in nuisance of mosquitoes as a result of successful IRS could result in a diminished perception of risk, and therefore lower usage and/or ownership of nets.

As summarized in the introduction (section 5.1), there is a lack of research on the impact of nets on LF transmission in areas with a *low* prevalence of LF or in the context of *decreasing* net coverage. This study suggests that in the absence of MDA, vector control can lead to a reduction in LF exposure over time, suggesting a slowing of LF transmission. However, decreases in seroprevalence were not uniform across sites receiving IRS. This raises the possibility that in areas of low LF endemicity, net ownership may play a greater role in reducing LF transmission than IRS. Additionally, these results suggest that *maintaining* high net coverage may have more of an impact on LF transmission than the addition of IRS to an environment with low net coverage. WHO advises that in relation to malaria control, IRS

should not be introduced to compensate for low net coverage (WHO, 2014). Additional evidence is needed to determine the effectiveness of IRS in low LF transmission settings.

The results of this study also demonstrate the limitations of rapid LF mapping strategies and the diagnostics used for mapping, particularly in low-endemic settings. Rapid LF mapping protocols were not designed to measure prevalence and are assumed to identify areas at greatest risk of LF (WHO, 2016c). However, antigen tests have reduced sensitivity as infection intensity decreases (Lammie et al., 2004). In addition, the sampling strategy used for mapping LF is not designed to detect small foci of transmission (Drexler et al., 2012). Because of these limitations, areas of residual or low infection may be missed during rapid mapping. Interestingly, in 2014 a comparison study of the ICT and the FTS was conducted in Nyambori and Igulwa – an intervention and control site in the present study, respectively. In both sites children and adults aged 5-80 years old were tested for antigenemia with ICTs and FTS. In Igulwa, no antigen-positive individuals were identified. However, in Nyambori, 9.45% of the population tested was antigen-positive (WHO, 2016c). Later in 2014 and 2015, LF 're-mapping' was conducted by the MOHSW using a revised sampling strategy in all districts of the Lake Zone to determine whether MDA was still required (Gass et al., 2017). The results led to the conclusion that all the districts in the Lake Zone, including those in this study, were no longer LF-endemic and do not require MDA.

One limitation of this study was the inclusion of Wb123 seropositivity as the only outcome measure used to assess LF exposure in the study population. With additional resources, it could have been useful to compare antifilarial antibody reactivity to the recombinant antigen Bm14 to those of Wb123. Similarly, utilizing laboratory-based antigen testing, such as Og4C3, would have enabled measurement of quantitative filarial antigen levels in the study population. Additionally, although ideally the control and intervention sites would have had similar baseline Wb123 seroprevalence, site selection in this study was constrained by the lack of village-level LF endemicity data available at the time.

In summary, this study suggests that LF transmission was ongoing in districts in Tanzania that were documented as being non-endemic, and thus not requiring MDA, only a year after the study concluded. The implications of localized areas of ongoing LF transmission within a district not targeted for MDA are unclear and there are currently no programmatic guidelines regarding what level of antibody prevalence constitutes a public health problem that warrants MDA. Nevertheless, it is important that areas of potential low LF prevalence are adequately assessed well before endemic countries reach the later stages of the GPELF, when interruption of LF transmission at the national level is assessed.

Chapter Six

Conclusions and Recommendations

6.1 Conclusions

This study documents high antifilarial antibody rates to Wb123 among young children living in communities throughout the Lake Zone of Tanzania. Positive antibody responses were found in children born during the study period, indicating recent LF exposure. This suggests the potential of ongoing transmission of LF in the study areas, which could be of concern since the Lake Zone is considered non-endemic for LF and has been determined not to require MDA. While the risk posed by focalized areas of ongoing LF transmission remains unclear, the results from this study strongly support the need for additional monitoring of LF transmission in the Lake Zone.

This study found dramatic localized decreases in household net ownership in the Lake Zone despite implementation of a nationwide UCC undertaken during the study period. These findings are consistent with national and regional trends reported in the 2015-16 DHS, which indicated that net ownership was declining before implementation of a second UCC in 2015-16. While it is likely that the second UCC implemented in 2015-16 (after the present study concluded) increased net ownership, the temporary gains made after the previous UCC in the Lake Zone should be considered as strategies to maintain stable ITN coverage are developed.

Despite the overall decline in household net ownership over the study period, household net ownership was found to be significantly associated with a decrease in Wb123 seroprevalence. This finding underscores the potential for vector control activities undertaken by malaria programmes to directly contribute to reductions in LF transmission. In this study, this impact of increased net coverage on LF transmission was unintentional; however, it demonstrates the potential for planned strategies aimed at both diseases to be effective.

Surprisingly, IRS was found to be associated with reduced net ownership, and in turn, with higher Wb123 seroprevalence. No published literature or reports could be found in which a similar effect of IRS on net ownership, or usage, has been demonstrated. This may represent a novel finding; however, follow-up studies are required to assess a causal relationship. Nevertheless, WHO now recommends prioritizing the delivery of either LLINs or IRS at high coverage rather than introducing the second intervention to make up for shortcomings in the coverage of the first (WHO, 2014). Thus, a potential negative impact of IRS on net coverage should not be a major concern in countries following this guidance.

Several overall themes emerge from this study and are discussed in turn below.

6.1.1 The Need to Address Areas of Low LF Endemicity

The current approach to mapping LF to determine the need for MDA relies on antigen testing. Although rapid antigen tests, including the ICT and more recently the FTS, can be utilized in the field without the need for a laboratory or special equipment, their sensitivity is reduced in settings of low LF prevalence. Further, the sampling strategy employed is not designed to detect small foci of transmission. Similarly, there are areas in which the need for programmatic interventions is unclear and tools to confirm the absence of LF transmission are needed (Won, Sambou, et al., 2018). To address these challenges, new antibody-based assays, such as the Wb123 ELISA used in this study, are becoming increasingly recognized for their ability to detect early exposure to LF (Steel et al., 2013). As these tools are advanced it will be important to develop an understanding of the appropriate approach to infection indicators in areas of low LF prevalence, especially since such areas will become increasingly common as national LF programmes come to an end. Critically, guidelines are needed that define the conditions for appropriate use of the Wb123 assay as well as the interpretation of results to guide programmatic decisions (de Souza et al., 2017).

6.1.2 The Importance of Sustaining Gains in Vector Control for LF

Following the 2011 UCC, a national review was undertaken to develop recommendations for implementing strategies to maintain the high ITN coverage that had been achieved through the campaign (Koenker et al., 2013). The NMCP ultimately adopted a strategy of continuous distribution through the TNVS described in Chapter 3, along with the piloting of school-based distribution in the southern part of the country (PMI, 2013). Despite these efforts, as shown in Chapters 3 and 4, the gains made through the massive efforts to achieve universal coverage of ITNs were being lost just four years later in many areas. The 2015-16 DHS did not fully reflect the impact of Tanzania's second UCC implemented in 2015-16 since it was administered in most regions before the campaign was initiated. However, importantly, the results indicated that ITN ownership was decreasing between implementation of the UCCs in many regions.

Waning ITN coverage could have an impact on LF transmission. Indeed, in this study, the village of Mwaliga was shown to have a significant increase in Wb123 seroprevalence while experiencing a decline in net ownership. Similarly, there was not a significant decline in Wb123 seroprevalence in Igulwa, where net ownership also decreased. Local areas in which high ITN coverage is not achieved and *sustained* may not benefit from the community-wide effect of reducing mosquito populations (Binka, Indome, & Smith, 1998; Hawley et al., 2003). Persistent mosquito populations can contribute to ongoing LF transmission through the

continued uptake of microfilariae from LF-infected humans - as long as adult *W. bancrofti* worms are present and producing microfilariae (Richards et al., 2013). Given that the life span of an adult worm is four to eight years (Kazura, 2002; Michael et al., 2004), transient increases in net ownership in an area not receiving MDA should be of concern to LF Programmes.

6.1.3 The Significance of High Variability in Local Level Data

Household ITN ownership increased by nearly 140% from the 2007-08 MIS (38%) to the 2011-12 MIS (92%). This is undoubtedly a major achievement; however, as shown in Chapters 4 and 5, examination of local data reveals high variability of net ownership. For example, in 2011, village-level net ownership in this study ranged from 20% to 98%. Further, after the implementation of the 2011 UCC, village-level net ownership in 2012 ranged from 53% to 89%. Yet, net ownership at the national level on the Mainland was 94.8% in the 2011-12 MIS, while that in the Lake Zone was 96.5%. This suggests that reliance on large population-based surveys conducted every two to three years may not provide timely and adequate data that may be critical to address barriers to sustaining high coverage. This has been argued by the NMCP in Tanzania (National Malaria Control Programme, 2012). Indeed, these results were a precursor to the 2015-16 DHS, which showed a significant decrease in national ITN coverage to 65.4%, just two years after the present study concluded.

6.1.4 The Potential Value of Coordinating LF and Malaria Programmes

Programmes targeting malaria and LF are rarely integrated or even co-implemented. Whilst there are cases of focused efforts to integrate LF and malaria activities that are demonstrating success (Rajagopalan, Panicker, & Das, 1987), the positive benefits for LF are typically a collateral benefit from malaria programmes (Bockarie et al., 2002; Burkot et al., 1990; Rebollo et al., 2015; Reimer et al., 2013b; Webber, 1977). Yet, they share several commonalities that could be further exploited to benefit both programmes (van den Berg et al., 2013). Several examples of commonalities between the diseases and their respective programmes where they share common vectors are highlighted in Figure 6.1. Despite these commonalities, opportunities for pre-elimination coordination remain, in many programmes, untapped. Indeed, this is not a one-way relationship - LF programmes provide opportunities for malaria programmes as well. For example, in Haiti, implementation of integrated TAS, which included assessments for malaria in addition to LF and STH, demonstrated the feasibility of integrating assessments required for each programme (Knipes et al., 2017). In the post-elimination environment, integration of efforts may prove to be essential (WHO Global Malaria Programme, 2015). For instance, once elimination is achieved, maintaining

political will and sufficient resources will undoubtedly become a challenge (Groce, Banks, & Stein, 2018). It is at this point, which will occur at different times in different countries, when well-funded effective surveillance strategies will need to be in place to detect and respond to possible recrudescence. Integrated surveillance represents an opportunity to help ensure both programmes maintain their achievements (Arnold, Scobie, Priest, & Lammie, 2018).

6.2 Learning from the Study Design and Implementation

The overall design and implementation of this study was multi-faceted with both field and laboratory components. From the time I developed the study questions and study design to ultimately carrying out the field and laboratory work, it was important to me that this body of work contribute to the overall goals of the National NTD Programme in Tanzania. Critical to this was engaging the MOHSW NTD team from the inception phase and utilizing their vast field experience to assist with field activities. It is my hope that the results of this study will prompt additional activities in the Lake Zone of Tanzania to confirm the presence or absence of ongoing LF transmission so that if MDA is required, it can be implemented as soon as possible by the National NTD Programme.

In retrospect, there are several aspects of the study that I would alter if I could repeat this project. First, I would use mobile technology for all three years of data collection. This was not done until the third year of the study and would have saved time and funding if it had been utilized in the first two years of field work. Second, I would limit the scope of the household questionnaire to make it simpler and more efficient for field teams to administer. For example, I would reduce the number of questions pertaining to household bed net details that were not directly relevant to my study questions. Additionally, during training of field teams I would ensure that all survey questions and variables are consistently defined, such as the household commodities “iron” and “lamp”. These were defined differently by field teams resulting in their ultimate removal from analysis. Third, given additional funding, I would include laboratory-based antigen testing (e.g., the Og4C3 assay) of the blood spot samples I collected from children. In addition to LF exposure, this would enable assessment of LF infection in the study population and allow for comparison between community antibody and antigen levels in this age group. Fourth, with additional resources, a detailed census of the study villages, including micro-mapping of their geography, would enable more comprehensive spatial analysis at the village level to investigate local patterns of LF exposure, IRS, and net ownership. Finally, it would have been ideal for all study sites to have similar levels of LF prevalence at the outset of the study. However, as discussed previously, the best

data available at the time was used to select study sites that were most likely to have ongoing LF transmission.

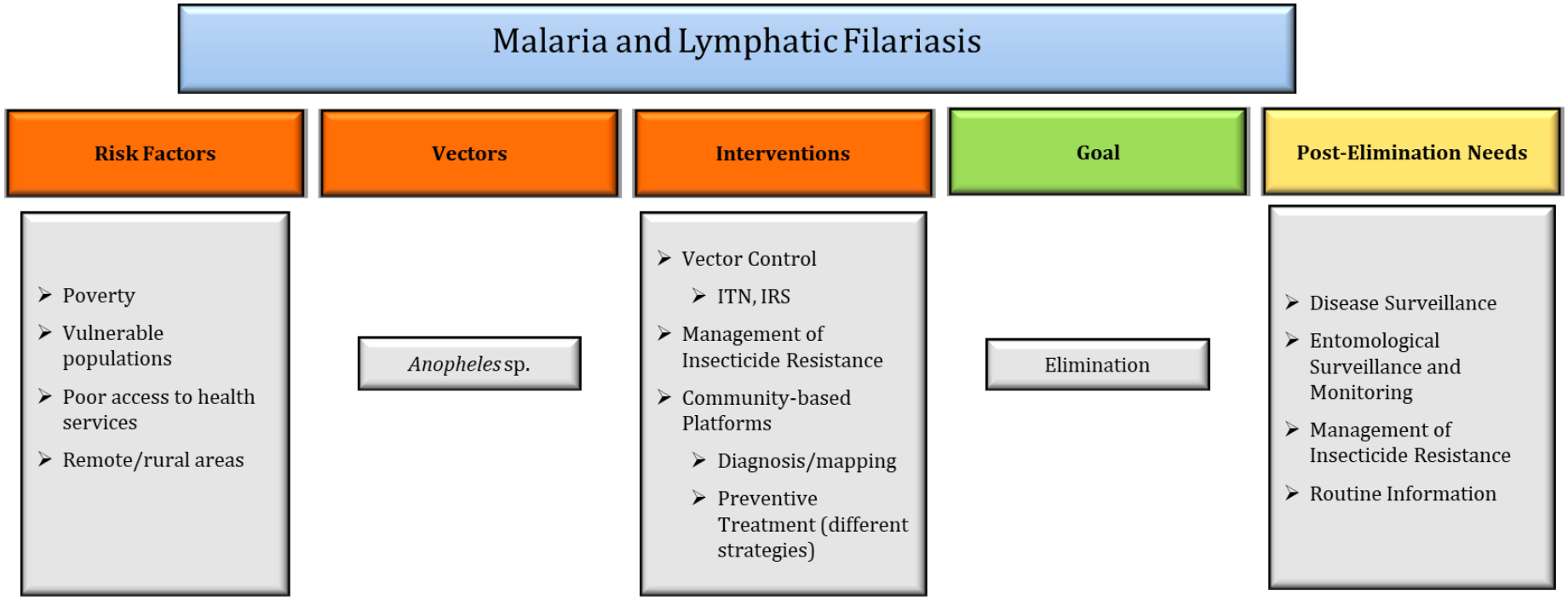


Figure 6.1. Examples of Commonalities Between LF and Malaria where they share common vectors (not intended to be exhaustive).

6.3 Programmatic Recommendations

1. It is advised that the LF and malaria programmes in Tanzania seek further opportunities to integrate monitoring and evaluation efforts, particularly as post-elimination strategies are developed. Opportunities for integrated surveillance should be explored.

2. It is suggested that the national LF Programme in Tanzania seek guidance from the Regional Programme Review Group of WHO/AFRO regarding the implications of this study with respect to possible ongoing LF transmission in focalized areas of the Lake Zone.

3. Additional evaluation of LF transmission in the Lake Zone is recommended to ensure MDA is not required and to ensure confidence in the LF-status of the Lake Zone when Tanzania eventually presents its LF elimination dossier to WHO.

6.4 Research Recommendations

1. Follow-up LF transmission studies are recommended to investigate the implications of ongoing focalized transmission of LF in low prevalence settings. These should include entomological components.

2. Rapid, field-friendly, sensitive, and specific diagnostic tools are essential to the success of the GPELF. Research on new serological tools shows promise and needs to be further developed with the goal of making inexpensive commercialized tests available to LF programmes.

3. Studies to inform programmatic guidelines on cut-offs for serological results are urgently needed. Further evaluations of the new Wb123 rapid test and guidelines that define its use are required.

Ultimately the success of the GPELF, both in Tanzania and globally, will depend on sustained efforts beyond the 2020 elimination goal. The availability of field-friendly and sensitive diagnostic tools coupled with effective strategies for monitoring and evaluation are critical to the long-term success of the programme. Joining efforts with other disease programmes, especially malaria programmes, can help ensure the communities suffering from these diseases are most effectively reached.

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Appendices

Appendix 1: IRS Interventions in the Lake Zone, 2006-2016

Year	Region*	No. Districts Sprayed	Insecticide Used	No. Structures Sprayed	Population Protected
2006/07	Kagera	1 (Muleba)	Pyrethroid	34,745	167,871
2007/08	Kagera	2 (Muleba & Kagera)	Pyrethroid	95,584	448,690
2008/09	Kagera	2 (Muleba & Kagera)	Pyrethroid	185,217	872,378
2009/10	Kagera	All & districts	Pyrethroid	425,118	2,138,299
2010/11	Kagera, Mwanza, Mara	All 18 districts	Pyrethroid	1,144,621	6,343,091
2011/12	Kagera, Mwanza, Mara	All 18 districts	Carbamate in Muleba & Karagwe; Pyrethroid in others	1,224,095	6,518,120
2012/13	Kagera, Mwanza, Mara	Targeted spraying in 18 districts	Carbamate in Kagera Region and 3 districts of Mwanza and 2 districts of Mara; Pyrethroid in others	773,929	4,052,353
2013/14	Kagera, Mwanza, Mara	Targeted spraying in 15 districts	Carbamate in 9 districts, Pirimiphos-Methyl CS (OP) in 6 districts	493,425	2,473,683
2014/15	Kagera, Mwanza, Mara	Targeted spraying in 7 districts	Pirimiphos-Methyl CS (OP)	419,753	2,110,198
2015/16	Kagera, Mwanza, Mara	Targeted spraying in 8 districts	Pirimiphos-Methyl CS (OP)	487,553	1,912,391

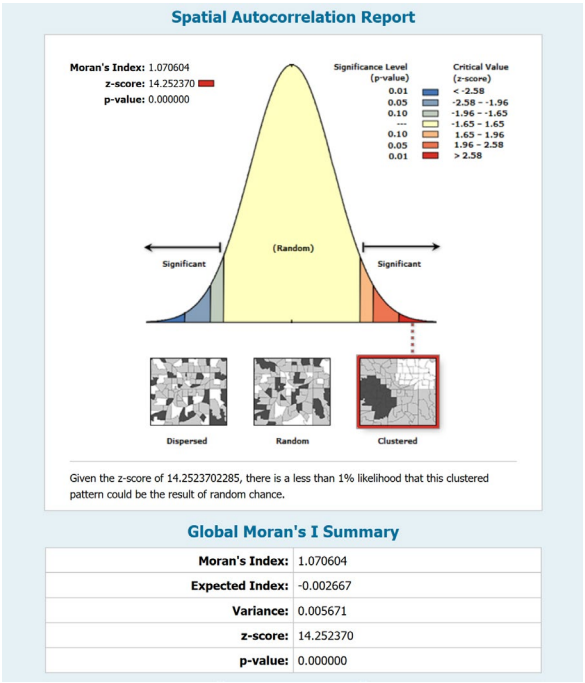
Sources: PMI Malaria Operational Plans (PMI, 2013, 2015)

* Several districts formerly in the regions listed became part of the new regions of Geita and Simiyu at the time of administrative border changes in 2012.

Appendix 2: Spatial Autocorrelation Reports

Moran's I Summaries for ITN and IRS Spatial Analysis

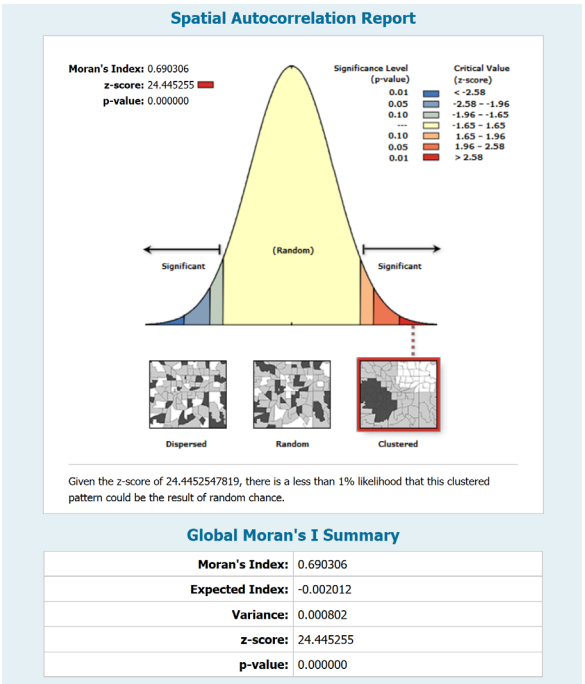
A. ITNs 2007-08



Global Moran's I Summary

Moran's Index:	1.070604
Expected Index:	-0.002667
Variance:	0.005671
z-score:	14.252370
p-value:	0.000000

B. ITNs 2011-12

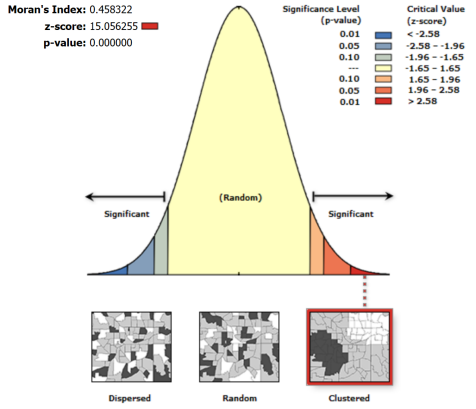


Global Moran's I Summary

Moran's Index:	0.690306
Expected Index:	-0.002012
Variance:	0.000802
z-score:	24.445255
p-value:	0.000000

C. ITNs 2015-16

Spatial Autocorrelation Report



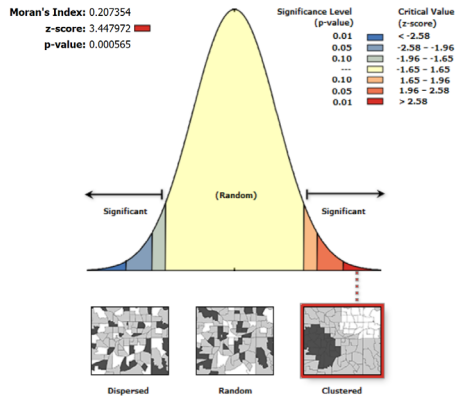
Given the z-score of 15.0562552522, there is a less than 1% likelihood that this clustered pattern could be the result of random chance.

Global Moran's I Summary

Moran's Index:	0.458322
Expected Index:	-0.001901
Variance:	0.000934
z-score:	15.056255
p-value:	0.000000

D. IRS 2007-08

Spatial Autocorrelation Report

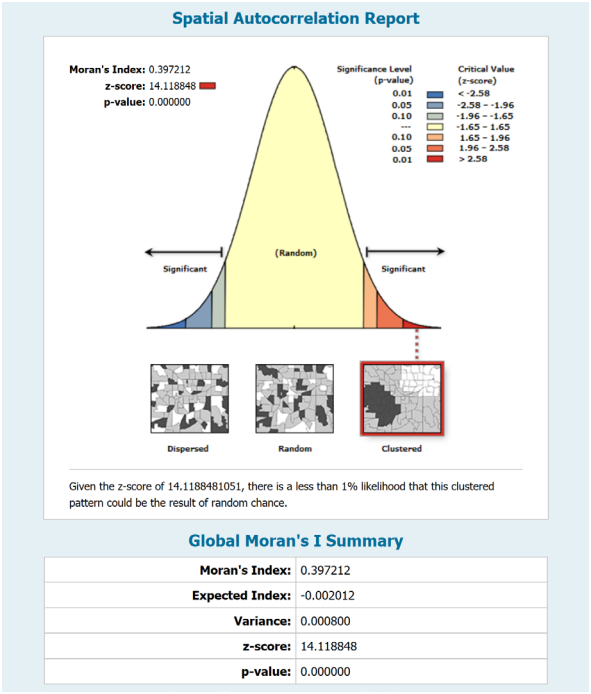


Given the z-score of 3.44797158635, there is a less than 1% likelihood that this clustered pattern could be the result of random chance.

Global Moran's I Summary

Moran's Index:	0.207354
Expected Index:	-0.002667
Variance:	0.003710
z-score:	3.447972
p-value:	0.000565

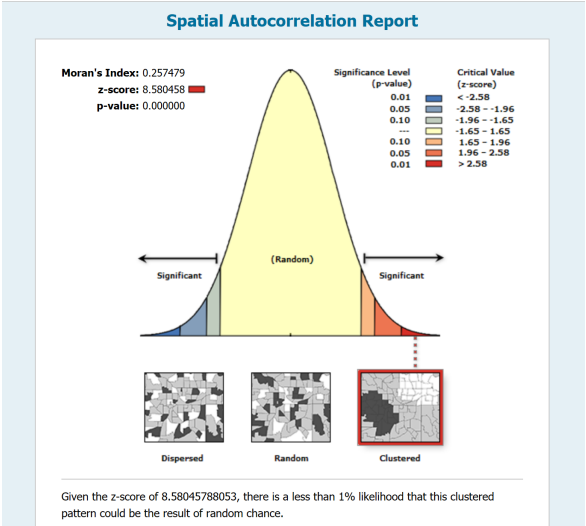
E. IRS 2011-12



Global Moran's I Summary

Moran's Index:	0.397212
Expected Index:	-0.002012
Variance:	0.000800
z-score:	14.118848
p-value:	0.000000

F. IRS 2015-16

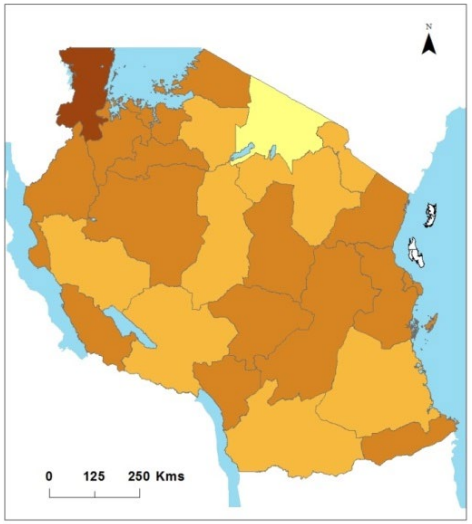


Global Moran's I Summary

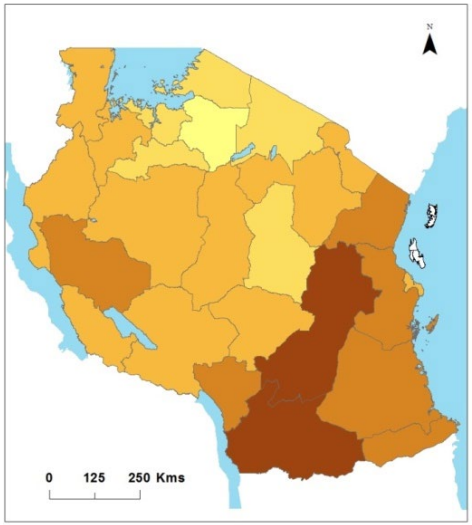
Moran's Index:	0.257479
Expected Index:	-0.001901
Variance:	0.000914
z-score:	8.580458
p-value:	0.000000

Appendix 3: Modelled Mosquito Species Distribution by Region

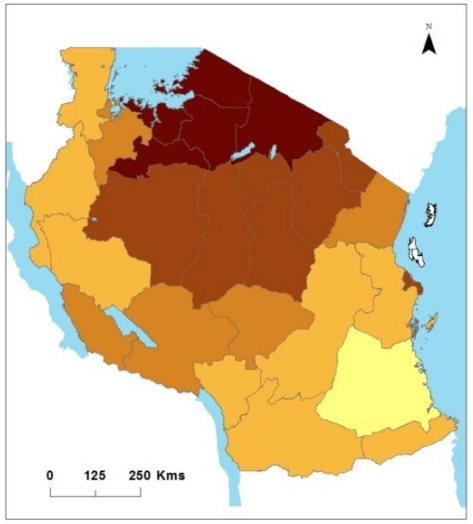
a. An. gambiae

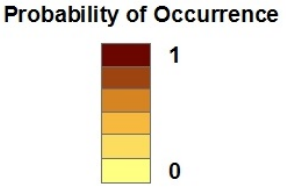


b. *An. funestus*



c. *An. arabiensis*





Appendix 4: Household Questionnaire

Note: For each household in which any person is sampled, one questionnaire is to be completed for the entire household.

SECTION ONE: HOUSEHOLD IDENTIFICATION

1	**Name of Interviewer**		Iname
2	**Date**	(DDMMYY)	date
3	**Region name**		region
4	**District name**		district
5	**District number**	**(see codes below)**	dnumber
6	**Village name**		vname
7	**GPS Reading**	Latitude= Longitude=	GPScords
8	**Household ID (GPS Way point number)**	(3 digit waypoint)	waypoint
9	**Name of Person Interviewed**		nperson
10	**Name of Head of Household**		nheadh

SECTION TWO: HOUSEHOLD MEMEBERS

Instructions: Please give me the names of the persons who usually live in your household and guests who stayed here last night. Start with the head of the household.

1	2	3	4	5	6	7	8
Line No.	**Names**	**Relationship to Head of Household** 01=Head 02=Wife or Husband 03=Son or daughter 04=Brother or Sister 05=Son- or Daughter-in-law 06=Grandchild 07=Parent 08=Parent-in-law 09=Co-wife 10=Adopted/Foster/Step child 11=Other Relative 12=Not Related 13=Don't Know	**Sex** M= male F= female (circle one)	**Age** (in years, If less than one year old record '00')	**Does (name) live here?** (circle Y or N)	**Did (name) stay here last night?** (circle Y or N)	**If older than 15, what is (name's) marital status?** 01=Married or living together 02=Divorced or separated 03=Widowed 04=Single
01			M F 1 2		Y N 1 2	Y N 1 2	
02			M F 1 2		Y N 1 2	Y N 1 2	
03			M F 1 2		Y N 1 2	Y N 1 2	
04			M F 1 2		Y N 1 2	Y N 1 2	
05			M F 1 2		Y N 1 2	Y N 1 2	
06			M F 1 2		Y N 1 2	Y N 1 2	
07			M F 1 2		Y N 1 2	Y N 1 2	
08			M F 1 2		Y N 1 2	Y N 1 2	
09			M F 1 2		Y N 1 2	Y N 1 2	
10			M F 1 2		Y N 1 2	Y N 1 2	

(Continue on extra sheet if more than 10 people in household)

SECTION THREE: HOUSEHOLD FACILITIES

12	Does your household have:	Yes	No
	Electricity?	1	2
	A paraffin lamp?	1	2
	A radio?	1	2
	A television?	1	2
	A mobile telephone?	1	2
	A non-mobile telephone (land line)?	1	2
	An iron (charcoal or electric)?	1	2
	A refrigerator?	1	2

13	Record the Main Material of the Floor		Record only ONE Choice
	Earth, Sand or Dung	01	
	Wood plants, bamboo or palm	02	
	Parquet or polished wood	03	
	Vinyl or asphalt strips	04	
	Ceramic tiles, terrazzo	05	
	Cement	06	☐☐
	Carpet	07	
	Other _____ (specify)	99	

14	Record the main Wall Material of the House		Record only ONE Choice
	Grass	01	
	Poles and Mud	02	
	Sun-Dried Brick	03	
	Backed Bricks	04	
	Wood or Timber	05	
	Cement Blocks	06	☐☐
	Stones	07	
	Other _____ (specify)	99	

15	Record the main Material of the Roof of the House		Record only ONE Choice
	Grass/Thatch/Mud	01	
	Iron/Metal Sheets	02	
	Tiles	03	
	Concrete	04	☐☐
	Asbestos	05	
	Other _____ (specify)	99	

16	How many rooms in your household are used for sleeping? (include rooms outside the main dwelling)	
	(Indicate Number of Rooms)	☐☐

SECTION FOUR: MOSQUITO CONTROL MEASURES

17.	**At any time in the past 12 months, has anyone sprayed the inside of your house with canned/tin mosquito spray (like the kind you would buy at the market) to prevent/kill mosquitoes?**	
	Yes = 01, No = 02 Don't Know = 03	☐☐

18.	**At any time in the past 12 months, has anyone sprayed the interior walls of your dwelling against mosquitoes?**	
	Yes = 01, No = 02 Don't Know = 03	☐☐

If yes, answer questions 19 and 20. If no, skip to question 21.

19.	**How many months ago was the house sprayed?**	
	(if less than 1 month, record '00'), 99=NA	☐☐
20.	**Who sprayed the house?**	
	01 = government program 02 = private company 03 = Household member 04 = Other _____ (specify) 05 = Don't know 99= NA	☐☐

21.	**Does your household have any mosquito nets that can be used while sleeping?**	
	Yes = 01, No = 02 Don't Know = 03, No answer = 99	☐☐

22.	**How many mosquito nets does your household have?**	
	(Indicate number of nets)	☐☐

ASK THE PERSON BEING INTERVIEWED TO SHOW YOU THE NET(S). FOR EACH NET OBSERVED COMPLETE THE COLUMNS OF THE TABLE.

		1	2	3	4	5	6	7	8
		How many months ago did your household obtain the mosquito net? Enter No. of Months (if less than one month, write '00')	Where did you get the mosquito net from? 1= Shop 2 = Machinga 3 = Health facility 4 = Government Program 5 =Market 6 = Gift 7 = Other 8 = Don't know	When you got the net was it already treated with an insecticide to kill or repel mosquitoes? (circle Y, N or Don't Know)	Observe or ask the type of mosquito net. 01 = Permanent net 02 = Pretreated net 03 = Other 04 = Not Sure If permanent net, skip Q5 & Q6 and go to Q7	Since you got the net has it ever been soaked or dipped in a liquid to repel mosquitos or bugs? (circle Y, N or Don't Know)	If yes, how many months ago was the net last soaked or dipped? Enter No. of Months (if less than one month, write '00')	Did anyone sleep under this mosquito net last night?	Who slept under this mosquito net last night? (Record the person's Name and Line Number from Section 2 of this Questionnaire) Name Line No.
1	Net # 1	☐☐	☐☐	Y N 1 2 Don't Know 3	☐☐	Y N 1 2 Don't Know 3	☐☐	Y N 1 2 Don't Know 3	_____ ☐☐ _____ ☐☐ _____ ☐☐ _____ ☐☐
1	Net # 2	☐☐	☐☐	Y N 1 2 Don't Know 3	☐☐	Y N 1 2 Don't Know 3	☐☐	Y N 1 2 Don't Know 3	_____ ☐☐ _____ ☐☐ _____ ☐☐ _____ ☐☐

(Use next sheet if more than 2 nets are observed in the household)

Bed Net List (continued from previous page, if needed)

		1	2	3	4	5	6	7	8
		How many months ago did your household obtain the mosquito net? Enter No. of Months (if less than one month, write '00')	Where did you get the mosquito net from? 1= Shop 2 = Machinga 3 = Health facility 4 = Government Program 5 =Market 6 = Gift 7 = Other 8 = Don't know	When you got the net was it already treated with an insecticide to kill or repel mosquitoes? (circle Y, N or Don't Know)	Observe or ask the type of mosquito net. 01 = Permanent net 02 = Pretreated net 03 = Other 04 = Not Sure If permanent net, skip Q5 & Q6 and go to Q7	Since you got the net has it ever been soaked or dipped in a liquid to repel mosquitos or bugs? (circle Y, N or Don't Know)	If yes, how many months ago was the net last soaked or dipped? Enter No. of Months (if less than one month, write '00')	Did anyone sleep under this mosquito net last night?	Who slept under this mosquito net last night? (Record the person's Name and Line Number from Section 2 of this Questionnaire) Name Line No.
1	Net # 3	☐☐	☐☐	Y N 1 2 Don't Know 3	☐☐	Y N 1 2 Don't Know 3	☐☐	Y N 1 2 Don't Know 3	_____ ☐☐ _____ ☐☐ _____ ☐☐ _____ ☐☐
1	Net # 4	☐☐	☐☐	Y N 1 2 Don't Know 3	☐☐	Y N 1 2 Don't Know 3	☐☐	Y N 1 2 Don't Know 3	_____ ☐☐ _____ ☐☐ _____ ☐☐ _____ ☐☐

(Use additional sheet if more than 4 nets are observed)

Appendix 5: Laboratory Form

(one form to be completed for each 2-7 year old child whose blood is collected on filter paper)

1	Date	Day ____ Month ____ Year ____	Date
2	Region name		region
3	District name		district
4	District number	____ ____	dnumber
5	Village name		name
6	GPS reading	Latitude= Longitude=	GPSCord
7	Household ID (GPS Way Point number)	____ ____ ____	HouseID
8	Individual ID number [District no.][Way point no.][HH member line no. from Questionnaire]	____ ____ ____ ____ ____ ____ ____	IDnum
9	Name of Subject (3 names)		name
10	Sex	1 = Male, 2 = Female ____	sex
11	Age (Year)	____	age
12	Date of Birth	Day ____ Month ____ Year ____	dob
13	Name of Household Leader		Hhead
Filter Paper Blood Sample			
14	Parental Consent Received	1 = yes, 2 = no ____	Pconsent
15	Storage/Future Testing Consent Received	1 = yes, 2 = no ____	Sconsent
16	Sample Collected	1= sample collected on filter paper, 2=Not done ____	sample

Name of Examiner: _____ Signature: _____

Name of Team Leader: _____ Signature: _____

Appendix 6: Age Distribution of Children Sampled for Wb123 Seropositivity

Age		2011	2012	2013	Total
2	n	382_a	410_a	345_a	1137
	% within year	17.5%	16.9%	15.4%	16.6%
3	n	372_a	447_a	373_a	1192
	% within year	17.0%	18.4%	16.6%	17.4%
4	n	366_a	411_a	347_a	1124
	% within year	16.7%	17.0%	15.5%	16.4%
5	n	381_a	395_a	345_a	1121
	% within year	17.4%	16.3%	15.4%	16.4%
6	n	304_a	309_a	310_a	923
	% within year	13.9%	12.8%	13.8%	13.5%
7	n	381_a	451_a	525_b	1357
	% within year	17.4%	18.6%	23.4%	19.8%
Total	n	2186	2423	2245	6854
	% within year	100.0%	100.0%	100.0%	100.0%

Each subscript letter denotes a subset of Year categories whose column proportions do not differ significantly from each other at the .05 level.