PREVENTIVE CHEMOTHERAPY FOR ELIMINATION OF LYMPHATIC FILARIASIS AND ONCHOCERCIASIS IN SIERRA LEONE

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

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DECLARATION

This work has not been previously accepted in substance for any other degree and is not being currently submitted in candidature for any other degree. Part of this project has been published with multiple authorship including Dr. Joseph B. Koroma (JBK), Dr. Santigie Sesay (SS), Mustapha Sonnie (MS), Dr. Mary H. Hodges (MHH), Dr. Foday Sahr (FS), Dr. Yaobi Zhang (YZ), Professor Moses J. Bockarie (MJB), Momodu M Bangura (MMB), and Mohamed S Bah (MSB). MJB was the author's PhD supervisor.

Signed……(Candidate)

Date…….

The project described in this thesis was conceived and designed by the author, JBK. He was the national coordinator for the National Onchocerciasis Control Programme and later the Neglected Tropical Diseases (NTD) Control/Elimination Programme in Sierra Leone from 2005 to 2009. Since 2009 he has been the technical advisor for the NTD programme in Sierra Leone. The results presented in chapters three, four, five and six were conducted in collaboration with others whose contributions were as follows:

Chapter 3

SS, the national coordinator for the NTD control/elimination programme in Sierra Leone, and MHH, the Country Director for Helen Keller International in Sierra Leone, assisted with the coordination of the fieldwork. YZ, MHH, and MJB assisted with data analysis.

Chapter 4

MMB led and conducted the field work. MSB and MHH conducted the data entry and initial analysis. JBK and MHH drafted and revised the paper, and conducted correlation analysis. MJB provided support during the revision of the paper. YZ conducted the final data analysis, spatial analysis and contributed to the revision of the paper. All authors reviewed and approved the final manuscript.

Chapter 5

SS, MS, MHH, FS, YZ, and MJB participated in field activities. SS, FS, and YZ assisted with laboratory analysis. MHH and YZ participated in data analysis. MJB contributed to the manuscript writing. JBK, SS, and MS coordinated the study. JBK, SS, MS, MHH, FS, YZ and MJB revised the paper. JBK, SS, MS, MHH, FS, YZ, and MJB reviewed and approved the final manuscript. FS conducted quality control.

Chapter 6

JBK, SS, and MHH designed the study. SS was the NTD programme manager and coordinated the field work. JBK supervised the study. YZ and JBK conducted the data analysis. MJB and MHH provided support during data analysis.

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ABSTRACT

Lymphatic filariasis (LF) and onchocerciasis are highly endemic in Sierra Leone. Using World Health Organization (WHO) guidelines for monitoring national programmes where both infections are co-endemic, this study aimed to determine the impact of preventive chemotherapy on transmission intensity by measuring changes in human infection status using standard epidemiological indicators.

Separate longitudinal studies designed to deliver WHO outcomes for programmes targeting the elimination of both diseases were conducted. Onchocerciasis mapping surveys from 1988-2005 revealed that twelve of fourteen health districts were endemic. The baseline average mf prevalence was 53.1%, and mf densities in positive-only or entire populations were 28.87 and 15.33 mf/snip, respectively. Mf prevalence and density increased with age and was higher in males than females.

Baseline prevalence and intensity surveys showed that LF was endemic in all 14 districts (*Wuchereria bancrofti* antigenaemia prevalence > 1%). Mean LF prevalence by ICT cards was 21% (males 28%; females 15%) with higher prevalence in the northeast (Bombali 52%; Koinadugu 46%; Tonkolili 37%; Kono 30%) and lower in the southwest (Bonthe 3%; Pujehun 4%). Mf prevalence was also relatively higher in the northeast (Bombali 6.7%; Koinadugu 5.7%; Port Loko 4.4%; Kono 2.4%). Mf prevalence was higher in males (males 2.9%; females 1.8%) and infection rate was higher in the over 20 years age-group (2.5%) than younger (1.7%). Arithmetic mean mf density was 50.30 mf/ml among mf-positive individuals and 1.19 mf/ml in the population examined.

Nationwide mass drug administration (MDA) using ivermectin plus albendazole was applied to eliminate both diseases. In 2010, after five rounds of MDA (2005-2009) with effective treatment coverage for onchocerciasis during 4/5 years, overall onchocerciasis mf prevalence was reduced by 60.26% (from 53.10% to 21.10%), overall mf density among positive-only individuals was reduced by 71.29% (28.87 to 8.29 mf/snip) and overall mf density among the entire population studied was reduced by 88.58% (15.33 to 1.75 mf/snip). Mf prevalence and density were higher in males, lowest in the 1-9 and highest in the 40-49 year age groups. Mf prevalence was reduced by >50% in 10/12 districts, and reduction in skin mf density was ≥50% among positives-only in 11/12 districts.

After MDAs with effective treatment coverage in 2008-2010, LF mf prevalence decreased to less than 1% in 11/12 districts. Mf prevalence fell by 88.5% to 0.3%, with decreases of 70-95% in seven and 100% (0 prevalence) in four districts, respectively. Overall arithmetic mean mf density after three MDAs was 17.59 mf/ml among mf positive individuals and 0.05 mf/ml for the entire population examined.

After five MDAs, the overall mf prevalence was 0.54% and was higher in males (0.7%) than females (0.36%). Eight of twelve districts with <1% mf prevalence passed the pre-transmission assessment survey (TAS) and therefore qualified for a TAS to determine whether MDA could be stopped. Four districts failed the pre-TAS: Koinadugu (0.98% *i.e.* close to 1%), Bombali (2.67%), Kailahun (1.56%) and Kenema (0%). Following WHO recommendations, Kenema and Kailahun districts were paired to form a unit of approximately one million. Kenema, the spot check site, was considered to have failed the pre-TAS even though the mf prevalence was 0% because Kailahun, the sentinel site, failed.

A qualitative study examining the impact of the Ebola virus disease (EVD) outbreak on the NTD programme found that despite a one-year absence of interventions, two rounds of MDA had been completed, including one during the ongoing outbreak in May/June 2015. Although it compromised the likelihood of achieving the 2020 targets of LF elimination and onchocerciasis control, the EVD outbreak has enhanced awareness about the important role of community volunteers in ensuring its success. While it may be the 'endgame' for LF, the NTD community and collaborating research institutions must address additional challenges if onchocerciasis is to be eliminated from Sierra Leone.

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LIST OF ABBREVIATIONS

ADB	African Development Bank
ADL	Adeno-lymphadenitis
ADLA	Acute dermatolymphangioadenitis
AFRO	World Health Organization Regional Office for Africa
AG	Antigen
APOC	African Programme for Onchocerciasis Control
APOD	Acute Papular Onchodermatitis
ARI	Acute Respiratory Infection
AsDB	Asian Development Bank
BBIN	Bangladesh, Bhutan, India and Nepal
BMGF	Bill & Melinda Gates Foundation
CBTI	Community-based Treatment with Ivermectin
CDD	Community-directed Drug Distributor
CDI	Community-Directed Intervention
CDTI	Community Directed Treatment with Ivermectin
CFA	Circulating Filaria Antigen
CHC	Community Health Centres
CHP	Community Health Post
CHO	Community Health Officer
CIs	Confidence interval
CMO	Chief Medical Officer
CNTD	Center for Neglected Tropical Diseases
CPOD	Chronic Papular Onchodermatitis
DALYs	Disability-adjusted life years
DERC	District Ebola Response Centres
DFID	Department for International Development
DHMT	District Health Management Team
DMO	District Medical Officer
DPC	Disease Prevention and Control
DSA	Disease Specific Assessment
ECOWAS	Economic Community of West African States
EDCA	Endemic diseases control assistant
EDTA	Ethylenediamine Tetraacetic Acid
END in Africa	End Neglected Tropical Diseases in Africa
EOC	Emergency Operation Center
EPI	Expanded Programme on Immunization
ESPEN	Expanded Special Project for Elimination of Neglected Tropical Diseases
ETC	Ebola treatment Centre
EU	European Union
EVD	Ebola Virus Disease
FDS	Filaria Dance Sign
FGS	Focus group discussion
FHI360	Family Health International 360
FPSU	Filarial Programme Support Unit
FTS	Filaria test strip
GAELF	Global Alliance to Eliminate Lymphatic Filariasis

GDP	Gross Domestic Product
GNI	Gross National Income
GoSL	Government of Sierra Leone
GPELF	Global Programme for the Elimination of lymphatic filariasis
GMS	Greater Mekong Subregion
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
HKI	Helen Keller International
ICC	International Certification Committee
ICT	Immunochromatographic test
IEC	Information, education and communication
IRS	Indoor residual spraying
ITN	Insecticide-treated bed nets or insecticide impregnated bed nets
IU	Implementation units
JAF	Joint Action Forum of APOC
LF	Lymphatic Filariasis
LLIN	Long-lasting insecticidal net
LOD	Lichenified Onchodermatitis
LSDI	Lubombo Spatial Development Initiative
LSTM	Liverpool School of Tropical Medicine
MCHA	Maternal and Child Health Aide
MCHP	Maternal and Child Health Post
MDA	Mass Drug Administration
MDP	Mectizan Donation Program
M&E	Monitoring and Evaluation
MEC	Mectizan Expert Committee
MMDP	Morbidity management and disability prevention
MF	Microfilariae
MOHS	Ministry of Health and Sanitation
MRU	Mano River Union
MSD	Merck, Sharpe and Dome
NBS	Night Blood Survey
NERC	National Ebola Response Centre
NGDOs	Non-Governmental Development Organisation
NOCP	National onchocerciasis Control programme
NTDP	Neglected Tropical Disease Program
NTD	Neglected Tropical Disease
OCP	WHO Onchocerciasis Control Programme
OEC	Onchocerciasis elimination committee
OEPA	Onchocerciasis Elimination Programme for the Americas
PacELF	Pacific Programme to Eliminate LF
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health
PC	Polymerase Chain Reaction
PC NTDs	Neglected Tropical Diseases targeted through Preventive Chemotherapy
PCR	Preventive Chemotherapy
PCT	Preventive chemotherapy and transmission control

PHC	Primary Health Care
PHU	Peripheral Health Unit
Pre-TAS	Pre- Transmission Assessment Survey
RAGFIL	Rapid assessment of the geographic distribution of Bancroftian Filariasis
RAPLOA	Rapid Assessment Procedure for Loiasis
RDT	Rapid diagnostic test
REMO	Rapid epidemiological mapping for onchocerciasis
RTI	Research Triangle Institute
SAC	School Aged Children
SAE	Severe adverse event
SCH	Schistosomiasis
SCS	Spot check site
SECHN	State enrolled community health nurse
SIZ	Special Intervention Zone
SS	Sentinel site
SSB	Survey Sample Builder
STH	Soil Transmitted Helminthes
STI	Sexually Transmitted Infection
TAS	Transmission Assessment Survey
TB	Tuberculosis
TBA	Tradition Birth Attendant
TBF	Thick Blood Film
TF	Trachomatous inflammation-follicular
TT	Trachomatous trichiasis
USAID	United States Agency for International Development
WA	Western Area
WAHO	West African Health Organisation
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

NEGLECTED TROPICAL DISEASES

The significantly improved and excellent strategic investment in neglected tropical diseases (NTD) control globally has paved the way for the potential elimination of some NTDs such as lymphatic filariasis (LF) and onchocerciasis as public health problems in Sierra Leone (Hodges *et al.* 2011). NTDs are poverty-promoting parasitic and bacterial diseases with often stigmatising conditions that occur mainly in rural areas of low-income countries. NTDs are ancient afflictions even described in the Bible and other ancient literature (Molyneux, Hotez, Fenwick 2005) and have afflicted humanity for millennia (Molyneux, Hotez, Fenwick 2005). Apart from affecting mainly the poor and exacerbating their poverty, there is strong evidence that when infected with NTDs one becomes increasingly susceptible to, or there is worsening of, the progression of morbidity from Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS), Tuberculosis (TB), and Malaria. Therefore, NTD control/elimination is an indirect effective, low-cost means of reducing morbidity and mortality associated with these three global health problems (Gloeckner *et al.* 2010). NTDs affect over a billion people including over half a million children. It is estimated that annually 46-57 million disability-adjusted life years (DALYs) are lost through NTDs (World Health Organization (WHO) Regional Office for Africa (AFRO) 2016).

The momentum of the fight to combat NTDs has reached a peak unprecedented for public health programmes with the formation of a coalition of partners including donors, international health-oriented Non-Governmental Development Organisation (NGDOs), and pharmaceutical companies that are prepared to support endemic countries globally with their efforts to eliminate NTDs. This big development started in 2012 with the London Declaration on NTDs during which key donors pledged their support for this development and committed to either continuing to donate drugs or to provide the funds needed for the interventions. The key aspects of this coalition is joint support to control NTDs, coordination and collaboration at national and international levels, and regular reviews of progress through publication of reports that show how the key milestones established for the WHO 2020 targets for NTDs are being achieved (Bockarie et al. 2013; Uniting to combat NTDs 2015).

Among the 15 most common NTDs, seven have similar strategies to address their control, namely, single doses of effective treatment termed preventive chemotherapy (PC) given once, twice or four times a year, to broad segments of the population within communities that are endemic for these NTDs. These seven NTDs affect mainly the poorest communities in countries that usually have weak health systems (Baker *et al.* 2010). They are LF, onchocerciasis, schistosomiasis, three soil transmitted helminthiasis[1] (ascariasis, trichuriasis, hookworm), and trachoma (Linehan *et al.* 2011). It has been suggested that NTDs rank sometimes higher than malaria and TB when DALYs lost is considered (Liese *et al.* 2010).

The African region contributes an estimated 40% of the NTD global burden. All 42 countries in Africa have at least two of the NTDs that are targeted through PC and 36 are endemic for up to seven PC NTDs (WHO AFRO NTDP 2016). An estimated 169 million people need treatment for onchocerciasis and 468 million need treatment for LF in the WHO African region (WHO AFRO NTDP 2016). Due to increasing political commitment and government leadership in delivering treatments, there has been significant progress in tackling NTDs in the African region (WHO AFRO NTDP 2016).

Since NTDs affect mainly the poorest communities in countries that usually have weak health systems (Baker *et al.* 2010), the affected countries themselves have not been able to address the NTD problem without substantial financial and technical input and assistance from international donors. Strategic investments in the control of NTDs mainly by the US Government through the United States Agency for International Development (USAID), the British Government through the Department for International Development (DFID), the Bill & Melinda Gates Foundation (BMGF), and pharmaceutical companies such as Merck and Co. Inc., GlaxoSmithKline, Pfizer, Johnson & Johnson, Merck and MedPharm, has enabled treatment for these seven debilitating NTDs targeted through PC (PC NTDs) paving the way for elimination of some of these NTDs as public health problems (Hodges *et al.* 2011). Since 2007, USAID, DFID and BMGF have pledged new funding to support the implementation of PC programmes globally (Baker *et al.* 2010). Each year pharmaceutical companies donate drugs to address

[1] In other sections I refer to these seven NTDs as five NTDs because these 3 belong to the same group (helminthiasis).

NTDs at an estimated cost of US$3.8 billion, and it is estimated that 600 million DALYs will be averted between 2011 and 2030 if NTD goals are attained (Uniting to Combat NTDs 2015). The pharmaceutical companies Merck and Co. Inc., GlaxoSmithKline, Pfizer, Johnson & Johnson, Merck and MedPharm have also committed to donating NTD drugs needed by endemic countries for as long as needed (Baker *et al.* 2010).

Many NTDs show significant geographic overlap and in many cases, are syndemic. There is usually, therefore, need to integrate activities targeting the seven NTDs to save costs and also allow the limited health workforce to maximise their effectiveness in controlling/eliminating these diseases (Molyneux, Hotez, Fenwick 2005). Since most countries in Africa and other parts of the world are endemic for more than two PC NTDs and are challenged in terms of human resource capacity, it is good that NTDPs use an integrated approach in addressing the NTD problem to reduce cost and ensure that health systems, though challenged in terms of human resource, can maximize their effectiveness against the NTDs. In 2006, WHO developed guidelines for PC of human helminthiasis using integrated approaches (WHO 2006; Baker *et al.* 2010). Among the PC NTDs, Onchocerciasis, LF, and trachoma are currently targeted for elimination (Baker *et al.* 2010). The current minimal cost of 0.40 US$ per person treated per annum for NTDs will bring multiple health benefits to many and will have a socioeconomic impact in the affected countries (Molyneux, Hotez, Fenwick 2005). Some NTD experts believe that NTD control is one efficient way to combat poverty as most of these NTDs can be effectively treated at minimal cost. NTDs rank sometimes higher than malaria and TB when DALYs lost is considered (Liese *et al.* 2010). NTD experts urge the international NTD community including those from the countries affected to be committed to eliminating NTDs so that future generations can be protected from the disability, stigma, and blindness linked with diseases like LF and onchocerciasis (Molyneux 2009).

WHO AFRO recently (23rd May 2016) launched the 5-year (2016-2020) Expanded Special Project for Elimination of NTDs (ESPEN) that will coordinate and guide countries endemic for NTDs in Africa to use effective and efficient strategies for controlling/eliminating PC NTDs. ESPEN is expected to make a significant contribution in accelerating the reduction of the

burden of PC NTDs in Africa through technical support and guidance to endemic countries (WHO AFRO NTDP 2016; WHO 2016b).

STUDY AREA

Sierra Leone is a poor West African country that belongs to what MacKinnon and MacLaren (2012) describe as "fragile and conflict-affected states" with health indicators that paint a dire picture for residents and the way forward for the health service appears bleak. Between 1991 and 2002 there was a civil war in the country that had a devastating socio-economic effect and almost brought the entire health care delivery system to a standstill. However, the socio-economic situation started improving after the end of the civil war in 2002, and the economic prospects were seen by many experts to be more optimistic. The neglected tropical diseases programme (NTDP) that started with the national onchocerciasis control programme (NOCP) in 1989 was integrated in 2007 to include, besides onchocerciasis, other NTDs such as LF, schistosomiasis, soil-transmitted helminthiasis, trachoma, Guinea worm disease (Dracunculiasis), and Buruli Ulcer. The NTDP made significant achievements between 2005 and 2013 with financial and technical support from the WHO Headquarter, AFRO, the WHO African Programme for Onchocerciasis Control (APOC), USAID, Helen Keller International (HKI), Sightsavers and the Centre for Neglected Tropical Diseases (CNTD) of the Liverpool School of Tropical Medicine (LSTM) (Pose and Rabinowitz 2014). Unfortunately, this was marred temporarily by an outbreak of Ebola Virus Disease (EVD) in West Africa that started in neighbouring Guinea in December 2013 and spread to Liberia in March 2014 and Sierra Leone in May 2014 (Boisen *et al.* 2015; Hersey *et al.* 2015). The EVD outbreak is believed to have caused almost the same devastating socio-economic effect as the civil war of 1991-2002 and appeared to have derailed the NTDP (Bartsh *et al.* 2015; Boisen *et al.* 2015; Helleringer and Noymer 2015; Hersey *et al.* 2015).

General information on Sierra Leone

The general information on Sierra Leone is provided in terms of the geography and climate, population and demographic situation, political and administrative organisation, and economic and socio-economic profile.

Geography and climate

Sierra Leone is situated on the West coast of Africa between latitudes 70 and 100 north of the equator, and longitude 10.50 and 13.50 west of Greenwich. The country is bounded on the west by the Atlantic Ocean, on the north and east by Guinea and the south-west by Liberia. Population movement across these borders is high, and the three countries (Sierra Leone, Guinea, and Liberia) have had a recent history of civil strife. The country has a surface area of about 72,000 square kilometres or 28,000 square miles (Government of Sierra Leone (GoSL), Ministry of Health and Sanitation (MOHS) 2009; GoSL, MOHS 2012a).

Figure 1: Map of Sierra Leone showing rivers - risk factor for onchocerciasis (Online, available from: http://www.mapsofworld.com/sierra-leone/river-map.html)

There are ten major rivers (Figure 1 above) running from north-east to the south-west of Sierra Leone that are connected to large tributaries (Wikipedia, (online) available from: https://en.wikipedia.org/wiki/List_of_rivers_of_Sierra_Leone; Accessed 29/06/2016).

The country is tropical, and the tropical climate consists of two distinct seasons: the dry season that starts in November and ends in April, and the rainy season that starts in May and ends in October. The vegetation ranges from mangrove along the coasts to forest covered hills and savannah as one moves further inland (GoSL, MOHS 2009; WHO Sierra Leone 2009; GoSL, MOHS 2010; GoSL, MOHS 2012a; WHO AFRO NTDP 2013; WHO Sierra Leone 2014).

Population and demographic situation

There are 20 distinct language groups in Sierra Leone that reflect the diverse culture and traditions among which the largest ethnic groups are the Temne-35%, Mende-31 and Limba-8% (GoSL, MOHS 2009; GoSL, MOHS 2012a; Wikipedia, (Online) available from: https://en.wikipedia.org/wiki/Ethnic_groups_in_Sierra_Leone; accessed 19/10/2016). The estimated total population in 2015 is 6.45 million people (African Health Observatory, WHO AFRO 2016). The country has a young population with relatively high proportion below 15 years (>40%). The proportion of the population living in urban areas in 2008 was 38% (GoSL, MOHS 2009; WHO AFRO 2009; GoSL, MOHS 2010).

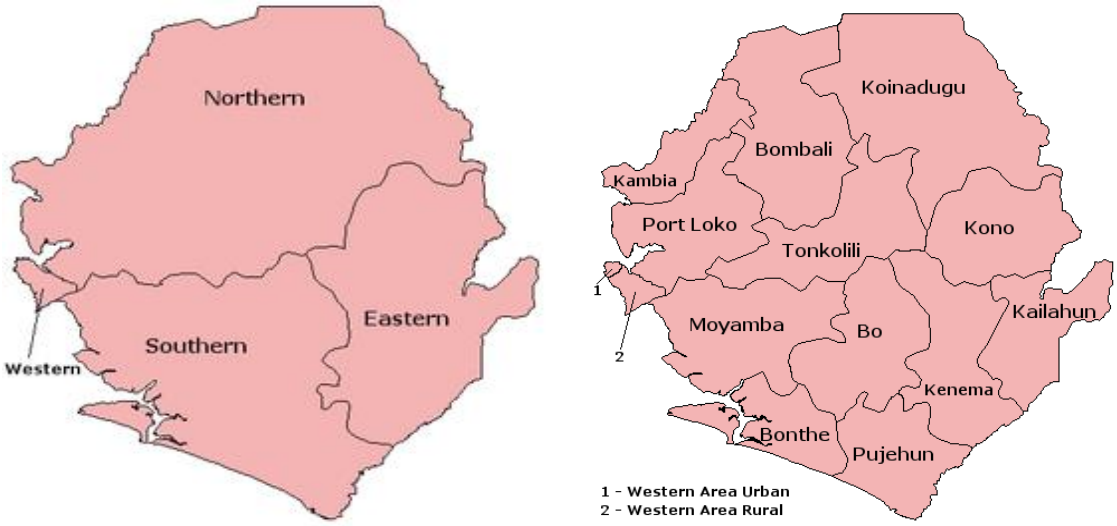
Political and administrative organisation

Sierra Leone is administratively divided into four regions (Figure 2): The Western Area and three provinces – Eastern, Northern, and Southern provinces. The three provinces are further divided into twelve districts (Eastern- Kailahun, Kono and Kenema districts; Northern- Koinadugu, Bombali, Kambia, Port Loko and Tonkolili districts; and Southern- Bo, Bonthe, Moyamba and Pujehun districts). The Western Area has been operationally divided into Western Urban district (mainly the capital) and Western Rural District, which comprises of the towns and villages surrounding the capital Freetown (GoSL, MOHS 2009).

The twelve districts are sub-divided into chiefdoms that are governed by traditional Paramount Chiefs. Chiefdoms are subdivided into sections (governed by Section Chiefs), and Sections are

divided into villages (governed by Village Chiefs). There are 149 chiefdoms in the 12 districts of the three provinces that are governed by traditional Paramount Chiefs while the entire Western Area is subdivided into 30 wards headed by Councillors. Recent devolution of services to local communities has led to the creation of 19 local councils (14 district councils headed by elected district council chairmen and five city councils headed by elected Mayors) (GoSL, MOHS 2009; GoSL, MOHS 2010; GoSL, MOHS 2012a). Excluding the Western Area, Sierra Leone has 14,413 villages with populations between 100 and 500 inhabitants (Koroma, Turay and Moihua 2006).

Figure 2: Sierra Leone maps showing health regions and districts (Online, available from: https://commons.wikimedia.org/wiki/Atlas_of_Sierra_Leone#/media/File:Sierra_Leone_Provinces.png)



Politically Sierra Leone is a constitutional democracy with a unicameral parliament that has one chamber with 124 seats. After gaining independence from Great Britain on 27th April 1961, Sierra Leone became a Republic on 19 April 1971 (GoSL, MOHS 2009; GoSL, MOHS 2010; GoSL, MOHS 2012a). The 11 year (1991-2002) civil war in Sierra Leone resulted in tens of thousands of deaths, internal displacement of a third of the population including health personnel, brought health services to a standstill in large parts of the country and resulted in the destruction of health-related properties that needed a long time to be replaced. The negative socio-economic impact of the war was still noticed even 12 years after the end of the civil war.

The health workforce was severely affected either through the death of many health workers or migration of health workers to other countries during the war (MacKinnon and MacLaren 2012; Pose and Rabinowitz 2014).

The rebuilding of governance infrastructure after the civil war started in February 2002 with disarmament and demobilisation of ex-combatants through the support of the United Nations and other development partners, followed by a successful presidential and parliamentary elections on 14th May 2002. Another set of successful presidential and parliamentary elections were repeated five years later, 28th July 2007, that resulted in a smooth transition of power from the then ruling party to the opposition party. This event is viewed by many as a major milestone in the re-establishment of strong constitutional democracy in the country, which signaled the end of the recovery phase and the start of a peacebuilding and development phase of post-conflict Sierra Leone (GoSL, MOHS 2009; GoSL, MOHS 2010; GoSL, MOHS 2012a; WHO Sierra Leone 2009; WHO Sierra Leone 2014).

Economic and socio-economic profile

Sierra Leone is classified as one of the least developed countries in Africa and the world in general. The 2007 Human Development Report ranked the country 177 out of 177, the least developed country in the world (WHO Sierra Leone 2009); 178 out of 178 in 2008 (GoSL, MOHS 2009); and 183 out of 187 countries in 2012 with a human development index of 0.374 (United Nations Development Programme (UNDP) 2014a,b). However, the human development report of 2015 ranks the country 181 out of 188 and notes that the human development index has improved from 0.268 in 1980 to 0.413 in 2014 (a 50% increase) (WHO AFRO 2009; UNDP 2015; Focus 1000 2016). Gross national income (GNI) per capita in 2011 was US$ 1,815.1 (GoSL, MOHS 2009; UNDP 2014a,b). In 2006 it was estimated based on the 2004 census that 71% of Sierra Leoneans are poor (earning below $1.00 a day) and 26% of the population live in extreme poverty (*i.e.* they are unable to afford 2,700 calories of food per day) (UNDP 2009). About 70% of Sierra Leoneans lived below the poverty level in 2007 (GoSL, MOHS 2009). The country's main economic sector includes mining, agriculture, and fisheries. Diamond, bauxite and rutile mining is the main source of foreign exchange. Two-thirds of the country's population are involved in agriculture, mostly subsistence farming and contribute an estimated

51% of the overall national gross domestic product (GDP). Most of what is produced is used for domestic consumption, and income is low. The manufacturing sector is still developing and involves mostly processing of raw materials and light manufacturing for the domestic market. Living standards are expected to rise if the current stabilising macro-economic policy of the government is maintained. Post-conflict growth performance has been relatively better averaging 7.5% per year between 2005 and 2009 (GoSL, MOHS 2009). Gross national income per capita in 1990 was 430$, in 2000- 350$, and in 2008-750$ (UNDP 2014a,b).

Inter-country collaboration takes place through the Mano River Union (MRU), which involves Sierra Leone and her neighbours, Liberia, Guinea and Cote D'Ivoire, and the Economic Community of West African States (ECOWAS), which comprises of all 15 West African states. Although the economy has recently improved, it is still dependent on the maintenance of peace and continued receipt of substantial external financial aid, which is needed to offset the severe trade imbalances and supplement limited government revenues. The country receives significant budgetary support from the European Union (EU), DFID, USAID, the African Development Bank (ADB), the World Bank, the Governments of China, Libya, Iran, Malaysia, and Morocco (WHO Sierra Leone 2009; WHO Sierra Leone 2014).

General information on health services

The information on the health situation and health services in Sierra Leone is provided in terms of the health indicators, health system organisation, health sector priorities, human resources for health and health sector financing.

Health indicators

Sierra Leone is among the poorest in the world as the health situation in Sierra Leone is critical compared even to other sub-Saharan African countries (GoSL, MOHS 2009; GoSL, MOHS 2010; GoSL, MOHS 2012a; MacKinnon and MacLaren 2012; Pose and Rabinowitz 2014). Communicable diseases including NTDs contribute over 70% of the burden of disease (African Health Observatory, WHO AFRO 2016).

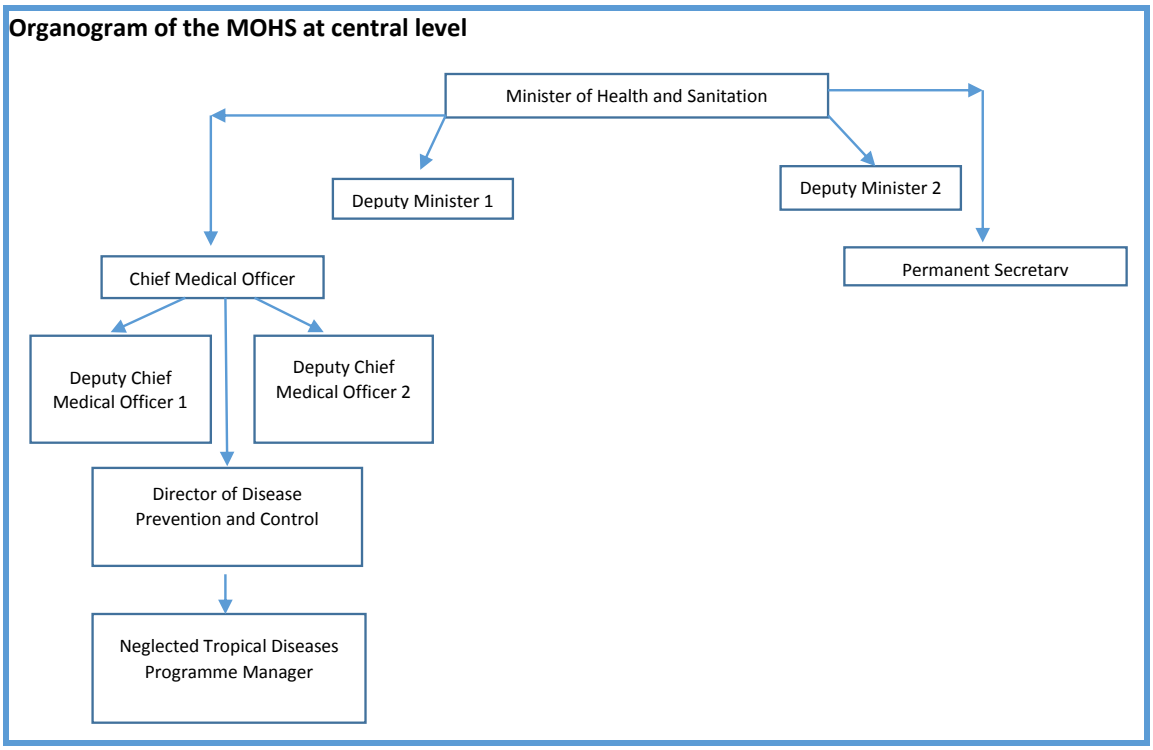
Rural populations bear the greatest burden of diseases especially females within the rural population. Therefore, women are also more likely to stop economic activities due to illness than men. Health care costs remain high resulting in poor utilisation of health services (0.5 visits per person per year). Out of pocket expenses for the health of about 61.3% is among the highest in Africa (African Health Observatory, WHO AFRO 2016). The Government has tried to address the inequality in utilisation of health services by devolving responsibility and accountability to the local level for effectiveness and efficiency of service delivery (GoSL, MOHS 2010; GoSL, MOHS 2012a). The government introduced a free health care initiative in 2010 that targets pregnant women, lactating mothers and children under five years to address the high maternal, child and under-five morbidity and mortality (WHO Sierra Leone 2014).

Health system organisation

The MOHS at the central level is currently headed politically by the Minister of Health and Sanitation, and two Deputy Ministers of Health and Sanitation (Figure 3 below). As part of public sector reforms initiated in 2003, the MOHS was divided into two main divisions at the central level: medical services and management services. The medical services division is currently headed by a Chief Medical Officer (CMO), who is assisted by two Deputy CMOs. The management services division is headed by a Permanent Secretary, who is usually a Chief Administrative Officer within the Ministries. Between the two main divisions of the MOHS, there are 13 directorates and 12 programmes. The NTDP is supervised directly by the Director of Disease Prevention and Control (DPC) (GoSL, MOHS 2009; GoSL, MOHS 2015).

At the district level, health service is coordinated by a district health management team (DHMT) headed by a District Medical Officer (DMO). The DHMT is responsible for overall planning within districts; implementation of the national health policies in the districts; coordination and management of district health services; health education; ensuring provision of safe water and environmental sanitation; M&E of district health services, including health data collection, management, interpretation, dissemination and utilization (GoSL, MOHS 2010; GoSL, MOHS 2012a; GoSL, MOHS 2012b).

Figure 3:



The health care system within districts is organised in a three-tier system: the first tier includes the frontline health facilities called peripheral health units (PHUs); the second includes district hospitals; and the third, the referral hospitals. PHUs (Table 1) are the first line health services and are divided into three groups: community health centres (CHCs), community health posts (CHPs) and maternal and child health posts (MCHPs). Currently, health care service within communities is delivered through a network of about 1,195 PHUs (GoSL, MOHS 2009; GoSL, MOHS 2010; GoSL, MOHS 2012b).

Table 1: Details on types of peripheral health Units and the service they provide (GoSL, MOHS 2009; GoSL, MOHS 2010; GoSL, MOHS 2012a,b).

S. No	Type of PHU	Population covered	Usual Location	Area covered	Staffing	Services provided	Supervision
1	CHC	10,000 to 30,000 people	Chiefdom headquarter	Entire chiefdom or five-	community health officers (CHOs), State	Management of communicable diseases -malaria, acute	Supervise activities in lower level PHUs- CHPs and MCHPs.

				ten-mile radius	enrolled community health nurses (SECHN), midwives, laboratory and pharmacy technicians	respiratory infection (ARI), and diarrheal diseases; normal deliveries; minor surgical emergencies such as abscesses and injuries; inpatient care and some laboratory services	Severe cases are referred to them from CHPs and MCHPs when necessary. They also supervise traditional birth attendants (TBAs) within chiefdoms
2	CHP	5,000 to 10,000 people	Section headquarter	Entire sections or 5-mile radius	Endemic diseases control assistants and SECHN	Maternal and child health care services, communicable diseases	Supervise MCHPs and TBAs within the section
3	MCHP	500 and 5,000 people	Relatively large villages	3-mile radius	Maternal and Child health Aides (MCHAs)	Maternal and child health care services, communicable diseases	TBAs within area covered

The district hospitals form the secondary level facilities providing support and referral points for PHUs. They provide outpatient care for patients referred from PHUs and the population living within the immediate environs; in-patient and diagnostic services; management of accidents and emergencies; and technical support to PHUs. There are about 37 hospitals (secondary health institutions) among which 23 are government owned, and the rest are owned by private, mostly faith-based organisations, and NGOs. There are nine tertiary health facilities among which seven are in the Western Urban District (the capital Freetown). These facilities are inadequately equipped and under-staffed, thus providing limited health care services (GoSL, MOHS 2009; GoSL, MOHS 2010; GoSL, MOHS 2012a,b).

Health sector priorities

One of the key priorities of the GoSL is to improve the health of the nation. However, Sierra Leone has one of the highest under-five mortality rates in the world with almost one out of three children dying before the age of five years from malaria, diarrhoea, and/or pneumonia. Sierra Leone also has one of the highest maternal mortality rates in the world because of obstructed labour, haemorrhage, anaemia, and toxaemia in pregnancy (WHO Sierra Leone 2009; Pose and Rabinowitz 2014). The health situation in Sierra Leone is therefore still in a dire position although significant progress has been made in reducing infant and maternal mortality

rates, improving immunisation coverage and use of long-lasting insecticide-treated bed nets (Sierra Leone Government, MOHS 2006; Pose and Rabinowitz 2014).

To ensure effective implementation of the national health priority areas, the National Health Sector Strategic Plan 2010-2015 was developed around strengthening the six pillars of the national health system: (1) leadership and governance; (2) service delivery; (3) HRH; (4) medical products and technologies; (5) health care financing; and (6) health information system (GoSL, MOHS 2009; WHO Sierra Leone 2009; GoSL, MOHS 2010; GoSL, MOHS 2012a).

Human Resources for Health

According to MacKinnon and MacLaren (2012), human resources for health is key for accessibility of health services and determines the overall health of the country's population. Accessibility to health care services is poor especially in rural areas due to an acute shortage of trained health professionals; the significant dichotomy of staff between rural and urban health facilities and among health cadres; and poor access to good quality healthcare, medical technology, and equipment. WHO has set benchmarks to determine if a country is facing a health workforce crisis. WHO determines that a country should have 2.28 health care professionals per 1,000 population as a minimum threshold for public health access. Countries with less than 2.28 health workers per 1,000 population are said to have a critical shortage of health professionals as this indicator sheds light on a country's capacity to meet basic health needs (MacKinnon and MacLaren 2012). Sierra Leone in 2008 had a health care worker (physicians, nurses and midwives) density of 0.39 trained health workers per 1,000 population, which represents about one sixth of the minimum recommended by WHO (MacKinnon and MacLaren 2012). The current total workforce is estimated at over 8000 health personnel with over 50% of staff in the Western Area alone (GoSL, MOHS 2012a).

As poor post-conflict countries, such as Sierra Leone, strive to rebuild their public health systems, the role of bilateral and multilateral donors in strengthening health service delivery becomes crucial. The donors and developing partners that support the MOHS in Sierra Leone have also supported the building of public management capacity in general including for

human resources for health, and also technical assistance and training to improve health service delivery (MacKinnon and MacLaren 2012; WHO Sierra Leone 2009).

Health Sector Financing

Expenditure on health as a percentage of GDP increased over the years from 4.3% in 2000 to 7% in 2006. However, a high proportion (about 61.3%) of total health expenditure is out-of-pocket spending (WHO Sierra Leone 2009; GoSL, MOHS 2012b). The main source of financing the public health sector is therefore through budget allocations still being strengthened by financial support from development partners such as the USAID, EU, DFID and ADB (WHO Sierra Leone 2009). In 2013, external resources as a percentage of total expenditure on health were 31.3%. Per capita total expenditure on health in 2013 was US$228.00. Total expenditure on health as a percentage of GDP was 11.8% in 2013, and general government expenditure on health as a percentage of GDP was 1,7% (African Health Observatory, WHO AFRO 2016).

Neglected Tropical Diseases Programme

Before 2007, only the NOCP existed (which was established in 1989). The NOCP was charged with nationwide surveillance for Guinea Worm Disease from 2005 to 2007 when the disease was declared eradicated in Sierra Leone. Consequently, reliable data on the prevalence of NTDs, especially for LF, before the NTDP was formed in 2007 are scarce (unpublished NTDP Reports 2008-2015; WHO Sierra Leone 2009; WHO Sierra Leone 2014).

Epidemiology studies conducted using skin snip method between 1988 and 2005 have shown that 12 out of the 14 health districts are endemic for onchocerciasis. The NOCP was set up in 1989, and by 1990 both preventive chemotherapy and vector control had been established in all 12 endemic districts with support from the WHO Onchocerciasis Control Programme (OCP) for West Africa and Sightsavers. However, between 1991 and 2002 the civil war which disrupted all programme activities led to the complete halt of programme activities in 1997. Onchocerciasis control activities restarted in 2003 under the Special Intervention Zones (SIZ) programme established for ex-OCP countries following the closure of the OCP in 2002. The SIZ programme was managed by APOC (unpublished NTDP Reports 2008-2015).

In 2005, with support from APOC, Sightsavers and the World Bank, the onchocerciasis control activities were reviewed and reorganized both technically (more staff were appointed) and administratively (the leadership changed) due to poor performance as the treatment coverage was 35% in 2003 and 28% in 2004, and geographic coverage could not be determined. In 2005 the NOCP continued onchocerciasis control mainly through mass drug administration (MDA) using the community directed treatment with Ivermectin (CDTI) strategy under the guidance of APOC (Bockarie et al. 2013). Treatment results improved gradually and by the end of 2006 MDA results for onchocerciasis increased to over 70% epidemiological coverage[2] and 100% geographic coverage (unpublished NTDP Reports 2008-2015; Pose and Rabinowitz 2014).

After advocacy by AFRO in 2006, the MOHS decided, in 2007, to integrate onchocerciasis control with the elimination/control of other NTDs starting with LF and the NOCP was renamed the National NTDP. Baseline surveys to determine LF microfilaraemia prevalence and density were conducted using 'night blood survey (NBS) and the thick blood film (TBF) method' in 2007 (in six districts) and in 2008 (in the eight remaining districts) before LF MDA was launched. A phased integrated MDA for the treatment of onchocerciasis and LF starting with six districts in 2007 was conducted (the remaining six of the 12 onchocerciasis-endemic districts were treated only for onchocerciasis) and upscaled to another six districts in 2008. Thus, integrated LF/onchocerciasis MDA was conducted for the first time in all 12 previously onchocerciasis-endemic districts since 2008. The two districts that are not co-endemic for onchocerciasis and LF started treatment for LF separately in 2010. Since 2007 the NTDP Sierra Leone has been responsible for control/elimination of onchocerciasis, LF, schistosomiasis, soil transmitted helminthiasis, Buruli Ulcer, and Human African Trypanosomiasis (unpublished NTDP Reports 2008-2015).

Indicators for NTDs in Sierra Leone

This study focuses on PC NTDs that include onchocerciasis, LF, schistosomiasis, soil transmitted helminthiasis, and trachoma. Although details of the onchocerciasis and LF situation in Sierra Leone will be provided in subsequent chapters, it is worth noting here that mapping/baseline

[2] Epidemiological coverage is the coverage of an intervention among the total population expressed in percentage and is calculated as the total number of people treated divided by the total population of the area treated multiplied by 100 (WHO 2013).

studies conducted for onchocerciasis, LF, schistosomiasis, soil transmitted helminthiasis, and trachoma have shown that onchocerciasis is endemic in 12 out of 14 districts; LF is endemic in all 14 districts; schistosomiasis is endemic in 12 out of 14 districts; soil transmitted helminthiasis is endemic in all 14 districts. None of the 14 districts are endemic for trachoma. No schistosomiasis control activities were conducted in Sierra Leone before the arrival of USAID funding in 2008. Earlier studies indicated that both intestinal and urinary forms of schistosomiasis were prevalent in the north-east and baseline studies in 2008 showed moderate to high prevalence of *Schistosoma mansoni* in seven districts (Kono, Koinadugu, Kenema, Kailahun, Bo, Bombali and Tonkolili districts that involves 1.8 million people at risk) and low prevalence in the five coastal districts (Port Loko, Kambia, Moyamba, Pujehun and RWA). Bonthe and Urban Western District had zero schistosomiasis prevalence. Baseline survey/mapping was conducted with USAID funds for trachoma in 2008 in the five northern districts that border with districts in Guinea that have been demonstrated to be endemic for trachoma in neighbouring Guinea. Since 2008 the NTDP has received financial and technical support from the USAID NTDP initially through the NTDP Control Programme that was managed by Research Triangle Institute (RTI) International (2008-2010) and later through the End NTDs in Africa (END in Africa) project (2011 – to date) to implement programme activities for the control/elimination of NTDs. After several country and field visits to conduct a situational analysis by members of the International Certification Committee (ICC) for Guinea Worm Disease between 2005 and 2007, Sierra Leone was certified by WHO based on the ICC recommendation as GWD free in 2007. No studies have been conducted for diseases such as Buruli Ulcer and Human African Trypanosomiasis and no activities have been started in respect of these diseases (unpublished NTDP Reports 2008-2015; Koroma *et al.* 2010; Koroma *et al.* 2011).

Implementation of the NTDP

The NTDP is under the direct supervision of the DPC Directorate of the MOHS and has an NTD Task Force chaired by the Director of DPC that supports coordination of NTD activities in the country. The NTDP is headed by a Programme Manager who is responsible for implementation of NTDP activities in the country with support from the NTD Task Force. The NTDP has technical officers responsible for the various NTDs - onchocerciasis, LF, SCH, and soil

transmitted helminthiasis (GoSL, MOHS 2009; unpublished NTDP reports 2008-2015). The core function of the NTDP at the central level is policy formulation and ensuring adherence to WHO guidelines; setting of standards and quality assurance; resource mobilisation; capacity development and technical support; provision of nationally coordinated services such as MDAs and impact assessment surveys; M&E for NTDs and training conducted at national level (unpublished NTDP Reports 2008-2015).

At the district level, NTDP activities are coordinated by a district NTD focal point/coordinator who operates within the DHMT that is headed by a DMO (GoSL, MOHS 2009; GoSL, MOHS 2012a; WHO AFRO NTDP 2013).

The health care system within districts is used by the NTDP to reach every village in districts endemic for the targeted NTDs. Activities within communities are coordinated by PHU staff and implemented by community-directed drug distributors (CDDs) who are trained, supervised and supported by PHU staff. Each PHU staff covers villages that are in their catchment areas (WHO AFRO NTDP 2013). The second tier (district hospitals) and third tier (referral hospitals) are involved in NTDP activities such as management of severe cases of adverse events following treatment for NTDs and passive treatment for people who go to these institutions after missing any of the MDAs. Depending on the number of PHUs in districts, all the 1,195 PHUs are involved in the MDAs and PHU staff train, supervise and monitor treatments conducted by CDDs. CDDs are usually people within affected communities (men and women) that are literate (mostly primary school teachers) or semi-literate community members that are selected by their community members to implement MDAs within communities. It is worth noting that due to the high number of severe adverse events reported in the first MDA that was conducted for SCH using praziquantel tablets it was decided that only PHU staff will distribute praziquantel tablets for treatment of SCH with the support of teachers in school and CDDs in communities (GoSL, MOHS 2009).

Human Resources for the NTDP

Since accessibility to health care services is poor especially in rural areas due to an acute shortage of trained health professionals, the NTDP implements activities within communities

using community volunteers or CDDs who are supervised, trained and monitored by PHU staff. This way, all communities within the 12 endemic districts have been treated for onchocerciasis and LF since 2008. The PHU staff are, in turn, supervised by DHMT members. Activities within districts are also supported, supervised and monitored by NTDP staff at the central level, and also by representatives of locally based NTD partners such as Sightsavers and HKI (Sierra Leone Government MOHS 2006; unpublished NTDP Reports 2008-2015). There are currently 1,195 PHUs throughout the country that are staffed by different cadres of health workers: CHOs, MCHAs and SECHNs who oversee approximately 25,000 volunteer CDDs. These CDDs are the backbone of all the NTDP activities in the rural setting. While in the rural areas CDDs serve as volunteers within the NTDP, in the Western Area there are no volunteer CDDs and NTD drugs are distributed by paid health workers for a fixed number of days (normally five days) (unpublished NTDP Sierra Leone Reports 2008-2015; Pose and Rabinowitz 2014).

NTDP Financing

The main source of financing NTDP activities in Sierra Leone is through support from NTD partners such as USAID, Sightsavers, AFRO, APOC, the World Bank, LSTM CNTD and HKI. The method of financing NTDP activities is such that the most remote villages, some of which are hard to reach, are accessed by DHMT staff and PHU staff at no cost to the community members themselves. Budgets include provision for movement to all areas of land and sea and include involvement of community volunteers as CDDs who receive only per diems during training but work for free as a service to their communities. In general, NTD funds move directly from the funding agencies to the NTDP central level and then the DHMTs with different partners requiring different methods of accounting. The different NTD partners also supervise field activities to ensure proper use of the funds they provide. NTDP funding before 2003 was from the OCP and Sightsavers; between 2003 and 2007 from APOC (through the SIZ programme), Sightsavers and the World Bank; and from 2008 to date from USAID, Sightsavers, APOC (SIZ programme closed in December 2007 and APOC closed in December 2015) and HKI. USAID support provided through the END in Africa project is managed locally in Sierra Leone by HKI (unpublished NTDP report 2008-2015).

Currently, USAID provides over 80% of the financial support needed by the NTDP. Funds from the different sources are pooled for overall integrated implementation of interventions. The CNTD supported refurbishment of the NTD laboratory in Makeni and two key operational research projects for endemic NTDs in the past six years ('Transmission of lymphatic filariasis in two post-conflict urban cities in West Africa' and 'Impact assessment surveys to define the factors determining the successful implementation of MDA to eliminate LF in a fragile health system in post-conflict Sierra Leone'). Johnson & Johnson has supported the training/retraining of 70 doctors, mostly from the Northern Province, on surgical procedures for hydrocele, one of the complications of LF. The NTDP has also received, in recent years, financial support through HKI for the second round of de-worming of school-aged children in some districts. Funds for extra deworming efforts in 2010 came from the World Food Programme and in 2011 and 2012 from the World Bank's Fast Track Initiative through the Ministry of Education, Science and Technology. Mebendazole/albendazole for soil transmitted helminthiasis treatment has been donated from the Saint Andrews Clinic for Children in Sierra Leone, De-worm the World, Feed the Children, and World Vision Sierra Leone. TOMS Shoes and HKI established a partnership in 2013 that has led to the donation and distribution of shoes to all CDDs (unpublished NTDP Reports 2008-2015).

JUSTIFICATION, RATIONALE, AIM AND OBJECTIVES OF THE STUDY

Results of onchocerciasis baseline studies[3] showed that 12 out of the 14 districts are onchocerciasis-endemic while LF mapping studies showed that all 14 districts are LF endemic. Integrated MDA for the treatment of onchocerciasis and LF has been ongoing in the 12 districts co-endemic for both diseases since 2008 (unpublished NTDP reports 2008-2015). This study will document the progress and achievements made, and the experiences gained in the management of the programmes for the elimination of onchocerciasis and LF from the establishment of the respective programmes to date. The study will also discuss the way forward for the two diseases up to verification of elimination by WHO.

[3] For onchocerciasis, the mapping results obtained are used also as baseline data as opposed to LF for which there is WHO guidelines on how to do mapping and baseline studies separately.

The study and associated publications also serve as an archive for LF and onchocerciasis data needed for verification of elimination of both diseases and will guide the NTDP towards the elimination of both diseases with minor adjustments as the programme continues depending on new strategies and diagnostic tools that will be adopted in the future by WHO.

Why do the planned research studies in Sierra Leone?

Available literature suggests that both onchocerciasis and LF can be eliminated as a public health problem and transmission of both diseases can be stopped completely with the implementation of the right strategies recommended by WHO. Furthermore, drugs for treating some of these parasitic infections (especially onchocerciasis and LF) are donated to the NTDP by pharmaceutical companies. Also, most of the strategies used for the elimination of onchocerciasis and LF are similar or the same. For example, the strategies for controlling/eliminating onchocerciasis and LF rely on the use of the same drug regimen (Ivermectin/Mectizan and albendazole) administered on a massive scale via treatment of entire communities. When the decision to integrate LF and onchocerciasis treatment was taken in 2007, albendazole was added to be co-administered with ivermectin and CDTI became CDTI plus albendazole. The addition of albendazole to the already existing onchocerciasis treatment with ivermectin facilitated integrated MDAs for onchocerciasis and LF. Both these drugs are donated to NTDPs by the manufacturers for as long as required (unpublished NTDP Reports 2008-2015).

Many poor rural communities in Africa live in areas endemic for two or more of these NTDs, and 12 out of 14 districts of Sierra Leone are endemic for both diseases. Fortunately, only the NOCP existed in Sierra Leone before the idea of having an integrated NTDP was recommended by WHO to the MOHS, and so it was a straightforward exercise for the NOCP to be responsible for all NTDs in the country. The NOCP activities were completely integrated into the health system since the formation of the NOCP in 1989 and activities were coordinated at central level by the NOCP but coordinated at the lower levels (districts, chiefdoms, and villages) by health service personnel within the MOHS that operate at these levels. Therefore, with the NOCP responsible for LF elimination since 2007, the same applied to LF activities, which were in almost all cases co-implemented with onchocerciasis activities at all levels. Since health

workers at district, chiefdom and village levels have to visit the same communities several times in a year to deliver different interventions for different diseases the co-implementation of onchocerciasis and LF activities has reduced the burden of health workers and, to some extent, it has fostered integrated implementation at lower levels, rational and efficient use of human and financial resources, savings on time of implementers and beneficiaries, synergistic impact on the targeted NTDs where these are co-endemic, and also strengthened health services delivery systems. Integrated programmes are also easier to sustain as financial, human and other resources are shared. Integration is particularly important at this time of dwindling resources from donor nations and agencies. Sierra Leone has emerged from a vicious 11-year civil war that destroyed the economy, infrastructure and interrupted virtually all health services, other social sectors and developmental activities. During this phase of rehabilitation, reconstruction and recovery, it is good that the country can integrate disease control programmes and avoid having to run many vertical programmes that are expensive to sustain especially so when the bulk of the health budget is externally funded (unpublished NTDP Reports 2008-2015).

The aim of the study

The aim of the study is to determine the impact of integrated treatment of onchocerciasis and filariasis using the community directed treatment with ivermectin plus albendazole strategy and make recommendations on the way forward to achieve elimination of transmission of both diseases in Sierra Leone.

Objectives of the study

- To evaluate the impact of vertical treatment of onchocerciasis between 2005 and 2006 plus integrated onchocerciasis/LF treatment between 2007 and 2009 on the transmission of onchocerciasis in Sierra Leone.
- To evaluate the impact of vertical treatment of onchocerciasis in Sierra Leone before 2007 on the LF transmission and intensity.
- To evaluate the impact of integrated onchocerciasis/LF treatment in Sierra Leone at mid-term (*i.e.* after three effective MDA rounds) on the LF transmission intensity

- To evaluate the impact of integrated onchocerciasis/LF treatment in Sierra Leone after five effective rounds of MDA on the LF transmission intensity.
- To determine the way forward to achieve elimination of both diseases as a public health problem using the latest available WHO guidelines and diagnostic tools.

Expected Output/Outcome of the Study

The author of this study is working with the National NTDP of the MOHS in Sierra Leone to conduct these research studies in strict adherence to WHO guidelines and the policies, rules, and regulations of the MOHS. The author of this study has supported and will support the national NTDP to conduct, analyse and document all research relating to onchocerciasis and LF control in Sierra Leone. The research studies conducted for this thesis are a requirement of WHO for successful completion of the onchocerciasis and LF programmes and are all conducted strictly in line with WHO recommendations for the two diseases. Data collection and archiving are relatively poor in Sierra Leone, and through this study, the studies conducted relating to onchocerciasis and LF elimination are documented, and the data and information available can be used by the NTDP for decision making as the programme is implemented. According to WHO recommendations and requirements, the NTDP will need to put together a dossier of survey and treatment data that will be used in the near future by the Elimination Committees that will be set up to verify elimination of onchocerciasis and LF in Sierra Leone. This study and its content will serve as a good collection of all data needed by the NTDP for verification of elimination of onchocerciasis and LF in the near future. The international scientific community will benefit from the documented onchocerciasis/LF elimination experiences obtained from co-implementation of activities for the two diseases and integration of programme coordination within the MOHS service delivery system in Sierra Leone, a post-conflict country that has also recently been through an EVD outbreak. It is also hoped that countries with similar challenges (post-conflict, and with co-endemicity of onchocerciasis and LF), especially in Africa, can learn from the experience in Sierra Leone. The NTDP in Sierra Leone and the MOHS, in general, can use the experiences gained in the integrated management of onchocerciasis and LF for the integration of other disease control programmes.

It is expected that the study will demonstrate the following:

- How onchocerciasis control activities can be co-implemented with LF control activities in areas where both diseases exist and the effectiveness of co-implementation for control of both diseases.
- How the onchocerciasis and LF control programmes can be integrated into a country's health care delivery system.
- How an integrated control programme can be conducted in a post-conflict country with a weak health system and weak human resources for health.
- The outcome in terms of reduction in prevalence and distribution of onchocerciasis and LF.

METHODOLOGY

Study design

This is a nationwide longitudinal observational study of filariasis infection dynamics conducted in 14 districts undergoing MDA for the elimination of LF and onchocerciasis. The study will quantify and test the hypothesis that annual rounds of PC can significantly reduce transmission intensity and eliminate LF as a public health problem after five-six years and onchocerciasis after 15-17 years. The study design will be consistent across all study districts and represents an observational study of human infection status and demographic information related to the force of transmission. The primary study design in each district is a community-based longitudinal investigation of changes in the mean trends and variability in parasitological and serological variables. Changes in the community infection load are monitored following the WHO PC guidelines.

The original maps of the previously studied sentinel sites are updated using Geographic Information Systems. New maps are created of spot check sites that change over time. A census of the population is performed by house-to-house visits. All members of the households are registered and name, sex, birth date, declared familial relationship, occupation, and duration of residence recorded. Informed consent to participate in this observational study is obtained from all individuals 18 years old. Consent is obtained from a parent or guardian of younger individuals. Prior to obtaining demographic information and obtaining

informed consent, repeated community meetings are held in all villages to communicate the purposes of the study and answer questions at the individual and community level. Local district health workers are used as spokesmen as an integral part of the research team.

The primary analysis quantifies the presence and community levels of microfilariae (MF), and antigen (Ag), indicators stratified by age, sex, and village using univariate statistical methods. Multivariate analysis will be performed to examine the risk of LF and onchocerciasis infection with factors such as prior level of endemicity and MDA coverage.

Review of longitudinal survey data

All treatment results for the period 2005-2015 (for onchocerciasis and LF), and all research studies conducted at baseline (1988-2005) and during universal treatment (2008-2013) for monitoring the impact of treatment are reviewed. Apart from NTDP data and information, extensive literature search will be conducted using the appropriate search words. Information obtained will be used to review the data from treatment and research studies conducted by the NTDP. Some of the data obtained from the research studies have been published already in international peer-reviewed journals. This study and all the data it contains will also be made available to the MOHS for use in the future as part of the dossier to be prepared for verification of elimination of onchocerciasis and LF in Sierra Leone.

Sources of information and data for the study

The following are used as sources of information for the review:

- Mapping/Baseline data for onchocerciasis obtained using the skin snip method for the period 1988 – 2005.
- Mapping/Baseline data for LF including mapping results obtained using ICT cards in 2005 and baseline survey results obtained using NBS/TBF method in 2007/2008.
- Results of onchocerciasis evaluation conducted in 2010.
- Results of mid-term evaluation conducted for LF in 2011 after three years (2008-2010)
- Results of pre-transmission assessment survey (pre-TAS) conducted in 2013 for LF after five years of treatment (2008-2012).
- Results of MDA for onchocerciasis (2005-2015) and LF (2007-2015).

- Annual Implementation Plans for the period 2005-2015.
- Annual NTDP Reports for the period 2005-2015.
- Publications on NTDs in general with a focus on onchocerciasis and LF.

Ensuring good representation for each study

Sampling for each study was done in accordance with WHO guidelines and recommendations for each disease-specific study. All mapping and baseline surveys were conducted in all 14 districts, and subsequent impact assessment surveys were conducted in the districts that were determined to be endemic based on mapping and baseline surveys conducted. Selection of sentinel sites for all impact assessment studies is based on the mapping results. The mapping sites with the highest prevalence rates were selected for the baseline study (for LF) and the sites selected for baseline studies are kept as sentinel sites for impact assessment studies. For onchocerciasis, the mapping sites with highest results were selected for impact assessment studies. The NTDP selected areas of highest risk to demonstrate reduction in disease prevalence or interruption of transmission with the assumption that reduction of prevalence in areas with the highest risk of exposure increases the confidence that areas in the lower transmission zones, covered by the same intervention strategy, would have also reduced disease prevalence or interrupted interruption (unpublished NTDP Reports 2008-2015).

Ethical considerations

This study involves several research studies for onchocerciasis and LF and involves participants that are ≥5 years. The author has received ethical approval for the studies from the LSTM Ethics Committee (see appendix 1 of page 290). Since all studies conducted were coordinated by the NTDP Sierra Leone, and within the NTDP Sierra Leone by technicians belonging to the NTDP itself, the MOHS and the University of Sierra Leone, ethical approval was sought and received for each of the studies by the NTDP from the Ethics Committee of the MOHS. Details on ethics will be provided for each of the research studies in subsequent chapters where the studies are discussed in detail. The following ethical issues were addressed during all the studies discussed for this thesis: ensuring that all guidelines are followed for the protection of participants and members of the research teams from infection; ensuring that investigators receive all the relevant materials for their protection and the protection of participants;

treatment and follow-up of all those who are found to be positive; provision of enough information to participants of the study such as the reality that not all those affected with the disease can be cured but those affected can work with the NTDP to prevent spread of the diseases; proper disposal of blood specimen and materials after the survey; and proper cleaning of instruments and equipment before and after surveys. The research studies were designed and implemented to avoid any litigation and to avoid any conflict with routine health services. Litigation was avoided by ensuring the safety of the research teams and research participants and by properly engaging with community leaders and participants of the studies first during meetings with community leaders and then subsequently with entire communities where the surveys were conducted. Measures were put in place to avoid any conflict with the implementation of routine health services. The NTDP has in place a team of investigators for the studies that involved central level staff of the NTDP, the MOHS and the University of Sierra Leone. District health workers were not involved in the actual implementation of the studies but supported the research teams in identifying villages to be investigated and also leading the discussions with community leaders and communities. By covering only sites located within their areas of supervision the district health workers were not kept away from their jobs for more than two days.

CHAPTER 2: LITERATURE REVIEW ON ONCHOCERCIASIS AND LYMPHATIC FILARIASIS

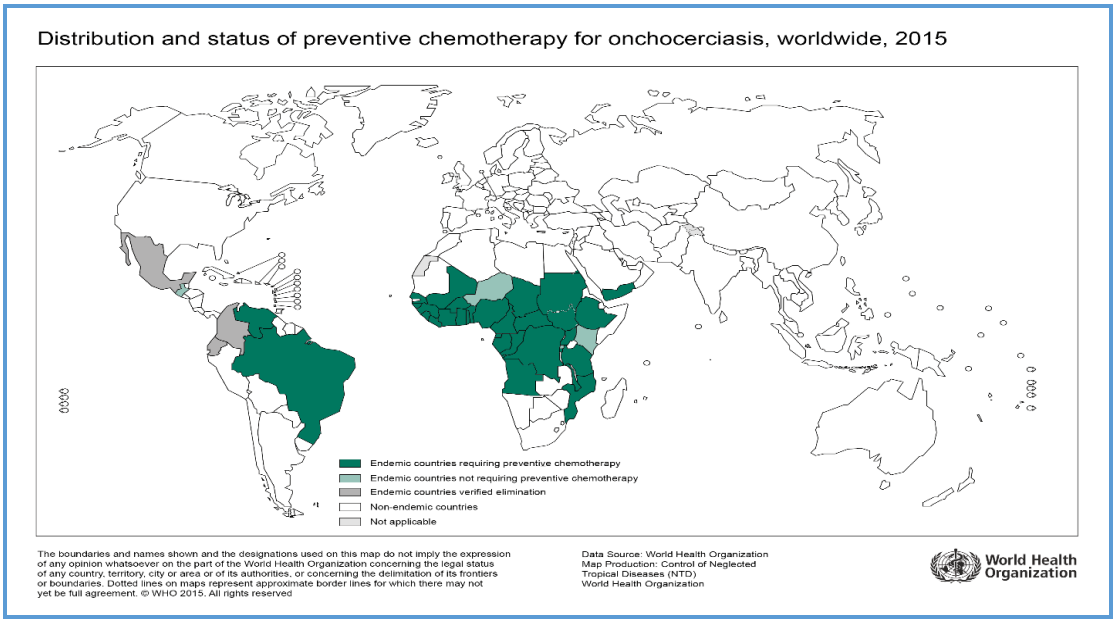
GLOBAL OVERVIEW OF ONCHOCERCIASIS

Introduction

Onchocerciasis, known as River Blindness and Robles' disease, is a parasitic disease that affects over 37 million people and can lead to permanent changes mostly in the skin, the eye and can end in total blindness. The disease is caused by infection with *Onchocerca volvulus (O. volvulus)*, a microscopic nematode (Taylor 2003; Boatin and Richards 2006; Basanez *et al.* 2006; WHO APOC 2010; Traore *et al.* 2012; Katabarwa *et al.* 2013; WHO 2016b). The disease is transmitted to humans by the blackfly (*Simulium spp.*), and disease pathology is linked with the death of the MF in the skin and eyes (Basanez *et al.* 2006; Gloeckner *et al.* 2010; Traore *et al.* 2012). Humans are known as main reservoirs for *O. volvulus (*APOC 2010). Some animals such as elands and buffalos are possible reservoir hosts, which makes control of the disease in areas where these animals co-exist more difficult (Crump *et al.* 2012). Other forms of the onchocerciasis parasite (besides *O. volvulus*) affect various animals including wild game, livestock, draught animals and dogs (Crump *et al.* 2012). Figure 4 shows the global distribution of onchocerciasis in 2015.

Currently, there are an estimated 187 million people at risk of onchocerciasis (living in endemic areas) among which 37 million are onchocerciasis-infected. Among those infected, 4 million people live with skin manifestations of the disease and an estimated two million are either visually impaired or blind. The vast majority of infection is in sub-Saharan Africa (about 99% of reported cases) (Taylor 2003; Basanez *et al.* 2006; Traore *et al.* 2012; Uniting to Combat NTDs 2015; WHO 2016b). With South Sudan, the total number of endemic countries in sub-Saharan Africa is 31 (20 ex-APOC and 11 ex-OCP) and Nigeria alone accounts for an estimated 25% of the total global burden of infection. The other 1% of the global infection is in Yemen and six Latin American countries (Brazil, Colombia, Ecuador, Guatemala, Mexico, and Venezuela) (APOC, 2010; Crump *et al.* 2012; Uniting to Combat NTDs 2015). The disease in Yemen and Latin America appears to have been imported from Africa (Hopkins and Boatin 2011; Lipner *et al.* 2006; Weil *et al.* 2000; Taylor, Hoerauf and Bockarie 2010).

Figure 4: Distribution and status of preventive chemotherapy for onchocerciasis, worldwide, 2015 (WHO, Online; available from: ttp://www.who.int/mediacentre/factsheets/images/Onchocerciasis_2015.png?ua=1)

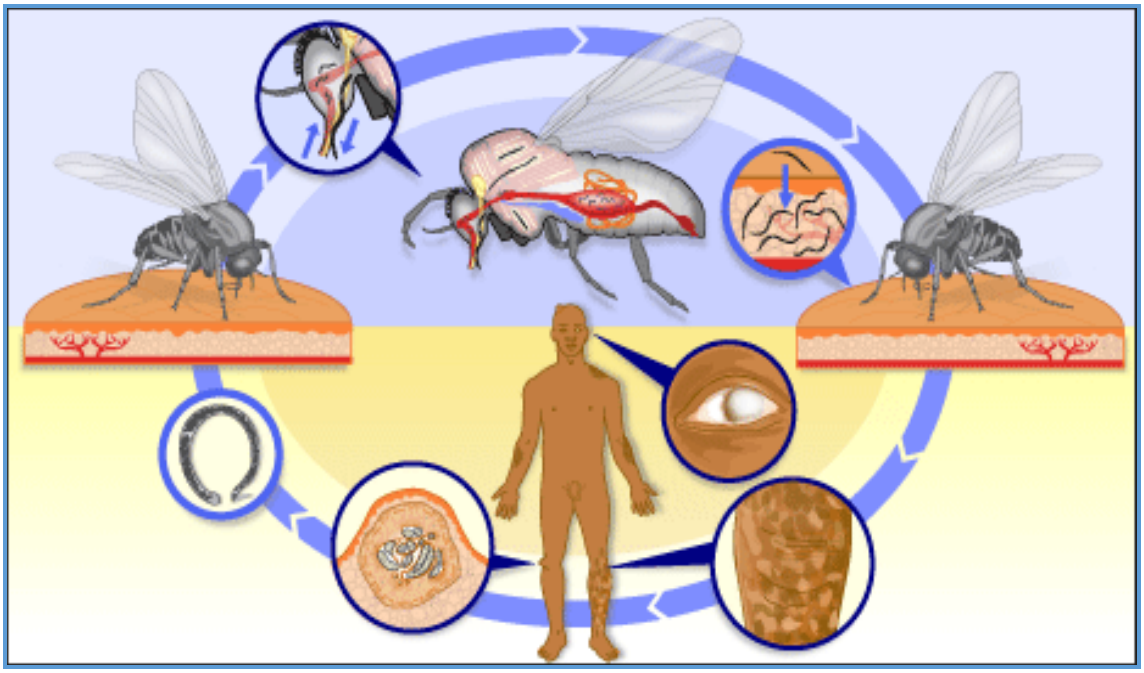


Onchocerciasis is a disabling disease that causes significant morbidity, psychosocial problems and reduces the ability to work, especially agricultural productivity, within populations affected. Onchocerciasis is the world's second leading cause of blindness after cataract, and onchocerciasis-related blindness brings its own consequences as it can perpetuate poverty of families and communities. Blindness from onchocerciasis in people occurs early in life (20-30 years) and usually, children stay from school to lead their blind parents around, which devastates the life of affected families and creates socio-economic problems for affected communities and countries. The cost to individuals and families of treating ailments relating to blackfly bites can be catastrophic for people who depend on subsistence farming for a living. It is also suggested that the nuisance of black fly bites can also reduce tourism and onchocerciasis can cause deaths among wild animals and livestock (Basanez *et al.* 2006; APOC 2010; Gloeckner *et al.* 2010; Crump *et al.* 2012; Traore *et al.* 2012).

Transmission

Among the many Onchocercal species available only *O. volvulus* is hosted by man and man is known as the main animal reservoir for the onchocerciasis parasite *O. volvulus (*Taylor *et al.* 2009). Transmission of *O. volvulus* occurs in several stages (Figure 5). The female *Simulium* ingests the MF (baby worms) of *O. volvulus* while taking a blood meal from the skin of an infected person. After ingestion, the MF enters the gut and thoracic flight muscles of the fly developing to the 1st larva stage (L1), then the 2nd larva stage (L2) that moves to the proboscis of the fly, and finally to the 3rd larva stage (L3) that moves to the saliva. The larvae take seven days after being ingested to reach the L3 stage in the black fly, which is the infective stage. The L3s pass on to the next human while the fly takes another blood meal through the wound created in the skin when the fly bites the skin, remains in tissues for a few days and then transforms into the L4 stage (Taylor *et al.* 2009; APOC 2010; Hopkins and Boatin 2011, Tekle *et al.* 2012; Katabarwa *et al.* 2013).

Figure 5: Transmission cycle of *O. volvulus* including stages in humans and flies *(*APOC; Online, available from: http://www.who.int/apoc/onchocerciasis/lifecycle/en/)



After one week, they are transformed into juvenile worms (L5 stage). It takes a further 7-15 months before the juvenile worm becomes mature and the adult worm moves towards the nodule where mating takes place. Adult worms mate in the subcutaneous layer of the human skin and females produce 700-1500 larvae or MF each day. Although a vast majority of MF are found in the skin of an infected person, some are located in the eyes and other tissues. The cycle is restarted when the black fly takes another blood meal ingesting newly reproduced MF. To develop to the adult stage, the MF must enter the black fly, develop to the L3 stage and re-enter the body of a human when the fly takes a blood meal. The adult lives for 10-14 years. The MF not ingested by the fly during a blood meal after reproduction live 6-24 months in the human host and then die. It has been noted that the vector is a day biting fly (Taylor *et al.* 2009; APOC 2010; Hopkins and Boatin 2011, Tekle *et al.* 2012; Katabarwa *et al.* 2013).

Black flies breed in rapids and fast-flowing water (streams and rivers) because the black fly needs well-oxygenated water to lay its eggs that also serves as a place where the larvae can develop. Rapid flowing water provides the oxygenation needed for the development of the vector larvae. Most larvae and pupae develop on rocks or vegetation just below the water surface although those of *S. neavei* develop on amphibious *Potamonautes* crabs. Aquatic stages of the fly require ten days to complete development depending on temperature and nutrients available. Eggs hatch after 36-48 hours, and the larval stage lasts for five-ten days depending on water temperature. Pupation and emergence of adult flies occur after further two-three days, and the black flies live for up to four weeks. The female fly mates only once on the day after emergence; then seeks a blood meal, which is necessary for maturation of her eggs; and is ready for oviposition four or five days after the meal. The time between blood meals varies from six to 12 days. Consequently, the transmission is most intense and the disease most severe within communities that are close to fast flowing rivers or streams. The risk of blindness is, therefore, higher for such communities that live close to rivers hence the name 'river blindness'. Development of the black fly and transmission of the disease is therefore linked to the flow of rivers and streams. For areas where rivers run throughout the year, transmission continues throughout the year, while in areas where the rivers run only during the rainy season, transmission occurs only during the rainy season. Therefore, some authors have suggested the need to provide onchocerciasis treatment to communities just

before the period or during the period when transmission by black flies is most intense (Samba 1994; Boatin *et al.* 1998; Taylor *et al.* 2009; Hopkins and Boatin 2011).

The black fly feeds as close to the breeding site as possible and so populations within 5km of the breeding site are most exposed although communities 12-15km away may be affected. Transmission of onchocerciasis takes place when the fly moves from the breeding site to feed on human blood by biting the skin (Kutin *et al.* 2004). Because the risk of infection is greater the closer a community is to a river; it appears as if those close to the river protect those that are far away from the river (Kutin *et al.* 2004; Taylor *et al.* 2009; Hopkins and Boatin 2011). *Simulium* rarely enters the house to bite and biting is usually in the mornings and late afternoon hours when people need the rivers for water, washing, and food. There have been reports of villages being abandoned because of the nuisance created by the continuous biting of the black fly and fear of being blind (Taylor *et al.* 2009; Hopkins and Boatin 2011).

Recent studies have also shown that *S. damnosum* can fly 400-500km by moving with the prevailing wind in West Africa: from Guinea and Sierra Leone in the south to Mali in the north during the rainy season; and back from Mali to the south during the harmattan season (Hopkins and Boatin 2011). The issue of migration should be considered when discussing disease transmission especially the possibility of migration between neighbouring transmission zones. Therefore, it is important to ensure that neighbouring transmission zones are treated adequately with ivermectin and that geographic and therapeutic coverage are adequate in all zones within an endemic country (APOC 2010). As some of the fly species can travel long distances in Africa care must be taken when constructing dams as the fast runoff of the water is ideal to establish new breeding sites for *Simulium* black flies. This must be considered during construction and maintenance of new dams (Hopkins and Boatin 2011).

Male/female nuances of onchocerciasis transmission

The male/female differences in prevalence, the density of infection and clinical disease due to onchocerciasis is reviewed and related to differential exposure of females to infective vectors. Sex differentials are most marked in savannah areas of high transmission, and in these areas, worm burden is lower from early childhood in females as are ocular lesions. In forest areas, sex

differences are less significant, and ocular lesions are similar in men and women. Sex differences are most evident under conditions of high transmission, and it has been suggested that females are more resistant to infection than males. Further research is needed to obtain substantive evidence that onchocerciasis is less frequent in females. Little is known about onchocerciasis in pregnancy but increased resistance could influence the risk of transmission of infection from mother to child in highly endemic areas. Onchocerciasis infection in pregnancy is also likely to affect the immune response to tetanus toxoid vaccination in mothers and birth weight of children. Onchocerciasis, therefore, represents an important public health problem for women and their offspring (Brabin 1990).

Transmission from mother to child

A study analysed the impact and extent by which parental *O. volvulus* infection, intensity, and transmission of *O. volvulus* infective stage L3 larvae can influence transmission of onchocerciasis from mothers to their children. The study results showed that children from *O. volvulus* infected mothers were more likely to be infected with onchocerciasis than children from non-infected mothers. They were also more likely to acquire the infection earlier in life and developed higher infection levels (Kirch *et al.* 2003).

Pathogenesis

Adult worms (males and females) are found in fibrous nodules or onchocercomata found in subcutaneous tissues especially over bony prominences (although others can be found in deeper tissues). The adult worms found in the nodules under the skin of infected individuals can live 10-14 years. Female worms are larger than males (30-80 cm versus 3-5 cm long) and are found entwined around each other in the nodules. Each nodule may contain one/two male worms and 2/3 female worms, although larger nodules may have up to 509 adult worms (Taylor *et al.* 2009; APOC 2010; Hopkins and Boatin 2011; Tekle *et al.* 2012; Katabarwa *et al.* 2013). Adult *O. volvulus* female worms live for up to 14-15 years producing millions of microscopic baby worms or larvae known as MF. Adult worms, which take a year to mature from the microfilaria stage, lodge in nodules under the skin releasing millions of MF into surrounding tissues, which then migrate through the body living up to 9-18 months (Omura and Crump 2004; Geary 2005). Since the adult worm is usually located in the subcutaneous

layer of the human skin, this limits access to the immune system towards them. However, the principal symptoms of onchocerciasis are due to MF because they can be spread all over the body. Live MF are no problem to the human host until they start to die after six months if not ingested by the black fly. The dead MF release *Wolbachia* surface protein inducing an immune response that leads to inflammatory reaction and local systemic changes. *Wolbachia* endobacteriae (symbionts of anthrops and filarial nematodes) contribute to the inflammation pathology associated with the disease. *Wolbachia* species are endosymbionts for adult onchocercal worms as well as MF. Although the immune reaction relating to one MF is small, the overall effect is devastating because of the large numbers of MF reproduced and that subsequently die thus provoking widespread and chronic reactions. At first, reactions are reversible but later permanent changes occur in the tissues (mainly the skin and the eyes) (Boatin and Richards 2006; Hopkins and Boatin 2011). The MF can enter all areas of the eye and when they die the ocular conditions can involve any part of the eye - conjunctiva, cornea, uvea and the posterior segment, including the retina and the optic nerve. Blindness is the result of anterior segment lesions, posterior segment lesions and secondary glaucoma or cataract (Boatin and Richards 2006). MF are found in the tissue of the eye of an infected individual from the conjunctiva to the optic nerve posteriorly. MF in the conjunctiva provokes itching. In the posterior segment, MF can be seen in the vitreous humour (Hopkins and Boatin 2011). The intensity of infection is an important indicator of the disease because the more the number of adult worms, the more MF they produce and the more severe are the manifestations of the disease (APOC 2010).

The pathogenicity of *O. volvulus* varies with different strains of the parasite. Savannah strains provoke much more blindness than the forest strain. Both savannah and forest strains provoke skin changes. Both strains are adapted to specific vector species; forest strains are transmitted by species of the vectors that are adapted to the forest areas and likewise with Savannah strains (Hopkins and Boatin 2011). Prolonged stays of several years and exposure to the fly bites and parasite introduction are needed for the disease to develop (Wikipedia (Online), available from: http://en.wikipedia.org.wiki.onchocerciasis; accessed 28/10/2013). However, there is a report of onchocerciasis infection after a 10-day stay in Cameroon, which was

completely cured with a single dose of ivermectin and additional treatment with doxycycline (Ezzedine *et al.* 2006).

Vectors

At least 15 simuliids species can transmit onchocerciasis depending on location (Taylor *et al.* 2009). In Africa, the main vectors are members of the *Simulium damnosum sensu lato* (*S. damnosum s.l*) complex, which can travel long distances (up to 400km from their origin flying with the prevailing winds) (Brown 1962; Burnham 1998; Hopkins and Boatin 2011; Crump *et al.* 2012). The *S. damnosum s.l* species includes an estimated 60 cytoforms and is responsible for transmission of 95% of all onchocerciasis cases. *S. damnosum* is a complex of sibling species with minor variations between the species, but they show adaptation to local circumstances. *S. damnosum* sub-complex contains species that are mostly responsible for transmission in Savannah areas whereas the *S. sanctipauli*, and *S. squamosum* subspecies are found more in forest areas. The vectors in East Africa in areas of Uganda, Tanzania, Ethiopia, and the Congo are members of the *S. neavei* complex that breeds on the carapaces of crabs. The *S. neavei* complex is usually restricted to localised areas and does not fly long distances. *S. albivirgulatum* is a separate species, which is found in the "Cuvette Central" of the River Congo. The larvae of this species are found on the underside of leaves floating down the River Congo and its tributaries, thus finding enough oxygen and nutrition for larval development. In the Americas, the principal vectors are *S. ochraceum*, *S. metallic*um, *S. guianenses* and *S. exiguum*. While in Africa the disease exists only in areas where the vectors are found, there are areas in the Americas where vectors exist in the absence of infection. Among the vector complexes, some bite humans almost exclusively while others are to varying degrees zoophilic (Brown 1962; Burnham 1998; Basanez *et al.* 2006; Crump *et al.* 2012).

In hyper-endemic areas, an individual can receive several thousand bites a day from the flies. This can lead to an overall lowering of productivity, ill-health, disfigurement, and often abandonment of infested areas that can also devastate socio-economic wellbeing in affected communities (Crump *et al.* 2102). The seriousness of the disease within affected communities is determined by the number of black flies. The greater the number of black flies relative to the human population, the greater the intensity of disease transmission and the higher is the

endemicity level in terms of prevalence and density of infection in the human population (APOC 2010).

Manifestations

The people infected with onchocerciasis have symptoms of onchodermatitis (severe skin lesions), musculoskeletal pain and various stages of blindness. The most severe complications of onchocerciasis are irreversible ocular lesions of both the anterior and posterior segment of the eye, resulting first in impaired vision and finally in total blindness. Blindness is caused by the endosymbiont of the nematode, *Wolbachia pipientis*, which causes a severe inflammatory process in the eye that leads to blindness (Taylor 2003; Hopkins and Boatin 2011). Also, those affected may have decreased body mass index, work productivity, and social stigmatisation (Gloeckner *et al.* 2010). MF are found in the tissue of the eye of an infected individual from the conjunctiva to the optic nerve posteriorly and when in the conjunctiva can provoke itching of the eye (Hopkins and Boatin 2011). *O. volvulus* infection also causes some systemic changes such as low body weight, general debility, and diffuse musculoskeletal pain. Bleeding and ulceration of the skin, secondary infections, bone pain, headache, and fatigue have also been reported. Evidence suggest that onchocerciasis is a risk factor for epilepsy and may be responsible for a type of hypo-sexual dwarfism in some endemic areas (*e.g.* the Nkalanga syndrome in Uganda). With a heavy MF load, there may be generalised lymphadenopathy and some dilatation of lymph vessels, leading to tissue swelling and mild elephantiasis (Hopkins and Boatin 2011). People who suffer from onchocerciasis suffer from more problems than the primary dermatological and ocular clinical symptoms. They suffer social stigma, diminished income generating capacity associated with persistent itching that leads to discomfort for the affected and financial woes for them and their families (Amazigo *et al.* 2007; Amazigo *et al.* 2012). In most parts of the world, onchocerciasis has been not only an important public health problem but also a major obstacle to socio-economic development. Outside of the West and Central African Savannah, except certain areas in DRC, onchocercal blindness is not a major public health problem, but other complications of the disease can be highly prevalent. Skin lesions can affect more than a third of the adult population in hyper-endemic communities, ranging from unsightly and itchy papular onchodermatitis to gross depigmentation of the shins (leopard skin). In these communities, more than half the adult population suffers from severe

itching due to onchocerciasis. For the affected population, this itching can be maddening and disturbing and is thus seen as the most severe complication of the disease as it affects their well-being and those affected perceive it as a important public health problem (WHO 1995).

Ocular disease and blindness

Blindness is defined as visual acuity of less than 3/60 or a restriction of the visual field to less than 10 degrees of fixation in the better eye. Low vision is defined as visual acuity of less than 6/18 but equal to or better than 3/60 in the better eye. The assessment of visual impairment and blindness in epidemiological surveys of onchocerciasis is usually based on a simple visual acuity test, such as the illiterate E- or the Sjogren hand test, at defined distances. Onchocerciasis can also cause a severe reduction in peripheral fields and it has been shown that some 25% of those functionally blind would have been missed if the examination were limited to the visual acuity test without peripheral field assessment. Studies conducted during the OCP suggest that in the absence of control, the prevalence of ocular lesions is more than three times the prevalence of blindness as measured by visual acuity testing (WHO 1983).

Skin diseases of onchocerciasis

Distribution and severity of onchocercal skin disease have been poorly studied and hardly anything was known about the importance of onchocercal skin disease for the affected populations. This was partly due to the absence of a standard classification scheme for documenting skin changes in onchocerciasis and also the difficulty in interpreting available literature on onchocercal skin disease because of the variety of non-standard clinical classification and examination methods used in the past. A simple standard classification and grading system for cutaneous changes in onchocerciasis was developed that was adopted by the WHO Expert Committee on onchocerciasis and recommended as the standard method to be used in surveys of onchocercal skin disease (Murdoch et al. 1993). This method classified the main onchocercal skin lesions into Acute Papular Onchodermatitis (APOD), chronic Papular Onchodermatitis (CPOD), Lichenified Onchodermatitis (LOD), Atrophy and Depigmentation. The method defines grades of severity for all lesions as well as grades of activity of the reactive skin lesions APOD, CPOD, and LOD. The main limitation of the method is that it is based on the differentiation of clinical, morphological groups that are consistent with cutaneous

onchocerciasis but for which the cutaneous changes are not specific or diagnostic of the disease and differential diagnosis will often be required. Field testing has shown that this method produces reliable results that can be reproduced, especially if the clinicians involved undergo a few days training in the application of the method (Murdoch et al. 1993; WHO 1995).

Geographic variations of onchocerciasis epidemiology

The epidemiological pattern of onchocerciasis, especially the severe ocular disease, varies considerably between geographical zones. The differences in ocular pathology between the West Africa Savannah and forest areas is well documented. While onchocercal blindness can be more frequent in hyper-endemic communities in the Savannah, virtually no blindness is found in forest communities with similar intensity of infection. Some experts believe the explanation lies in the existence of various *O. volvulus* strains of different pathogenicity. The vector-parasite complex in the West African Savannah is responsible for the most severe form of ocular onchocerciasis in the world, as blindness can affect more than 10% of the population in the most affected villages, which are located in the river valleys where breeding sites of the vector are found, thus earning the disease this infamous name of River Blindness. However, the level of infection varies significantly among communities that are located in river valleys. The severity of onchocerciasis is closely related to the intensity and duration of the infection. In the West African Savannah, onchocerciasis is not apparent when the prevalence of MF in the skin snip remains below 35%, and severe blindness rates are found only in hyper-endemic villages (where MF prevalence is 60% or above). In the West African Savannah, the prevalence of onchocercal eye lesions and blindness are directly related to this index. Onchocerciasis becomes a major public health problem when the community MF load reaches 15-20mf per skin snip (mf/s), and blindness will affect more than 5% of the population when the community MF load exceeds 40mf/s. With such high blindness rate, the disease becomes insupportable and threatens the survival of the affected village itself. Fear of this disease has therefore led to the depopulation of many relatively fertile river valleys in the Volta River Basin and several neighbouring river basins in the West African Savannah (Duke, Lewis and Moore 1966; Prost, Hervouet and Thylefors 1979; Prost 1980; Dadzie et al. 1989; Zimmerman et al. 1992). The severity of onchocerciasis is related to the prevalence and intensity of infection at the

community level, and so the community diagnosis of endemicity is important to identify communities most in need of treatment (Taylor, Duke and Munoz 1992; WHO 1991).

Diagnosis

Diagnosis of onchocerciasis can be done through studies that detect the adult worm (macrofilariae) and the baby worms (MF) in individuals that live within at-risk communities. The detection of nodules on bony prominences is taken as a proxy for detection of adult worms that can be confirmed through nodulectomy (surgical opening of nodules and detection of adult worms within the nodules). MF can be detected using the skin snip method, during which the top layer of the skin of both sides of the groin (right and left iliac crest) is cut off using specially designed punches (2mm Holth corneoscleral punch) and the subcutaneous layer is examined under a compound microscope to detect the MF. Slit lamp can also be used by trained ophthalmologists to detect MF in the eyes of infected individuals because the MF can be seen in the posterior segment of the eye. OCP that covered 11 West African countries including Sierra Leone for the control of onchocerciasis between 1974 and 2002 mainly used the skin snip method to determine communities that should be treated for onchocerciasis. The cut off prevalence of 40% was used as a threshold for treatment because the skin snip method is relatively more sensitive and specific for detection of MF of *O. volvulus*. Communities that had ≥40% of people studied positive for MF in the skin were treated. APOC had used rapid epidemiological mapping for onchocerciasis (REMO) to obtain baseline data and determine communities that should be treated. This method is based on detection of nodules in specific areas of the body of individuals that live in communities suspected to be at-risk. Since this method is less sensitive and specific for the diagnosis of onchocerciasis because other diseases can also cause similar nodules in the skin of individuals, the cut-off point for treatment is 20%. Communities that have ≥20% of individuals studied having nodules are treated for onchocerciasis (Taylor 2003; Traore *et al.* 2012; Taylor *et al.* 2009; Thylefors, Alleman 2006). Since the MF can invade many organs and tissues, it is possible to detect them sometimes in blood and urine (Taylor *et al.* 2009; Hopkins and Boatin 2011; Dowell *et al.* 2013). Diagnosis of onchocercal ocular disease demands an ophthalmological examination that is conducted using slit lamps and ophthalmoscopes. MF is identified in the cornea and also in the anterior chamber of the eye when the head of the patient is positioned down for several minutes

before the examination. Ocular lesions of onchocerciasis include anterior segment lesions- sclerosing keratitis, and iridocyclitis; and the posterior segment lesions- choroidoretinitis and optical atrophy. Sometimes, lesions of the posterior segment of the eye are not visible due to obstruction by the anterior segment lesion. An ophthalmologist highly experienced in ophthalmological surveys of onchocerciasis is needed to obtain reliable results (Dadzie et al. 1986; Dadzie et al. 1989). Since onchocerciasis endemic areas are usually remote and difficult to access, the impact of using optometrists for diagnosis is limited. This is in addition to the limited number of such experts in the endemic countries in general (Berger and Nnadozie 1993).

Skin snip methodology

The standard and most reliable method to diagnose onchocerciasis infection and to determine its intensity is through microscopic examination of the skin snips for the presence and number of *O. volvulus* MFs. This method is highly specific but is not so sensitive for light infections. Sensitivity can, however, be increased by taking as many as six skin snips from areas of the body that harbour the parasites. The practice, however, is to take two skin snips from the right and left iliac crests, which is the site that usually has the highest concentration of skin MFs. Skin snip is done in all selected villages 11-12 months after last treatment, and the survey is usually cross sectional. All subjects above one year[4] who agree to participate (or whose parent agree on their behalf) and voluntarily present themselves for the study are selected. They are asked for identification data - name, age, sex, occupation, and number of years resident in the village. Two skin biopsies are obtained from the right and left iliac crests of those studied. A two mm Holth corneoscleral punch is used to obtain the two bloodless skin snip biopsies. The scleral punch is sterilised with sodium hypochlorite solution and distilled water and then autoclaved under pressure for 15 minutes after taking biopsies from each participant. This was to prevent the transfer of HIV and other blood-borne infections. The samples are then microscopically examined for the presence and number (quantity) of *O. volvulus* MFs after incubation for 30 minutes in distilled water. Negative skin snip samples are further kept in saline solution for 24 hours and microscopically re-examined (currently, all snips are examined

[4] This was recently changed from one year to five years for ethical reasons considering the pain experienced by participants when skin snipping is done. Currently participants are those ≥five years.

24 hours after collection). The number of MFs are counted, and the results are recorded for each person examined. Migration history is taken for each person during the last ten years before the survey. Pre- and post-treatment skin snip data are then analysed to determine and compare onchocerciasis infection levels using indicators of prevalence of microfilaria and community MF load. The results are expressed as a proportion of positive/negative people in the sample (Wanji *et al.* 2005; Afework *et al.* 2012; Katabarwa *et al.* 2013).

Rapid Epidemiological Mapping for Onchocerciasis

Since ivermectin treatment was introduced, researchers have focused on developing and testing simple and rapid methods for community diagnosis. The prevalence of palpable subcutaneous nodules is closely related to the prevalence of infection as determined by skin snip, with the prevalence of MF being about twice the prevalence of nodules. Furthermore, in the West African Savannah the prevalence of onchocerciasis has been shown to be directly related to the prevalence of nodules. The rapid assessment of endemicity of a community is now usually done through palpation for nodules in a sample of 30-50 adult males per community. The rapid assessment method though more rapid and acceptable than skin snipping still requires a visit and a rapid survey in all potentially endemic communities. A method for REMO was developed and successfully tested in Cameroon. These surveys are conducted only in a special sample of two to four percent of all communities, and the results are extrapolated to estimate the approximate endemicity level of the remaining communities. For REMO, researchers initially identify and select “high risk” communities every 30km along the river and additional primary communities located 10km away from those at “high risk”. Thereafter, if necessary, secondary communities are selected 10km away from the primary communities and tertiary communities and 10km away from secondary communities until members of the research team reach onchocercal nodule-free communities. Assessment of nodule rates is undertaken among 30-50 adults who are at least 20 years old and have lived in the community for 20 years or more. The results are expressed as a proportion of the number of positive people in the samples (Katabarwa *et al.* 2008; Katabarwa *et al.* 2012).

Rapid Assessment Procedure for Loiasis

Since people or individuals with high microfilarial loads of *Loa loa* are at increased risk of neurological serious adverse events following ivermectin treatment against onchocerciasis, it is usually necessary to identify areas of onchocerciasis/*Loa loa* co-endemicity (Gardon *et al.* 1997). This is done using the Rapid Assessment Procedure for Loiasis (RAPLOA), a newly developed rapid assessment procedure for loiasis that relates the prevalence of a key clinical manifestation of loiasis (history of eye worm) to the level of endemicity of the infection. This method is proven to be a useful tool for identifying areas of potential risk of *Loa loa* post-Ivermectin treatment encephalopathy (Wanji *et al.* 2005).

Treatment

Control/elimination programmes for onchocerciasis focus mainly on prevention as the blindness resulting from the disease is irreversible. Before the concept of onchocerciasis elimination in Africa, onchocerciasis was considered a serious public health problem when microfilaridermia prevalence was greater than 40%, and treatment was based on this. Areas with less than 40% prevalence were not treated (APOC 2010). The two main treatment strategies for onchocerciasis control are vector control through larviciding and chemotherapy using ivermectin. Other possible interventions such as personal protection from exposure to vector biting with adequate clothing that is usually impractical, use of deodorants/insect repellants that are not so effective and can be expensive, or large-scale nodulectomy campaign have little practical value for onchocerciasis control (Taylor 2003; Thylefors, Alleman 2006). The OCP (1974-2002) began mainly with the vector control strategy to interrupt transmission of the parasite long enough for the human reservoir to die out (Hopkins and Boatin 2011; Molyneux et al. 2014). For APOC countries onchocerciasis control has almost exclusively been based on large-scale ivermectin treatment of at-risk populations conducted annually or six-monthly with a recommended therapeutic coverage of ≥65% and geographic coverage of 100% to control the disease as a public health problem (APOC 2010).

A single dose of ivermectin per annum can kill first stage larvae (MF) in those infected and prevent transmission within communities (Diawara *et al.* 2009). Ivermectin is effective as microfilaricide and kills 99% of MF with a single treatment. Since MF are responsible for most

manifestations of the diseases, treating with Ivermectin provides an immediate health benefit. However, ivermectin does not kill the macrofilariae (adult worm) and most macrofilariae start reproducing MF a few weeks after treatment with ivermectin resulting in a renewed increase in MF load. There is evidence that ivermectin affects the viability and reproductivity (fertility) of the adult worm and even though ivermectin does not kill the adult worm, the rate of increase of the MF load is less after each treatment. Computer simulation shows that the prevalence bounces up after each treatment but the MF load increases at a slower rate than before to a maximum level that is lower than the level reached after the previous treatment (APOC 2010).

Vector control

Vector control through routine aerial and ground application of larvicides and application by boat was the main strategy of OCP throughout its mandate. Vector control experience in West and East Africa has shown that vector control can be an effective strategy to achieve transmission interruption and parasite reservoir elimination as demonstrated in Kenya in the 1950s (Roberts et al. 1967) and at a much larger scale in the OCP countries. In the OCP countries, vector control was highly effective especially in the Savannah areas where vector breeding sites are relatively easy to identify, limited in number and fairly accessible by helicopter (Philippon 1990). The cost of implementing vector control is high and should be maintained over a large area in at least the many foci where *S. damnosum s.l* is the vector to reduce the risk of reinvasion of transmission zones under control by infective vectors from other transmission zones that are still being treated. This suggests therefore that vector control is more feasible when managed by a multi-national project such as OCP and may be beyond the means of individual endemic countries themselves (Remme 2004). The use of DDT applied to the water at a concentration as low as 0.1 p.p.m. for 30 minutes leads to the elimination of the larvae of *Simulium*. Such larvicidal methods have eradicated *S. neavei* from Western Kenya and virtually eradicated *S. damnosum* from the Victoria Nile in Uganda (Brown 1962). This was expensive but considered necessary. Vector control is no longer considered feasible or cost-effective after the closure of OCP in 2002 although it was implemented briefly in some of the Special Intervention Zones (SIZ) such as the north of Togo (Taylor *et al.* 2009). Vector control led to the interruption of transmission of the parasite causing human

onchocerciasis *(O. volvulus*) in many areas and introduction of ivermectin treatment in addition to vector control interventions led to a decline in anterior-segment lesions of the eye and the reduction of posterior-segment lesions (Boatin, 2008). The impact of vector control for controlling onchocerciasis was demonstrated in Uganda (Lakwo *et al.* 2006).

Vector control versus vector control plus ivermectin MDAs

It was demonstrated that the combined use of vector control and ivermectin treatment is more effective in reducing infectivity among black flies and reducing MF prevalence and density in humans than vector control alone. It is currently recommended by experts that only selective vector control should be conducted while the focus should be on ivermectin treatment (Guillet *et al.* 1995).

Nodulectomy

Nodulectomy has been used as a third form of onchocerciasis control, especially in Mexico, Ecuador, and Guatemala, where health workers went from village to village removing nodules mainly around the head. This approach can lessen the number of MF entering the eye though there is no strong evidence that this can prevent blindness (Burnham 1998). Although Mexico and other countries have used nodulectomy with significant impact on the reservoir, these campaigns may be impractical especially in Africa where 99% of those infected live (Remme, 2004).

Effect of ivermectin on transmission of onchocerciasis

Ivermectin (otherwise known as Stromectol or Mectizan) is a semi-synthetic macrocyclic lactone and is considered an excellent tool for the treatment of onchocerciasis and reduction of blindness rates (Eezzuduemhoi and Wilson 2010). Initially, it was proposed that ivermectin was an agonist for neurotransmitter function because of its rapid and specific antiparasitic and anthelmintic action. Experiments confirmed this later when it was demonstrated that inhibition occurred via glutamate-gated chloride ion channels in nerve and muscle cells of the parasite. Ivermectin interacts with these channels and prevents their closure. As a result, synapse membranes become increasingly permeable to chloride ions which leads to hyperpolarization of the neuronal membrane and decreases or prevents neuronal

transmission. This, in turn, leads to paralysis of the somatic muscles, particularly the pharyngeal pump causing the death of the parasite. ϒ-aminobutyric acid (GABA)-related chloride ion channels that are present only in nematodes, insects and ticks are only inhibited with greater drug concentrations. In mammals, GABA receptors and neurones are found in the central nervous system while in arthropods and nematodes they are found in the peripheral nervous system. This plus the relatively low dose concentrations needed to kill arthropods and nematodes ensures that mammals can ingest ivermectin with a high degree of safety (Omura and Crump 2004; Geary 2005).

Ivermectin kills the MF of the parasite by attacking its nervous and muscular system causing paralysis so that they can be killed by eosinophils and macrophages produced by the human body. With ivermectin treatment, the intense itching of the skin stops and the progression to blindness also stops. High treatment coverage within at-risk communities is needed to reduce infection rates and parasite loads of fly populations (Kutin *et al.* 2004). Although some studies have suggested that ivermectin inhibits production of additional offspring by reducing the fertility of the adult onchocercal worm thus preventing morbidity and transmission, the drug has mainly microfilaricidal effect and does not kill the adult worm. The adult onchocercal worms continue to produce MF a few months after treatment with ivermectin necessitating many years of treatment to control microfilarial loads (Diawara *et al.* 2009; Taylor *et al.* 2009). Mass treatment with ivermectin significantly reduces but does not stop transmission during first years of treatment and cannot kill the adult *O. volvulus* parasites. Long-term annual treatments are needed or at least 14 years of annual treatment is needed after the first dose because it is expected that the adult onchocercal worms will die naturally during the 14 years of treatment (Eezzuduemhoi and Wilson 2010). Computer simulations with the ONCHOSIM model predicted that treatment should continue for over 25 years before local transmission of the infection can be stopped in Africa. The model indicated the possibility of elimination in most endemic foci in Africa, but treatment is needed for as many as 25 years (Winnen *et al.* 2002).

The CDTI strategy adopted by APOC since 1997, after the multi-country study, promotes community participation as the key aspect of ivermectin distribution to improve access to

ivermectin and ensure community ownership of the process. The strategy is first introduced to communities by local health workers and NGDO representatives in a participatory manner. Through subsequent community meetings, they explain the roles and responsibilities of communities in the CDTI process. The communities are then encouraged to direct the planning and implementation of the interventions by first collectively selecting CDDs and then later planning the distribution process by deciding the method used (house to house or central location), the place where the distribution is conducted if a fixed location is accepted, when the distribution is conducted, by whom activities will be implemented, how all activities will be monitored, and the support, if any, that CDDs will receive (financial or otherwise) from the community. With CDTI communities collect their supply of ivermectin from a central point agreed upon with the health services and store it within the community until the distribution period. The health workers, with support from NGDO representatives, train, supervise and monitor the CDDs while the community directs the process. It has been suggested that when the community takes charge of onchocerciasis control, mass treatment can be sustained for up to 20 years. Overall programme implementation costs also reduce significantly because the community plays the leading role in all aspects of programme implementation. In addition to training communities to assume leadership of the CDTI process, NGDOs have also made a significant contribution to the CDTI process through operational research, provision of resources to complement national programmes by supporting health staff in remote communities, and through technical and financial support to NOCPs. An NGDO coalition was created in 1991 for onchocerciasis control that meets regularly to coordinate collaboration at international and national levels (Dadzie, De Sole and Remme 1992; Amazigo 1999; Boatin and Richards 2006; Taylor *et al.* 2009). The Community-Directed Intervention (CDI) Study Group 2010; WHO APOC 2010; Meredith, Cross and Amazigo 2012).

Ivermectin needs to be taken only once or twice a year, needs no refrigeration during handling and storage and is relatively safe so that it can be administered by minimally trained community health workers (Wikipedia, available from: https://en.wikipedia.org/wiki/Ivermectin; accessed: 19/10/2016). It has been demonstrated that ivermectin has less side effects than diethylcarbamazine (Greene *et al.* 1985; Albiez *et al.* 1988). Other studies were also able to demonstrate that ivermectin has less ocular side effects

than diethylcarbamazine and significantly improves ocular status when used as opposed to diethylcarbamazine for the treatment of patients with ocular manifestations of onchocerciasis (Lariviere *et al.* 1985; Taylor *et al.* 1989; Taylor 1990a,b). When given as a single dose of 150 mcg/kg it reduces MF in the skin by more than 90% after a few months and the reduction rate is maintained up to 1 year after a single dose (Basanez *et al.* 2008). Ivermectin does not kill adult worms (macrofilariae) but can cause them to cease releasing MF, possibly by paralysing their reproductive tract thereby preventing morbidity and transmission (Duke *et al.* 2002; Duke 2005; Basanez *et al.* 2008).

Transmission is significantly reduced also, though not interrupted completely, because of the reduction of the microfilarial load after each successive treatment which translates into a significant drop in the annual transmission rate. The mean MF load is further reduced with each subsequent treatment round, and the annual level of transmission continues to reduce or decline. The population of the adult worm also reduces although at a slower rate through natural or treatment-induced death or sterilisation of old worms without replenishment. As this continues, the adult worm population can reach a low level at which the parasite can move irreversibly to its extinction even without any further ivermectin treatment. Thus, the parasite density is considered to have fallen below its "breakpoint" and ivermectin treatment can be stopped, bringing an end to the treatment phase (stage one) of the elimination process. The concept of breakpoint means that treatment can be safely stopped even when infection and transmission are not completely zero. In the Senegal and Mali study conducted by APOC, it was demonstrated that no renewed transmission and infection was detected after treatment was stopped for three years even though there were some MF-positive individuals when treatment was stopped. Predictions were made in the 1990s even before empirical evidence that in the long-term interruption of transmission and elimination of the parasite reservoir is possible with just ivermectin treatment. First empirical evidence of the feasibility of onchocerciasis elimination with ivermectin treatment was made available through studies in three onchocerciasis foci in Senegal and Mali that showed that after 15-17 years of annual or six monthly treatments with ivermectin the prevalence and intensity of infection falls below thresholds for elimination of the disease (Diawara *et al.* 2009; APOC 2010; Traore *et al.* 2012; Bockarie et al. 2013).

Severe adverse events after treatment with ivermectin

Ivermectin causes reactions that are known and do not last for long (less than a week to be resolved) and programme guidelines usually encourages staff to inform treated communities and individuals of the possible side effects so that when they occur they are reported and those affected receive the correct care. Reporting side effects is important and reporting forms do include areas for reporting side effects. According to the information on ivermectin from drugs.com (Online, available from: http://www.drugs.com/mmx/ivermectin.html; Accessed: 25/05/2015) ivermectin reduces the number of MF in the eye slower than with diethylcarbamazine and thus reduces the possibilities of tissue changes relating to immune reaction of surrounding tissue to the dead *O. volvulus* and its endosymbionts *Wolbachia pipientis*. The drug does not cross the blood-brain barrier in humans, and most mammals and so no major reaction has been reported relating to the central nervous system (Drugs.com, Online, available from: http://www.drugs.com/mmx/ivermectin.html; Accessed: 25/05/2015). Ivermectin is proven to be teratogenic in experiments with mice and therefore not recommended for treatment of pregnant women (Drugs.com, Online, available from: http://www.drugs.com/mmx/ivermectin.html; Accessed: 25/05/2015). According to drugs.com (Drugs.com, Online, available from: http://www.drugs.com/mmx/ivermectin.html; Accessed: 25/05/2015), ivermectin is secreted with breast milk and so not recommended for breastfeeding women in the first two weeks after delivery. Since safety and efficacy of ivermectin are not established for children weighing less than 15kg, it is not recommended for children below 15kg or five years to take the drug. The frequency of side effects is found to be related to the level of parasite infection and last for up to three days (Drugs.com, online http://www.drugs.com/mmx/ivermectin.html, 22/05/2015). Side effects of ivermectin can include Mazzotti type reactions (pruritus, edema, headache and rash), severe headache, orthostatic hypotension, confusion/disorientation, stupor, coma and death, especially in areas where loiasis is co-endemic (Pacque *et al.* 1990; Pacque *et al.* 1991; Chijioke and Okonkwo 1992; Kamgno *et al.* 2004). APOC conducted an intensive study across Africa to determine the *Loa loa* areas where ivermectin treatment can cause a severe reaction that can lead to coma and death (Zouré *et al.* 2011). Some authors suggest the use of a six-week treatment with doxycycline, which kills the MF and sterilises and kills the female adult worm by killing the *Wolbachia* bacteriae that live in the worms, in areas where it is not safe to administer

ivermectin (Taylor *et al.* 2009). Pirmohamed *et al.* (2007) recommend good pharmacovigilance when treating communities with ivermectin so that side effects can be detected and managed early.

Possible O. volvulus resistance to ivermectin

Evidence has shown that ivermectin kills the MF of *O. volvulus* and can have embryostatic effect on female adult worms (Bockarie et al. 2013), but there are suggestions that the onchocerciasis parasite *O. volvulus* is developing resistance to ivermectin (Awadzi 2004; Eng and Prichard 2005; Ardelli, Prichard 2007; Hodgkin *et al.* 2007; Lustigman, McCarter 2007; Osei-Atweneboana *et al.* 2007a; Osei-Atweneboana *et al.* 2007b; Boatin 2008; Gloeckner *et al.* 2010; Frempong *et al.* 2016). It has been recommended that more research be conducted on resistance of *O. volvulus* to ivermectin including the use of genetic markers for monitoring sub-optimal or atypical responses of *O. volvulus* to ivermectin (Awadzi 2004; Eng and Prichard 2005; Ardelli and Prichard 2007; Burnham 2007; Cupp *et al.* 2007; Mackenzie 2007; Osei-Atweneboana *et al.* 2007a; Osei-Atweneboana *et al.* 2007b; Bourguinat *et al.* 2008; Churcher *et al.* 2009; Taylor *et al.* 2009). Many authors agree that resistance to ivermectin by *O. volvulus* will disrupt the global onchocerciasis control and elimination programme as ivermectin is currently the only available drug for onchocerciasis treatment. They also agree that although there is some sub-optimal response to ivermectin treatment and probably selection for development of resistance, more studies are needed to produce actual evidence of *O. volvulus* resistance to ivermectin (Burnham 2007; Cupp *et al.* 2007; Hodgkin *et al.* 2007; Mackenzie 2007; Taylor *et al.* 2009). Currently, there are many ongoing onchocerciasis studies sponsored by big donors such as the BMGF to develop alternative drugs for treating onchocerciasis that can replace ivermectin (Turner *et al.* 2010).

Other possible alternative treatments for onchocerciasis

There is increasing concern that there are currently no alternatives to ivermectin and there is no vaccine for onchocerciasis, especially when some onchocerciasis experts have suggested the possibility that *O. volvulus* is developing resistance to ivermectin. There are other antibiotics being tried for treatment of onchocerciasis such as doxycycline, described below (Basanez *et al.* 2006). Trials of Rifampicin and Azithromycin to determine if they can deplete

Wolbachia from *O. volvulus* was unsuccessful, and the conclusion was that short courses of the two drugs cannot clear *Wolbachia* from *O. volvulus* (Richards *et al.* 2007). It should be noted that in areas where there is co-endemicity of onchocerciasis and LF, LF treatment (ivermectin plus albendazole) is a treatment for onchocerciasis and if onchocerciasis threshold for stopping MDA is reached, onchocerciasis evaluations can be conducted together with LF evaluations (APOC 2010).

Moxidectin, an analogue of Ivermectin, is also a veterinary anthelmintic. Many clinical trials have shown Moxidectin to be a substitute for ivermectin but has no macrofilaricidal effect on *O. volvulus* (Cotreau *et al.* 2003; Tagboto and Townson 1996). In addition to efforts to discover new medicines, researchers are currently trying to discover other medicines for tropical diseases using strategies such as 'piggy-back discoveries' or testing of medicines already in use for treating other diseases caused by similar causative agents. These efforts need an extended period of time invested in testing and subsequent approval when a suitable drug is discovered. Drug repositioning or identification and development of new uses for existing drugs can potentially be less time consuming and more cost-effective. One such effort has targeted Moxidectin an analogue of ivermectin for replacement of ivermectin when necessary. Both Ivermectin and Moxidectin were initially only marketed as veterinary anthelmintics. The successful use of ivermectin has validated repositioning for the discovery of new drugs for NTDs (Hodgkin *et al.* 2007; Gloeckner *et al.* 2010).

Effect of doxycycline on Wolbachia

The importance of the endosymbiotic bacteria *Wolbachia*, found in *O. volvulus*, has become clear to researchers. Living MF cause little or no inflammation even in the anterior chamber of the eye. However, when they die the host response to degenerating worms can result in ocular inflammation causing progressive loss of vision and blindness that tend to occur in adulthood after many years of infection. Treatment with diethylcarbamazine can cause the Mazzotti reaction, the severity of which is dependent on the number of MF containing *Wolbachia* in the skin and eyes (Greene *et al.* 1985; Albiez *et al.* 1988). Acute and severe inflammatory responses in people infected with *O. volvulus* are associated with the release of *Wolbachia* into the blood following death or damage to worms, suggesting that *Wolbachia* may be the cause

of acute inflammatory disease. Post-treatment reactions might also be related to *Wolbachia* products that induce inflammatory responses. Anti-*Wolbachia* products could minimise inflammatory responses seen after treatment, a view supported by treatment of *O. volvulus* -infected individuals with doxycycline, resulting in the elimination of skin MF, presumably through direct effects on the endosymbionts (Crump *et al.* 2012). The excellent impact of doxycycline on the onchocerciasis MF with little or no side effects has been demonstrated in several studies although treatment with doxycycline is needed daily for up to six weeks (Hoerauf *et al.* 2008; Wanji *et al.* 2009; Tamarozzi *et al.* 2012).

The role of Merck & Co. Inc. in drug donation

In 1987 Merck and Co. Inc. offered to donate ivermectin for treatment of onchocerciasis for as long as it was needed and this has been ongoing since 1988. Merck launched the Mectizan Donation Program (MDP) in 1987, a unique collaboration between public and private enterprises, a unique multi-sectoral coalition involving Merck, the Mectizan Expert Committee (MEC), the Task Force for Child Survival and Development (now the Task Force for Global Health), WHO, the World Bank, UNICEF, national Ministries of Health, more than 35 NGDOs, and thousands of local community health workers. The generous donation of ivermectin by Merck and Co. Inc. has increased general interest in health-related public-private partnerships and generated the momentum for other donations to tackle other NTDs. Mectizan has also been donated for the elimination of LF since 1998 in African countries and in Yemen where onchocerciasis and LF are co-endemic. Ivermectin is co-administered with albendazole donated by GlaxoSmithKline for LF elimination. The MDP works in collaboration with the Mectizan Expert Committee/Albendazole Coordination and its scientific advisory committee. The programme achieved important notable results including positive health impacts, economic benefits, strengthened health systems, and the empowerment of communities where the delivery and administration of ivermectin is managed. MDP also laid a foundation for efforts to integrate the management of NTDs. (Alleman, Twum-Danso and Thylefors, 2006; Boatin, 2008; Colatrella, 2008; Thylefors, Alleman, Twum-Danso, 2008; Thylefors, 2008; Hopkins and Boatin, 2011; Meredith, Cross and Amazigo 2012; Pose and Rabinowitz 2014; WHO 2016b). Yameogo (2008) describes the donation of ivermectin in 1987 as a key factor for success with onchocerciasis control because vector control efforts were proving costly and ineffective in

certain areas and ivermectin distribution has become the primary strategy for onchocerciasis control.

Paradigm shift towards onchocerciasis elimination

Worldwide eradication of onchocerciasis could be challenging with ivermectin treatment alone, but analysis shows that the elimination of onchocerciasis using mass treatment programmes is feasible only in areas where high treatment coverage can be maintained throughout the treatment period which is long for onchocerciasis. Since relying on a single drug is high risk, priority should be given to research for alternative drugs, and safe, effective and affordable alternative elimination strategies such as the use of macrofilaricides (Alley *et al.* 2001; Boatin and Richards 2006; Winnen *et al.* 2002). However, since 2009 there has been a paradigm shift from controlling onchocerciasis as a public health problem to eliminating the disease by stopping local transmission after studies in Senegal and Mali showed that it was possible to reduce the disease to a level where it reaches its demise and transmission is completely stopped. The recommended therapeutic coverage during treatment with ivermectin is ≥80% and geographic coverage of 100% if a country wishes to move towards elimination of onchocerciasis (Hodgkin *et al.* 2007; Diawara *et al.* 2009; APOC 2010; Tekle *et al.* 2012; Traore *et al.* 2012; Bockarie et al. 2013). However, a few studies have indicated that elimination might not be so easy in some foci in Africa. In Cameroon and Uganda, 10-13 years of ivermectin treatment did not interrupt onchocerciasis transmission (Katabarwa *et al.* 2008), nor did 15 years of annual treatment in West Cameroon interrupt transmission (Katabarwa *et al.* 2013). The Joint Action Forum (JAF) of APOC has strongly recommended the use of alternative approaches including twice yearly treatments with ivermectin, where appropriate, to scale-up and speed up elimination in problematic areas, and also to address cross-border issues (APOC 2011).

Community empowerment and ownership

In sub-Saharan Africa and other undeveloped parts of the world many public health programmes and projects have to address the issue of delivering services in remote rural areas within poor countries with inadequate infrastructures (Amazigo *et al.* 2012). Despite large financial commitments at international level, challenges still exist with service delivery.

Community driven approaches used in the fight against onchocerciasis show that engaging communities in the delivery process maximise access and performance. This way communities can be empowered to extend access to health services themselves (Amazigo *et al.* 2012). The empowering of communities to be part of the solution of the onchocerciasis problem is important (Crump *et al.* 2012; Pose and Rabinowitz 2014). As part of community participation, CDDs who are usually literate or semi-literate members of their communities are selected to be able to complete basic reporting forms. The challenge in many African communities is that CDDs are mostly men because of local traditions and this can limit women's access to treatment (Amazigo 1999). The involvement of communities in efforts to control onchocerciasis can also improve the sustainability of onchocerciasis treatment that should continue for at least 15 years (Amazigo *et al.* 2007).

Although the concept of expecting communities to work without pay is still controversial and many programmes like the polio campaign pay volunteers, studies in four countries funded by APOC has highlighted possible problems with payment of volunteers such as fragmentation of remuneration (different rates by different programmes within the same country), lack of coordination at national level, and difficulty in sustaining cash incentives in the long term in such under-resourced countries where they are implemented (Amazigo *et al.* 2012). It is suggested that the following alternative forms of incentive be considered: transport money provided during training; and provision of working tools such as boots, raincoats, and rainproof bags to protect treatment registers (Amazigo *et al.* 2012). With CDTI, CDDs are not taken from their other responsibilities for too long and communities sometimes find ways of compensating CDDs such as by helping them with their farm work or building a house for them (Meredith, Cross and Amazigo 2012). Several other studies have been conducted in Nigeria and Ethiopia that show that community adherence to treatment through CDTI is generally good and identified key factors for improving adherence to treatment and the strategies needed to improve adherence (Brieger *et al.* 2002; Nuwaha *et al.* 2005; Yirga *et al.* 2010; Brieger *et al.* 2011).

CDTI and other interventions

A three-year study was conducted in Cameroon, Nigeria and Uganda between 2005 and 2007 demonstrated the use of CDTI as a vehicle for delivering other public health interventions such as Vitamin A supplementation, distribution of insecticide-treated nets (distribution plus retreatment), home management of malaria and detection and referral of TB cases for short-course directly observed treatment. It was shown that with the right training and support community implementers could deliver multiple interventions correctly and sustain them over time. It is suggested that CDTI coverage is better when the strategy is integrated with other interventions such as Vitamin A supplementation, home management of malaria and bed net distribution (CDI Study Group 2010).

Effect of ivermectin on other diseases

Several authors have conducted studies that show the effect of ivermectin on other diseases such as soil transmitted helminthiasis, pediculosis and scabies. A study conducted within communities receiving annual or biannual ivermectin treatment showed that among school-age children living in endemic areas, ivermectin has significant effects on the prevalence and intensity of *Trichuris trichiura* infection, but appeared to have no impact on *Ascaris lumbricoides* or hookworm infection (Moncayo *et al.* 2008). Pediculosis and scabies are caused by ectoparasites and patients of both diseases present with itching. ivermectin is not officially approved for their treatment, but the effect can occur in areas treated for onchocerciasis (Meinking *et al.* 1995; David, Flinders and De Schweinitz 2004; Burkhart and Burkhart 2006). Every year malaria afflicts an estimated 500 million people worldwide and kills more than one million people, mostly in sub-Saharan Africa. Recent field studies in Senegal have suggested that ivermectin can kill the malaria vectors. ivermectin MDA reduced the proportion of *Anopheles gambiae sensu stricto (s.s.)* infected with *Plasmodium falciparum* in treated villages in southeastern Senegal (Kobylinski *et al.* 2011).

History of onchocerciasis control

It is suggested that the disease onchocerciasis has been around for centuries but was first scientifically observed almost 140 years ago**.** In 1874-1875, John O'Neil, a British naval surgeon who was based in Ghana (then Gold Coast) detected an irritating and intractable skin disease

among locals that was similar to scabies and known locally as ‘kra kra’ or ‘craw craw’. Through microscopic examination of specimens taken from papules of patients, he detected easily visible minute worms that contorted violently. He noted that there were two small dots at the head or blunted extremity of the worms, but their nature could not be determined (Crump *et al.* 2012).

Between 1890 and 1945, Scientists described the worm, disease transmission and manifestation, and the vector. In 1915 Dr. Rodolfo Robles Valverde discovered that the disease is caused by filaria worms while caring for patients in Guatemala and also shed light on the life cycle and mode of transmission. His publication from Guatemala in 1917 on the “new disease” associated the disease with subcutaneous nodules, anterior ocular lesions, dermatitis and MF. In 1922 Blacklock started investigating the mode of transmission of onchocerciasis in Sierra Leone. As the MF were found in skin, not blood, he proposed that an anthropod transmitting the disease must damage the skin to be able to introduce the larvae in the skin in its efforts to reach the blood. He later noticed that a common small black fly named *Simulium damnosum* was biting people. He noticed that the flies do not actively seek a host but wait in short grass for an individual to pass biting low on the body, usually around the lower leg and ankle (Blacklock 1926). In 1945 Sir Harold Ridley inventor and surgical pioneer of the intra-ocular lens, was able to demonstrate the importance of onchocerciasis as a blinding disease after extensive research in Ghana (Crump *et al.* 2012).

By 1946 vector control was suggested as the only feasible control intervention since no therapeutic drugs were available. It was suggested that the vector be killed in their breeding sites using the then successful insecticide dichlorodiphenyltrichloroethane (DDT). Subsequently, in 1946 vector control was initiated in Kenya that resulted in the eradication of *Simulium neavei.* In 1948 vector control was extended in Congo basin, and later to the Victoria Nile in 1954 (Crump *et al.* 2012).

In 1954, skin snip diagnosis was developed that allowed detection of MF in the skin (Crump *et al.* 2012).

In 1972 the World Bank President visited West Africa and saw many people blind from onchocerciasis with the blindness rate in some villages as high as 50%. This led to the formation of the OCP in 1974 under the coordination of the World Bank (Crump *et al.* 2012; Bockarie et al. 2013; Molyneux et al. 2014).

Between 1971 and 1988, ivermectin was developed and approved for use in humans through a collaboration between the Kitasato Institute in Japan and Merck, Sharpe and Dome (MSD) laboratories in the US to discover new antibiotic agents from natural microorganisms. By 1981 avermectin/ivermectin was marketed as an anthelmintic veterinary drug and became a best seller. MSD started manufacturing ivermectin for veterinary use, to deworm dogs, sheep, cattle, horses, pigs and other animals (Taylor 2003; Omura and Crump 2004; Crump *et al.* 2012).

By 1982 MSD reported activity against *O. volvulus*, thus revealing the possibility of using the drug in human public health and disease control. Clinical trials in many countries including Liberia and Sierra Leone confirmed the safety of the use of ivermectin for the treatment of human onchocerciasis. In 1987, the French government decided to approve the use of the drug for treatment of diseases in humans, following which MSD decided to donate the drug free of charge to help eliminate onchocerciasis. By 1987 ivermectin was registered for treatment of onchocerciasis in humans and MSD started its donation in 1988 for treatment in endemic communities (Taylor 2003; David, Flinders and De Schweinitz 2004; Omura and Crump 2004; Geary 2005; Burkhart and Burkhart 2006; Crump *et al.* 2012; WHO AFRO NTDP 2016).

In 1988 MSD started the donation of the drug under the brand name Mectizan. Merck, Sharpe and Dome formed MDP, the first ever mass drug donation programme. Since its introduction more than 30 years ago ivermectin has proved to be one of the most successful therapeutic drugs in veterinary medicine, as well as the basis for one of the most successful public health programmes in the past century (Crump *et al.* 2012; Molyneux et al. 2014).

Between 1975 and 2002, OCP was responsible for onchocerciasis control in 11 West African countries including Sierra Leone. Large scale onchocerciasis control started in the 1970s

through the OCP in West Africa (1974-2002). The OCP goal was to eliminate onchocerciasis as a public health problem and mitigate its negative impact on the social and economic development of affected areas. OCP started in 1975 as a vertical programme with its vector operations. The objective of vector control was to interrupt transmission of the parasite for sufficient periods to allow the adult parasites in the human reservoir to die out (Hopkins and Boatin, 2011; Molyneux et al. 2014). OCP is described as the first large successful public-private partnership established by WHO to address a public health problem and it was expected that the programme will improve accessibility to fertile land through vector control in OCP countries, lead to enhanced agricultural yields, elevated crop diversity, improved human nutritional status, and remove two important public health problems namely blindness and skin disease resulting from infection (Hodgkin *et al.* 2007). OCP's history started in 1975 with support in 7 countries: Benin, Burkina Faso, Cote d'Ivoire, Ghana, Mali, Niger, and Togo. The programme later spread to a further four countries including Sierra Leone, and the name was changed from Onchocerciasis Control Programme to "the Onchocerciasis Control Programme in West Africa" maintaining the acronym OCP (Fobi *et al.* 2015). Initially, aerial larviciding was used in the absence of a safe drug for treatment, but chemotherapy started in 1989 with the donation of ivermectin by Merck and Co. Inc. in 1988, and the two strategies were continued up to the end of OCP in 2002 (Samba, 1994; Fobi *et al.* 2015).

In 1992, the Onchocerciasis Elimination Program for the Americas (OEPA) was launched with the goal of eliminating morbidity and interrupting disease transmission in 13 foci in endemic Latin American countries, using intensive twice yearly ivermectin treatment and an aim of reaching 85% of the estimated 503,000 people deemed to be at risk. Marked gains in controlling onchocerciasis have been achieved more in the Americas than in Africa under the coordination of Onchocerciasis Elimination Programme for the Americas (OEPA). The effort to eliminate the disease from the region was launched in response to the Pan American Health Organization (PAHO) resolution in 1991 to eliminate the disease as a public health problem by 2007. Onchocerciasis was found to be endemic in 13 foci in 1,845 endemic communities of 6 countries (Brazil, Colombia, Ecuador, Guatemala, Mexico and Venezuela) (Vieira *et al.* 2007; Sauerbrey, 2008; Rodríguez-Pérez *et al.* 2008; Gustavsen *et al.* 2011).

In 1995, APOC was launched (Molyneux et al. 2014). APOC was established in 1995 with the objective of establishing "effective and sustainable CDTI in all endemic areas". The goal of APOC was to permanently protect an estimated 120 million at risk in 19 countries (now 20 with the independence of South Sudan) from the debilitating and disfiguring disease through CDTI that can be sustained by communities themselves after APOC may have closed. Duration of treatment was determined to be dependent on the initial or baseline endemicity level and treatment coverage (Hodgkin *et al.* 2007). APOC before its mandate ended in December 2015 was another example of good public-private partnership coordinated by WHO since 1995 and was a partnership between affected communities, governments, bilateral and multilateral agencies, foundations, NGDOs, the scientific community, and the private sector including the pharmaceutical company Merck and Co. Inc.[5] (Fobi *et al.* 2015). APOC evaluations between 2008 and 2015 show that at least 25 million people live in previously endemic areas that now have few or no people MF positive due to years of onchocerciasis treatment. APOC had saved 17.4 million DALYs during 20 years of existence using only US$27 per DALY (WHO 2016b).

In 2003, SIZ was formed. The SIZ of the former OCP was launched in December 2002 under the coordination of APOC, following the closure of OCP in 2002 to sustain the momentum that had been gained for onchocerciasis control through ivermectin distribution and vector control (Hodgkin *et al.* 2007, Yameogo, 2008). Survey data obtained before the close of OCP in 2002 was used to determine areas within the ex-OCP countries that still needed special attention, areas where the poor impact of treatment resulted in results in 2002 that were not in line with achievements of the OCP objectives and the situation suggested the possibility of recrudescence. SIZ was created in 2003 in five ex-OCP countries (Benin, Ghana, Guinea, Sierra Leone and Togo) to continue treatment for onchocerciasis under the coordination of APOC that lasted up until December, 2007 (Yameogo *et al.* 2008; Fobi *et al.* 2015).

In 2009 - CDTI strategy was recommended to be used to deliver other integrated disease interventions including Vit A supplementation and antimalarial treatment (CDI Study Group 2010). In December, 2015 the APOC mandate ended and in January, 2016 ESPEN was launched to last for an initial period of five years (WHO AFRO NTDP 2016; WHO 2016b).

[5] This is the current name of what was once MSD.

History of onchocerciasis control in Sierra Leone

Sierra Leone has a high burden of all five PC NTDs like many other African countries. Endemicity of NTDs was known in Sierra Leone as early as 1926 when Blacklock first described the transmission of onchocerciasis through the black fly, *S. damnosum* in the Kono district of Sierra Leone (Blacklock 1926). Onchocerciasis control efforts started as early as 1957 with insecticide treatments along the Tonkolili River that was found to be the most severely affected. It has also been documented that onchocerciasis is the second most common cause of blindness after cataract in Sierra Leone and so in the late 1980s the former OCP extended its activities to four other countries including Sierra Leone and vector control through larviciding with insecticides continued along rivers in hyper-endemic areas (Hodges *et al.* 2011).

Vector control was conducted in the northern part of Sierra Leone in areas where blindness rate was as high as 6%. Sierra Leone was among the first countries where ivermectin treatment trials were conducted, and integrated vector control and ivermectin treatment was established. Considerable work was done in the 1950's, 1960's and then later in the 1990's during OCP and demonstrated that onchocerciasis prevalence in Sierra Leone was between 30% and 50% along the main rivers, and black flies were found to exist in the entire country except in areas around the capital Freetown and the southern coastal plain of the Bonthe district. Between 1988 and 2005 the distribution of onchocerciasis was mapped by the NOCP using the skin snip method for detecting *O. volvulus* MF and all districts were found to be endemic except the Western Area (Western Urban and Western Rural districts) (Hodges *et al.* 2011).

Although the OCP started activities in Sierra Leone in 1989, the civil conflict between 1991 and 2002 impacted negatively on onchocerciasis control activities and in 1997 all onchocerciasis activities were stopped nationwide. So, for the last five years of the OCP, no activities were conducted in the country due to insecurity. With support from APOC, the NOCP of Sierra Leone restarted interventions in 2003 after the end of the civil war in 2002 through the SIZ. By then the CDTI strategy had already been developed and established as a principal strategy for onchocerciasis control by APOC since 1997, and so CDTI was implemented nationwide in meso-

endemic and hyper-endemic areas under the SIZ (Yameogo, 2008; Hodges *et al.* 2011; APOC 2012; Fobi *et al.* 2015).

As the onchocerciasis situation in Sierra Leone was still unsatisfactory in December 2007 when SIZ closed, it was decided that APOC's financial and technical support would continue and this was the situation until APOC finally closed in December 2015 (unpublished NTDP Reports 2005-2015).

Mapping for onchocerciasis was started in Sierra Leone in the 1980's, early 1990's and refined between 2003 and 2005 after the end of the civil conflict with technical and financial support from OCP, SIZ, and APOC (Linehan *et al.* 2011). Integration of onchocerciasis treatment with LF treatment started in 2007 with support from WHO/AFRO (Hodges *et al.* 2011). Social mobilisation was intensive in the beginning and continued on a smaller scale later in areas with poor coverage (Koroma *et al.* 2010; Hodges *et al.* 2011; Koroma *et al.* 2011). The successful implementation of the NTDP in Sierra Leone demonstrates the improvements that took place in the health system post-war. It is believed that the NTDP has had some socio-economic impact in the country. Furthermore, the NTDP has contributed significantly to health system strengthening in the country plus the reduction in NTD-related morbidity has also had a significant impact on poverty reduction in the country (Molyneux, Hotez, Fenwick 2005; Hotez *et al.* 2009; Hotez and Thompson 2009; Hodges *et al.* 2011).

Other onchocerciasis studies conducted in Sierra Leone

It was estimated through results of epidemiological mapping by OCP in 1990 that there was a total of 701,000 people infected with onchocerciasis out of an estimated total population of 4.2 million, with an estimated 8,300 people blind due to onchocerciasis. In neighbouring Guinea and Liberia, the estimates were similar: estimated 510,000 infected within a population of 5.8 million and 9,000 blind for Guinea, and 600,000 infected with 2,600 blind within a total population of 2.6 million for Liberia (Remme 2004).

Ophthalmological surveys were conducted in 13 highly infected villages located in various rivers basins of southern Sierra Leone to assess the pattern of onchocercal ocular disease and

blindness. The most significant finding was the high blinding potential of onchocerciasis in the degraded forest area where the prevalence of onchocercal blindness reached levels of up to 6%. This finding is contrary to previous findings that indicated that onchocerciasis in the forest causes little blindness. Ocular onchocerciasis, without a doubt, is a problem of public health importance in south Sierra Leone. The rates of onchocercal ocular disease and blindness, on the other hand, were significantly lower than those found in Savannah villages with similar levels of endemicity. The problem this poses is that it is difficult to tell if the pattern of ocular onchocerciasis in south Sierra Leone is of the forest type or a pattern on its own (Dadzie *et al.* 1992).

O. volvulus infection in Sierra Leone was first reported by Blacklock in 1926, and he also suggested that the clinical manifestations varied within the regions of the country (Blacklock 1926). The eastern region has the forest strain of the parasite, and so the disease is clinically characterised by low intensity of infection, mild skin disease, and relatively lower blindness rates. In the south, there is a mixture of forest and Savannah strains of the parasite with high infection intensity, mild skin disease, and relatively higher blindness rates that are sometimes higher than blindness rates recorded for the Savannah area. The northern region has the Savannah strain of the parasite with high infection intensity, mild skin disease, and a relatively high blindness rate (Gbakima and Sahr, 1996). A microfilaraemia survey conducted and reported by Sierra Leonean researchers in the south (Moyamba district) showed an MF prevalence of 39.1% in men and 35.9% in women for *O. volvulus*. Prevalence was lower in children 5-9 years (13.3%) compared to older age groups (61.9% among those 40-49 years) (Gbakima and Sahr 1996).

Entomology situation for onchocerciasis in Sierra Leone

Regular entomology data collection on the vector of onchocerciasis was undertaken in five countries (Guinea, Guinea-Bissau, Mali, Senegal and Sierra Leone) of the Western Extension of OCP between 1986 and 1990 by national teams with personnel that were employees of the governments of the countries. The strategy was changed in the zone (*i.e.* the western extension of the OCP) in 1990 to include ivermectin treatment in addition to vector control. Before that, the strategy for onchocerciasis control was to interrupt transmission of the

disease through vector control. Some of the rivers in Sierra Leone and Guinea run throughout the year while others do not have water during the dry season (Sékétéli *et al.* 1993).

Integrated MDA in Sierra Leone

Treatment of onchocerciasis has always been annual as there has never been any need for biannual treatment in Sierra Leone. The NOCP continued MDA for onchocerciasis between 2003 and 2006 before the NTDP was formed in 2007. Integrated MDA has been conducted since 2007 for onchocerciasis and LF elimination in Sierra Leone by unpaid community volunteers or CDDs. Other community-based health campaigns such as 'Mother and Child Health Weeks' pay community volunteers for their service and these same volunteers who work as CDDs are then called Community Health Workers. This, therefore, creates a major challenge for the NTD control programme (Hodges *et al.* 2012a). One unique intervention introduced to ensure good coverage is independent monitoring by students of the University of Sierra Leone. Independent monitoring helps ensure that MDAs are conducted with effective coverage even in hard to reach areas within rural and urban locations where vulnerable populations reside. Individuals eligible for MDA are interviewed by the independent monitors and those who recall having taken ivermectin and albendazole during the MDA are recorded. The programme coverage[6] and results reported by the monitors by phone are compared daily with the expected targets. CDDs in areas where targets are not met are encouraged by the monitors in collaboration with the DHMTs to continue distribution, trace and treat absentees, and ensure the expected targets are met. Coverage in rapidly urbanised towns is also monitored this way during MDA. Monitoring of coverage is conducted in randomly selected sites in all 12 districts, in urban and rural areas after the MDA and the results are compared with coverage calculated from the pre-MDA census and reported as treatment figures. So far this method in addition to the supportive supervision provided at all levels by the NTDP, NTD partners, and the health service personnel at the different levels has ensured that coverage targets are met and maintained as high as possible. The effective epidemiological coverage of

[6] Programme coverage is the coverage of an intervention among the eligible population expressed in percentage and is calculated as the total number of people treated divided by the total number of people eligible for the treatment within the population of the area treated multiplied by 100 (WHO 2013).

65%, programme coverage of 80% and geographic coverage of 100% for both onchocerciasis and LF have been met since 2008 (Hodges *et al.* 2012b).

The NTDP has had to address several challenges of MDA in Sierra Leone. There have been instances when donated drugs for onchocerciasis or onchocerciasis/LF MDA arrive later than anticipated, and this triggers a cascade of delays that end with delayed implementation of MDA. CDDs have been making stronger demands for incentives in place of salaries in the past five years. Extra incentives in the form of donated TOMS shoes to CDDs and their families, T-shirts to CDDs, fliers on the houses of CDDs, rain boots, and bags have been provided to CDDs in the past five years as extra motivation to keep them committed. This has also however increased the overall cost of programme implementation. With the addition of treatment for LF and other PC NTDs, some CDDs now see their role as a full-time job and demand payment for their services. Since payment of salaries to CDDs cannot be accommodated by the NTDP currently, the policy of maintaining CDD participation in NTD control/elimination as volunteering leads to frequent attrition of CDDs that must be replaced. The new CDDs also should be trained to bring their performance to the same level as other CDDs. There are sometimes delays in programme implementation that lead to MDA being implemented at periods when other public health programmes such as the Expanded Programme on Immunization (EPI) and the Malaria Programme should conduct community-based activities. These programmes use the same community volunteers for their activities within communities and pay a certain fee for their services. This means that distribution relating to NTDs that is based on volunteering has to wait until after they complete activities for these other programmes. It is worth noting that the spirit of volunteering is still strong within rural communities albeit with some of these challenges (Hodges *et al.* 2011; Hodges *et al.* 2012b). The recent EVD outbreak has had its toll on programme implementation such that 2014 treatment was delayed and conducted only in June 2015 (GoSL 2015).

GLOBAL OVERVIEW OF LF

Introduction

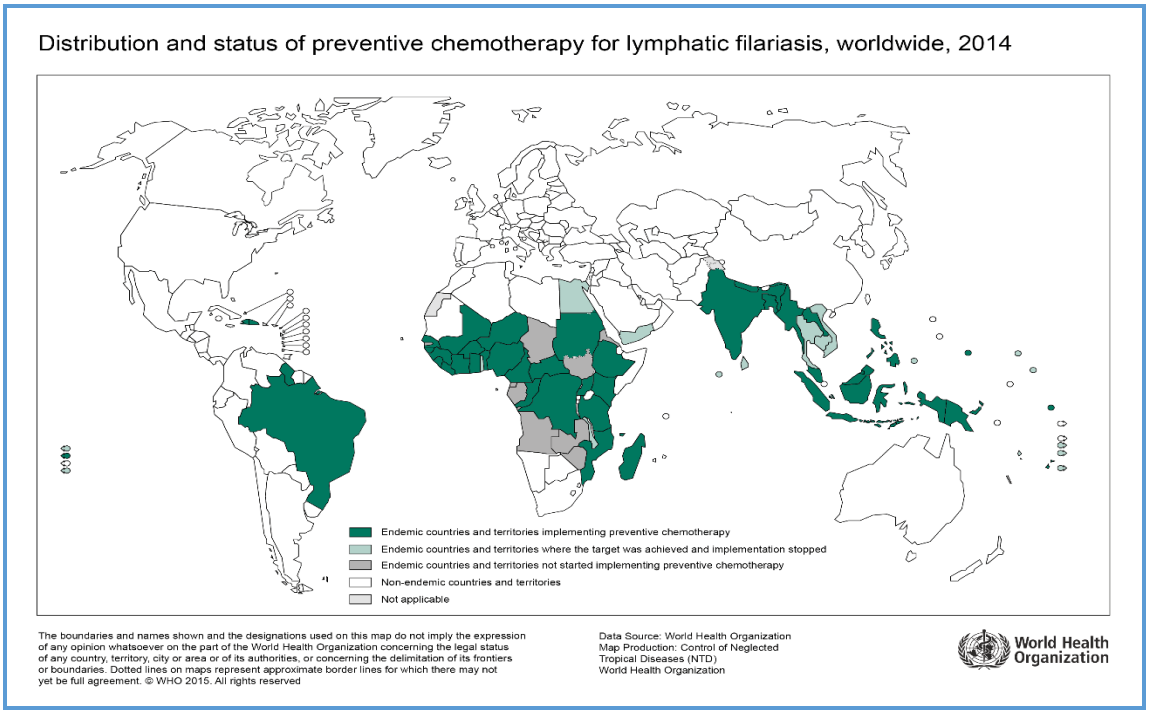
LF, described as a disease that affects poor people, is endemic in 73 countries in the tropics and subtropics (see Figure 6). NTDs are poverty-promoting diseases with often stigmatising conditions that are found mainly in rural areas of low-income countries. NTDs such as LF are ancient afflictions even described in the Bible and other ancient literature that have afflicted humanity for millennia (Molyneux, Hotez, Fenwick 2005). Marginalised people are usually affected, especially those living in areas with poor sanitation, and poor housing conditions (Ramaiah and Ottesen, 2014). LF is a major cause of physical and emotional suffering and also an economic loss (Huppatz *et al.* 2009). The 39 LF endemic countries in Africa are all low income (Grady *et al.* 2007; Bockarie and Molyneux 2009).

An estimated 40 million people in the world have clinically significant LF manifestations (lymphoedema, elephantiasis, and urogenital disorders such as hydrocoele in men) (WHO 1995; WHO 2015). LF is thus the second leading cause of permanent and long-term disability and has indirect losses associated with it due to diminished productivity or incapacitation of those affected. LF also creates a severe drain on local and national economies due to the acute and chronic manifestations, sub-clinical pathology of the renal and lymphatic system that affect all those infected with LF (Ottesen *et al.* 1997). LF thus leads to personal suffering as a result of the disabling and disfiguring lesions, and is also a significant impediment to socio-economic advancement, both locally (at the community, district or regional levels) and nationally (Ottesen *et al.* 1997). LF experts suggest that eliminating LF in poor countries will reduce poverty, improve well-being, prevent disability, and improve health care services because LF is distributed globally, has socio-economic impact on those affected, is recognized by WHO as a key disabling disease, has 1.3 billion people at risk, 120 million infected, and an estimated 40 million persons have gross pathology relating to the disease (Molyneux 2003; Grady *et al.* 2007).

LF is a parasitic infection that is transmitted by mosquitoes and is responsible for long-term chronic morbidity in the form of lymphoedema, genital pathology (especially hydrocele), recurrent disabling fevers (lymphangitis) and elephantiasis in over 40 million people around

the world" (Ottesen et al. 2008 cited in Bockarie, Kelly-Hope, Haskew 2010). LF affects an estimated 120 million people globally and is ranked by WHO as the second most common cause of long-term disability (WHO 1999). Since 70% of those infected with LF do not show symptoms of the disease but almost all those infected have subclinical damage to the lymphatic vessels (Sodahlon et al. 2013), a filariasis case can now be defined as all those persons who have evidence of active infection or all those who show positive LF antigen test irrespective of microfilaraemia status and presence or absence of chronic pathology (Melrose 2004).

Figure 6: Global distribution of LF in 2014 (WHO, online, available from: http://gamapserver.who.int/mapLibrary/Files/Maps/LF_2014.png)



The microscopic MF of the parasite that causes LF was first observed by a British physician, Timothy Lewis, in 1870 in the urine of patients (Bockarie and Molyneux 2009). Currently, it is known that LF is transmitted in humans by three mosquito-borne microscopic worms: *Wuchereria bancrofti (W. bancrofti*), *Brugia malayi* and *Brugia timori*. LF is linked by many with elephantiasis (swelling of limbs and scrotum). However, in most endemic areas only a small minority of those infected with LF proceed to elephantiasis. Over 90% of LF cases are Bancroftian filariasis (*i.e.* caused by *W. bancrofti*), and this form is spread all over the tropics

and some sub-tropical areas. *Brugia malayi* is confined to Asia (Southeast and Eastern Asia); and *Brugia timori* is found only in Timor and its adjacent islands (WHO 2015). Brugian filariasis is highly endemic in India and China (before elimination), Indonesia, Thailand, Malaysia, Philippines, Viet Nam and Republic of Korea (Ottesen *et al.* 1997). *W. bancrofti* affects only humans and is the only LF parasite in Africa and the Americas that accounts for 90% of an estimated 120 million cases of LF worldwide. *B. malayi* and *B. timori* are exclusively found in Asia (Bockarie, Kelly-Hope, Haskew 2010).

Table 2: Proposed classification of LF by Kumar 1996

Infection rate	Endemicity
<10%	Low
10-20%	High
20-40%	Hyper-endemic
>40%	Holoendemic

Several attempts were made to classify LF using parasitology data and subjective clinical findings that are usually difficult to standardise. Kumar in 1996 proposed the use of microfilaraemia for classification of LF because it closely correlates with other LF-related indices and is, therefore, easier to use for setting cut-off points of different endemicity levels. The classification proposed by Kumar (1996) is as indicated in Table 2 above.

The International Task Force for Disease Eradication completed a review of an estimated 100 medical conditions including infectious diseases in 1993 and decided that six of them (including LF) were eradicable or potentially eradicable based on diagnostic tools and treatment strategies that were available. Since this review was conducted by independent experts, awareness and interest were raised over the plausibility of LF elimination among scientists and public health experts (Ottesen, 2000; Huppatz *et al.* 2009). In 1997 the World Health Assembly formulated resolution WHA50.29 that urged endemic communities to strengthen efforts for the elimination of LF as a public health problem (Ramaiah and Ottesen 2014; Bockarie and Molyneux 2009). LF is currently targeted for elimination as a public health problem while eradication is a more long-term objective (Ottesen *et al.* 1997). The motivation to move

towards elimination of LF as a public health problem was stimulated by the elimination of LF as a public health problem in countries such as Japan, Taiwan and mainland China. In China the drive to eliminate LF was based on the negative impact of the disease on agricultural productivity and the socio-economic impact was a 15:1 return after the disease was eliminated. It is estimated that a billion US$ is lost annually in India alone and this is in addition to the personal anguish, suffering, disability and stigmatisation experienced by about 50 million clinically affected persons worldwide. The prevention of infection, suffering, and disability among children that are to be born should also be considered (Ottesen 2000).

The optimism for the elimination of LF as a public health problem and possible eradication globally in the future is based on the availability of simple, rapid diagnostic tools, safe and effective donated drugs by Merck & Co Inc. and GlaxoSmithKline, and knowledge that *W. bancrofti* has no non-human host and *B. malayi* has only few animal hosts (Bockarie, Kelly-Hope, Haskew 2010). Field diagnosis of infection is possible through simple finger-prick antigen detection tests that are conducted any time of day, and the clinical diagnosis is also now possible through ultrasound identification of living adult parasites (Ottesen 2000). The two principal goals of LF elimination are therefore interruption of transmission of infection, and alleviation and prevention of suffering and disability resulting from the disease (Ottesen 2000). NTD experts now believe that LF elimination is feasible through cheap affordable health interventions that provide benefits greater than just treating LF (Ottesen 2000).

Between 2000 and 2012 over six billion treatments were given and over four billion treatments were taken within LF endemic communities (Molyneux 2003; Ramaiah and Ottesen 2014). The WHO publication on the LF situation in 2014 shows that there were 73 countries considered LF endemic among which 18 have progressed to the post-MDA surveillance stage, and 55 countries still have to continue mass treatment of affected communities. Among this group of 55 countries, 11 countries are yet to start MDA and have not shown evidence that they do not need MDA; MDA is yet to be upscaled to 100% geographic coverage in 23 countries (*i.e.* not all implementation units (IUs) or administration units at which the programme is implemented are being treated); and 21 countries have conducted at least one round of MDA in all endemic IUs (*i.e.* they have achieved 100% geographic coverage). In the 18, where surveillance is

ongoing to determine whether the targets for elimination have been achieved, MDA is continuing in some areas (WHO 2015). Significant progress is being made in the 35 LF endemic countries in Africa. MDA has been started partially in 25 countries but is yet to be scaled up to 100% geographic coverage for elimination targets to be met. Two countries have stopped MDA nationwide (Togo and Malawi), and seven countries have achieved 100% geographic coverage and can stop MDA nationwide before 2020: Benin, Burkina Faso, Comoros, Ghana, Mali, Niger and Sierra Leone (WHO 2015). Among the 73 LF-endemic countries, 18 countries no longer needed MDA in 2015 and are conducting post-MDA surveillance, and the other 55 still need MDA. Among the 55 still needing MDA, 10 countries are yet to start MDA (WHO 2016a). Currently, Togo is the first country in sub-Saharan Africa to reach the stage of eliminating LF as a public health problem (Sodahlon *et al.* 2013). By 2014, the population requiring MDA was determined to have been reduced by 314.7 million, and based on mapping and TAS results the population requiring MDA has decreased from 1.410 billion in 2011 to 1.103 billion in 2014 (WHO 2015). Over 6.2 billion treatments have been administered for LF to over 820 million people between 2000 and 2015. The estimate for people requiring treatment for LF has dropped from 1.410 billion in 2011 to 947 million in 2015 (WHO 2016a).

Transmission

A typical life cycle of the LF parasite starts when the vector mosquito takes a blood meal and ingests MF of the parasite in the process. The MF then shed their sheaths, penetrate the mosquito's midgut and migrate to the thoracic muscles. The MF develop into L1 larvae, L2 and L3 larvae; then migrate to the head of the mosquito and the mosquito proboscis so that when the mosquito takes the next blood meal the L3 larvae enter the skin of the next host. Within the human host the L3 larvae develop into adult worms and are located in the lymphatic system; and the adult parasites produce sheathed MF that migrate into the lymphatic and blood system (McMahon and Simonsen 1996).

It has been demonstrated that the mosquito infection rate (this is the number of mosquitoes that have MF after feeding on blood and the number of ingested MF per mosquito) increases with an increase in the number of MF in the blood of a human host. Bockarie (1997) was able to demonstrate that there is a positive correlation between the annual infective biting rate and

the annual transmission potential on the one hand and the MF rate, MF density, and prevalence of leg oedema. This suggests that transmission intensity is a key determinant of patent infection and morbidity. Kazura *et al.* (1997) also showed through a study in Papua New Guinea that the prevalence of leg oedema was highly and positively related to the annual transmission potential. The incidence of acute filarial attacks also has a direct relationship with transmission intensity.

The concept of "facilitation" (that is the concept that the proportion of MF that develop generally increases as the number of ingested MF increases) should be considered by any programme moving towards elimination of LF. This is because theoretically, it is possible to reach a stage (called the 'breakpoint" by some experts) when the circulating MF within a given population is insufficient to support transmission. However, it should be noted that MF density as low as 3 MF per ml can still cause infection in mosquitoes and that people with low MF densities after MDA can still potentially cause a rapid resurgence of LF. Mosquitoes that have blood meals from individuals with medium and low-level MF densities can still, therefore, maintain transmission especially if the main vector is *Culex* and not an *Anopheles*. The difference in transmission capacity of the two types of vector species is explained through the concept of limitation (*i.e.* that the *Anopheles* mosquito has a well-developed pharyngeal armature that destroys MF when they pass through during ingestion). Therefore, if the number of MF ingested is low during a blood meal, then the number that subsequently survives or is viable to infect the mosquito may be zero. MF can also be reduced/lost when ingested by the *Anopheles* mosquito through the fluid that is expelled from the anus of the mosquito species but not with *Culex*. It has therefore been suggested that there is a critical level of man/mosquito contact at which the disappearance of the LF infection from a population is possible (Pichon 2002).

Gender difference in LF transmission

Animal studies suggest that oestrogen hormones play a part in reducing filarial infection in females as several studies have shown that LF MF density is lower in women of reproductive age when compared to men of the same age. This difference could not be explained by differences in exposure (such as differences in clothing), is not associated with pregnancy but

could be related to the hormonal activity (Kaur 1997; Alexander and Grenfell 1999). A specific age distribution of microfilaraemia is consistent in all endemic areas, and this is that prevalence and density rise with age and peak between the ages of 15 and 25 years and a decline in adulthood (Sasa 1976). A study by Lammie *et al.* (1994) in Haiti showed 24.5% prevalence in children aged 1-5 years that increased to 70% in adults older than 50 years. More males are infected than females and incidence of the disease is higher in males. The prevalence of antigenaemia and microfilaraemia and the microfilaraemia density are closely related to transmission intensity (Day et al. 1991a,b). It was also demonstrated that higher MF prevalence in younger people is linked with the increased vector biting rates (Farid et al. 1997).

Pathogenesis

A British Physician Timothy Lewis was the first to observe the minute MF of the parasite that causes LF in 1870 in the urine of patients (Bockarie and Molyneux 2009). Patrick Manson on the 10th August 1887 fed some mosquitoes with the blood of his microfilaraemic gardener Hin-Lo and succeeded in demonstrating the development of the larva within the insect. The mosquitoes used by Manson in the first experiment were confirmed to be *Culex quinquefasciatus* that is still regarded as one of the most important LF vectors. By 1976 other species of *Culex* and *Anopheles*, *Aedes*, and *Mansonia* were added as vectors of LF and the list currently has several hundreds of vectors (Manson 1878a, 1878b, 1884).

LF parasites are long hair-like nematodes that dwell in tissues. Together with the onchocerciasis parasite they have arthropods as intermediate hosts and have a life cycle that involves a maturation stage in a blood-sucking insect and a reproductive stage in the tissues or blood of the human host (McMahon and Simonsen 1996). The adult male and female worms live in the lymphatic system or other tissues. MF produced by female worms, circulate in the blood and are ingested by the vector. Larval development takes place within the vector's muscles. The infective L3 stage moves to the proboscis of the vector and is transmitted to the new host during subsequent blood meals. Unlike malaria, the infective stage is deposited onto the skin of the new host and finds its way through the skin generally through the puncture the mosquito makes during the bite, and are not injected directly into the skin of the new host. Filaria worms can be found in all classes of vertebrates except fish and are also common in

birds. Both filaria worms that cause LF and onchocerciasis in humans belong to the family *Onchocercidae* (Roberts and Janovy 1996).

Intracellular bacteria were discovered in the 1970s in some species of female LF parasites that were later identified as belonging to the genus *Wolbachia* and have the same role as the symbiont bacteria found in arthropods that have a significant influence on the growth and reproduction of the host arthropod. It was then suggested that these symbionts could be implicated in the pathogenesis of LF and should be targeted through the antifilarial activity for elimination of the disease (Hoerauf et al. 1999; Hoerauf et al. 2000).

Patrick Manson was able to demonstrate nocturnal periodicity of LF through his laboratory assistants. One worked during the day and the other during the night and the one that worked during the night found more filaria than the one that worked during the day. He, therefore, set up an experiment in which serial blood samples were taken from the same patients during the day and night, and he found more MF in large numbers from the blood collected in the night, but MF were almost absent in the blood samples collected during the day. His findings were met with disbelief, but Myers and MacKenzie confirmed Manson's findings. MacKenzie (1881) reversed the nocturnal periodicity by asking his patients to sleep during the day and remain awake in the night. Manson (1883) also did the same the following year. Changes in nocturnal periodicity have been obtained with as little as a three-day reversal in sleeping patterns. Manson later confirmed this finding in a human case in 1897. Thorpe in 1896 and Lynch in 1905 reported that the MF (which was subsequently called *W. bancrofti var pacific*) had no periodicity. Turner and Edeson (1957) demonstrated that there are nocturnal and sub-periodic forms of *Brugia malayi*. Seventy percent (70%) of those infected with LF do not show symptoms of the disease, but almost all those infected have sub-clinical damage to the lymphatic vessels (Sodahlon *et al.* 2013). Damage to the lymphatic system places people at risk of secondary infection (WHO 1995).

LF Vectors

LF is a mosquito-transmitted parasitic infection (Grady *et al.* 2007). The detection of mosquitoes as vectors of *W. bancrofti* in China in 1877 by the British physician Patrick Manson

was the first time any association had been made between an insect and active transmission of an agent of an animal or human disease (Bockarie and Molyneux 2009). The parasite that causes LF can be transmitted by five genera of mosquitos: *Anopheles, Aedes, Culex, Mansonia, Ochlerotatus* (Bockarie and Molyneux 2009). Therefore, unlike malaria whose transmission cycle is dependent only on the *Anopheles* species, LF has a wide range of mosquitoes that serve as vectors, of which the most widespread and important species is *Culex quinquefasciatus*. Since this species breeds in collections of heavily polluted water in urban and semi-urban settings, this results in the high prevalence of LF in areas where rapid growth overtakes the available sanitation services. It is a night-biting mosquito, and LF in areas where it is the main vector show nocturnal periodicity. Other *Culex* species are capable of transmitting LF and are important vectors in some areas (Manson-Bahr 1959; WHO 1992). *Aedes polynesiensis* and *Ae. Samoanus* are the key vectors in the Pacific. They breed in crab holes and tree holes which make it difficult to control using conventional methods for other mosquitoes. They are also day-biting mosquitoes that account for the diurnal periodicity of LF in that region. *Ae. poecilius*, a night-biting mosquito, is the key vector in the Philippines (Manson-Bahr 1959; WHO 1992). *Mansonia* species are also important vectors of *B. malayi*, and sometimes *W. bancrofti* in areas where large parts of aquatic plants exist (Manson-Bahr 1959; WHO 1992). *Anopheles* species are the key vectors for *W. bancrofti* in parts of Africa, Southern Asia, and Papua New Guinea. *A. barbirostris*, which breeds in open rice paddies, is the only vector known to transmit *B. timori* (Manson-Bahr 1959; WHO 1992). Bed bugs (*Cimex species*) can be naturally and experimentally infected with *B. malayi* and *W. bancrofti* with some limited larval development, but the extremely high mortality of the larvae within bed bugs means they cannot be seriously considered as a vector of filariasis (Burton 1963). In West Africa, the vector for LF and malaria are the same *Anopheles* species and vector control for one can impact the control of the other. The effect of vector control for malaria on LF endemicity status has been documented in several studies (Kelly-Hope *et al.* 2006; Reimer *et al.* 2013; de Souza *et al.* 2015).

Manifestation

LF causes acute and chronic morbidity of humans in tropical and sub-tropical parts of Asia, Africa, Western pacific and parts of the Americas (Bockarie and Molyneux 2009). An estimated

40 million individuals have the principal morbidities of LF (lymphoedema and hydrocoele). The Global Programme to Eliminate LF (GPELF) objectives are to interrupt transmission of causal parasite and alleviate suffering from the morbidities linked with the disease (Sodahlon *et al.* 2013).

Current literature suggests that there are usually five groups of people within LF endemic communities:

1. People who are exposed with no evidence of disease. These are endemic normal people or people who are not microfilaraemic and have no clinical manifestation of the disease even though exposed to the disease. The possibility that they are immune to the disease is still debatable (Ottesen 1989; Kazura et al. 1993; Weil et al. 1996). They still have antigens to the worm and ultrasound has shown that they can have adult worms in their scrotum, which suggests that they are in the pre-patent stage of the disease (Simonsen et al. 1997b; Dreyer et al. 1996a). It has been shown in animals that some level of immunity occurs for LF that is probably T-cell mediated. People in this group could be immune to LF because there is conclusive evidence that herd immunity exists for LF in some communities. This may explain the reduction of MF intensity among older people; *i.e.* they develop immunity with long term exposure to the disease. The LF-related immunity noted is more directed against L3 larval stages of the worm (Weil et al. 1982; Michael and Bundy 1998).
2. People who are microfilaraemic but asymptomatic. This is a more common manifestation of LF and can occur in children as young as 14 months. The individuals in this group usually have many MF in their blood but show no sign of the disease, and this may persist for decades. Most people in this group (about half) can be demonstrated using ultrasound to have motile adult worms in the lymphatics of their scrotum also known as the "filarial dance sign" (Lowman 1944; Ottesen 1992; Amaral et al. 1994).
3. People who have an acute filarial disease with or without MF in the blood. LF is usually linked with elephantiasis when most people with LF do not have this condition. When people say, LF is not a problem they usually mean elephantiasis is not a problem. Acute LF can occur without MF in the blood and could be misdiagnosed in endemic communities as malaria or any other tropical infection. This results in wrong treatment and waste of resources for health. Acute attacks can be experienced by patients as young as three

months but the frequency increases in older children, teenagers and persists throughout life. The acute attacks can be experienced by people with or without MF in the blood and more among people with chronic LF. Sometimes filarial markers such as filarial antigen and antifilarial IgG4 antibody may be absent. This may be explained by the inflammatory response to L3 stages before adult worms are formed although some studies have shown that up to 30% of people with acute attacks have adult worms. Acute filariasis is usually manifested by acute adeno-lymphadenitis (ADL), characterised by intense lymphangitis and lymphadenitis that starts from the affected lymph node and shows reddening of the overlying skin. The attacks go with chills and fever. Males can have orchitis, epididymitis, and acute transient hydrocoele. An episode lasts for one week and can end or be resolved spontaneously (Wartman 1947; Dasgupta 1984; Nanduri and Kazura 1989; Addiss et al. 1994; Roberts and Janovy 1996).

4. People who have chronic disease with or without MF in the blood. The first sign of the chronic disease is either lymphoedema or hydrocoele after an acute attack. The onset of lymphoedema and hydrocoele is usually gradual. Efforts have been made to reduce chronic manifestation of LF using different techniques to increase lymph flow and prevent lymphoedema: hyaluronidase was used with some success; coumarin (a drug that increases macrophage-associated proteolysis and reduces stasis of protein in tissues) reduces lymphoedema and elephantiasis; surgical procedures such as establishment of a shunt between lymphatic and venous system or lymphatics and omentum can reduce lymphoedema in some patients; and lymphosuction was proposed as a new treatment for chronic lymphoedema. The risk of getting chronic disease increases as the MF density increases (Jordan 1959; Goldsmith 1974; Nanduri and Kazura 1989; Casley-Smith et al. 1993; Dreyer et al. 1994; Clodius 1998). Lymphoedema can be graded as indicated in Table 3 below (Gyapong *et al.* 1994; McMahon and Simonsen 1996).

Table 3: Grading of lymphoedema cases (Gyapong *et al.* 1994; McMahon and Simonsen 1996)

Manifestation	Grade symptoms
Elephantiasis of the limb	0. normal
	1. Loss of contour or lymphoedema
	2. Thick skin and loss of elasticity

	3. Evident elephantiasis
Hydrocoele	0. normal
	1. Swelling of spermatic chord
	2. Swelling up to 10 cm in diameter
	3. Swelling greater than 10 cm
Scrotal elephantiasis	0. normal
	1. Lymphoedema
	2. Thick skin and loss of elasticity
	3. Evident elephantiasis

5. People with tropical pulmonary eosinophilia. This is the least common manifestation of LF. There is usually severe hypersensitivity response with pronounced eosinophilia, extreme levels of serum IgE and high titres of antifilarial IgG and IgE. MF is not usually found in the blood, but adult worms can be detected by ultrasound. This type is clinically manifested as coughing in the night and asthma. Pulmonary infiltration is detected through a characteristic x-ray feature known as the “snowflake lung”. Fibrosis and permanent lung damage can occur due to the accumulation of eosinophils in the lung with subsequent release of cationic proteins and free radicals. This form is more common in Southern India and parts of Southeast Asia but less common in Papua New Guinea and Africa (Ottesen et al. 1982; Pinkston et al. 1987; Nanduri and Kazura 1989; Lobos et al. 1992; Ray et al. 1993; Magnussen et al. 1995; Dreyer et al. 1996b).

Besides the five groups presented above, some LF patients have other manifestations of the disease such as chyluria. Chyluria is the presence of chyle in the urine following rupture of dilated lymphatic vessels in the bladder or kidneys into the urinary system. This is a rare complication of LF (Cahill 1965; McMahon and Simonsen 1996). It has been detected that parasites induce some level of immunosuppression to ensure their survival in the host (Nussenzweig 1982). Many studies have been documented to determine the prevalence of LF morbidity (Simonsen *et al.* 2002; Njenga *et al.* 2007; Jullien *et al.* 2009). Simonsen *et al.* (2002) showed that examination of scrotal tissue can be used to determine signs of adult worms through detection of the filarial dance sign (FDS) using ultrasound (Simonsen *et al.* 2002). It is worth noting that the goals of GPELF include the interruption of transmission and provision of

care for those with LF disease manifestation (*i.e.* morbidity control) such as acute inflammatory episodes, lymphoedema, and hydrocoele. Bacteria is the cause of acute episodes known as acute dermatolymphangioadenitis (ADLA).

Community social attitudes to LF

LF is seen as a terrible disease because it causes disfigurement (Rauyajin *et al.* 1995) and some of those affected are completely shunned by their families and communities. This is usually worse for women, and they refuse to leave the house, and marriage prospects for them are slim within their communities (Rauyajin *et al.* 1995). Those affected do not seek help or usually would turn to traditional medicine. It was reported that during the advanced stages of the disease traditional medicine is combined with western medicine to lower body heat (Rauyajin *et al.* 1995).

Loss of income was reported in all families with someone affected by LF not only the poor. Poor families were pushed to near destitution. People with LF are reported as marginalised and forgotten (Perera *et al.* 2007). People refuse to sit, eat with them or marry them. In Tanzania having LF is considered an embarrassment, in Polynesia during the 1950's men with elephantiasis of the scrotum were seen as social and procreative handicaps. In Ghana mild to moderate elephantiasis is accepted but those affected themselves are embarrassed about their disease and so prefer to stay at home. People with hydrocoele are teased, and those with chronic manifestations of LF cannot become chiefs in their villages (Kessel 1957; Evans et al. 1993; Muhondwa 1983; Gyapong *et al.* 1996a,b).

LF-related stigma is worse for women. Women with labial enlargement in the Philippines are seen to be promiscuous, and so there is poor reporting of this aspect of the disease by women. In Ghana, young women have problems getting married because young men think they (women with the disease) will not be able to work and he will also have to pay the cost of her treatment of the disease. In Nigeria, women with LF have problems getting married, or if they get married, there is no stability in the marriage and these women are deprived of happiness in the marriage. This unwillingness to marry women with LF is compounded by a belief that the offspring will also get the disease. In India, LF is considered to cause "grave social wounds",

especially for women and most women with LF, have low self-esteem and fear of being rejected by their husbands (Gyapong *et al.* 1996a,b; Gyapong *et al.* 2000).

Women had similar reactions about marrying men with manifestations of LF, but the decision was not usually theirs because relatives arrange the marriage. In Tanzania, it was documented that people from villages with low endemicity avoid marrying girls from villages with high endemicity, but within hyper-endemic communities, girls can be married even when they have some manifestation of the disease. However, although this happens the women cannot have 'good' husbands and marital happiness is diminished. In Ghana, the divorce rate is higher than normal when women with LF are involved (Hunter 1992; Mujinja et al. 1997; Coreil et al. 1998; Ahorlu et al. 1999).

Children unfortunately also suffer social effects of LF due to attacks of ADL that result in interruption of education. They also have medical and social effects of chronic pathology. They can also stop attending school because of the shame, embarrassment and ridicule suffered. It is reported that boys with hydrocoeles could not cycle, or walk to school, play or take part in sport because of the associated scrotal pain that results from exercise (Ramaiah et al. 2000).

Beliefs on aetiology of LF

Beliefs on the origin of LF varies widely. In developing countries, LF is attributed to sorcery and other supernatural causes. In Ghana, it is believed that one gets elephantiasis of the leg by stepping on spiritual things put on the ground by witch doctors at funeral festivities. It is believed that one gets elephantiasis of the arm by accidentally picking up the tail of an animal that a witch doctor drops on the ground. Some believe LF can be passed on in-utero to children when the father's semen is infected. Few people know that mosquitoes transmit LF and minimising contact with mosquitoes can reduce the chances of getting the disease (Gyapong *et al.* 1996a,b; Gyapong *et al.* 2000).

Socio-economic impact of LF

Productivity is reduced especially during the late stages of the chronic disease when the complications such as hydrocoele and lymphoedema are more pronounced although people

with such late stages of the disease are beyond their most productive years (Kessel 1957; Muhondwa 1983). The impact of LF in similar communities can be severe. Gyapong *et al.* (1996b) estimate that 4.1% of the productive female labour force and 20% of the productive male labour force are disabled by between 10 and 60% because of chronic LF. An estimated 20% of people with chronic advanced LF often give up their primary food producing role and do eventually settle for more sedentary occupations like weaving. This can overall reduce the food producing capacity of some communities. Elephantiasis, hydrocoele, and attacks of adeno-lymphangitis can physically incapacitate those affected and reduce their level of participation in socio-economic activities within communities they live in (Wynd *et al.* 2007). WHO member states are committed to eliminating the disease as a public health problem cognisant of its economic impact and the disability and social stigma it causes (WHO 2016a).

Diagnosis

Diagnostic tools help make decisions on where to treat, how to measure the impact of treatment, how to define targets, how to determine end points for stopping MDA and how to monitor for a possible resurgence of LF transmission after it is stopped (Weil and Ramzy 2007). Surveillance and other M&E results are important for establishing, determining and modifying strategies, reporting public health successes, and can be key for advocacy to obtain and maintain financial and technical support nationally and internationally (Baker *et al.* 2010).

Currently, two methods are being recommended for diagnosis of LF:

1. Demonstration of the existence of MF through direct techniques. Baseline survey (in sentinel sites only), and monitoring survey at midterm (after three years of post-mapping MDA) and after at least five years of post-mapping MDA (pre-TAS) are still recommended in sentinel and spot check sites. The baseline survey is required to obtain baseline data against which data obtained in impact monitoring surveys can be compared while the monitoring surveys at mid-term, and the pre-TAS are conducted to determine the decline in LF prevalence and intensity following MDAs and to determine eligibility for a transmission assessment survey (TAS) respectively. These studies are conducted using microscopy approach to examine night blood films. Samples of 60µl of blood taken between 10pm and 4am from 300-500 adults provide key information (WHO 2005; WHO

2010; WHO 2011a,b,c; WHO 2013). In areas where the LF parasite shows nocturnal periodicity blood can be collected two hours before or after midnight when the MF density is expected to be highest. In cases of diurnal periodicity, blood is taken two hours before or after midday (Sasa 1976). MF testing (through microscopy of thick blood films) is determined to be insensitive for active infections and misses people with low MF density and people with amicrofilaraemic LF infection that can lead to irreversible major lymphatic damage in these patients and they (the patients) can still contribute to LF transmission in the future within their communities. Thus, MF testing can lead to under-diagnosis and exclusion of areas with active LF transmission (Braga *et al.* 2003; Weil and Ramzy 2007). Other challenges of MF testing are the unsociable hours that the tests are conducted (before and after midnight) with high refusal and the extensive microscopy needed that requires extensive training. It has been therefore determined that other approaches are needed for endpoint assessments of LF infection in endemic communities and other methods such as exposure antibodies in children and polymerase chain reaction (PCR) methods for xenomonitoring filarial parasites in mosquitoes have been recommended (Farid *et al.* 2001).

2. Detection of LF antigen. LF antigenaemia is linked with active LF infection, and several assays for LF antigen using polyclonal and monoclonal antibodies raised against various antigens have been developed. The ICT antigen test (ICT Diagnostics, Sydney, Australia) is a rapid immuno-chromatographic technique that uses specific monoclonal and polyclonal antibodies. The test is conducted using capillary and venous blood and is simple enough for use in the field by people who receive minimal training (Hamilton 1985; Weil et al. 1987; Zheng et al. 1987). While some authors (Phantana *et al.* 1999) consider the test highly sensitive (100%) and specific (96.3%) with predictive positive value of 70.7% and predictive negative value of 100%, others (Pani *et al.* 2000) think that the test is less sensitive for detecting low-level microfilaraemia. One significant development in the diagnosis of bancroftian LF is the introduction of the LF antigen test that does not depend on MF presence and so makes the NBS and the TBF method unnecessary. It has also been suggested that antigenaemia testing is far more superior for diagnosis of LF (prevalence and intensity) because microfilaraemia surveys alone can underestimate the prevalence of LF by up to 30%. The ICT test (and recently the filaria test strip (FTS)) test can be

undertaken using finger prick stick in the field and the results are obtained fast (WHO 2016c). ICT cards were developed for the diagnosis of Bancroftian LF in human serum or plasma and had more advantages than MF tests. The survey is done in daytime and has high sensitivity and specificity when performed in serum. It is also done within short time and are simple to use with minimal training needed. Specificity of ICT cards ranges from between 72.4% and 100%. However, ICT is susceptible to classification errors as faint lines can be misread; and there could be cross reaction with soil-transmitted helminth infection since the antigens that the test can detect have not been clearly identified. It was also demonstrated that individuals remain positive up to two years after treatment with diethylcarbamazine (Braga *et al.* 2003). Currently, WHO recommends antigen detection with FTS, a similar test to ICT, that detects circulating LF antigen to decide where to treat (*i.e.* for mapping LF distribution), and to monitor progress towards elimination end points (for pre-Transmission Assessment Survey (TAS) and TAS) for LF (WHO 2016c). Alternative to ICT/FTS for measuring antigen is the ELISA-based approach that uses Og4C3 monoclonal antibody (Molyneux 2009). Some level of training is still needed in the use of ICT and FTS to avoid the misreading of slides leading to false positives. The ICT cards have been shown to have limited shelf life at ambient temperature (3 months at 30-degree centigrade) and have a longer shelf life when stored at four-degree centigrade. They should not be frozen. One hundred (100) microlitre of blood collected from finger prick into calibrated capillary tube or microtiter pipette coated with anticoagulant (ethylenediamine tetraacetic acid (EDTA) or heparin) or finger prick blood is collected in a microcentrifuge blood collection tube coated with EDTA or heparin. Blood should not be added directly from finger to the card. Two cards from each lot should be tested before the survey using a weak positive control. Test line with this control is faint, and so cards that are negative with the control should not be used. For transportation to the field, cards do not have to be put in a cool box but should also not be exposed to extreme heat for long. Lighting should be adequate when reading results to avoid missing the faint lines, especially at night. Results should be read ten minutes after closing card. The FTS has now replaced ICT and is being donated for TAS to some countries through WHO. FTS is developed by ALERE (Scarborough, ME, United States) through financial support from the pharmaceutical companies, MDP and the BMGF. A field study conducted to compare the ICT and FTS showed that the two tests had

similarly high rates of sensitivity and specificity and >99% agreement but the FTS detected 26.5% more people with filarial antigenemia and had better test result stability than ICT (Weil and Ramzy 2007; Weil *et al.* 2013). TAS is a standardised tool recommended for deciding when to stop MDA (TAS1) and after stopping MDA to monitor and confirm that infection has been maintained below the pre-requisite elimination thresholds (TAS2 and TAS3) (WHO 2011a; WHO 2013; WHO 2015; WHO 2016b). TAS is conducted to determine if MDA can be stopped within an LF evaluation unit after at least 5 rounds of annual MDA. Lot quality assurance sampling forms the basis of the TAS survey design, but survey site is dependent on school enrolment rate in the evaluation unit. Eligible population for the survey is 1st and 2nd graders (6-7) year olds and their exposure to LF should be less because they have lived most of their lives during MDAs. The methodology provides critical cut-off values for positives based on sample size. This is a statistically powered threshold below which transmission is expected to be no longer sustainable. TAS survey design depends on net primary school enrolment in each EU (if ≥75% then the school-based survey is done, and if <75% then the community-based survey is done). The target population, vector type, and parasite species also help determine the required survey site, the target population for the survey, survey type, sample size, critical cut-off, and diagnosis tool. The survey sample builder (a Microsoft Excel computer tool) is used to assist principal investigators to navigate the TAS protocol and input required data. The survey sample builder, after the necessary input are made, provides random number lists and automated survey design calculations such as sample size, sampling intervals for a rigorous sampling. Survey methodologies for all TAS are the same (whether for stopping MDA (TAS1) or for post-MDA surveillance-TAS2 and TAS3 (Chu *et al.* 2013).

Treatment

MDA is the PC strategy recommended for delivering safe, anthelminthic drugs within populations known to be at risk of LF to prevent the morbidity resulting from the infection and also to interrupt transmission (WHO 2015). LF MDA involves annual administration of a combined dose of medicines to all within endemic areas that are eligible for treatment for at least five years (WHO 2015). MDA is stopped when after at least five years of annual treatment

it is demonstrated that the level of infection has been reduced to below already established target thresholds (WHO 2015).

Interruption of infection transmission is achieved by treating the entire at-risk population long enough so that the levels of microfilaraemia are kept below the levels that allow transmission. The two-drug regimen involves 400 mg of albendazole plus diethylcarbamazine 6mg/kg or 400mg albendazole plus ivermectin 200mcg/kg and is administered at least annually for between four-six years. This period corresponds with the lifespan of the parasite. For areas where fortified diethylcarbamazine salt is used treatment period is six-12 months of daily fortified salt intake (Ottesen 2000; Hotez 2011; WHO 2016a).

Ivermectin and diethylcarbamazine rapidly decrease microfilaraemia, and the anti-MF effect is further increased when they are administered together with albendazole (a broad spectrum anthelminthic) that reduces adult worm viability and MF production (Ramaiah and Ottesen 2014). The impact of MDA is noted right from the first round and increases with each treatment round. One round (assessment after 12 months) reduces MF by 26% to 41% and five-six rounds lead to 88%-90% reduction (Ramaiah and Ottesen 2014). Two rounds of treatment can clear LF infection in 0-5-year-old children, and 2-4 MDA rounds can free 1-10-year-old children from LF infection. Single dose treatment can reverse LF pathology in children. Newly born children are protected from acquiring the infection as MDA has an impact on transmission from the first treatment round. Therefore, within communities treated for LF children 0-5 years are free from microfilaraemia and the disease (Ramaiah and Ottesen 2014). Using a model based on empirical observations of the impact of treatment on the clinical signs of LF it was estimated that 96.71 million LF cases, 79.20 million MF carriers, 18.73 million hydrocoele cases, and at least 5.49 million lymphoedema cases were prevented between 2000 and 2014, but there are still up to 36 million cases of hydrocoele and lymphoedema globally (Ramaiah and Ottesen 2014; WHO 2015).

Key factors responsible for the success of one programme and failure of others include the following: initial level of LF endemicity; efficiency/effectiveness of vector mosquitoes; MDA drug regimen; and population adherence (Kyelem *et al.* 2008). Other factors crucial for success

include high-level political commitment, development of appropriate social mobilisation strategies, involving communities in MDAs, and the introduction of morbidity management (Mohammed *et al.* 2006).

LF programmes aim at 65% coverage of entire at-risk population and 80% coverage of the eligible population annually for a minimum of five years to interrupt transmission of the parasite (Bockarie and Molyneux 2009). Drug cost is not a barrier to elimination of LF because GlaxoSmithKline donates albendazole and Merck and Co. Inc. donates Ivermectin for LF and onchocerciasis treatment for as long as necessary (Bockarie and Molyneux 2009). The efficacy of MDA for stopping the spread of infection is demonstrated by countries continuing to show eligibility for MDA through mapping and implementation of TAS1 before stopping MDA. A programme must achieve a minimum of 65% coverage of the entire at-risk population in at least five annual rounds of MDA and show that less than 1% microfilaraemia or 2% antigenaemia has been achieved in each sentinel and spot check site that are evaluated (WHO 2015).

MDA for NTDs can be administered for as little as US$0.50 or less per person per year (Molyneux, Hotez, Fenwick 2005). The low cost of NTD interventions is driven by several factors: (1) commitment of pharmaceutical companies to provide NTD drugs free of costs; (2) the scale of the programmes (use of strategy that involves MDA, endemicity of many countries and high number of people and communities at risk); (3) many opportunities that exist for synergy in the delivery of interventions for NTDs (especially onchocerciasis and LF); and (4) volunteer contribution of communities and teachers in MDA (Conteh, Engels, Molyneux 2010). There has been an expansion of MDA due to increased commitment of endemic countries, bilateral donors and NGDOs (Molyneux and Malecela 2010).

An estimated US$21.8 billion of direct economic benefits is gained over the lifetime of about 31 million individuals that received treatment in the first eight years of the GPELF. Among this, more than US$ 2.3 is realised through protection of an estimated three million children from the disease when they are born in areas where LF transmission is interrupted. Moreover, 28 million persons already infected benefit for prevention of disease progressing to the gruesome

manifestations. Moreover, this results in a lifetime economic benefit of approximately US$19.5 billion. Another benefit is that health systems have fewer patient services to attend to relating to LF due to reduced LF morbidity and this saves US$ 2.2 billion that would otherwise be used for this service. MDA for LF offers great economic benefits and is an excellent investment in global health (Chu *et al.* 2010).

Since albendazole, ivermectin and diethylcarbamazine show some but limited macrofilaricidal effect on LF, ivermectin is claimed to cause worm sterility and higher death rate of *O. volvulus* administered using more frequent doses), MDA for onchocerciasis and LF with albendazole, ivermectin or diethylcarbamazine may not fully address needs of individual patients that may be seeking treatment for symptoms. Chemotherapy against the endosymbiont *Wolbachia* with doxycycline has higher parasitic efficacy for onchocerciasis and LF and also more improvement of the disease is seen (Hoerauf 2008). Six-weeks of administering 200mg of doxycycline per day sterilises adult female OV worms. 200mg of doxycycline per day for 4-6 weeks show 50% and 60% macrofilaricidal effects respectively (Hoerauf *et al.* 2008). With *Bancroftian* LF there is a reduction of 80-90% adult worms with 200mg of doxycycline per day for 4-6 weeks. Reduction of lymph vessel dilatation and hydrocoele was also observed with this regimen. Lymphoedema was halted and reversed in early stages. This treatment can be applied to individual cases (Hoerauf *et al.* 2008).

Community participation improves programme interventions. In American Samoa churches and multiple media channels for health promotion led to sustained programme improvements. Other programmes may benefit from this use of MDA approach for disease control (King *et al.* 2010). Training and motivation of drug distributors are important because they interact directly with populations treated and their behaviour can affect adherence by families and individuals (Krentel, Fischer, Weil 2013). Also important are the thorough preparation of personnel, supplies, and logistics for implementation and preparation of population towards the MDA (Krentel, Fischer, Weil 2013). Demographic factors such as age, sex, income level, and area of residence are often linked with adherence. Decisions to comply or not are affected by individual or community perception of potential benefits of participation against the risk of adverse reactions (Krentel, Fischer, Weil 2013).

Effect of ivermectin, albendazole and diethylcarbamazine on LF transmission

Diethylcarbamazine: Diethylcarbamazine is a piperazine derivative that has proprietary names of Hetrazan, Banocide, and Notezine. Diethylcarbamazine is still the most widely used for LF in areas where there is no onchocerciasis as there is the severe reaction in these areas due to the mass death of *O. volvulus* that occurs with diethylcarbamazine (Campbell and Rew 1986; Molyneux et al. 2014). Diethylcarbamazine is given orally, rapidly absorbed, reaching peak blood levels after just 1-2 hours of taking. It reaches all parts of the body in about 25 minutes after taking; plasma half-life varies from 6.1-8.1 hours. Excretion is mainly renal, and plasma levels drop to zero in 48 hours. The exact mechanism by which diethylcarbamazine destroys, MF is still a subject of debate. Effect on MF is through the effect of the drug itself on the parasite and the facilitation of host-parasite interaction. It is suggested that diethylcarbamazine has macrofilarial and microfilarial effects but the macrofilarial effect is still questionable. A single annual dose of 300mg of diethylcarbamazine for adults and 150mg for children (combined with ivermectin and sometimes albendazole) is used. Low dose diethylcarbamazine significantly reduces prevalence and intensity of MF in treated communities and reduced prevalence of chronic pathology. Panicker *et al.* (1991) documented a 74.9% reduction of MF prevalence with annual treatment and 90% reduction with biannual treatment. Attacks of filarial fever and incidence of oedema cases also significantly reduce after diethylcarbamazine treatment.

Ivermectin: Ivermectin has been used successfully for the treatment of onchocerciasis; this is discussed elsewhere. A single annual dose of 400mcg/kg, either alone or with diethylcarbamazine, has proved to be effective in producing long-term MF suppression in *Bancroftian* LF in some countries, or is also equally effective against Brugian LF. Nguyen *et al.* (1996) note that at 400mcg/kg dose of ivermectin, MF prevalence drops from 21% to 7%and the MF density dropped to 0.5% of the initial value. Zheng *et al.* (1991) also noted mild reactions to ivermectin and noted that acute cases of LF were less likely with ivermectin treatment than with diethylcarbamazine. Cao *et al.* (1997) noted that the severity of reaction or adverse events was directly related to the pre-treatment MF density but was noted to be independent of the dose. Weil *et al.* (1991) argue that adverse reactions such as nodule

formation, lymphangitis and epididymitis do not occur with ivermectin treatment because it does not kill the macrofilariae and it is the death of the macrofilariae that cause these reactions. A total of 15 men who were known to have living adult *W. bancrofti* detected through use of ultrasound were treated with 400mcg/kg of body weight every 2 weeks for 6 months (total dose of 4.8mg/Kg). The MF were suppressed, but there were no changes in the motility or location of the adult worms. Dreyer in another study (Dreyer *et al.* 1995a,b) was able to remove live adult worms eight months after treatment with 400mcg/kg of ivermectin. Strong evidence exists that ivermectin ingested by a mosquito from a treated person during a blood meal reduces mosquito survival and fertility (Tesh and Guzman 1990; Nasr *et al.* 1996; Bockarie *et al.* 1999).

Albendazole: Albendazole was used for the treatment of intestinal worms but recently is used as an anti-filarial. Addiss *et al.* (1997a,b) have demonstrated that at a standard dose of 400mg per person works well as a microfilaricide for LF treatment, and this effect is, even more, when albendazole is combined with diethylcarbamazine or ivermectin. Adverse reactions are not worse or less with albendazole than with diethylcarbamazine or ivermectin (Addis *et al.* 1997a,b).

Combination therapy: Combining diethylcarbamazine and ivermectin or albendazole and ivermectin is demonstrated to be effective in providing rapid and long-term LF MF clearance. Diethylcarbamazine and ivermectin were more effective than when used alone in clearing circulating filarial antigen in persons who are amicrofilaraemic and those who are microfilaraemic (Molyneux et al. 2014). Addiss *et al.* (1997) have demonstrated that 200-400mcg/kg of ivermectin plus 400mg of albendazole are more effective in MF clearance than when used alone.

Other effects of PC for LF

Other non-LF benefits include treatment of children and women of childbearing age for soil transmitted helminthiasis (effect of albendazole), also for onchocerciasis, lice and scabies (effect of ivermectin) (Ottesen *et al.* 2008; Molyneux et al. 2014; WHO 2015). Beach *et al.* (1999) showed in a randomised placebo-controlled trial that six monthly dose of a combination

of ivermectin and albendazole was effective in controlling *W. bancrofti*, *A. lumbricoides, T. trichuria* and hookworm (*Necator americanus* and *Ancylostoma duodenale*) among Haitian primary school children. This combination also has the benefit of improving the height and weight of the children treated. The effect of ivermectin on onchocerciasis, scabies and lice has been described above.

Search for new antifilarial agents

There is an active global search to develop safe and effective macrofilaricides, including search within the marine environment involving a synthetic marine alkaloid, aplysinopsin (Singh et al. 1997). Another novel approach suggested is to deliver antifilarial drugs into the lymphatic system rather than the blood. Since adult worms live in the lymphatic system (the lymph nodes) and have good contact with lymph, this approach may lead to the discovery of a microfilaricide (Loiseau et al. 1997). It has also been demonstrated that administration of ivermectin, albendazole and diethylcarbamazine together as triple drug therapy is safer and more effective in reducing the MF of *W. bancrofti* in non-onchocerciasis areas than the usual combination of diethylcarbamazine and albendazole (Thomsen *et al.* 2016). Hoerauf *et al.* (1999, 2000) had suggested the targeting of the endosymbiont bacteria that live within the filaria worms and believes this can have a beneficial effect on the growth and survival of the filaria worms. Treatment of onchocerciasis patients with tetracycline also leads to sterilisation of female adult worms.

Adverse reactions to anti-filarial drugs

Reactions post-treatment are common in LF and onchocerciasis (it is called Mazzotti reaction with onchocerciasis), and most cases are relatively mild. They can, however, cause communities to be afraid of taking treatment and can result in failure of control/elimination programmes. Fever is the most common manifestation, but there could be lymphadenitis, arthralgia, chills, drowsiness, headaches and hypotension. The reaction is not caused by the drugs used for the treatment but occurs because of an inflammatory reaction induced by the dying MF. The severity of the reaction, therefore, tends to increase depending on the number of circulating MF. Laigret (WHO unpublished report 1983) discovered that reactions to diethylcarbamazine decrease and are less frequent as the treatment rounds increase. The

exact cause of the reaction is still unknown, but Turner *et al.* (1994) had shown that cytokines such as Interleukin 6 (IL-6) and tumour necrosis factor are implicated. Nodule formation, lymphadenitis, and epididymitis are sometimes seen near sites where dying adult worms are located. This reaction is more common with diethylcarbamazine because of its partial macrofilaricidal effect (Weil *et al.* 1991).

Integration for NTD control/elimination

Essential NTD drugs are currently being delivered as a package that targets multiple NTDs simultaneously. NTD control is now considered an important and vital global public health solution. ivermectin is effective in killing MF in persons with LF and is co-administered with albendazole as preventive chemotherapy to interrupt transmission of LF in sub-Saharan Africa (Hotez *et al.* 2009). Integration is needed when there is an overlap of geographic areas of high prevalence for multiple NTDs such as LF and onchocerciasis. Vertical MDA programmes can be integrated using a package of donated or low-cost generic drugs. In Africa, one such combination is ivermectin and albendazole. In Asia and the Caribbean ivermectin is replaced with diethylcarbamazine because onchocerciasis is not prevalent in these regions. The rapid packages can be administered for as little as $0.40-0.50 per person per year (Hotez *et al.* 2009).

Opportunities for integration through the USAID NTDP currently exist, but several possible challenges have been identified for integration. Integration can lead to increased bureaucratic burden that can, in turn, lead to reduced effectiveness of health services. As the number of activities increases this becomes aligned to a full-time job for CDDs, and as CDDs, have limited time for other economic activities they demand payment. This can also affect the performance of a CDD. To address this concern, it is possible to increase the number of CDDs to address this. Another challenge/concern is that it is possible that a parallel health delivery system can be created when vertical programmes integrated with separate funding, drugs, delivery channel, and staff. Another challenge is harmonisation of information, education and communication (IEC) materials. Safety and efficacy of drug combinations also have to be considered. M&E activities should be carefully designed and implemented to answer operational questions (Kolaczinski *et al.* 2007).

Challenges of LF treatment through preventive chemotherapy

There are always challenges in implementing health programmes in post-conflict settings (Molyneux and Malecela 2010). NTDPs must be implemented within a health system context and the health systems in most endemic countries are weak. This creates a challenge for NTD control programmes that usually means the capacity building is needed for successful implementation of the NTDPs (Molyneux and Malecela 2010). There has been a relatively weak contribution from governments of endemic countries to the direct implementation of NTDPs. Endemic countries themselves need to commit their own resources (financial or otherwise) for successful implementation of NTDPs (Molyneux and Malecela 2010). Different drug combinations involving diethylcarbamazine cannot be used in areas of Africa where onchocerciasis is prevalent because treatment with diethylcarbamazine induces severe and lethal reaction in areas that are also coendemic for Loiasis (Bockarie et al. 2013; Molyneux et al. 2014). Loiasis is caused by *Loa loa* (sometimes called 'the African eye worm') infection that is spread by *Chrysops* flies. The disease is present in Central and West Africa. Signs and symptoms include fugitive or 'Calabar' swellings, itching and joint pains. Sometimes there is an asymptomatic invasion of the eye by the worm that gives the name 'eye worm'. Among filaroids, it infects travellers from non-endemic zones the most (McMahon and Simonsen 1996; Roberts and Janovy 1996). Most affected communities are remote and rural and therefore in most cases difficult to access. Health services can have difficulty accessing these communities and community members can have problems accessing health services. CDTI is a cornerstone for APOC's success that involves communities themselves. In many areas where onchocerciasis and LF are co-endemic, drug delivery can be owned by communities. With CDTI trained health workers play a supervisory and technical role. They provide professional expertise and conduct household and community surveys to ensure programme requirements are met while community volunteers do the actual distribution (Bockarie, Kelly-Hope, Haskew 2010). The capacity of some LF endemic African countries to deliver PHC to rural poor is severely affected by civil conflicts. The experience gained from CDTI strategies in resource-poor settings has led WHO to develop a pro-poor strategy for health care delivery in countries with the challenges of conflict and poor infrastructure. This involves an integrated approach for PC. The CDTI approach has been successful in post-conflict and fragile states (Bockarie, Kelly-Hope, Haskew 2010). Overall successful implementation of NTDPs depends on supervision and monitoring of

activities at all levels. Monitoring is not just an activity to gather data and report back to higher levels but can serve to inform managers of the current status of their elimination programmes (Bockarie, Kelly-Hope, Haskew 2010).

Other challenges include the need to develop other antifilarial drugs. Although available drugs are effective, there is need to develop other anti-filarial drugs, especially macrofilaricides. There is currently no evidence of resistance but this can occur in the future, and the availability of other drug alternatives will be key when this occurs. Currently, it is necessary to develop techniques for monitoring drug resistance (Alley *et al.* 2001).

Vector control

Vector control has an impact on LF elimination since *W. bancrofti* requires a mosquito host to complete its life cycle and the disease can be eliminated through vector control (Bockarie and Molyneux 2009; Kelly-Hope *et al.* 2011). Integrated vector management, including distribution of bed nets, insecticide-treated or insecticide-impregnated bed nets (ITNs), and long-lasting insecticidal nets (LLINs), and indoor residual spraying (IRS), is recommended by WHO as the best approach that can improved efficacy, cost-effectiveness, ecological soundness and sustainability of vector control (van den Berg, Kelly-Hope and Lindsay 2013). Vector control reduces human-vector contact and can have a significant impact in reducing transmission of Malaria and LF both transmitted by *Anopheles* in West Africa (van den Berg, Kelly-Hope and Lindsay 2013). With Vector biting rates below 0.66 bites/man/hour, transmission of Malaria and LF is unlikely to be maintained. Therefore, vector control can have a significant impact on transmission of Malaria and LF in Africa (de Souza *et al.* 2015). One of the objectives of the Roll Back Malaria initiative is that at least 60% of children below 5 years and pregnant women should be sleeping under ITNs by 2010 and mass distribution of bed nets is needed to achieve this (Molyneux and Nantulya 2004; Blackburn *et al.* 2006). Vector control can reduce morbidity

and mortality due to Malaria among the poor and within hard-to-reach communities, and the same may be true for LF (Molyneux and Nantulya 2004).

Vector control is an important tool for diseases transmitted by mosquitoes, in particular against Malaria and LF in West Africa where the vector is the same for both diseases (Blackburn *et al.* 2006; Kelly-Hope *et al.* 2006; de Souza *et al.* 2010). *Anopheles* transmits Malaria and LF in Africa (Blackburn *et al.* 2006). *An. Gambiae* and *An. funestus* are the predominant rural vectors for *W. bancrofti* (Bockarie *et al.* 2013), and control is enhanced using impregnated bed nets that can reduce the duration of required MDAs during the endgame (Bockarie *et al.* 2013). High ITN and LLINs use for Malaria control can, therefore, reduce the prevalence of *W. bancrofti* (Bockarie *et al.* 2013). There is currently increased suggestion to combine control efforts for Malaria (caused by the protozoa of the genus Plasmodium) and NTDs especially LF (van den Berg, Kelly-Hope and Lindsay 2013). In Sierra Leone like in other West Africa countries, LF is transmitted by *Anopheles* that transmit Malaria (de Souza *et al.* 2015).

It has been suggested that the vector control effect of ITNs is limited because there are many vectors of LF among which some bite during the day and night when people are not under bed nets (Charlwood and Dagoro 1987). However, it is reported that *Anopheles* mosquitoes are susceptible to ITNs and LLINs (Stanton, Bockarie and Kelly-Hope 2013) and attempts to control one parasite in Malaria/LF co-endemic areas through vector control can lead to a change in prevalence of the other (Kelly-Hope *et al.* 2006). Vector control for Malaria control can, therefore, supplement MDAs for LF and reduce treatment years (Bockarie *et al.* 2013). Vector

control for LF is even more effective than for Malaria because unlike Malaria the parasite does not multiply in the vector and so a person must be exposed to many bites of infected mosquitoes to become infected (Bockarie and Molyneux 2009; Kelly-Hope *et al.* 2011). Overall, insecticide-treated bed nets (ITNs) are more effective in reducing transmission of Malaria than spraying, and this could be true also for LF (Bockarie and Molyneux 2009).

Studies have indicated that vector control alone can interrupt LF transmission in areas where the vector is *Anopheles* mosquitoes and no transmission occurs afterwards (de Souza *et al.* 2015). Increased distribution of bed nets can, therefore, accelerate LF elimination (Stanton, Bockarie and Kelly-Hope 2013). There is a suggestion that it is good to distribute ITNs and LLINs within entire population, especially in hard to reach areas (Stanton, Bockarie and Kelly-Hope 2013). Schuurkamp *et al.* (1987) estimate a period of 11 years to bring LF prevalence to less than 2% in the Tabubil area of the Western Province of Papua New Guinea through vector control alone.

Culex plays little, or no role in LF transmission in West Africa (de Souza *et al.* 2015) and usually resurgence of LF infection following vector control efforts occurs only in countries where the vector is Culex such as Zanzibar in the United Republic of Tanzania (de Souza *et al.* 2015).

The impact of vector control through ITNs and LLINs is determined by the extent of distribution of ITNs and LLINs for Malaria control (Bockarie *et al.* 2013). There are currently suggestions of investigating the impact of ITNs/LLINs distribution on LF (Stanton, Bockarie and Kelly-Hope 2013; Molyneux *et al.* 2014).

There is limited recognition of the number of bed nets distributed for Malaria control in the last decade and the impact this can have on LF prevalence in the absence of MDA for LF in Malaria/LF co-endemic areas (Molyneux *et al.* 2014). Recent scale-up of ITNs/LLINs distribution and use and IRS for Malaria can have a positive impact in reducing LF transmission in areas where the LF parasite is transmitted by *Anopheles* mosquitoes (Kelly-Hope, Molyneux and Bockarie 2013). Bed net use was low in Africa (Blackburn *et al.* 2006). In Central Nigeria in 2004, 38,600 ITNs was distributed during MDA campaigns for LF (with ivermectin and albendazole) that increased ITN ownership to 80%, 9 times more than in 2003 (Blackburn *et al.* 2006). Integration of ITN distribution and MDA improved ITN ownership and use significantly and did not adversely affect MDA coverage (Blackburn *et al.* 2006). Between 2008 and 2010, an estimated 294 million ITNs was distributed in sub-Saharan Africa for Malaria control (van den Berg, Kelly-Hope and Lindsay 2013). According to the Sierra Leone National Malaria Control Programme database of 2013, over 6 million ITNs was distributed nationwide in the past 5 years (Gerstl *et al.* 2010; Bennett *et al.* 2012; Statistics Sierra Leone and ICF International 2013). IRS was also conducted in selected chiefdoms (sub-district) of 4 districts- Bo, Bombali, Kono and Rural Western District (Statistics Sierra Leone and ICF International 2013).

In Sierra Leone, 40% of households owned mosquito nets in 2008 but this increased to 65% of households in 2013 (Statistics Sierra Leone and ICF International 2013). A reported 37% of households owned ITNs in 2008 but this improved to 64% in 2013 (Statistics Sierra Leone and ICF International 2013). In 2013, only 15% of households had universal coverage of LLINs (*i.e.* one LLIN per two persons who slept in a household the night before the survey) (Statistics Sierra Leone and ICF International 2013). 49% of children slept under ITNs the night before the

survey (Statistics Sierra Leone and ICF International 2013). Among households with ITNs, 73% of children slept under ITN the night before the survey (Statistics Sierra Leone and ICF International 2013). 60% of households are protected either through ownership of ITN or after receiving IRS in the past 12 months (Statistics Sierra Leone and ICF International 2013). 19% of households are protected through ownership of ITNs for every 2 persons or after receiving IRS in the past 12 months (Statistics Sierra Leone and ICF International 2013).

There are many examples of successful use of ITNs, LLINs and IRS to control/eliminate LF in countries that support the suggestion that widespread use of vector control can have an added effect on reducing LF transmission. Gambia, Sao Tome and Principe, and Togo had the highest coverage rates for ITNs, and it is believed that MDA has either stopped or is considered unnecessary due to this. In Costa Rica, Suriname, and Trinidad and Tobago there is no evidence of ongoing LF transmission probably because of IRS done for a limited period during the Malaria eradication campaign of the 1970s (Bockarie, Kelly-Hope, Haskew 2010). In Solomon Islands and parts of Papua New Guinea, vector control through IRS has led to the interruption of LF transmission (Bockarie *et al.* 2013; de Souza *et al.* 2015). Vector control alone has led to the interruption of transmission of LF in the Solomon Islands (Bockarie and Molyneux 2009; Kelly-Hope *et al.* 2011). In East Africa and PNG, bed net distribution for Malaria prevention reduced LF prevalence even when the bed nets used then were not impregnated with insecticides (Molyneux and Nantulya 2004). Recent studies have shown that LF transmission has possibly been interrupted in The Gambia because of extensive ITN use for decades to control Malaria (Rebollo *et al.* 2015). Prevalence of LF (*W. bancrofti*) in The Gambia was among the highest in Africa. In the 1950s, the prevalence of *W. bancrofti* mf among those equal to or

older than 10 years was between 24.1% and 48.4% (Rebollo *et al.* 2015). The Malaria vectors in The Gambia are also responsible for transmission of LF and *An. arabiensis*, *An. gambiae* s.s., *An. melas*, and *An. funestus* are the key vectors of *W. bancrofti* in the country that are all susceptible to ITNs and IRS (Rebollo *et al.* 2015). ITNs were introduced in the country in the 1990s (Rebollo *et al.* 2015). By 2008, 60% or more of ITN ownership coverage was reported (Rebollo *et al.* 2015). The absence of transmission in the whole country demonstrated through TAS (Rebollo *et al.* 2015). In 2013, the absence of transmission of *W. bancrofti* among children after 6-7 years of effective vector control in The Gambia strongly suggested the interruption of transmission of LF after 2 decades of ITN use (1950-1970s) and no MDA campaign has ever been conducted for LF in the country (Rebollo *et al.* 2015).

The newly proposed strategy of combining coordinated vector control and MDA using albendazole monotherapy for LF elimination in areas where there is co-endemicity with Loiasis has not been applied by any national LF programme (WHO 2015). The breaking of vector-host contact by use of repellents and bed nets has been recommended as a strategy for NTD control in addition to chemotherapy (Reimer *et al.* 2013).

Vector control for *Anopheles* is mainly through the use of synthetic pyrethroids currently recommended for bed net impregnation and IRS. However, resistance is already widespread to pyrethroids in some areas of West and Southern Africa. Dichlorodiphenyltrichloroethane (DDT) has been reintroduced to increase insecticide choice after its use was suspended for 3 decades. Unfortunately, the resistance of the vector is also already beginning to re-emerge to DDT. Resistance may, therefore, end up being a major challenge for Malaria and LF control or

elimination (de Souza *et al.* 2010; Bockarie *et al.* 2013; van den Berg, Kelly-Hope and Lindsay 2013). It has therefore been suggested that the pattern of insecticide resistance among Malaria and LF vectors be assessed to find ways of avoiding the worsening of this problem (Molyneux *et al.* 2014).

Morbidity management

WHO (2016a) has indicated that LF patients and their caregivers experience co-infection with other diseases and mental illness, that LF is responsible for 2.8 million DALYs lost. Alleviation of suffering and prevention of disability from LF is based on reducing secondary bacterial and fungal infection of limbs and genitals that already have their lymphatic function compromised due to the infection as the secondary infection is already proven to be the main pathogenetic factors that enhance worsening of lymphoedema and elephantiasis. Strategies used include the introduction of the use of meticulous hygiene, and motivation of those affected through the creation of hope and understanding among patients, caregivers and the community in general (Ottesen 2000). Since opportunistic infections (bacterial and fungal infections) play a role in progression to chronic obstructive filarial disease, attention to basic hygiene, use of antibiotics and antifungals, local physiotherapy, can slow progression, prevent or sometimes even reverse elephantiasis (Melrose 2004). Morbidity management and disability prevention (MMDP) includes a basic package of health care services that should be provided to those with hydrocoele and lymphoedema that are required to alleviate suffering and prevent the disease from progressing further (WHO 2015). National programmes should include morbidity management and disability prevention (MMDP) in their strategies so that care can be provided to those affected by LF after transmission has been interrupted. Those affected have a right to health care and programmes need to realise this right (WHO 1995). Some experts also believe that MMDP can also improve adherence to MDA within communities (WHO 1995).

The GPELF focusses MMDP on lymphoedema, elephantiasis and hydrocoele surgery. For other conditions, such as chyluria, lymphocele, scrotal lymphoedema, tropical pulmonary eosinophilia, adenopathy and haematuria standard practices for clinical management and

referral have to be used as there are no public health approaches available to address these conditions (WHO 1995).

Disability encompasses limitations in specific body functions (also called impairment), whole body limitations or limitation in a social sense through inability to participate in social functions within their own communities. Those affected therefore need psychological and social support for reintegration into their communities and economic life (WHO 1995). Patients need continued care and support throughout their life to manage and prevent progression to advanced stages of the disease (WHO 1995). WHO and partners have developed strategies and activities for managing lymphoedema (home based care) and increasing access to surgery for hydrocoele (Brantus 2009). There is now the integration of MMDP and PC for LF, and some progress has been made, but there are still many challenges to reach all those that need care as highlighted by Brantus (Brantus 2009).

Lymphoedema

Lymphoedema is debilitating and a chronic complication of LF that results from lymphatic insufficiency and can have serious physical, social and psychological consequences for the person affected (Barclay *et al.* 2006). The current management strategy for morbidity management and disability prevention involves a combination of strategies that aim to protect and decongest the oedematous limb/s and stimulate the development of supplementary lymphatic pathways thus controlling swelling in the long term. Aromatherapy has been proposed anecdotally as one such strategy because it is suggested that adding aromatherapy oils in massage cream can provide relief for people with cancer. Results of a trial conducted indicate that self-massage and skin care using aromatherapy oils provide improved relief to patients and, also slightly reduced the limb volume. This can be proposed to those who can afford it (Barclay *et al.* 2006). About 15 million people mostly women have lymphoedema or its advanced form elephantiasis mainly of the lower limb (WHO 1995). Lymphoedema and elephantiasis can be managed with simple measures such as improved hygiene and skin care aimed at preventing acute inflammatory episodes of adenolymphangitis. Proper wound care, exercise, elevation of affected limb and use of proper footwear can also provide relief. These

methods can reduce adenolymphangitis episodes and improve the quality of life of those affected and can be maintained as home-based care (WHO 1995).

Hydrocoele

Globally about 25 million men suffer from the urogenital disease of LF mainly hydrocoele that can be cured through surgery. The patient's and his family's economic situation and quality of life can improve significantly and also result in more participation within communities (WHO 1995).

Examples of successful LF programmes

LF transmission has been interrupted in the following countries: Japan, South Korea, endemic areas of China, Sri Lanka, Thailand, Malaysia, Solomon Islands, Costa Rica, Suriname, Thailand and Trinidad and Tobago using different approaches: mass treatment with diethylcarbamazine tablets or use of diethylcarbamazine salt, selective treatments of infected persons, vector control or a combination of several approaches. Sri Lanka has eliminated Brugian filariasis and Brazil, Malaysia, Cost Rica, Suriname, Trinidad and Tobago have eliminated LF in smaller foci (Molyneux 2003). Japan has eliminated LF and other parasitic diseases through integrated nationwide community-driven campaigns of the 1960s and 1970s that also created a cadre of experienced clinicians, scientists and public health workers that had excellent operational and technical knowledge and, also the right positive attitude towards LF elimination (Ichimori, Graves, Crump 2006). Japanese experts have supported LF elimination efforts in neighbouring countries since the 1970's and since 1999 have been working on this through the Pacific Programme to Eliminate LF (PacELF) that was created that year. PacELF has demonstrated that the successful model for LF elimination in Japan can be extended at the regional level (Ichimori, Graves, Crump 2006). Post-World War II conditions in Japan were the same as those in developing countries today, and the 15-year programme was successfully implemented through disease detection, drug distribution, prevention, and extensive health education. There were over 1 million people infected with LF in Japan in 1962 when a nationwide LF eliminate campaign was started with over 20% LF prevalence in some islands (Ichimori, Graves, Crump 2006).

China was one of the most heavily endemic countries of the world for LF with 864 endemic counties/cities in 16 provinces and a total population of 330 million at risk of getting LF. Among the 864, 542 were hypo-endemic (<5% microfilaraemia prevalence); 287 were meso-endemic (MF rate 5% - ≤20%); 33 were hyper-endemic (MF rate 20% - ≤30%); and 2 were super-endemic (MF rate >30%). LF elimination became a priority after the People's Republic of China was founded in 1949. The ultimate goal of eliminating LF was achieved in 2006 (De-jian, Xu Li, Ji Hui 2013).

In Africa, two countries (Togo and Malawi) have succeeded in interrupting transmission of LF and are currently going through the necessary procedures for verification of elimination by WHO. Togo started MDA for LF after mapping and baseline studies for LF in 2000. By 2009 it was demonstrated that a break in transmission has been achieved after passing a TAS and MDA was stopped nationwide followed by post-MDA surveillance for six years that demonstrated interruption of transmission (Sodahlon *et al.* 2013; WHO 2016a). Malawi passed a TAS in 2014 and stopped MDA nationwide in 2015. Post-MDA surveillance is currently ongoing (American Society of Tropical Medicine 2015).

Effect of other disease control interventions on LF

Several authors have reported studies that have shown that distribution of ivermectin for onchocerciasis control has an impact on LF intensity and prevalence. It was noted that reduction of onchocerciasis MF prevalence can be as high as 100% (to zero MF prevalence) in some villages (Kyelem *et al.* 2003; Kyelem *et al.* 2005; Kelly-Hope *et al.* 2011). However, similar studies in Nigeria showed that 2-5 years of Ivermectin treated with good coverage had no significant effect on LF transmission (Richards *et al.* 2005a,b).

History of LF control

Not all elephantiasis is caused by LF and elephantiasis is not the most common sign of LF. Elephantiasis is, however, the most visible manifestation of LF and has been known since ancient times. Elephantiasis features in Greece, Roman and Indian mythology (talk of beings with enlarged or swollen legs); in Egyptian history statues of Pharaoh Mentuhotep 111 (200 BC) and "Queen of Punt" Stella are depicted with deformities resembling elephantiasis of the

limbs); and in artwork from Nigeria and South America depicting scrotal swelling (Neisius 1927; Andrews 1959; Lawrence 1967; Lawrence 1990; Routh and Bhowmik 1993). Physicians and medical writers from early times knew the disease and even linked it to places where there is stagnant water (a relevant observation given the link between *Culex* mosquitoes that breed in stagnant water and LF transmission). Indians wrote of the disease as early as 600 BC, between 600 and 250 BC people with elephantiasis were not allowed to be Buddhist priests; the Roman writer Lucretius Carus noted elephantiasis as characteristic disease of Egyptians that was facilitated by the climate around the Nile; Persian physicians of 10^{th}–13^{th} centuries AD and medieval European physicians gave accurate descriptions of elephantiasis and hydrocoele; and in the 19^{th} century a firm link was made between elephantiasis, hydrocoele and chyluria (Lawrence 1967; Hoeppli 1969; Lawrence 1970; Routh and Bhowmik 1993).

Discovery of *W. bancrofti*: Jean-Nicholas Demarquay, a Cuban surgeon, discovered a worm-like creature in hydrocoele fluid in 1862 (Demarquay 1863); Otto Wucherer, a Brazilian, found the same organism in chylous urine in 1866 (Wucherer 1868); and MF was discovered in blood in 1872 (Lewis 1872). Joseph Bancroft, a Brisbane physician and parasitologist, discovered a female adult worm in an abscess from the arm of a butcher in 1876 and other examples were found in South America and China. Sibthorpe and Bourne discovered the male adult worm in 1888. In 1921, the name *Wuchereria bancrofti* was formally adopted (Seurat 1921). The detection of mosquitoes as vectors of *W. bancrofti* in China in 1877 by the British physician Patrick Manson was the first time any association had been made between an insect and active transmission of an agent of an animal or human disease (Bockarie and Molyneux 2009). The minute MF were also first observed by another British Physician Timothy Lewis in 1870 in the urine of patients (Bockarie and Molyneux 2009). The presence of *W. bancrofti* in *Anopheles* mosquitoes was first reported by Ronald Ross in 1900 (de Souza *et al.* 2014).

Discovery of the *Brugia* species: Lichtenstein and Brug discovered a microfilaria in the Dutch East Indies (now Indonesia) in 1927 that was morphologically different from *W. bancrofti* and named it *Filaria malayi* (Brug 1927; Lichtenstein 1927; Brug 1928). Although accepted as such, this may not have been the first description of *Brugia* as Ashburn and Craig had described a case from the Philippines in 1905 that had MF that differed from *W. bancrofti*, and they called

it *Filaria philippinesis* (Ashburn and Craig 1905). Manson-Bahr reviewed the findings in 1941 and reported that the MF were identical to the *F. malayi* discovered by Ashburn and Craig. In 1940 Rao and Maplestone first described the adult worm (Rao and Maplestone 1940). Brug's work was acknowledged in 1958 when Buckley proposed a new genus *Brugia* and *F. malayi* was renamed *Brugia malayi* (Buckley 1958; Buckley 1960). The zoonotic feature of *Brugia* was discovered in 1939 when MF that was later identified as those of *B. malayi* were discovered in a Kra monkey (Poynton and Hodgkin 1939). Another filarial species was discovered in the 1960s in Portuguese Timor and given the name *Microfilaria timori*. Partono infected Mongolian gerbils with this new species and developed adult worms. He confirmed the new species belonged to the genus *Brugia* and named it *B. timori* (David and Edeson 1965; Partono et al. 1977).

In 1988 Merck and Co. Inc. launched the donation of ivermectin under the brand name Mectizan. Merck formed the MDP, the first ever mass drug donation programme. ivermectin is now donated for two global disease elimination programmes (onchocerciasis and LF) that are benefiting millions of the world's poorest people after ivermectin/albendazole and diethylcarbamazine/albendazole combinations were approved by late 1990s for use to treat for elimination of LF (Thylefors, Alleman 2006; Thylefors 2008; Thylefors, Alleman, Twum-Danso 2008). In 1997 the World Health Assembly formulated resolution WHA50.29 that urges endemic communities to strengthen efforts for control and elimination of LF (Ramaiah and Ottesen 2014; Bockarie and Molyneux 2009). In 2000 the GPELF in 2020 was established (Ramaiah and Ottesen 2014; Molyneux 2003; WHO 2015; Bockarie, Kelly-Hope, Haskew 2010).

In 2009, the CDTI strategy was expanded to be used to deliver other integrated disease interventions including Vit A supplementation and antimalarial treatment (CDI Study Group 2010). In January 2016, ESPEN was launched by WHO to last for five years (2016-2020) (WHO AFRO NTDP 2016; WHO 2016b).

Mapping/baseline surveys for LF

Mapping is needed to identify priority areas for MDA and to allow for planning for implementation of programme activities (Baker *et al.* 2010). Mapping/baseline studies on LF in

West Africa: Gyapong *et al.* (1996a) reported baseline studies on LF in Ghana that showed high MF prevalence (MF prevalence ranged between 1.8% and 20%) with considerable regional variation (northern Savannah and southern coastal areas had high prevalence while the middle forest belt had low prevalence). Dunyo *et al.* (1996a) also showed that LF microfilaraemia was common in four villages in the Western region of Ghana and overall prevalence ranged from 9.2%-25.4%. They also showed that *Anopheles gambiae s.l.* and *A. funestus* were vectors of LF in the endemic villages. Gyapong *et al.* (2002) conducted a multi-country baseline study that showed that ICT positive prevalence among adult populations was as high as 70% in some communities studied, in large areas of Burkina Faso ICT prevalence ranged from 30%-50%, in most of Togo, Southern Benin and the greater part of Southern Ghana the LF prevalence was between 10%-30%. However LF prevalence was low in coastal Togo and Coastal Benin. Nigeria has been identified through mapping and baseline studies in 2009 to be the country in sub-Saharan Africa with the highest number of cases of NTDs including LF and onchocerciasis (Hotez *et al.* 2012). Many other studies on mapping and baseline surveys for LF in other parts of the world have been reported (Simonsen *et al.* 1995; Onapa *et al.* 2001; Sunish *et al.* 2001; Nielsen *et al.* 2002; Murty *et al.* 2004; Chhotray *et al.* 2005; Das *et al.* 2006; Ngwira et a. 2007; Mishra, Bhadoriya 2009; Ruberanziza *et al.* 2009; Knight *et al.* 2010; Msyamboza *et al.* 2010; Foo *et al.* 2011).

History of LF in Sierra Leone

The presence of *W. bancrofti* in *Anopheles* mosquitoes was first reported in Sierra Leone by Ronald Ross in 1900 (de Souza *et al.* 2014). During the ten-year civil conflict that started in 1991, an estimated 47% of the pre-war population were displaced and had to settle in camps or urban areas in Sierra Leone and in the neighbouring countries of Liberia and Guinea. With the population of Freetown increasing from an estimated 750,000 pre-war to 1.5 million post-war in 1997, a rapid assessment for LF in seven camps showed an LF antigenaemia prevalence of 14.5% among internally displaced persons (De Souza *et al.* 2014). In West Africa LF is predominantly a rural disease and the principal vector for LF in West Africa are the *Anopheles* mosquitoes with *Anopheles gambiae* complex identified as the major vector. The role of *Culex* mosquitoes in the transmission of LF in West Africa is unknown although they are common in large cities and urban areas in West Africa (De Souza *et al.* 2014). LF was determined to be

common in rural and urban areas of Sierra Leone (Gbakima and Sahr 1996). *Anopheles* species was also determined to be the vector of *W. bancrofti* in Sierra Leone. The prevalence rate for *W. bancrofti* in Sierra Leone between 1913 and 1931 was 8.8% in 1930 and 20.6% in 1931.Thomas (1958 cited in Gbakima and Sahr 1996) showed LF microfilaraemia rate of 44.2% in the north, 27.4% for the south-east and 27.7% for the south-west and 12.1% for Freetown. Vectors were identified as *An. costalis* and *A. funestus* (Gbakima and Sahr 1996). Other studies conducted in the 1990s in the south (Moyamba district) showed that LF microfilaraemia rate for *W. bancrofti* was 10.2% (Gbakima and Sahr 1996).

A survey was conducted in 2011/2012 in Freetown and Monrovia (capitals of 2 neighbouring post-conflict countries that experienced significant rural-urban migration) to assess the impact of migration during the conflict period on LF transmission in urban areas. More *Culex* mosquitoes were collected than *Anopheles* in both countries (14,342 *Culex* against 1,731 *Anopheles gambiae*). The results showed that An. *gambiae* are in low numbers with a level of LF MF infection too low to maintain transmission of LF (De Souza *et al.* 2014). TAS also conducted in Bo and Pujehun districts. Antigen prevalence in children was 0.19% and 0.67% respectively, levels lower than the 2% recommended for stopping MDA in *Anopheles* transmission areas (De Souza *et al.* 2014).

There has been an excellent strategic investment in the control of NTDs led by the US and UK governments, the BMGF and key pharmaceutical partners that has enabled the treatment of millions of people for five targeted debilitating diseases (LF, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis and trachoma). This has paved the way for the potential elimination of some of these diseases as public health problems (Hodges *et al.* 2011). Sierra Leone has a high burden of these five NTDs and has a fragile health system. After emerging from a devastating 10-year civil war, the country has successfully implemented the National NTD Control Programme, reaching 100% national coverage in 2010 (Hodges *et al.* 2011). The NTD Control Programme had used the existing Onchocerciasis Control Programme as a platform to cover other PC NTDs that involve primary health care workers. The programme has provided extensive training opportunities to health workers at national, district and community levels. The country currently has over 30,000 trained community volunteers who conduct MDA

in about 14,500 villages (Hodges *et al.* 2011). There is evidence that investments in NTD control can contribute to strengthening health systems, particularly at the primary level, through the extensive capacity building of frontline health workers and community-directed distributors (Hodges *et al.* 2011). USAID support through RTI International as a prime contractor started in 2007. Technical and financial support from WHO and the USAID NTDP through RTI International enabled the completion of mapping of the five PC NTDs in Sierra Leone in 2005-2008. Drug distribution is integrated for onchocerciasis and LF and all related activities for the two diseases after mapping are integrated including training, supervision and drug distribution within communities. MDA is however reported separately for the two diseases (Hodges *et al.* 2011; Linehan *et al.* 2011).

CHALLENGES OF NTD CONTROL

Controlling NTDs has many challenges including the high cost of mass treatment programmes, poor patient adherence, emerging or existing drug resistance, and possible low therapeutic efficacy of ivermectin (Gloeckner *et al.* 2010). In areas of tropical rain forest in Africa, there is a common infection of patients with another filarial parasite, *Loa Loa*. Although the mobile *Loa loa* adult worm is found in the tissues often not far from the skin, the MF are located in the blood. When patients with high levels of MF in the blood are treated with ivermectin, the ivermectin treatment can provoke serious adverse events that can be as severe as an encephalopathy. The patient develops neurological symptoms such as drowsiness, slurring of speech, walking difficulties, and eventually coma may occur. If properly managed, the patient with coma will normally recover after a few days although some sequelae may remain. However, most of these cases live in remote areas with difficult access to suitable health services. In some cultures, patients in a coma are treated with local remedies which delays the transfer of the patient to a suitable health facility. Thus, patients already have major complications due to pressure sores and other infections by the time they reach health facilities putting the lives of these patients further at risk. Special measures are needed to manage these patients quickly and effectively where treatment is required for onchocerciasis (Hopkins and Boatin 2011). Civil conflicts have unfortunately been a reality for several African countries such as Sierra Leone. Conflict causes population movement, destroys infrastructure

and leads to significant brain drain when competent health workers look for jobs elsewhere where their skills can be better utilised. Annual treatment coverage in many parts of central Africa (especially in the Democratic Republic of Congo) remains far too low to have an impact on the transmission of the disease and efforts at scaling up are also difficult for the reasons mentioned above (Hopkins and Boatin 2011). Duration of treatment in onchocerciasis endemic areas is long because: (1) the adult form of the parasite lives so long that treatment with ivermectin has to continue until the adult parasites die after 14 years; (2) duration of treatment can depend on the pre-control endemicity level that reflects the initial worm load and the pre-control intensity of transmission; and (3) the treatment coverage during the control period has to be adequate. Since treatment takes long and should be maintained at high treatment coverage if the transmission is to be interrupted, it is to some extent difficult to maintain both donor and patient interest. It is therefore recommended that programmes be fully integrated into the PHC system and become part of the standard package of activities at this level to be sustainable (Hopkins and Boatin 2011). Several authors have indicated the possibility of cross-border transmission of NTDs including onchocerciasis and LF (Bhumiratana *et al.* 2005; Bhumiratana *et al.* 2010; Bhumiratana *et al.* 2013a; Bhumiratana *et al.* 2013b; Ramaiah 2013).

Cross-border transmission as a problem

Cross-border transmission of infectious diseases including NTDs is cited as a major problem for many infectious diseases and NTD control efforts (Kaferstein, Motarjemi, Bettcher 1997; Bhumiratana *et al.* 2005; Asian Development Bank 2010; Bhumiratana *et al.* 2010; HKI 2010; International Coalition for Trachoma Control 2011; NNN 2011; Centers for Disease Control and Prevention 2011; The Carter Center and MOH Uganda 2011; Bhumiratana *et al.* 2012; Hodges *et al.* 2012a; Hodges *et al.* 2012b; WHO 2012; Gustavsen, Sodahlon, Bush 2016). The HKI position paper on NTDs identifies cross-border population movement as a cause of cross-border transmission of NTDs and notes that achievements in controlling NTDs can be undermined if control efforts in neighbouring countries are not the same (HKI 2010). A recent publication by Gustavsen, Sodahlon, Bush (2016) has expressed similar cross-border concerns in relation to onchocerciasis among the MRU countries. The participants of the 2011 second session of the NTD NGDO Network (NNN) in Nairobi and several other authors recognise the

importance of cross-border issues for NTD control as control efforts are weaker in some countries. They have noted that surveillance challenges mean that we do not know the extent of the problem, especially in Africa although there are indications of continuing importation of infectious diseases by mobile populations due to increased trans-national trade, travel and migration. Cross-border movement was identified as a challenge for controlling NTDs (Kaferstein, Motarjemi, Bettcher 1997; Zhang *et al.* 2010; NNN, 2011; Pose and Rabinowitz 2014).

Migration is common in the world and may pose a problem for control of LF, onchocerciasis and other endemic diseases (Ramaiah 2013). There are four possible types of migration: movement from endemic to non-endemic areas; from rural to urban areas; from non-MDA areas to areas that have already reached LF control/elimination; and across borders (Ramaiah 2013; Pose and Rabinowitz 2014). Usually, migrants are not able to create active transmission foci and cause infection among local people, but urban areas can be at risk due to a large influx of infected people which can end in urban areas needing longer treatment period (Ramaiah 2013). The migration-facilitated resurgence in areas that have achieved LF elimination appears to be difficult, but the risk cannot be excluded especially in areas with a more efficient vector such as *Culex* (Ramaiah 2013). The problem of cross-border transmission through migration between Thailand and Myanmar has been highlighted in several publications (Bhumiratana *et al.* 2010; Bhumiratana *et al.* 2013a,b). Thailand had completed LF MDA and was waiting for verification that almost all previously endemic areas were free of LF in December 2012 (MDA 2002-2006; post-MDA surveillance: 2007-2010). However, it was noted that there were pockets of infection along the border with Myanmar that were later shown to be due to migration from Myanmar. It was noted that the LF among Thai populations along the border with Myanmar was caused by nocturnal sub-periodic *W. bancrofti*, the same as that in Myanmar while the LF in Thailand is caused by nocturnal periodic *W. bancrofti* (Bhumiratana *et al.* 2010; Bhumiratana *et al.* 2013a). Ramaiah (2013) also dwells on the same Thai-Myanmar cross-border issue. Cross-border challenges were identified along Thailand-Myanmar border as up to 6% LF microfilaraemia rate, LF Antigenaemia rate of 22-36.8% and LF antibody prevalence rate of 54% was reported in border areas within Thailand. It was demonstrated that the control efforts in Thailand were confounded by migrants from Myanmar. Microfilaraemia

rates among migrants ranged from 4.4% to 8%; Antigenaemia rates 10% to 24%, and antibody prevalence rate of 42% were reported (Ramaiah 2013). They recommended that sentinel sites and periodic monitoring and evaluation mechanisms be set up to assess LF infection levels to pick up areas of possible resurgence along the border with Myanmar (Ramaiah 2013).

Active trachoma prevalence in the Gambia is high only where cross-border movement from Senegal creates new pockets of infection (International Coalition for Trachoma Control 2011). Evidence indicated that *Schistosoma mansoni* was being spread in Sierra Leone in the 1980s due to cross-border population movement (Hodges *et al.* 2012a). While presently Uganda might have eliminated onchocerciasis, whose vector the black fly (*Simulium damnosum*) can move easily across borders and continue transmission in controlled zones, cross-border transmission along the border with the Democratic Republic of Congo and South Sudan remains a problem (The Carter Center and MOH Uganda 2011). The ongoing migration between Mozambique, Swaziland and South Africa was noted as a concern especially so when the malaria situation in Mozambique was relatively worse than in the other two countries and action was taken to address malaria control through a regional initiative (Sharp *et al.* 2007).

Human migration has been identified as a key determinant of the success of LF elimination programmes although information is scarce on the role of migration in creating new foci or on the reintroduction of infection in areas where local transmission has stopped (Ramaiah 2013). Presently, there is no indication of resistance in the West African sub-region, but it should be noted that it has been suggested in Ghana that there is resistance to ivermectin used for treating onchocerciasis in the country (Osei-Atweneboana *et al.* 2007a; Osei-Atweneboana *et al.* 2007b). This claim has so far not been confirmed by other authors but the possibility of atypical or sub-optimal response still exists that can create problems for onchocerciasis control in the sub-region. Some authors have indicated the possibility of transmission of certain strains of causative agents of infectious diseases that are resistant to available treatments (Awadzi 2004; Eng and Prichard 2005; Burnham 2007; Cupp *et al.* 2007; Churcher *et al.* 2009; Taylor *et al.* 2009; Bhumiratana *et al.* 2013a).

Possible ways of addressing cross-border NTD transmission

Cross-border transmission of infectious diseases including NTDs can be addressed by improving inter-country cross-border collaboration that will involve existing regional and sub-regional structures; by conducting surveillance for infectious diseases (in this case NTDs) along national borders; and learning from successful cross-border initiatives in Africa and Asia established for the control of Malaria and HIV. Countries can improve cross-border collaboration by providing technical support and services to each other and, also by holding cross-border meetings (Zhang *et al.* 2010; Gustavsen, Sodahlon, Bush 2016). Since many NTDs can spread across borders, endemic countries can work together to set clear plans for cross-border collaboration; share knowledge and experience in planning, programme implementation, training and advocacy; conduct active surveillance for infected individuals along border areas; and study vectors responsible for cross-border transmission of NTDs (Kaferstein, Motarjemi, Bettcher 1997; The Carter Center and the MOH Uganda 2011). In the Lubombo Spatial Development Initiative (LSDI) experts on malaria control from South Africa and Swaziland worked with the health authorities in Mozambique to improve control and surveillance activities for malaria control in Mozambique (Lubombo project 2008; Lubombo project 2009; Laas 2012). The MRU NTD meetings involving Sierra Leone, Guinea, Liberia and Cote d'Ivoire is one such forum that has been ongoing since 2006 (Gustavsen, Sodahlon, Bush 2016). The first objective of sharing experience and data on NTD control is clearly being achieved in the MRU, and so it was agreed that the annual meetings be continued at least for this purpose. However, it is noted that most of the recommendations made need to be addressed at higher levels in the MOHs or by international NTD partners and donors (MOHS Sierra Leone 2013; Gustavsen, Sodahlon, Bush 2016).

Cross-border collaboration can be improved by involving existing sub-regional structures. Many cross-border meetings are sometimes organised by major NTD partners but cross-border collaboration appears uncoordinated, and when meetings are held, and recommendations are made, follow-up is typically poor, and thus the recommendations are seldom implemented (The Carter Center and MOH Uganda 2011; Gustavsen, Sodahlon, Bush 2016). Such meetings can be coordinated at regional or sub-regional level thus making elimination/control of NTDs a sub-regional goal. Collaboration can be improved by taking advantage of existing sub-regional

structures such as the West African Health Organization (WAHO), the MRU and AFRO (Gustavsen, Sodahlon, Bush 2016).

The USAID-supported END in Africa project that covers Sierra Leone, Ghana, Burkina Faso, Cote d'Ivoire, Niger and Togo for NTD control decided to implement some of the recommendations of the 2013 MRU meeting by organising a cross-border meeting in Accra in October 2016. This meeting had to take place at the beginning of the United States' (US) fiscal year so the agreements can be finalised before activities are implemented. The purpose of this meeting was for countries within the project that share common borders (Ghana, Ivory Coast, Burkina and Togo) to sit and plan synchronised MDA and the project will use legal agreements for support to 'push' countries to synchronise MDA. As the project countries move towards the end game for elimination of both onchocerciasis and LF, the project will insert in the fiscal year 2017 a clause in the agreements for Ghana, Ivory Coast, Burkina and Togo that requires that onchocerciasis and LF MDAs are synchronized in some selected districts along the borders that represent known transmission zones. Participants from the countries in this meeting will include NTDP managers, onchocerciasis coordinators and LF coordinators. The countries together identified districts along their borders that need to synchronise treatment and planned the 'how' and 'when' to synchronise treatment for the border districts. All this will be inserted into agreements that the project leadership and country partners will enforce. This initiative can enhance coverage and increase the impact of the project as countries move toward the elimination goal. In this case, funding will be from the same source and sub-grantees of the project within the countries concerned are expected to resolve the challenges that have been linked with language and communication between countries (FHI360 2016).

Some authors have recommended developing a common surveillance and reporting system and the use of similar indicators and forms for reporting NTDs (WHO AFRO 2009). Regular epidemiological and entomological surveys can be conducted in selected sites on both sides of the border to monitor the transmission of NTDs between countries (Bhumiratana 2005; HKI 2010; International Coalition for Trachoma Control 2011; Ramaiah 2013). Others recommend routine surveillance in border areas (Khamsiriwatchara *et al.* 2011; Hodges et 2012b; WHO 2012). However, given the limited human resource for health in Africa, it might be difficult to

set routine surveillance for NTDs in all the official border crossing points. Furthermore, there are so many unofficial border crossing points between African countries that setting a system in the official border crossing points will not have a significant impact. It is, however, possible to have an international team that can be set up by AFRO in collaboration with WAHO, to coordinate epidemiological and entomological surveys in selected sites along the borders of the 15 West African countries. The challenge would be to develop agreements between countries, as well as protocols and plans for realising this recommendation. This can also be addressed by encouraging discussion among countries (Lubombo 2008; Lubombo 2009; WHO 2009; Laas 2012). Other small groups of countries such as the MRU countries can also establish similar surveillance mechanisms.

Recently, the World Bank launched the Sahel project involving Niger, Burkina Faso and Mali that aims to address cross-border issues relating to NTDs and malaria in the three countries. This project also seeks to improve regional collaboration for the control of malaria and NTDs within these countries (World Bank 2015). The need to have regional collaboration in addressing cross-border issues is key especially after the recent outbreak of EVD that clearly demonstrated that regional collaboration is needed and had to be established to end the outbreak (Gustavsen, Sodahlon, Bush 2016). The initiatives mentioned above have shown that there could be a diverse group of stakeholders for cross-border collaboration to address cross-border transmission of infectious diseases including NTDs in West Africa. There could be joint coordination by several international organisations. The author believes that in West Africa, WAHO, MRU and AFRO are the three best-positioned organisations to take on this challenge. WAHO, MRU and AFRO have a physical presence in the sub-region and in each country they cover that enables them to effectively foster international collaboration around cross-border initiatives. WAHO has a coordinator in each MOH within ECOWAS, WHO has a country office, and representation in all countries, and MRU has a secretariat in each of the four member states.

CHAPTER 3: IMPACT OF FIVE ANNUAL ROUNDS OF MASS DRUG ADMINISTRATION ON ONCHOCERCIASIS MICROFILARAEMIA PREVALENCE AND DENSITY IN SIERRA LEONE

ABSTRACT

Background

Studies to map onchocerciasis using skin snip method in 1988-2005 across Sierra Leone showed that 12 of the 14 health districts were onchocerciasis-endemic. Relatively better treatment coverage was achieved between 2005 and 2009 after the end of an 11-year civil conflict in the country in 2002.

Methods

To evaluate the impact of five years of effective treatment (2005-2009), 39 villages across the 12 onchocerciasis-endemic districts with the highest MF prevalence at baseline were selected and surveyed using skin snips in 2010, and results were analysed and compared with the baseline data from the same 39 villages.

Results

The average MF prevalence across 39 sentinel villages was 53.1% at baseline. MF prevalence increases with age. The lowest MF prevalence of 11.00% was within the age group 1-9 years and the highest was within the age group 40-49 years (82.31%). Overall MF density among positive-only was 28.87 mf/snip. MF load among positive-only also increases with age with the lowest within the age group 1-9 years and the highest in the age group 40-49 years. Males have higher MF prevalence and density than females. In 2010 after 5 rounds of MDA the overall MF prevalence reduced by 60.26%, from 53.10% to 21.10%; the overall MF density among positive-only reduced by 71.29% from 28.87 mf/snip to 8.29 mf/snip; and overall MF density among the entire population studied reduced by 88.58% from 15.33 mf/snip to 1.75 mf/snip. MF prevalence was higher among males than females, and MF density among males was twice as high for males than females. The age group 1-9 years had the lowest MF prevalence and MF density while the age group 40-49 years had the highest MF prevalence and density. Ten of 12 endemic districts (83.33%) had >50% reduction in MF prevalence. Eleven of 12 districts (91.67%) had ≥50% reduction in skin MF density among positive-only.

Conclusion

In just five years of good MDA using the CDTI strategy, there is a significant reduction in MF prevalence and MF load among positive-only with the greatest reduction in skin MF prevalence observed in the age group 1-9 years, which indicates a significant reduction in transmission.

INTRODUCTION

Sierra Leone is highly endemic for all seven PC NTDs like many other African countries. Endemicity of PC NTDs such as onchocerciasis was known in Sierra Leone since 1926 when Blacklock first described onchocerciasis transmission by the black flies *S. damnosum* in the Kono district of Sierra Leone (Blacklock 1926). Onchocerciasis control started in 1957 with vector control in Tonkolili district. Onchocerciasis was shown to be the second most common cause of blindness after cataract in Sierra Leone and so in the late 1980s the former OCP extended its activities to four other countries including Sierra Leone and vector control through larviciding with insecticides continued along rivers in hyper-endemic areas (Samba 1994; Yameogo 2008; Hodges *et al.* 2011; Fobi *et al.* 2015).

As indicated previously, many studies were conducted on onchocerciasis in Sierra Leone by the NOCP and other researchers linked to the then OCP and APOC. NOCP has baseline data for more than 100 study sites (villages) in all 14 districts with a prevalence that varied from 0% to 78.3%. Many sites had to be studied to determine areas that had to be treated, and it was determined that the Western Area (both Western Urban and Western Rural districts) and the southern coastal plain of the Bonthe district are non-endemic for onchocerciasis because the prevalence was 0% in these areas. Thus, it was determined that only the 12 provincial districts of Sierra Leone are endemic for onchocerciasis in Sierra Leone. Figure 7 shows point onchocerciasis MF prevalence for all sites studied at baseline and the areas where CDTI was being implemented in Sierra Leone in 2005.

Treatment in the 12 districts with ivermectin was based on *O. volvulus* micro-filaridermia prevalence and the treatment policy then was to conduct treatment only in areas that had *O. volvulus* MF prevalence ≥40% (*i.e.* in areas considered to be meso-endemic with *O. volvulus* microfilaridermia prevalence between 40% and 59.9%; and hyper-endemic areas with *O. volvulus* microfilaridermia prevalence ≥60%). It should be noted that within each of the 12 onchocerciasis-endemic districts there are hyper-endemic, meso-endemic and hypo-endemic areas (with *O. volvulus* microfilaridermia prevalence below 40%).

Although the OCP started activities in Sierra Leone in 1989, the civil conflict between 1991 and 2002 impacted negatively on onchocerciasis control activities and in 1997 all onchocerciasis activities were stopped nationwide. Finally, for the last five years of the OCP (1997-2002), absolutely no onchocerciasis control activities were conducted in the country due to insecurity. With support from APOC, the NOCP of Sierra Leone restarted interventions in January 2003 as part of the SIZ after the end of the civil war in 2002. By then the CDTI strategy had already been developed and established as a principal strategy for onchocerciasis control by APOC since 1997, and so CDTI was implemented nationwide in meso-endemic and hyper-endemic areas under the SIZ (Hodges *et al.* 2011; Yameogo 2008; Fobi *et al.* 2015**).** It is reported that treatment reports for the period 1989-2002 are unreliable because relatively few areas that needed treatment were covered due to insecurity. Furthermore, 2003 and 2004 epidemiological coverage was reported as 36% and 28% respectively, and geographic coverage (proportion of districts actually treated against the number targeted in each district) could not be determined for the two years. The year 2005 thus became the year of improvement in the efforts to control onchocerciasis, which coincided with management/administrative changes effected by the MOHS to improve onchocerciasis control efforts in the country, and treatment coverage has significantly improved since 2005 (unpublished NOCP/NTDP Reports 2005-2015).

The purpose of this study is to analyse the results of an epidemiological evaluation using the skin snip method that was conducted to assess the impact of five annual rounds of MDA (2005-2009) on onchocerciasis. A total of 39 villages spread across the 12 onchocerciasis-endemic districts, with baseline *O. volvulus* microfilaridermias prevalence ≥40%, were selected as sentinel sites for the 2010 evaluation. The current national policy is targeting onchocerciasis for elimination, and the use of the 39 sentinel sites for monitoring treatment impact is with the assumption that the reduction of onchocerciasis prevalence in these relatively high prevalence areas is an indication of an overall reduction of onchocerciasis prevalence.

METHODS

Ethics approval

The baseline and 2010 studies were conducted by the NOCP of the MOHS, Sierra Leone, with technical and financial support from the OCP and APOC/SIZ. Ethical approval for data collection was obtained from the Ethics Committee of the MOHS, and upon arrival at the randomly selected communities, the investigating teams met with community leaders and explained the nature of their work. All volunteers/participants aged one year or above (at baseline) or five years and above (2010 evaluation) in each site were eligible for inclusion without discrimination on gender, social status, religion or ethnicity. Volunteers participated in the studies after informed consent was verbally obtained and recorded by the team leader, as literacy rates are low in Sierra Leone. Consent was obtained from participants themselves, or from the parents of all participants below the age of 18 years. Data collection was conducted such that participants will remain anonymous during data entry and analysis. No individual's identity can be revealed upon publication.

Mass drug administration

In 2005 and 2006 MDA was conducted only for onchocerciasis with Ivermectin by the NOCP with support from APOC/SIZ. Integrated onchocerciasis/LF annual MDA with ivermectin and albendazole was piloted in 2007 in six rural onchocerciasis/LF co-endemic districts located in border areas with neighbouring Guinea and Liberia: Bombali, Kailahun, Kambia, Koinadugu, Kono, and Pujehun. The same year, onchocerciasis only MDA was conducted in the other six onchocerciases/LF districts. Integrated onchocerciasis/LF MDA was scaled up to cover all 12 onchocerciases/LF coendemic districts in 2008 with the following additional districts added to the previous six districts: Bo, Bonthe, Kenema, Moyamba, Port Loko and Tonkolili. The onchocerciasis programme has been using CDTI since the restart of onchocerciasis control efforts in 2003 after the end of the civil war in 2002. Besides the district headquarter towns and a few other commercial centres, the other areas of the districts are rural in Sierra Leone and consist of villages with population ≤500 people. Within rural communities ivermectin and later Ivermectin plus albendazole were distributed by CDDs who are literate members of different communities that are selected by their communities and trained by health workers to conduct MDA and report all incidence of adverse events following treatment to district health

workers. The CDDs were trained to use dose poles to determine the number of tablets of ivermectin to be administered depending on the height of the person treated. Between 1 and 4 tablets of 3mg ivermectin was administered to all those treated. District health workers conducted training of CDDs to prepare them for the MDA within their communities and provided supervision during MDA. NTDP staff and members of the DHMTs also supported training and supervision of the MDA. MDA is conducted once a year between September and December, which is the post-harvest period when communities have accepted MDA (unpublished NOCP/NTDP Reports 2005-2015).

Treatment for onchocerciasis (whether alone or integrated with LF treatment) is done using community registers. The NOCP (and later the NTDP) is supported to provide at least one register (depending on the population size) for each of the communities. The register is designed to capture all members of each community targeted for treatment, including those eligible for treatment and those not eligible for treatment, and is, therefore, a good source of demographic information for the communities that use them. Before each MDA, CDDs conduct a pre-MDA census and update the community register to reflect those that leave the community, those that join the community and the newly born. MDA details are also captured in the registers. After each MDA, the MDA details are summarised on village reporting forms by drug distributors and submitted to the supervising health workers. The supervising health workers prepare PHU summary reports for all villages areas targeted and submit the reporting forms to the DHMTs. Each DHMT then submits the district summary reports for the MDA to the NTDP, which collates MDA results from all districts (unpublished NOCP/NTDP Reports 2005-2015).

Baseline and 2010 onchocerciasis studies 1988-2005, and 2010

Onchocerciasis infection and its density were determined using the method of microscopic examination of the skin snips for the presence and number of *O. volvulus* MF. Two skin snips were taken from the right and left iliac crests, which is the site that usually has the highest concentration of skin MF. Skin snip was done in all selected villages 11-12 months after last treatment, and the survey was cross-sectional. All subjects who were one year or above who agreed to participate (or whose parent/s agreed on their behalf) and voluntarily presented

themselves (or are brought by their parents) were included in the study. They are asked for identification data - name, age, sex, occupation, and a number of years they are resident in the village. Two skin biopsies are obtained from the right and left iliac crests of those studied. A 2mm Holth corneo-scleral punch is used to obtain the two bloodless skin snip biopsies. The scleral punch is sterilised with sodium hypo-chlorite solution and distilled water and then autoclaved under pressure for 15 minutes after taking biopsies from each individual. This was to prevent the transfer of HIV/AIDS and other blood-borne infections. The samples are then microscopically examined for the presence and number (quantity) of *O. volvulus* MF after incubation for 30 minutes in distilled water. Negative skin snip samples are further kept in saline solution for 24 hours and microscopically re-examined. The number of MF are counted, and the results are recorded for each person examined. Migration history is taken for each person during the last ten years prior to the survey. Pre- and post-treatment skin snip data are then analysed to determine and compare onchocerciasis infection levels using indicators of MF prevalence and MF density. The results are expressed as a proportion of positive/negative people in the sample (Wanji *et al.* 2005; Katabarwa *et al.* 2008; Tekle *et al.* 2012; Katabarwa *et al.* 2012; Katabarwa *et al.* 2013). Since only those one year and above (for baseline) and five years and above (for 2010 evaluation) who volunteered for the study were snipped, the number of people studied per village varied significantly. Furthermore, the number of people studied in each district also varied significantly because the number of villages selected at baseline per district also depended on the size and population of the district. Training and refresher training of technicians in the survey teams were conducted to ensure standardisation of data collection and that all survey teams use the standard skin snip methodology recommended by the then OCP and APOC. At baseline, a total of 7,116 people were tested in all the 39 villages; males 3,461 (48.6%) and females 3,655 (51.4%). In 2010, For quality control, OCP and later APOC recruited scientists that worked in the field with the NOCP survey teams and examined all positive slides and 10% of the negative slides.

Statistical analysis

Results were entered into MS Excel and analysed in SPSS (IBM, Version 19). Prevalence and density of MF were calculated for all 12 districts, by sex and age groups and compared with the baseline data. For the villages, only MF prevalence was calculated and compared with baseline

MF prevalence data. The 95% confidence intervals (CIs) for prevalence were calculated using the Wilson score method without continuity correction (Newcombe 1998). The arithmetic mean MF density of infection with 95% CI was calculated using the total population examined and the positive samples only. The Chi-squared test was used to compare the differences in prevalence, and the Kruskal-Wallis test was used to compare the differences in MF density. Treatment coverage was calculated according to the WHO guidelines and reported using two indicators: epidemiological coverage and programme coverage (WHO 2011a). Epidemiological coverage is the proportion of people ingesting the drugs among the total targeted population in the endemic communities and districts. Programme coverage is the proportion of people ingesting the drugs among people in the endemic districts that are eligible for treatment. The total population used in rural areas was the total number of people registered during the pre-MDA census (Koroma, Turay, Moihua 2006), with an annual growth rate of 2.5%. Spatially smoothed contour maps of the interpolated onchocerciasis MF prevalence in the 39 sentinel sites at baseline and after five MDAs were produced (see Figure 8) as described previously (Zoure *et al.* 2011).

RESULTS

MDA results 2005-2009

A total of 8,451 villages were treated with ivermectin each year in 2005 and 2006 for onchocerciasis only, and 14,253 villages (including the 8,451 treated previously for onchocerciasis only) and urban areas were treated between 2007 and 2009 in the 12 districts for both onchocerciasis and LF using ivermectin and albendazole. Geographic coverage for onchocerciasis in these districts during this period was 100% although the treatment coverage was not always that required by WHO (≥65% epidemiological coverage and ≥80% programme coverage) (WHO, 2011a). As discussed previously, treatment coverage in 2003 and 2004 was so poor that it was considered ineffective and is not considered here. In 2005, coverage improved significantly but seven of the 12 districts achieved <65% epidemiological coverage and <80% programme coverage. Overall, epidemiological coverage was 61.6%, and programme coverage was 76.4%. With more concerted programme efforts and more technical/financial support from NTD partners, coverage significantly improved the next year and has been maintained

above 65% epidemiological coverage and above 80% programme coverage since 2007. Table 4 below shows treatment coverage between 2005 and 2009. It should be noted that between 2007 and 2009 treatment was conducted in all villages and urban areas of the 12 districts. Treatment, therefore, included villages and urban areas that were considered hypo-endemic (with <40% microfilaridermia prevalence) and were never treated before the introduction of LF treatment.

Dynamics of onchocerciasis distribution in Sierra Leone at baseline

Baseline studies conducted between 1988 and 2005 in an estimated 150 sites in all 14 health districts of Sierra Leone had shown that all the 12 provincial health districts of Sierra Leone were found to be endemic for onchocerciasis with the prevalence of skin snip MF positives ≥1%. Data from the 39 sites of the 12 onchocerciasis-endemic districts selected as onchocerciasis sentinel sites are analysed to determine the baseline onchocerciasis MF prevalence, onchocerciasis MF density for the entire population studied and onchocerciasis MF intensity for positives only. Table 5 summarises the results of the baseline and 2010 onchocerciasis MF prevalence, MF density for the entire population studied and MF density for positives-only for each of the 12 districts, by sex, and by age groups. The percentage reduction of MF prevalence, MF density for the entire population studied and MF density for positive-only and their corresponding p-values are also summarised in Table 5. Since for each district the sites selected as sentinel sites were those with the highest baseline prevalence, the baseline prevalence for each of the 12 districts varied from 39.01% (95% CI: 36.17-41.91) to 61.94% (95% CI: 54.09-69.20). The overall MF prevalence for all 7116 participants studied in the 39 sentinel sites was 53.09% (95% CI: 51.93-54.25). The MF prevalence for males was higher than the MF prevalence for females (55.19%, 95% CI: 53.52-56.84 for males and 51.11%, 95% CI: 49.49-52.73 for females). Onchocerciasis MF prevalence in the northern districts (Kambia 61.94%, 95% CI: 54.09-69.20; Tonkolili 60.40, 95% CI: 57.17-63.54; Koinadugu 58.83, 95% CI: 50.77-65.52; Bombali 57.88%, 95% CI: 52.78-62.82; and Port Loko 57.12, 95% CI: 53.29-60.86) tended to be higher than prevalence in the southern districts (Moyamba 58.20%, 95% CI: 55.20-61.14; Bo 54.30%, 95% CI: 51.77-56.81; Pujehun 53.57%, 95% CI: 49.43-57.66; and Bonthe 40.56%, 95% CI: 33.65-47.85), while the prevalence of the eastern districts are relatively the lowest (Kailahun 49.73%, 95% CI: 42.56-56.90; Kenema 45.12%, 95% CI: 39.44-

50.90; and Kono 39.01%, 95% CI: 36.17-41.91). The MF prevalence is lowest for the age group 1-9 years (11.05%, 95% CI: 9.80-12.43); increases sharply to 50.57% (95% CI: 47.87-53.26) for the age group 10-19 years; continues to increase and peaks at 82.31% (95%: 79.39-84.90) for the age group 40-49 years; and then drops to 76.17% (95% CI: 72.84-79.20) for the age group ≥60 years.

Dynamics of microfilaraemia density at baseline

The baseline data from the 39 sentinel sites were analysed to determine the microfilariae density for the entire population studied and also the density among those that were microfilariae positive. The overall arithmetic mean density for the entire population studied in the 39 sentinel sites is 15.33 mf/snip (95% CI: 14.43-16.24 mf/snip) and the mean arithmetic density among those MF positive is 28.87 mf/snip (95% CI: 27.29-30.46 mf/snip). The mean arithmetic density for the entire population studied is 21.11 mf/snip (95% CI: 19.49-22.72 mf/snip) for males and 9.94 mf/snip (95% CI: 9.09-10.79 mf/snip) for females. The mean arithmetic density for positives-only is 38.16 mf/snip (95% CI: 35.47-40.84 mf/snip) for males and 19.38 mf/snip (95% CI: 17.85-20.92 mf/snip) for females. The mean arithmetic density for entire population studied and for positives-only is twice higher for men than for women. The mean arithmetic density among the entire population studied ranges from 6.51 mf/snip (95% CI: 3.47-9.54 mf/snip) for Kenema to 22.09 mf/snip (95% CI: 19.28-24.91 mf/snip) for Tonkolili district. The mean arithmetic density among positives-only ranges from 14.42 mf/snip (95% CI: 7.91-20.94 mf/snip) for Kenema to 37.48 mf/snip (95% CI: 31.36-43.60 mf/snip) for Kono district. The trend between the regions observed for the MF prevalence is not clear cut for the mean arithmetic density. While the northern districts have relatively higher mean arithmetic density for entire populations studied (Tonkolili- 22.09 mf/snip, 95% CI: 19.28-24.91 mf/snip; Koinadugu- 18.38 mf/snip, 95% CI: 12.65-24.12 mf/snip; Kambia- 17.80 mf/snip, 95% CI: 11.02-24.58 mf/snip; Bombali- 16.85 mf/snip, 95% CI: 12.73-20.97 mf/snip; and Port Loko- 13.83 mf/snip, 95% CI: 11.12-16.53 mf/snip) than the southern and eastern districts, Bo district in the south has a mean arithmetic density for entire population studied of 18.91 mf/snip (95% CI: 16.59-21.23 mf/snip), higher than most of the northern district and Kono district has a mean arithmetic density for entire population studied of 14 mf/snip (95% CI: 12.01-17.25 mf/snip)

higher that some southern districts. The trend observed for the prevalence is also not clear-cut for the mean arithmetic density for positives-only.

The mean arithmetic density for entire population studied is lowest among the age group 1-9 years (0.91 mf/snip, 95% CI: 0.51-1.30 mf/snip), increases sharply to 6.91 mf/snip (95% CI: 5.92-7.91 mf/snip) in the age group 10-19 years, then increases further to peak at 35.94 mf/snip (95% CI: 31.44-40.44 mf/snip) in the age group 40-49 years and drops to 21.58 mf/snip (95% CI: 18.44-24.72 mf/snip) in the age group ≥60 years. The mean arithmetic density for positives-only follows the same pattern: lowest for the age group 1-9 years (8.24 mf/snip, 95% CI: 4.77-11.72 mf/snip), increases to 13.67 mf/snip (95% CI: 11.85-15.49 mf/snip) in the age group 10-19 years, peaks at 43.66 mf/snip (95% CI: 38.39-48.93 mf/snip) in the age group 40-49 years, and drops to 28.34 mf/snip (95% CI: 24.39-32.29 mf/snip) in the age group ≥60 years.

Prevalence of onchocerciasis microfilaridermia in 2010

The overall onchocerciasis microfilaridermia prevalence was 21.12% (95% CI:20.07-22.20%); or 24.49% (95% CI: 22.94-26.12%) for males, and 17.76% (95% CI: 16.39-19.21%) for females. The microfilaridermia prevalence among districts ranged from 6.90% (95% CI: 2.71-16.43%) for Koinadugu districts to 29.96% (95% CI: 27.19-32.89%) for Moyamba district. For the age groups, the lowest microfilaridermia prevalence is within the age group 1-9 years (1.71% (95% CI: 1.22-2.39%); then increases to 16.09% (95% CI: 13.82-18.65%) within the age group 10-19 years; peaks at 38.75% (95% CI: 34.74-42.91%) for the age group 40-49 years; and then drops slightly to 29.33% (95% CI: 25.73-33.21%) within the age group ≥60 years.

Microfilaridermia density in 2010

The overall arithmetic mean MF density was 1.75mf/snip (95% CI: 1.48-2.02mf/snip) in the total participants examined and 8.29 mf/snip (95% CI: 7.07-9.50mf/snip) among MF-positive individuals. For males, the arithmetic mean MF density was 2.55mf/snip (95% CI: 2.04-3.06mf/snip) in the total participants examined and 10.40 mf/snip (95% CI: 8.43-12.36mf/snip) among MF-positive individuals. For females, the arithmetic mean MF density was 0.96mf/snip (95% CI: 0.77-1.15mf/snip) in the total participants examined and 5.40mf/snip (95% CI: 4.40-6.40mf/snip) among MF-positive individuals. There was a significant difference in MF density in

males versus females (p<0.05) as density for the entire population among males was over twice as high as density among females and density for positives-only among males was almost twice as high as that for females. The mean MF density by the district was below 4mf/snip for all districts (and well below 1mf/snip in four districts- Koinadugu, Kono, Pujehun and Tonkolili) for the entire population examined; and below 12mf/snip among those who were mf positive. Among districts, the arithmetic mean MF density for entire population ranges from 0.05mf/snip (95% CI: 0.00-0.11mf/snip) in Koinadugu district to 3.10mf/snip (95% CI: 1.80-4.40mf/snip) in Port Loko district; and the arithmetic mean MF density for positives-only ranges from 0.75mf/snip (95% CI: 0.00-1.55mf/snip) in Koinadugu district to 11.91mf/snip (95% CI: 7.12-16.71mf/snip) in Port Loko district. Among the age groups, the arithmetic mean MF density for the entire population studied is lowest among the age group 1-9 years (0.04 mf/snip, 95% CI: 0.02-0.06mf/snip); increases slightly to 0.08 995% CI: 0.51-1.08 mf/snip in the age group 10-19 years; continues to increase and peaks at 4.09mf/snip (95% CI: 2.65-5.54mf/snip) in the age group 40-49 years; and then drops slightly to 2.10 mf/snip (95% CI: 1.47-2.73mf/snip) in the age group ≥60 years. The arithmetic mean MF density for positives-only is also lowest among the age group 1-9 years (2.47mf/snip, 95% CI: 1.49-3.45mf/snip); increases slightly to 4.49 (95% CI: 3.31-6.58mf/snip in the age group 10-19 years; continues to increase and peaks at 10.56mf/snip (95% CI: 6.99-14.13mf/snip) in the age group 40-49 years; and then drops slightly to 7.04mf/snip (95% CI: 3.18-10.89mf/snip) in the age group 50-59, and 7.17mf/snip (95% CI: 5.22-9.12mf/snip) in the age group ≥60 years.

Reduction in MF prevalence and density after five years of MDA

Reduction of MF prevalence

Overall, MF prevalence dropped by 60.22% (P=0.00); 54.24% among males (p=0.00), and 64.12% among females (p=0.00). Reduction in MF prevalence among districts was in general greater than 50% (P<0.05) except for Bonthe district and Moyamba district that had 34.25% (p=0.009) and 48.52% (P=0.000) reduction respectively. Koinadugu and Pujehun districts had over 80% reductions in MF prevalence (p=0.000). Among the age groups, the highest reduction in MF prevalence (82.55%) was recorded in the age group 1-9 years followed by the reduction in the age group 10-19 years (66.40%). The reductions were all statistically significant P<0.05) except for Gawula (P=0.1279) and Yakaji (P=0.1092).

Reduction of MF density

Overall, arithmetic mean MF density for the entire population studied dropped by 88.58% (P=0.00) while arithmetic mean MF density for positives-only dropped by 71.29% (P=0.000). For males, arithmetic mean MF density for the entire population studied dropped by 87.92% (P=0.000) while the arithmetic mean MF density among positives-only dropped by 72.75% (P=0.000). For females, the arithmetic mean MF density for the entire population studied dropped by 90.34% (P=0.000) while the arithmetic mean MF density among positives-only dropped by 72.14% (P=0.000). Among districts, reduction in arithmetic mean MF density for the entire population was in general >70% (PP<0.05) except for the Bonthe district that had 56.43% (P=0.004); and arithmetic mean MF density for positives-only was, in general, >50% (P<0.05) except for Bonthe district where the reduction of MF density among positives-only (33.80%) was not statistically significant (P=0.2470). The reduction of mean arithmetic MF density among positives-only was also not statistically significant for Kenema district (55.06%, P=0.2170). Koinadugu district had close to 100% drop in both densities for the entire population and positives-only (P=0.000). Among the age groups, the reduction of the arithmetic mean MF density for the entire population studied was in general above 80% with the highest reduction among the age group 1-9 years (95.60%); and the reduction of the arithmetic mean MF density for positives-only was in general above 60% with the highest reduction among the age group 50-59 years (81.13%).

DISCUSSION

Overall at baseline MF prevalence among the 39 sentinel villages was 53.09% with 55.19% for males and 51.11% for females. The following distinct epidemiological patterns were determined from the data analysed: (1) The MF prevalence was higher in males than females; (2) the prevalence is lowest for the age group 1-9 years followed by the age group 10-19 years; and (3) onchocerciasis MF prevalence was higher in the northern districts than in the southern and eastern districts. Distinct epidemiological patterns were also noted for the density: the mean arithmetic MF density for the entire population studied and for positives-only was

almost twice higher for males than for females; was lowest among the age group 1-9 years followed by the age group 10-19 years; and the age group 40-49 had the highest arithmetic mean MF density for entire population studied and for positives-only. The average density for northern districts was higher than that of southern and eastern districts although some southern and eastern districts had a density higher than some northern districts.

In general, males had higher infection levels than females. Although MF prevalence in males was only slightly higher than in females, the MF density for the entire population and positive-only was about twice as high in males than in females. The male/female differences in prevalence, the density of infection and clinical disease due to onchocerciasis have been discussed and are related to differential exposure of females to infective vectors (Brabin1990).

The prevalence is lowest for the age group 1-9 years followed by the age group 10-19 years. Lower age groups (1-9 years and 10-19 years) have the lowest MF prevalence and MF density even within highly endemic areas and peak MF prevalence, and MF density was observed in the age group 40-49 years. This also tends to indicate that onchocerciasis transmission to children may have reduced due to previous onchocerciasis control efforts although it may also be because children spend less time at the river banks and may be less open to bites of the black fly. A previous study analysed the impact and extent by which maternal *O. volvulus* infection can be transmitted to their children and showed that children from onchocerciasis-infected mothers are more likely to be infected with onchocerciasis (Kirch *et al.* 2003). One can, therefore, conclude that transmission of onchocerciasis to children in Sierra Leone has been low because females are less infected than men and children may be less exposed to the disease vector.

Onchocerciasis MF prevalence was higher in the northern districts than in the southern and eastern districts. The northern districts (Bombali, Kambia, Koinadugu, Port Loko and Tonkolili districts) have higher average MF prevalence and MF density than southern districts (Bo, Bonthe, Moyamba and Pujehun districts) that also have higher average MF prevalence and MF density than Eastern districts (Kailahun, Kenema, and Kono districts). A study was conducted in 1987-1988 to compare the onchocerciasis situation in forest areas and Savannah areas of the

country. Prevalence of *O. volvulus* MF, nodules and moderate or severe skin lesions was higher in the forest than in Savannah villages. In forest villages, the MF prevalence was 71.8% at the iliac crest while the corresponding MF prevalence for the Savannah villages were 51.9%. The study also showed that males were more infected with the disease than females (McMahon *et al.* 1988c). This observation made in the past might be the explanation for the regional variation noted in this analysis.

The MF prevalence reported for these villages was similar to the MF prevalence reported previously by other authors in Sierra Leone and elsewhere (McMahon *et al.* 1988a; Gbakima and Sahr 1996; Wanji *et al.* 2005). The overall MF prevalence of 55.09% is significantly higher than the 16.69% MF prevalence (701,000 infected among 4.2 million) reported by OCP for Sierra Leone in 1990 (Remme, 2004), but is similar to the >60% MF prevalence reported in 1988 for the northern districts (McMahon *et al.* 1988a). The results were also similar to MF prevalence reported in villages of one district of Cameroon (Wanji *et al.* 2005). The MF prevalence reported here for Moyamba district is higher than the prevalence reported in 1996 for Moyamba district in southern Sierra Leone. However, this study in 1996 also highlighted the relatively low MF prevalence (13.3%) observed among children 5-9 years compared to older age groups: 61.9% among those 40-49 years (Gbakima and Sahr 1996).

The 2010 evaluation in the same 39 sentinel sites revealed a significant decrease in onchocerciasis MF prevalence and density after just five rounds of annual MDA with ivermectin.

The same epidemiological dynamics at baseline was observed in the 2010 evaluations: mf prevalence was higher in males than in females and MF density was twice as high in males than females. The regional disease distribution observed at baseline (northern districts with relatively higher prevalence, followed by southern and then eastern having the lowest relative prevalence) appears to have changed slightly in the past five years. In 2010, the southern districts had relatively the highest average prevalence, followed by the average prevalence of eastern districts, and northern districts having relatively the lowest average mf prevalence.

Two studies discuss the regional dynamics for onchocerciasis in Sierra Leone. A study conducted to compare the onchocerciasis situation in forest areas (the northern region) and Savannah areas (the south-east) of the country shows that *O. volvulus* MF prevalence was higher in the forest (71.8%) than in Savannah villages (51.9%). This study also demonstrated that males are more commonly infected with onchocerciasis than females (McMahon *et al.* 1988c). Blacklock who first reported onchocerciasis endemicity in Sierra Leone in 1926 also suggested that the clinical manifestations of onchocerciasis vary within the regions of the country. It was suggested that the eastern region has the forest strain of the *O. volvulus* parasite and that the disease is clinically characterised by low intensity of infection, mild skin disease and relatively lower blindness rates. In the south, there is a mixture of forest and Savannah strains of the parasite with high infection intensity, mild skin disease and relatively higher blindness rate that are sometimes higher than blindness rates recorded for the Savannah area. The northern region has the Savannah strain of the parasite with high infection intensity, mild skin disease, and relatively high blindness rate ((Blacklock 1926; Gbakima and Sahr 1996). However, it appears that after five years of effective treatment this pattern has changed with northern districts now having relatively the lowest average MF prevalence compared to the eastern and southern districts.

For the age groups, the lowest microfilaridermia prevalence and density were observed within the age group 1-9 years, followed by the age group 10-19 years and was highest for the age group 40-49 years. This also tends to indicate that onchocerciasis transmission to children may have reduced even further with five years of treatment and probably also due to previous onchocerciasis control efforts before NOCP activities started, although it may also be because children spend less time at the river banks and may be less open to bites of the black fly. A previous study had shown that children from onchocerciasis-infected mothers are more likely to be infected (Kirch *et al.* 2003). Another study showed that after 4 years of MDA children 5-9 years who had not received any treatment for *O. volvulus* infection in the Mbam valley of Cameroon had low infection rate compared to older children because of reduced exposure to onchocerciasis as a result of the overall reduction in MF prevalence and density within the community (Pion, Clement and Boussinesq 2004). One can, therefore, conclude that transmission of onchocerciasis to children in Sierra Leone has been low because females are

less infected than men and that overall reduction in MF prevalence and MF density has reduced exposure of children to the disease.

Similar studies to determine onchocerciasis MF prevalence and MF density have been reported in Nigeria and Cameroon (Opara and Fagbemi 2008; Kamga *et al.* 2011; Sam-Wobo *et al.* 2012). Epidemiological studies conducted to determine onchocerciasis MF prevalence and MF density after repeated annual treatment with ivermectin in 11 selected communities along the Ogun River System, southwest Nigeria, showed that onchocerciasis prevalence ranged from 19.1% to 45.6% while community MF density ranged from 0.11 to 1.03mf/snip (Sam-Wobo *et al.* 2012). With over 60% baseline onchocerciasis MF prevalence in Fundong health district of Cameroon, the MF prevalence reduced to 3.5% after six rounds of continuous MDA using the CDTI strategy (Kamga *et al.* 2011). After seven years (1995-2001) of ivermectin treatment for onchocerciasis in 3 onchocerciasis-endemic villages of the Etung Local Government Area of Lower Cross River Basin, Nigeria, microfilaridermia prevalence reduced from 63.3% at baseline to 39.3% and community MF density dropped from 7.11 to 2.31mf/snip. It was also noted in this study that males were significantly more infected with *O. volvulus* than females and MF prevalence and intensity increased with age. Adults between the age group of 21 and 50 years accounted for 52.7% of MF-positive cases (Opara & Fagbemi 2008).

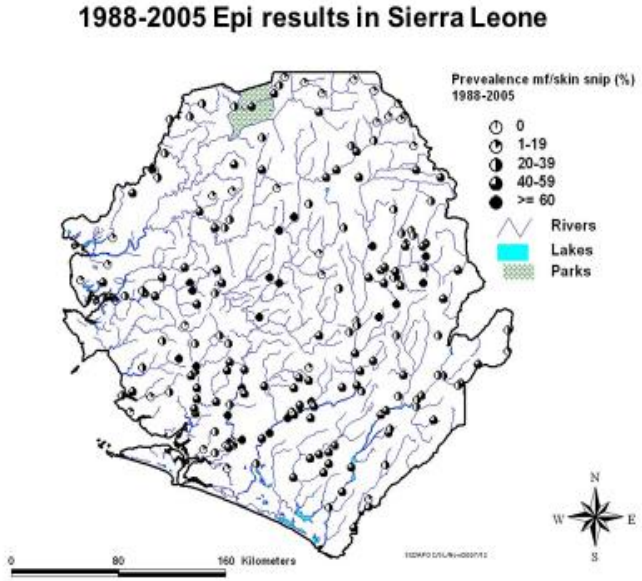
There are certain limitations for this analysis. The baseline data used for the analysis were obtained over a long period. Some villages were studied in 1988, others in 1989, then there was a break of about 11 years before more villages were studied in 2002, 2003, 2004 and 2005. It is possible the epidemiological situation may have changed in villages studied in 1988 and 1989. However, this was addressed during the selection of sentinel villages. The villages selected first were those with more recent data (2002-2005). Villages with older data (1988, 1989) were only selected when more recent data (2002-2005) were not available for a district. This way it was ensured that selection of the villages was based on more recent data. Convenient sampling was used to get participants in the studies and only those within the targeted villages who voluntarily accepted to participate in the study were included. Therefore, the number of participants for the study varied significantly between districts and villages. However, this sampling method is in line with current WHO/APOC guidelines for surveys to

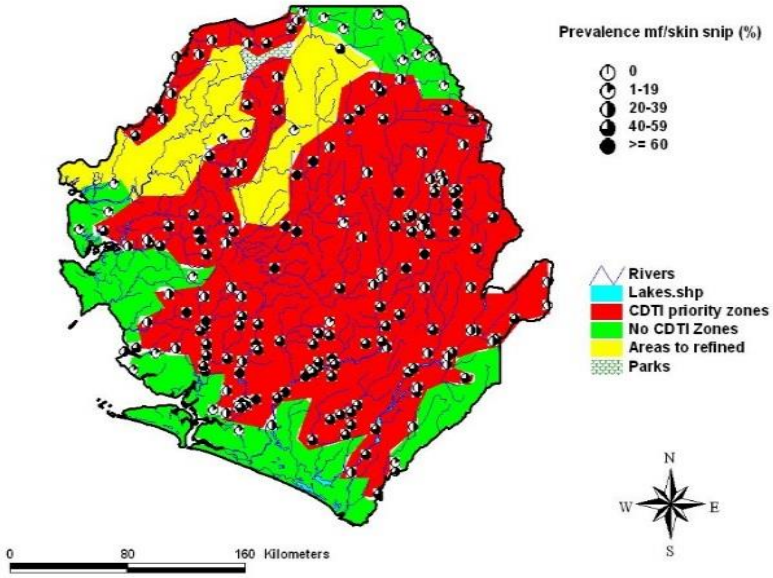
monitor the impact of onchocerciasis treatment on onchocerciasis MF prevalence and density. In the 2010 evaluations, only children ≥ five years of age were studied while children between 1 and 5 years were studied at baseline. This has resulted in fewer children 1-9 years examined in the 2010 evaluation. The decision not to study children below 5 years of age was made based on the high refusal rate observed in communities during baseline studies among parents when children below 5 years were to be studied. This decision has proven to be more ethical and will be maintained until a better methodology is developed for onchocerciasis evaluation that does not create so much fear in children and parents for their children. Another possible limitation of this study is that the focus for onchocerciasis has shifted from control to elimination. This means that areas previously considered hypo-endemic for onchocerciasis with <40% MF prevalence should be evaluated to know the impact of treatment. With this paradigm shift, it will be worthwhile to add control sites in future evaluations selected from hypo-endemic areas so the impact of treatment in all areas can be monitored.

CONCLUSION

There was a significant reduction of onchocerciasis MF prevalence and MF density across the 12 rural onchocerciasis-endemic districts of Sierra Leone after five annual MDA. Treatment coverage over this period also demonstrated that there is good MDA adherence. The results show that the onchocerciasis elimination programme in Sierra Leone is on course to reach the objective of eliminating onchocerciasis in Sierra Leone by the year 2025. However, MDA must continue in all onchocerciasis-endemic districts with good treatment coverage to reach the recommended number of rounds using positive experiences and lessons learnt from other countries.

Figure 7: Baseline (1988-2005) point prevalence and CDTI zones for onchocerciasis in Sierra Leone (APOC 2005*)





*** Maps were prepared for the NOCP in 2005 by APOC.**

Figure 8: Maps showing point onchocerciasis mf prevalence for the 39 sentinel sites at baseline and in 2010 after five MDA rounds

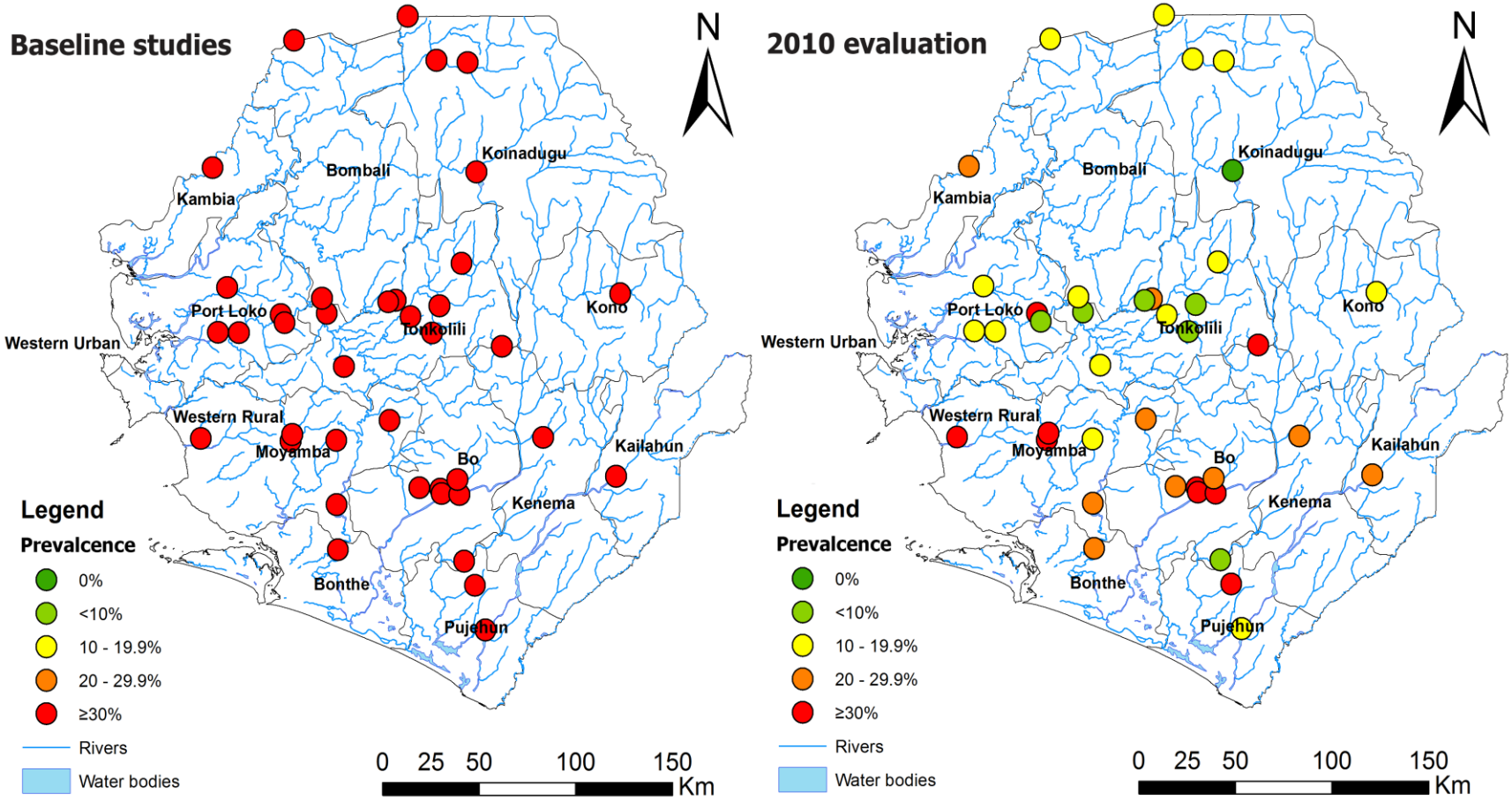


Table 4: Summary results of annual MDA carried out for onchocerciasis elimination in Sierra Leone 2005– 2009

	2005					2006					2007					2008					2009				
	Population		Treatment			Population		Treatment			Population		Treatment			Population		Treatment			Population		Treatment		
Districts	Eligible	Total	No. treated	Epid Cov	Prog Cov	Eligible	Total	No. treated	Epid Cov	Prog Cov	Eligible	Total	No. treated	Epid Cov	Prog Cov	Eligible	Total	No. treated	Epid Cov	Prog Cov	Eligible	Total	No. treated	Epid Cov	Prog Cov
Bo	201218	251523	193861	77.1	96.3	205955	257444	181006	70.3	87.9	246697	308371	219651	71.2	89.0	267153	333941	235427	70.5	88.1	291059	363824	268222	73.7	92.2
Bombali	197106	246383	170035	69.0	86.3	201746	252183	178195	70.7	88.3	208794	260993	197105	75.5	94.4	226285	282856	209378	74.0	92.5	316656	395820	303593	76.7	95.9
Bonthe	39626	49533	32347	65.3	81.6	40559	50699	40367	79.6	99.5	44830	56038	43493	77.6	97.0	72086	90108	59373	65.9	82.4	76100	95125	70821	74.5	93.1
Kailahun	178800	223499	91874	41.1	51.4	183009	228761	167859	73.4	91.7	186791	233489	177950	76.2	95.3	228464	285580	210281	73.6	92.0	199581	249476	193931	77.7	97.2
Kambia	84967	99961	84914	84.9	99.9	86967	102314	85622	83.7	98.5	84788	105985	82802	78.1	97.7	102602	128253	95393	74.4	93.0	100700	125875	84244	66.9	83.7
Kenema	170033	212541	117021	55.1	68.8	174036	217545	171765	79.0	98.7	175058	218823	164789	75.3	94.1	230055	287569	210935	73.4	91.7	183729	229661	172236	75.0	93.7
Koinadugu	111040	138800	85785	61.8	77.3	113654	142068	101258	71.3	89.1	111862	139827	105067	75.1	93.9	153577	191971	141749	73.8	92.3	157016	196270	142405	72.6	90.7
Kono	139026	173782	108005	62.1	77.7	142298	177873	131556	74.0	92.5	138281	172851	135745	78.5	98.2	141170	176463	127063	72.0	90.0	99605	124506	93520	75.1	93.9
Moyamba	150661	188327	101658	54.0	67.5	154208	192760	140934	73.1	91.4	160683	200854	149242	74.3	92.9	169114	211392	162675	77.0	96.2	162347	202934	156181	77.0	96.2
Port Loko	143167	168432	139170	82.6	97.2	137918	172397	134917	78.3	97.8	163872	204840	157423	76.9	96.1	127351	159189	106236	66.7	83.4	175292	219115	156077	71.2	89.0
Pujehun	120406	150508	91277	60.6	75.8	123241	154051	109061	70.8	88.5	158146	197682	145323	73.5	91.9	171640	214550	155988	72.7	90.9	186227	232784	180047	77.3	96.7
Tonkolili	188831	236038	101379	43.0	53.7	193276	241595	184953	76.6	95.7	202266	252833	192167	76.0	95.0	207034	258792	177206	68.5	85.6	272062	340078	256268	75.4	94.2
TOTAL	1724882	2139327	1317326	61.6	76.4	1756868	2189690	1627493	74.3	92.6	1882069	2352586	1770757	75.3	94.1	2096531	2620664	1891704	72.2	90.2	2220374	2775468	2077545	74.9	93.6

*Geographic coverage of villages for onchocerciasis was 100% in all 12 districts over the five years (2005-2009).

Table 5. Crude Onchocerciasis microfilaraemia prevalence and density by district, sex, and age groups in Sierra Leone after five annual rounds of MDA														
	Baseline survey				2010 Epidemiological Evaluation				Percentage reduction (%)			Significance test (P-values)		
	No of persons examined for MF	MF prev (%)	Pop mf density (mf/snip	Positive-only MF density (mf/snip)	No of persons examined for MF	Percentage MF prevalence (95% CI)	Population MF density (mf/snip) (95% CI)	Positive-only MF density (mf/snip) (95% CI)	MF prev	Pop MF density	Positive-only MF density	MF prev	Population MF density	Positive-only MF density
Overall	7116	53.09	15.33	28.87	5621	21.12 (20.07-22.20)	1.75 (1.48 - 2.02)	8.29 (7.07 - 9.50)	60.22	88.58	71.29	0.0000	0.0000	0.0000
By district														
Bo	1499	54.30	18.91	34.82	1079	25.77 (23.24-28.46)	2.95 (2.11 - 3.80)	11.46 (8.40 - 14.53)	52.55	84.40	67.09	0.0000	0.0000	0.0000
Bombali	368	57.88	16.85	29.10	494	16.19 (13.21-19.70)	1.58 (0.86 - 2.29)	9.72 (5.71 - 13.72)	72.02	90.62	66.60	0.0000	0.0000	0.0000
Bonthe	180	40.56	7.00	17.25	165	26.67 (20.51-33.16)	3.05 (0.41 - 5.68)	11.42 (1.71 - 21.13)	34.25	56.43	33.80	0.0090	0.0040	0.2470
Kailahun	183	49.73	12.06	24.25	118	23.73 (16.96-	2.01 (0.47 - 3.55)	8.46 (2.31 - 14.62)	52.28	83.33	65.11	0.0000	0.0000	0.0010

						32.16)								
Kambia	155	61.94	17.80	28.73	98	23.47 (16.18-32.76)	1.04 (0.43 - 1.65)	4.41 (2.24 - 6.58)	62.11	94.16	84.65	0.0000	0.0000	0.0000
Kenema	286	45.12	6.51	14.42	101	20.79 (14.02-29.70)	1.35 (0.18 - 2.51)	6.48 (1.09 - 11.86)	53.90	79.26	55.06	0.0000	0.0000	0.2170
Koinadugu	168	58.33	18.38	31.51	58	6.90 (2.71-16.43)	0.05 (0.00 - 0.11)	0.75 (0.00 1.55)	88.18	99.73	97.62	0.0000	0.0000	0.0050
Kono	1105	39.01	14.63	37.48	521	9.02 (6.85-11.79)	0.32 (0.18 - 0.46)	3.53 (2.31 - 4.75)	76.87	97.81	90.58	0.0000	0.0000	0.0000
Moyamba	1055	58.20	12.06	20.74	988	29.96 (27.19-32.89)	1.64 (1.27 - 2.01)	5.46 (4.35 - 6.58)	48.52	86.40	73.67	0.0000	0.0000	0.0000
Port Loko	653	57.12	13.83	24.21	738	26.02 (22.98-29.30)	3.10 (1.80 - 4.40)	11.91 (7.12 - 16.71)	54.45	77.58	50.81	0.0000	0.0000	0.0000
Pujehun	560	53.57	9.84	18.36	348	7.76 (5.39-11.03)	0.60 (0.06 - 1.14)	7.76 (1.03 - 14.49)	85.52	93.90	57.73	0.0000	0.0000	0.0020
Tonkolili	904	60.40	22.09	36.50	913	16.10 (13.86-18.63)	0.67 (0.43 - 0.91)	4.16 (2.81 - 5.50)	73.34	96.97	88.60	0.0000	0.0000	0.0000

By sex														
Male	3461	55.19	21.11	38.16	2805	24.49 (22.94-26.12)	2.55 (2.04 - 3.06)	10.40 (8.43 - 12.36)	54.24	87.92	72.75	0.0000	0.0000	0.0000
Female	3655	51.11	9.94	19.38	2816	17.76 (16.39-19.21)	0.96 (0.77 - 1.15)	5.40 (4.40 - 6.40)	64.12	90.34	72.14	0.0000	0.0000	0.0000
Age groups														
1-9	2182	11.05	0.91	8.24	1930	1.71 (1.22-2.39)	0.04 (0.02 - 0.06)	2.47 (1.49 - 3.45)	82.55	95.60	70.02	0.0000	0.1680	0.0200
10-19	1317	50.57	6.91	13.67	889	16.09 (13.82-18.65)	0.80 (0.51 - 1.08)	4.94 (3.31 - 6.58)	66.40	88.42	63.86	0.0000	0.0000	0.0000
20-29	780	78.21	19.94	25.50	648	38.27 (34.61-42.07)	3.68 (2.48 - 4.88)	9.58 (6.58 - 12.58)	49.09	81.54	62.43	0.0000	0.0000	0.0000
30-39	824	80.95	28.88	35.64	624	37.18 (33.48-41.04)	3.49 (2.34 - 4.64)	9.38 (6.43 - 12.33)	52.41	87.92	73.68	0.0000	0.0000	0.0000

40-49	735	82.31	35.94	43.66	542	38.75 (34.74-42.91)	4.09 (2.65 - 5.54)	10.56 (6.99 - 14.13)	51.20	88.62	75.81	0.0000	0.0000	0.0000
50-59	575	81.39	30.37	37.31	416	37.02 (32.52-41.76)	2.61 (1.15 - 4.06)	7.04 (3.18 - 10.89)	52.55	91.41	81.13	0.0000	0.0000	0.0000
≥60	684	76.17	21.58	28.34	566	29.33 (25.73-33.21)	2.10 (1.47 - 2.73)	7.17 (5.22 - 9.12)	59.74	90.27	74.70	0.0000	0.0000	0.0000

CHAPTER 4: LYMPHATIC FILARIASIS MAPPING BY IMMUNOCHROMATOGRAPHIC TEST CARDS AND BASELINE MICROFILARIA SURVEY PRIOR TO MASS DRUG ADMINISTRATION IN SIERRA LEONE

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ABSTRACT

Background

National mapping of LF was conducted using ICT in 2005 to determine endemicity and geographic spread of the disease. A baseline microfilaria survey was then conducted to determine LF prevalence and microfilaria intensity.

Methods

In 2005 1,982 persons of 15 years and over from 14 health districts were selected and fingertip blood samples were tested with ICT cards. In 2007-8 blood samples were taken between 10pm and 2am and examined for MF from 9,288 persons from 16 sentinel sites representing each district and two additional sites for districts with populations over 500,000 (Bo and Kenema).

Results

The overall LF prevalence by ICT cards was 21% (males 28%, females 15%). All districts had a prevalence of *W. bancrofti* antigen > 1%. Distribution of LF prevalence showed a strong spatial correlation pattern with high prevalence in a large area in the northeast gradually decreasing to a relatively low prevalence in the south-west coast. High prevalence was found in the northeast, Bombali (52%), Koinadugu (46%), Tonkolili (37%) and Kono (30%). Low prevalence was found in the south-west, Bonthe (3%) and Pujehun (4%). The MF prevalence was higher in the northeast: Bombali, 6.7%, Koinadugu 5.7%, Port Loko 4.4% and Kono 2.4%. Overall there was a significant difference in MF prevalence by gender: males 2.9%, females 1.8% ($p = 0.0002$) and within districts in Kailahun, Kono, Port Loko, Moyamba and Koinadugu (all $p < 0.05$). The MF prevalence was higher in people >20 years (2.5%) than in people ≤20 years (1.7%) ($p=0.043$). The overall arithmetic mean MF density was 50.30mf/ml among MF-positive individuals and 1.19mf/ml in the population examined which varied significantly between districts.

Conclusions

The ICT results showed that LF was endemic nationwide and that preventive chemotherapy (PC) was justified across the country. Both the ICT and microfilaraemia surveys found that prevalence was greater in males than females. The increase in microfilaraemia prevalence by age was evident when grouped as ≤20 versus >20 years demonstrating early exposure. Baseline LF microfilaria load will be used to monitor PC programme progress.

BACKGROUND

LF is a chronic, debilitating disease that affects people in tropical and sub-tropical areas of Asia, Africa, the Western Pacific and some areas of the Americas. LF is caused by the parasites *W. bancrofti* or *B. malayi* and transmitted by *Culex*, *Anopheles* and other mosquitoes (Ottesen 1997; Molyneux and Taylor 2001; Bockarie and Molyneux 2009). An estimated 90% of all LF cases worldwide and all cases in Africa are infections with the parasite *W. bancrofti*. The main LF vectors in West Africa are the *Anopheles* mosquitoes (Kelly-Hope *et al.* 2006).

Over 120 million people in over 80 countries worldwide in the tropics and sub-tropics and over 40 million people in Africa are infected with the parasite (Ottesen 2006; Ottesen *et al.* 2008). Bancroftian filariasis, which is prevalent in Africa, is endemic in rural as well as urban communities thriving within poor communities (Dunyo *et al.* 1996b; Kelly-Hope *et al.* 2006; Okon, Ibor and Opara 2010).

LF has a wide range of clinical manifestations from acute attacks of filarial fever, chronic conditions such as hydroceles, lymphoedema, elephantiasis of limbs, and enlarged breasts, to kidney damage, thus causing great morbidity and disability for those affected (WHO 1992). Filariasis is one of the most common causes of permanent disability worldwide creating the highest disease burden in terms of DALYs among tropical diseases (Ottesen *et al.* 2008). Those affected also suffer psychosocial stigmatisation and economic suffering as it can lead to job loss or inability to work. The disease is therefore a major cause of poverty as it creates economic burden for those affected, their dependants, their communities and the country as a whole (Dunyo *et al.* 1996b; Huppatz *et al.* 2009; Mishra and Bhadoriya 2009; Ruberanziza *et al.* 2009; Okon, Ibor and Opara 2010).

In 1993 the International Task Force on Disease Eradication identified LF as one of six diseases that could be eradicated, which led the World Health Assembly in 1997 to pass resolution WHA 50.29 calling for the elimination of LF as a public health problem in the world by 2020. By 2000, the GPELF was launched by WHO to support LF elimination programmes in endemic countries and a Global Alliance to Eliminate Lymphatic Filariasis (GAELF) was established as a partnership

of countries, NGDOs, academic and research institutions, pharmaceutical companies, international organizations, and advocacy and resource mobilization partners to support the GPELF (Ottesen *et al.* 1997; Mohammed *et al.* 2006; Bockarie and Molyneux 2009; Ruberanziza *et al.* 2009; Addiss 2010).

Circulating MF are responsible for transmission, therefore transmission can be broken/interrupted by reducing the number of people with microfilaraemia within affected communities through annual MDA for 4-6 years to ≥80% of the entire at-risk population which can reduce microfilaraemia to zero or close to zero (Gyapong *et al.* 2005; WHO 2008). Before MDA is started in a country, implementation units to be targeted should be determined through a rapid assessment study and also baseline data on LF MF level should be obtained to monitor the effectiveness of MDA. There are already countries that have succeeded in eliminating the disease (Cape Verde, China, Costa Rica, Solomon Islands, South Korea, Suriname, and Trinidad and Tobago) using a combination of strategies that include vector control and single annual doses of 2-drug treatments (albendazole together with ivermectin or diethylcarbamazine) (Gyapong *et al.* 2005; WHO 2008). The currently preferred strategy for LF elimination recommended by WHO is the preventive chemotherapy using the available drugs (WHO 2000a,b; WHO 2006). The GPELF has been strengthened by the donation of albendazole by GlaxoSmithKline and continued donation of ivermectin by Merck & Co. Inc. (Linehan *et al.* 2011). In Sierra Leone, reports from health facilities indicated endemicity of LF in all districts, and in 1996, a study in Moyamba district using the thick blood film method showed MF prevalence: 10.2% with 36.5% clinical manifestation (26.6% hydroceles and 9.4% lymphoedema/elephantiasis of the lower extremities) (Gbakima and Sahr 1996).

In 2004, a country profile of communicable diseases in Sierra Leone developed by WHO, quoting an anonymous 1999 study in 55 sites including the capital Freetown, showed that 14.5% of people tested for CFA of *W. bancrofti* were positive (WHO 2004). The Northern Province had the highest prevalence (19.6%), followed by Western Area (12.8%), Eastern Province (12.7%) and Southern Province (10.9%) (WHO 2004). Infection was noted in children, and this indicated ongoing transmission and infections acquired early in life.

In preparation for the national LF elimination programme, national mapping was conducted in 2005 using ICT cards. The national LF elimination programme started when the MOHS, Sierra Leone in consultation with WHO decided to conduct the integrated management of onchocerciasis, LF, schistosomiasis, soil-transmitted helminths and trachoma, and the existing NOCP became National NTDP in 2006 (Hodges *et al.* 2011).

Based on the mapping results, the implementation units (districts) for LF MDA were determined, and national baseline data on MF level were collected pre-MDA. The current paper presents the distribution and the level of infection of LF in Sierra Leone which formed the base for the national LF elimination programme.

METHODS

Ethics statement

The studies were conducted by the National NTDP of the MOHS, Sierra Leone. Ethical approval for data collection was obtained from the Ethics Committee of the MOHS and upon arrival at the randomly selected communities the investigating team met with the community leaders and explained the nature of their work. All participants aged 15 years or above in each site were eligible for inclusion without discrimination on gender, social status, religion or ethnicity. People participated in the studies after informed consent was verbally obtained and recorded by the team leader, as literacy rates are low in Sierra Leone. Data collection was conducted such that participants remained anonymous during data entry and analysis. No individual identity can be revealed upon publication.

National mapping of LF with ICT cards in 2005

Although previous studies and clinical records indicated that LF was prevalent particularly in the north, detailed data on distribution and level of risk throughout the country was not available, and all districts including the Western urban district and Western rural district were included in the mapping. Thirty-four (34) communities were randomly selected from all districts in consultation with WHO/AFRO with each district having at least one community selected. Participants who were 15 years of age or above were selected for the antigenaemia

study using ICT cards (WHO, 2006). During the survey, ICT cards were kept overnight at 8°C in district cold rooms for the expanded programme on immunisation and during the day the cards were transported in cold boxes and vaccine carriers with ice packs. The left index finger was pricked with a sterile lancet after cleaning with cotton wool soaked with spirit and 100µl blood collected and applied straight to the ICT cards. The survey teams were trained to read the results of the ICT cards at exactly 10 minutes after application, according to the manufacturer's instructions. No late reading of ICT cards was reported by the survey teams. Due to limited resources and the high sensitivity and specificity of the ICT (WHO, 2005), 50 persons were sampled in each randomly selected community and if a positive case was identified the sampling was complete and the teams moved on to the next site. If in the first 50 samples there was no positive case found, a further 50 persons were sampled bringing the total to 100 per site (WHO, 2005). Training of technicians in the use of the ICT cards to detect *W. bancrofti* antigen and data recording took place in Makeni and York Village, Western urban district. Three teams of three technicians (two for specimen collection and one for reading and recording of results) worked with a village volunteer (usually a school teacher) who served as registrar. Data included name, sex, village, chiefdom and district. A total of 1,982 people were tested; males 904 (45.6%) and females 1,078 (54.4%).

Baseline microfilaraemia data collection before MDA

Sampling was conducted in accordance with WHO guidelines (WHO 2005) of two sentinel sites per implementation unit (district for Sierra Leone) with a population of one million people. Ten of the fourteen health districts of Sierra Leone have a population below 500,000 and one sentinel site per district was selected representing a population ≤ 500,000. One sentinel site each was selected for Western rural district (232,294) and Western urban district (901,953). Bo district (Bo Town: Bo District, 222,561: 347,610) and Kenema district (Kenema Town: Kenema District, 188,869: 377,067) had a population above 500,000 and two sentinel sites were selected in these two districts, making a total of 16 sites. Communities/villages that showed the highest ICT prevalence in each district in 2005 were selected as MF sentinel sites (WHO 2005). The survey was performed in two phases according to funding availability: Bombali, Koinadugu, Kambia, Kono, Kailahun and Pujehun in 2007 and Tonkolili, Port Loko, Kenema, Bonthe, Moyamba, Bo, Western urban district and Western Rural district in 2008. Pre-

sensitization was carried out before the survey in each site. Five hundred participants of 15 years of age or above were recruited per site. In sites with less than 500 people selected, extra participants were recruited in neighbouring villages. To ensure the standardisation of activities and data, two-day practical training was performed before the study started for all technicians. Fingertip blood was collected between 10pm and 2am from each volunteer. A 60µl blood sample was collected, smeared gently and uniformly in a circular shape and allowed to air dry at room temperature for 12-24 hours. The following day the dried smear was dehaemoglobinized by flooding with distilled water for three-five minutes, air dried again, fixed with methanol for 30-60 seconds, stained with Giemsa for ten minutes then examined for MF under a light microscope by experienced examiners. Positive findings of MF were recorded, and individual MF density of infection was calculated and expressed as the number of MF per ml of blood (mf/ml) (26-29). A total of 9,288 night blood samples were examined. The mean age (± standard deviation) of the subjects examined was 37.7 ± 17.04 years (males: 37.27 ± 17.6, females: 38.12 ± 16.5). For quality control, all positive slides and 10% of the negative slides were preserved and examined by an experienced researcher.

Statistical analysis

Results were entered into Epi-Info version 3.5.2 and analysed in SPSS (IBM, Version 19). Prevalence of positive circulating LF antigen or microfilaraemia was calculated. The 95% CIs for prevalence were calculated using the Wilson score method without continuity correction (Newcombe 1998). The arithmetic mean MF density of infection with 95% CIs was calculated using the total population examined and the positive samples only (WHO 2005). Chi-square test was used to compare the differences in prevalence and Kruskal-Wallis test was used to compare the differences in MF density. Correlation analysis was conducted for the two sets of data (ICT and microfilaraemia prevalence) and the significance of the correlation tested (Trochim 2006). The coordinates of each sample site were recorded using hand-held units of global positioning system (site coordinates available upon request). Spatial analysis of the LF antigenaemia prevalence (ICT card data) was conducted using the kriging method in the Geostatistical Analyst Extension of ArcGIS version 10 (ESRI, Redlands, USA). Spatially smoothed contour maps of the interpolated prevalence of antigenaemia and the predictive probability for the ICT prevalence of greater than 1% were produced (Zoure *et al.* 2011).

RESULTS

Distribution of LF in Sierra Leone

Table 6 summarises the results of the survey using ICT cards for each district. All the districts of Sierra Leone were found to be endemic for LF with a prevalence of ICT positive tests ≥1%. Point prevalence for each survey site was shown in Figure 9. Among 34 sites surveyed, only one site in Bonthe district was shown to be negative. The median prevalence across the 34 sites was 20% ranging from 0% to 68% (inter-quantile range: 11.7-31%). Overall ICT positive prevalence was 20.8%. High prevalence was found in the northeast part of the country (Bombali 52%, Koinadugu 46%, Tonkolili 37% and Kono 30%). Relatively low prevalence was found in the south-west coastal districts (Bonthe 3.1% and Pujehun 4.4%). There were significantly more positive ICT tests in males (27.54%, 95% CI: 24.7-30.6%) than in females (15.2%, 95% CI: 13.2-17.5%) ($p < 0.00001$). Detailed analysis of prevalence among different age groups was not carried out as detailed age information was not recorded for the ICT card survey.

Microfilaraemia prevalence and density

Overall 9,288 night blood samples, male 4,335 (46.7%) and female 4,953 (53.3%), were examined for MF as shown in Table 6. There were less than 5% false positives and no false negative slides. All positive slides were reexamined, and three were redefined as artefacts. No MF of *Mansonella perstans* was detected.

In total, 220 persons (2.4%, 95% CI: 2.1-2.7%) had a positive blood smear and there was significantly higher MF prevalence in males 3.0% (95% CI: 2.6-3.6%) versus females 1.8% (95% CI: 1.4-2.2%) ($p=0.0002$). Age distribution of the MF prevalence is also shown in Table 6.

There was a significant difference in MF prevalence among age groups with higher prevalence in persons of 41-50 years ($p=0.041$). The point prevalence of microfilaraemia for each site is shown in Figure 10. There was a significant correlation between the MF prevalence and the ICT card prevalence ($r=0.86$, $p < 0.05$). In line with the ICT results, the MF prevalence (95% CI) was higher in the northeast part of the country: Bombali, 6.9% (5.3-8.8%), Koinadugu 5.7% (4.1-

7.7%), Port Loko 4.4% (2.9-6.6%), Kailahun 2.6% (1.6-4.1%) and Kono 2.4% (1.6-3.6%). No MF was found in persons examined in the Western urban district and Pujehun.

The overall arithmetic mean MF density was 50.30 mf/ml (95% CI: 39.89-60.71 mf/ml) among MF-positive individuals, and 1.19mf/ml (95% CI: 0.90-1.48 mf/ml) in the population examined (Table 6). There was significantly higher MF density in the male population than in the female population ($p<0.0001$). There was also a significant difference in MF density among age groups in the total population examined ($p=0.041$). There was no significant difference in MF density by sex or age groups of infected persons ($p>0.1$).

Spatial prediction of LF distribution

The spatial analysis of the ICT card data showed a strong spatial correlation pattern as the semi-variance in prevalence data in relation to the distance between survey sites (Figure not shown). The predicted spatial distribution of LF by kriging is shown in Figure 11. This shows a widespread distribution of LF prevalence with a clear geographical distribution pattern in Sierra Leone: high (>40%) in a large area spanning the northeast of the country with two clusters of predicted prevalence of over 50%, gradually decreasing towards the southwest, and ending with a low prevalence (<5%) in the coastal part of Bonthe and Pujehun districts. Figure 12 shows the predicted probability of the LF prevalence being over 1%, which shows high probability throughout the country with only two small clusters of relatively low probability (<50%) in Bonthe and Moyamba.

DISCUSSION

All districts in Sierra Leone were endemic with LF and qualified for MDA. Distribution of LF prevalence showed a strong spatial correlation pattern with high prevalence in a large area in the north-east gradually decreasing to relatively low prevalence in the south-west coast. ICT results showed two distinct patterns: males were more infected than females and districts in the north-east part of the country and had a higher prevalence than other districts. The ICT results obtained in this study were higher than in 2004, but the same pattern of a higher prevalence for CFA in the north than all other regions was repeated (WHO 2004). Three distinct

patterns were also noted in the microfilaraemia survey: microfilaraemia was higher in males (3.0%) versus females (1.8%), increased with age in the population peaking at 41-50 years, and showed a higher prevalence in the northeast than in other parts of the country. In two districts (Western urban district and Pujehun), microfilaraemia was not identified among the subjects examined, even though ICT prevalence was 11.7% and 4.4% respectively.

The MF prevalence was lower than that reported in 1996, but that study was conducted in an area with clearly visible signs of the disease to highlight the seriousness of the problem (Gbakima and Sahr 1996). There were many such areas in the districts where LF signs were clearly visible among the population but in this study, the sites were randomly selected to avoid bias. Therefore, the results of this study were more representative of the MF prevalence in the district population. The results acquired in this study on MF prevalence and MF density/intensity will form the basis for monitoring and evaluation of the effectiveness of MDA in interrupting LF transmission in each district.

Similar patterns are noted for both studies in geographical and sex distribution of the disease, which further strengthens the notion that these results are representative of the actual national picture. The ICT positive prevalence was nine times greater than the MF prevalence. Several authors have reported that ICT positive prevalence, which detects antigen released by adult *W. bancrofti*, can be 3-5 times higher than MF prevalence. People can be infected with the disease and still be amicrofilaraemic, which may explain the zero MF prevalence in Western urban district and Pujehun district in these studies (Braga *et al.* 2003; Weil and Ramzy 2007; Foo *et al.* 2011).

Previous studies demonstrated the impact of long-term treatment with ivermectin alone for onchocerciasis control on LF prevalence and transmission, which showed that in villages treated for many years with ivermectin, LF microfilaraemia prevalence and intensity were significantly lower than in untreated villages (Kyelem *et al.* 2003; Kyelem *et al.* 2005). Antigenaemia rates were significantly higher than microfilaraemia rates generally (Kyelem *et al.* 2003; Kyelem *et al.* 2005). Onchocerciasis was endemic in 12 of 14 health districts in Sierra Leone (Hodges *et al.* 2011). Community-based treatment with ivermectin for the control of

onchocerciasis in Sierra Leone started in the late 1980's but did not reach full geographical coverage due to insecurity at the beginning of the civil war in 1991 and were subsequently suspended in 1994. In 2003, CDTI was introduced but therapeutic coverage was low in the post-conflict setting. In 2005 the NOCP was reorganised, and therapeutic coverage reached the prerequisite ≥ 65% and has been maintained in all endemic districts since (Hodges *et al.* 2011). The relatively low microfilaraemia rates in our study and the difference between antigenaemia rates and microfilaraemia rates may have been due to the ivermectin treatment for onchocerciasis control in Sierra Leone before the surveys were conducted.

The current results are in line with other studies that males have a higher prevalence than females for CFA as well as for microfilaraemia (Murty *et al.* 2004; Mishra and Bhadoriya 2009; Upadhayula *et al.* 2010). The most probable reason for this is that males spend more time exposed to the bites of mosquitoes.

The distribution of MF prevalence increasing with age shown in this study is in line with results of many other studies (Okon, Iboh, Opara 2010; Mishra and Bhadoriya 2009; Foo *et al.* 2011; Murty *et al.* 2004; Upadhayula *et al.* 2010). This emphasises the socio-economic impact of the disease as the age groups affected most are the major workforce in the villages. In Sierra Leone, an estimated 70% of adults are farmers (Koroma, Turay, Moihua 2006), and disability from LF incapacitates those affected and increases poverty, which is a cause for concern as the country is among the poorest in the world and demands appropriate attention for the elimination of the disease. It has been suggested that adults could be more exposed to mosquito bites because of higher relative heat, more carbon dioxide output or simply because they have a relatively greater surface area that can be bitten by mosquitoes (Upadhayula et 2010). Similar studies on antigenaemia and microfilaraemia for *W. bancrofti* have been conducted in other countries that reflected similar gender and age pattern as our studies (Onapa *et al.* 2001; Gyapong *et al.* 2002; Ngwira *et al.* 2007).

There are certain limitations for the current studies. Firstly, children below 15 years were not selected for circulating filarial antigen and for microfilaria according to the WHO guidelines (WHO 2004). The WHO profile for LF in Sierra Leone in 2004 indicated that children were

infected and that the infection could be acquired early in life (WHO 2004). It has been suggested that excluding children below 15 years could bias the studies towards older people, and since it is common knowledge that filariasis infection increases with age, the prevalence might have been over-estimated for the general population compared to other studies that used population-based sampling methodology (Foo *et al.* 2011). While this may have been true in this study, considering the overall global objective is LF elimination, such slight over-estimation of LF prevalence due to the age bias should not have made much difference in terms of MDA decision in Sierra Leone. Secondly, it is recommended that ICT cards be stored at or around 8°C (Ruberanziza *et al.* 2009). Although efforts were made to keep the cards in a cold box during the field work, the relatively poor field conditions in the remote villages may have made it difficult to keep the box cold at all times. In such field conditions, reading every card within the time limit may not have been guaranteed. This may in part explain the higher ICT positive prevalence (9 times greater than the MF prevalence) in the current studies than in other studies (Braga *et al.* 2003; Weil and Ramzy 2007; Foo *et al.* 2011). However, taking both ICT and MF positive prevalence together, there is a strong correlation between the results of the two surveys for the 14 health districts as shown through correlation analysis. Therefore, the results can be considered to be representative of the true LF endemic situation in Sierra Leone.

Based on the information provided by these studies, the national NTDP started LF MDA in 2007 (Hodges *et al.* 2011). Four rounds of MDA with albendazole and ivermectin were delivered in 6 districts, three rounds in seven districts including the Western ruraL district, and two rounds in the Western urban district (Hodges *et al.* 2010). It is hoped that the assessment results will provide tools to evaluate the impact of the MDA and to adjust the course of MDA if necessary.

CONCLUSION

LF mapping using ICT cards was successfully conducted in 2005 in all districts of Sierra Leone which showed that all districts were endemic for LF and qualified for MDA. Baseline data collection with night blood smear was conducted in 2007-08 before MDA, which provided baseline values for MF prevalence and MF density and confirmed LF endemic status

determined by ICT card survey across the country. These surveys provided tools for the NTDP to design and implement MDA and provided the basis for future monitoring and evaluation of the national LF elimination programme.

Table 6: Crude LF prevalence with antigen detection and microfilaraemia tests by district, sex and age group in Sierra Leone						
	Mapping		**Baseline studies**			
	No of persons tested by ICT cards	**Percentage prevalence of antigen positives (95% CI)**	**No of persons examined for MF**	**Percentage prevalence of MF positives (95% CI)**	**Population MF density (mf/ml) (95% CI)**	**Positive-only MF density (mf/ml) (95% CI)**
Overall	1982	20.8 (19.1 - 22.7)	9288	2.4 (2.1 - 2.7)	1.19 (0.90 - 1.48)	50.3 (39.89 - 60.71)
By district						
Bo	173	15.0 (10.5 - 21.1)	1005	2.0 (1.3 - 3.1)	1.97 (0.84 -3.11)	99.17 (58.32 - 140.01)
Bombali	150	52 (44.1 - 59.8)	830	6.9 (5.3 - 8.8)	1.93 (1.28 - 2.57)	28.07 (21.70 - 34.44)
Bonthe	160	3.1 (1.3 - 7.1)	504	1.2 (0.6 - 2.6)	0.83 (0.02 - 1.63)	69.44 (13.68 - 125.21)
Kailahun	110	19.1 (12.8 - 27.4)	624	2.6 (1.6 - 4.1)	2.08 (0.00 - 4.89)	81.25 (0.00 - 195.58)
Kambia	110	15.5 (9.9 - 23.4)	619	2.1 (1.2 - 3.6)	0.97 (0.23 - 1.71)	46.15 (17.04 - 75.27)
Kenema	180	13.3 (9.1 - 19.1)	1016	0.6 (0.3 - 1.3)	0.34 (0.00 - 0.70)	58.33 (4.42 - 112.24)
Koinadugu	200	46 (39.2 - 52.9)	636	5.7 (4.1 - 7.7)	1.99 (0.95 - 3.04)	35.19 (19.83 - 50.54)
Kono	100	30 (21.9 - 39.6)	875	2.4 (1.6 - 3.6)	1.11 (0.37 - 1.84)	46.03 (20.09 - 71.97)
Moyamba	200	10.5 (7.0 - 15.5)	500	1 (0.4 - 2.3)	0.67 (0.00 - 1.36)	66.67 (6.33 - 127.00)
Port Loko	210	20.5 (15.6 - 26.4)	500	4.4 (2.9 - 6.6)	3.53 (1.48 - 5.59)	80.30 (44.49 - 116.12)
Pujehun	160	4.4 (2.1 - 8.8)	624	0 (0 - 0.6)	-	-
Tonkolili	100	37 (28.2 - 46.8)	500	2.4 (1.4 - 4.2)	0.63 (0.24 - 1.03)	26.39 (17.99 - 34.79)
WA Rural	69	7.3 (3.1 - 15.9)	500	1.2 (0.6 - 2.6)	0.33 (0.01 - 0.65)	27.78 (6.60 - 48.96)
WA Urban	60	11.7 (5.8 - 22.2)	555	0 (0 - 0.7)	-	-

By sex						
Male	904	27.5 (24.7 - 30.6)	4335	3.0 (2.6 - 3.6)	1.66 (1.11 - 2.20)	54.42 (38.81 - 70.02)
Female	1078	15.2 (13.2 - 17.5)	4953	1.8 (1.4 - 2.2)	0.78 (0.52 - 1.04))	44.13 (32.50 - 55.76)
By age group (yrs)						
15-20	-	-	1873	1.8 (1.3 - 2.5)	0.78 (0.38 - 1.19)	44.44 (26.37 -62.52)
21-30	-	-	2019	2.6 (2.0 - 3.4)	1.77 (0.73 - 2.80)	68.59 (31.79 -105.39)
31-40	-	-	1830	2.4 (1.8 - 3.2)	1.01 (0.55 - 1.47)	43.02 (27.55 -58.50)
41-50	-	-	1404	3.4 (2.5 - 4.4)	1.60 (0.94 - 2.27)	47.87 (32.75 - 62.99)
>50	-	-	2162	2.1 (1.6 - 2.8)	0.89 (0.49 - 1.30)	42.96 (27.40 - 58.53)

Figure 9: Geographical distribution of LF point prevalence by circulating antigen detection with ICT cards according to survey locations in Sierra Leone

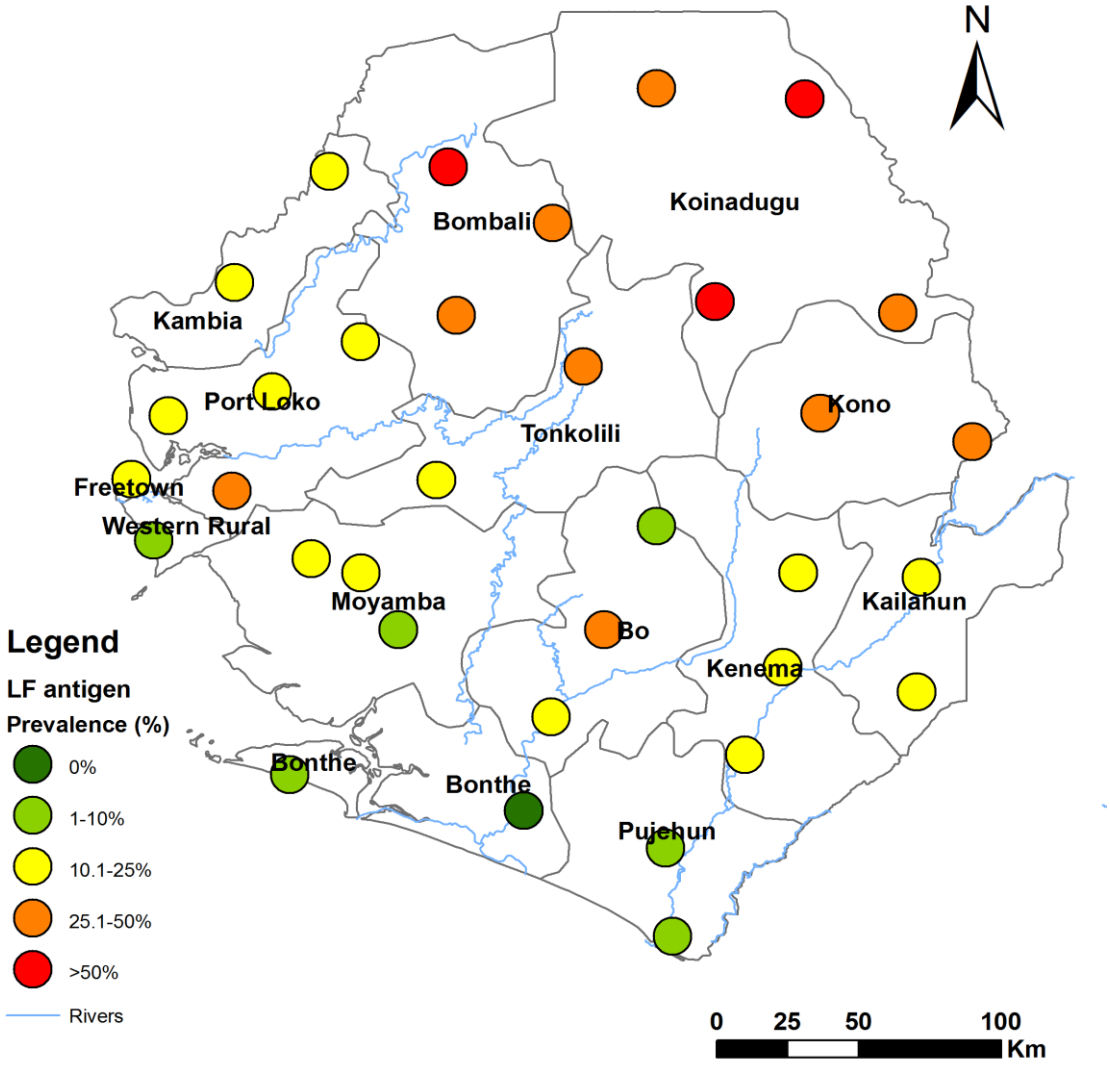


Figure 10: Geographical distribution of LF point prevalence by MF detection and point MF density according to survey locations in Sierra Leone

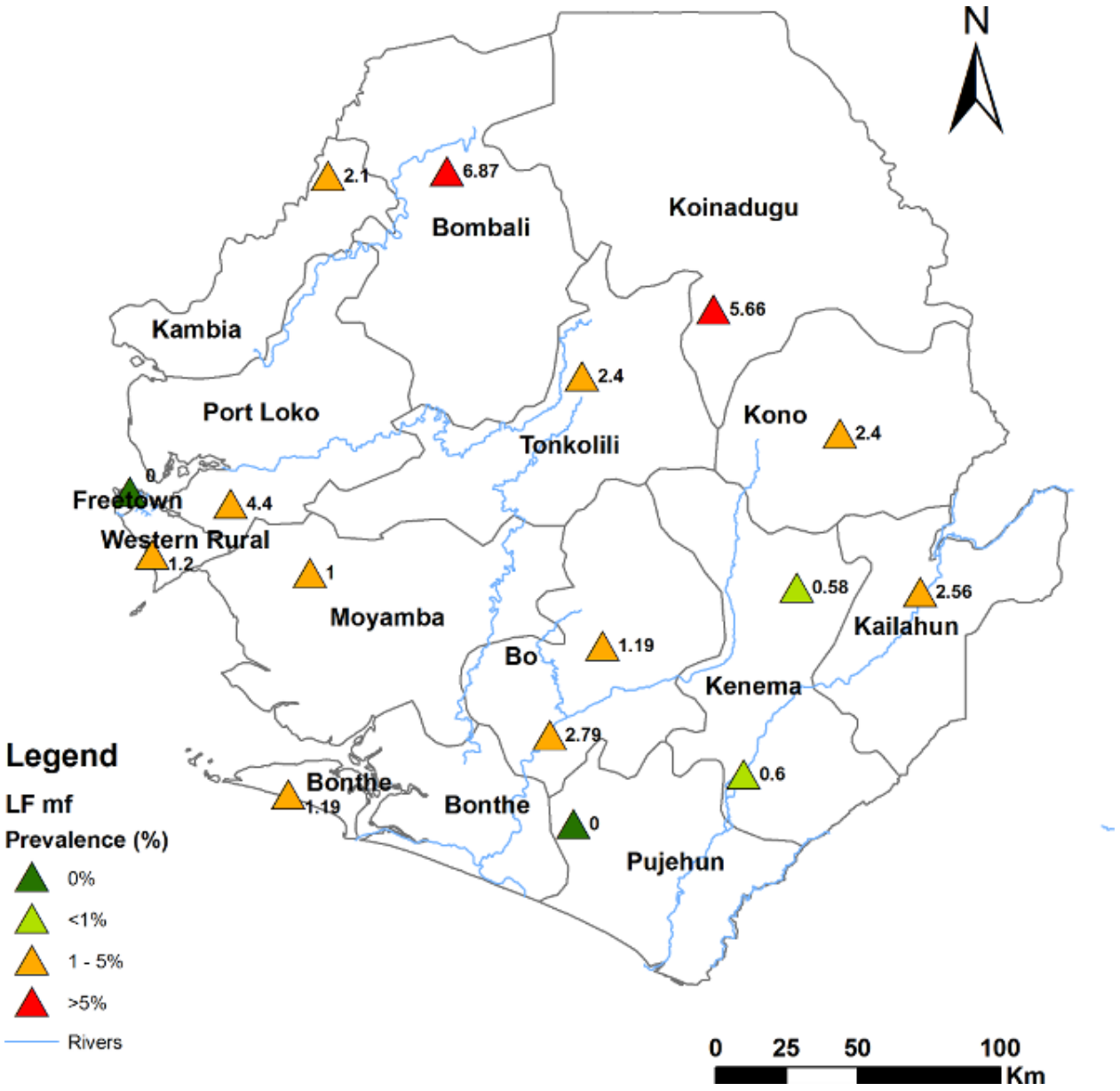


Figure 11 Spatially smoothed contour map of predicted LF prevalence by ICT cards in Sierra Leone.

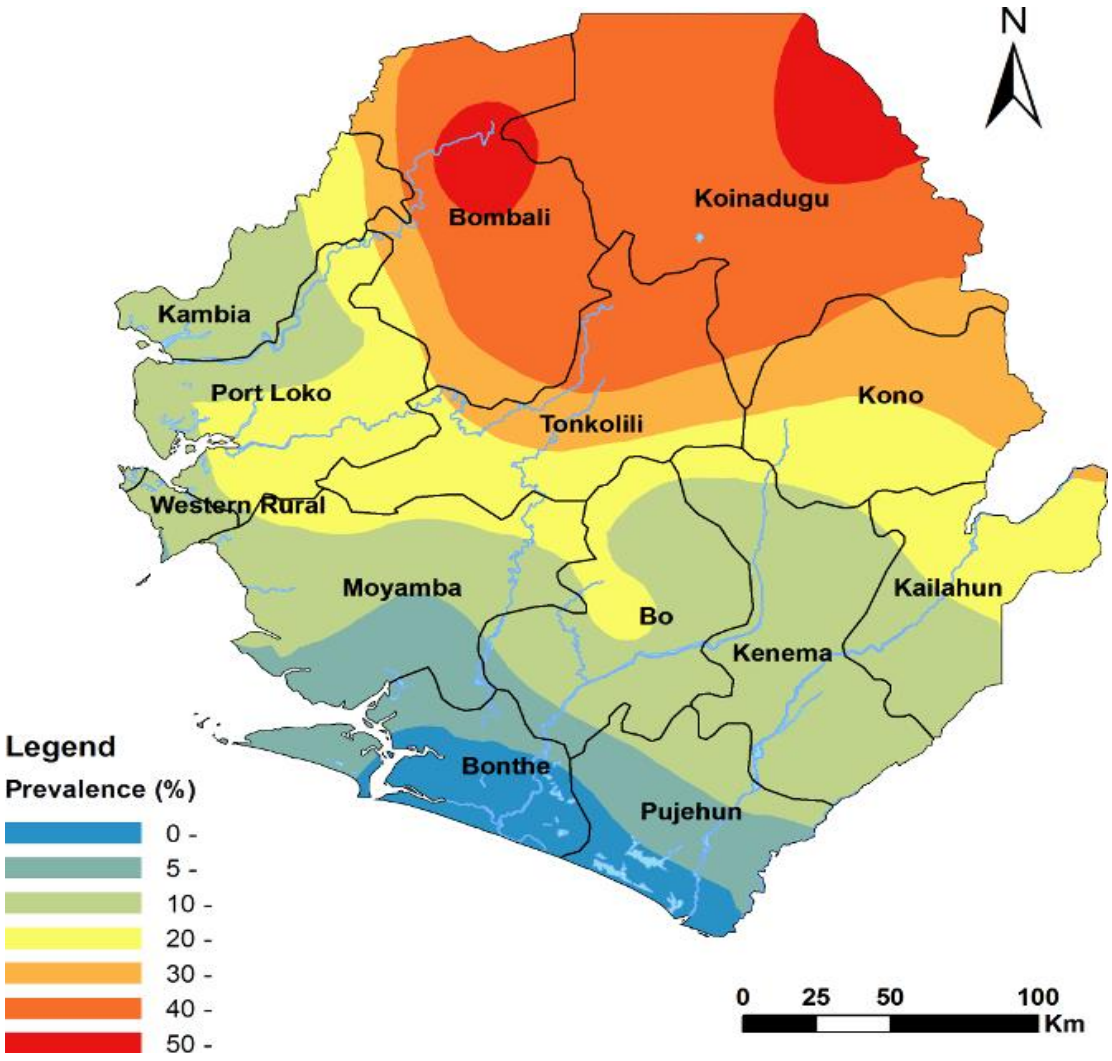
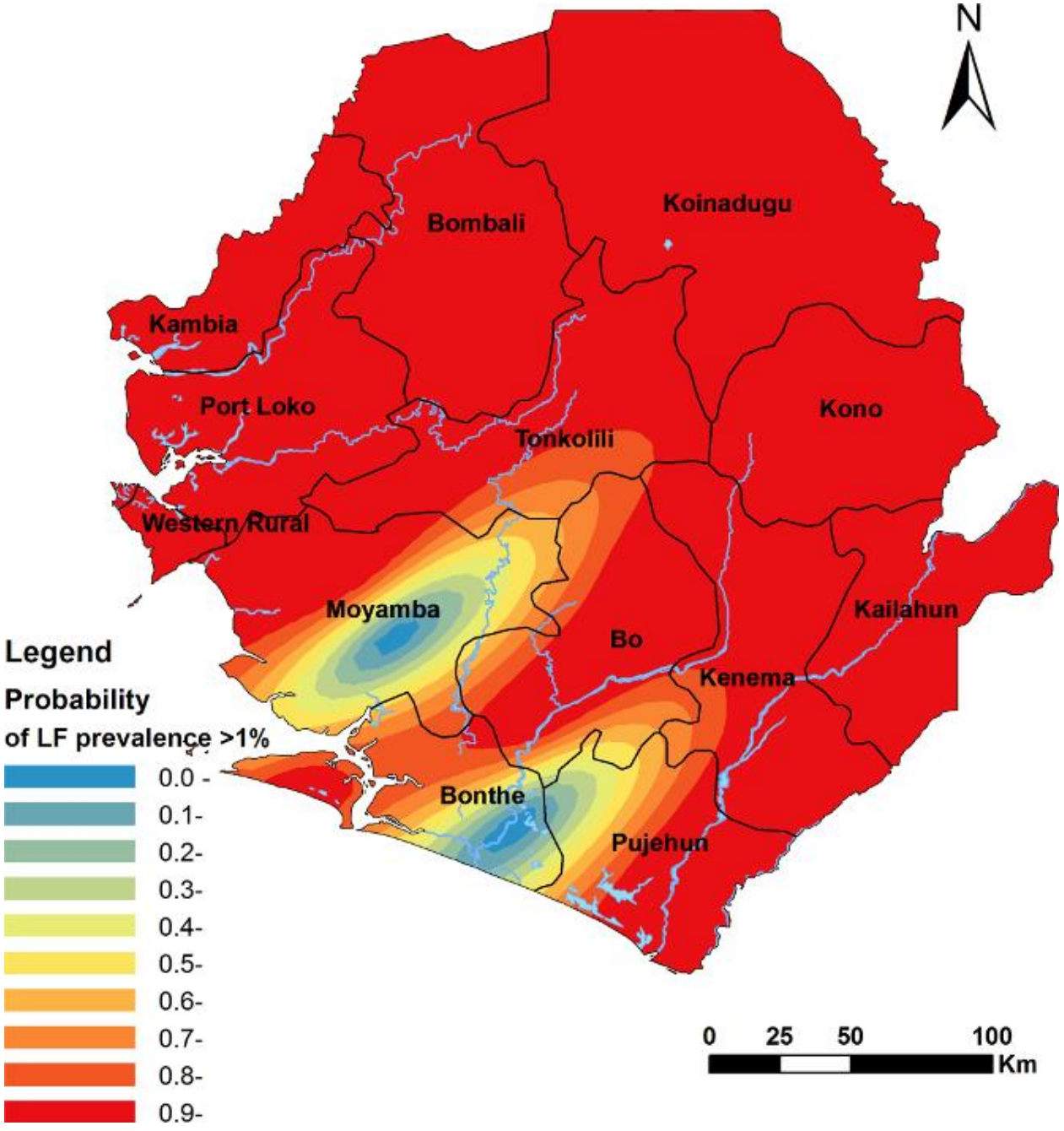


Figure 12 Spatially smoothed contour map of the predicted probability that the prevalence of LF antigenaemia exceeds 1%.



CHAPTER 5: IMPACT OF THREE ROUNDS OF MASS DRUG ADMINISTRATION ON LYMPHATIC FILARIASIS IN AREAS PREVIOUSLY TREATED FOR ONCHOCERCIASIS IN SIERRA LEONE

The results of this chapter have been published as the manuscript:

Koroma JB, Sesay S, Sonnie M, Hodges MH, Sahr F, Zhang Y and Bockarie MJ (2013) Impact of Three Rounds of Mass Drug Administration on Lymphatic Filariasis in Areas Previously Treated for Onchocerciasis in Sierra Leone. PLoS Negl Trop Dis 7(6): e2273. doi:10.1371/journal.pntd.0002273

ABSTRACT

Background

1974–2005 studies across Sierra Leone showed onchocerciasis endemicity in 12 of 14 health districts and baseline studies 2005–2008 showed LF endemicity in all 14 HDs. Three integrated annual MDA were conducted in the 12 co-endemic districts 2008–2010 with good geographic, programme and epidemiological coverage. The midterm assessment was conducted 2011 to determine the impact of these MDAs on LF in these districts.

Methodology

The MF prevalence and intensity in the 12 districts were determined using the TBF method and results compared with baseline data from 2007–2008.

Principal Findings

Overall MF prevalence fell from 2.6% (95% CI: 2.3%–3.0%) to 0.3% (95% CI: 0.19%–0.47%), a decrease of 88.5% (p = 0.000); prevalence was 0.0% (100.0% decrease) in four districts: Bo, Moyamba, Kenema and Kono (p = 0.001, 0.025, 0.085 and 0.000 respectively); and seven districts had reductions in MF prevalence of between 70.0% and 95.0% (p = 0.000, 0.060, 0.001, 0.014, 0.000, 0.000 and 0.002 for Bombali, Bonthe, Kailahun, Kambia, Koinadugu, Port Loko and Tonkolili districts respectively). Pujehun had baseline MF prevalence of 0.0%, which was maintained. Only Bombali still had an MF prevalence >1.0% (1.58%, 95% CI: 0.80%–3.09%)), and this is the district that had the highest baseline MF prevalence: 6.9% (95% CI: 5.3%–8.8%). Overall arithmetic mean MF density after three MDAs was 17.59 mf/ml (95% CI: 15.64 mf/ml–19.55 mf/ml) among MF positive individuals (65.4% decrease from baseline of 50.9 mf/ml (95% CI: 40.25 mf/ml–61.62 mf/ml; p = 0.001) and 0.05 mf/ml (95% CI: 0.03 mf/ml–0.08 mf/ml) for the entire population examined (96.2% decrease from baseline of 1.32 mf/ml (95% CI: 1.00 mf/ml–1.65 mf/ml; p = 0.000)).

Conclusions

The results show that MF prevalence decreased to,1.0% in all but one of the 12 districts after three MDAs. Overall MF density reduced by 65.0% among MF-positive individuals and 95.8% for the entire population.

BACKGROUND

LF and onchocerciasis are among two of the major NTDs, presently targeted for elimination using the WHO recommended strategy of preventive chemotherapy and transmission control (PCT) (Molyneux *et al.* 2003; WHO 2006; Ottesen *et al.* 2008). LF is a disease caused by the nematodes *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*, and transmitted by mosquitos. It is highly endemic in the tropics and subtropics (Africa, Asia, South Pacific and some parts of South America). The elimination strategy is through annual MDA with albendazole and ivermectin/diethylcarbamazine (Molyneux *et al.* 2003; WHO 2006). LF elimination is implemented through the GPELF which has expanded MDA coverage from three million people treated in 12 countries in 2000 to more than 450 million in 53 countries in 2010 (WHO 2010; WHO 2011a). During that period, the disease was eliminated in China and Korea. Nine countries no longer require MDA because of a natural decline in transmission intensity in areas of low disease endemicity. Globally, a total of 73 countries (including the recently independent Republic of South Sudan) are presently endemic for LF. Onchocerciasis, caused by *Onchocerca volvulus*, is transmitted by blackflies belonging to the *Simulium damnosum* complex. It is mainly endemic in Africa, Yemen and the Americas (Boatin and Richards 2006). Control of the disease in Africa is through APOC using the annual community-directed treatment with ivermectin (CDTI) (WHO APOC 2010). In 2008 alone, 56.7 million people received treatment in 19 endemic African countries (WHO APOC 2010).

In Sierra Leone, both diseases are widely distributed across the country and co-endemic in 12 of the 14 administrative districts. The early distribution and clinical manifestations of both diseases in Sierra Leone were described previously (McMahon *et al.* 1988a,b,c,d; Whitworth *et al.* 1991; Whitworth *et al.* 1992; Whitworth *et al.* 1993; Mabey *et al.* 1996; Post and Crosskey 1985; Dadzie, De Sole, Remme 1992; Gbakima *et al.* 2000;). The NOCP was established in the 1980s to control onchocerciasis, and with the support from APOC, CDTI started in 2002 in meso and hyper-endemic communities nationwide (Hodges *et al.* 2011). After further national mapping of LF in 2005 and baseline data collection on MF prevalence and density in 2007-2008 (Koroma *et al.* 2012), CDTI was expanded to include albendazole distribution to control LF in six co-endemic districts (Hodges *et al.* 2011). With support from the USAID NTD Program,

managed at the time by RTI International, the NOCP was transformed into the National NTDP in 2008 to integrate other NTDs into the control effort (Hodges *et al.* 2013).

Annual MDA with ivermectin and albendazole has been implemented since then. By early 2011, all 12 rural health districts (except Western Urban district and Western Rural district) had received at least three rounds of MDA. According to the WHO guidelines (WHO 2011a), a mid-term survey was conducted in July/August 2011 in sentinel and spot check sites in the 12 rural health districts to assess progress towards LF elimination and identify any implementation units (districts) that may require additional effort to reach the target of LF elimination. In this paper, we describe the remarkable impact of three rounds of MDA on LF prevalence and MF density in areas of low LF endemicity which may be related to previous treatment with ivermectin for onchocerciasis control.

METHODS

Ethics statement

This study was conducted by the National NTDP of the MOHS, Sierra Leone as part of the routine monitoring and evaluation activities of the national control programme. Ethical approval for the study was obtained from the MOHS Research and Ethics Committee. Informed oral consent was obtained from each participant before samples were collected and their acceptance was recorded on a form by the team leader, as literacy rates are low in the country. All participants aged five years and above in each site were eligible for inclusion without discrimination on gender, social status, religion or ethnicity. Participants' identities were protected by collecting, recording and analysing data such that participants remained anonymous.

Mass drug administration

Annual MDA with ivermectin and albendazole was piloted in 2007 in six rural districts located in border areas with neighbouring Guinea and Liberia: Bombali, Kailahun, Kambia, Koinadugu, Kono, and Pujehun. This was scaled up to cover 12 rural districts in 2008 with the additional districts added to the previous six: Bo, Bonthe, Kenema, Moyamba, Port Loko and Tonkolili.

Geographic coverage for the endemic districts targeted reached 100% in 2010 when MDA was scaled up to cover the remaining two health districts: Western Urban district and Western Rural district (Hodges *et al.* 2010). Within rural communities, ivermectin and albendazole were distributed by CDDs who are literate members of the respective communities selected by their communities and trained by health workers. In urban areas students in medical and nursing institutions are trained to conduct MDAs. District health workers conduct training for MDA and provide supervision during MDAs. NTDP staff and members of the DHMTs also support training and supervision for MDAs. MDA is conducted once a year between September and December, which is the post-harvest period that communities have accepted for MDAs.

Before each MDA, CDDs conduct a pre-MDA census. Details on all community members are recorded in the community registers and updated each year prior to subsequent MDA. MDA details are also captured in the registers. After each MDA, the MDA details are summarised in the reporting forms by drug distributors and submitted to the supervising health workers. The supervising health workers prepare summary reports for all villages/urban areas targeted and submit the reporting forms to the DHMTs. Each DHMT then submits the district MDA report to the NTDP, which collates MDA results from all districts.

Survey site selection

Sampling was conducted in accordance with WHO guidelines in one sentinel site and one spot check site per population of one million people. The 12 rural districts that had conducted at least three rounds of MDA were involved in this study. As the populations of the districts were small, the 12 districts were put in six groups of two districts depending on geographical proximity and epidemiological characteristics so that the total population for each group was about a million (WHO 2011a). For the baseline study in 2007 and 2008, sentinel sites were randomly selected for all 14 health districts according to WHO guidelines (Koroma *et al.* 2012; WHO 2011a). In each of the six groups, a sentinel site was selected in one district for this study, and a spot check site was selected in the other district, in consultation with the DHMTs. The groups included the following pairs of districts: Bonthe (sentinel site (SS)- Moboya) and Moyamba (spot check site (SCS)- Taninahun Kapuima); Koinadugu (SS-Kumala) and Bombali (SCS-Makoba Yelima); Bo (SS-Gelehun) and Pujehun (SCS- Kundorwahun); Port Loko (SS-

Gbabai) and Kambia (SCS- Kamasasa); Kailahun (SS-Manowa) and Kenema (SCS- Joru); Kono (SS- Tombodu) and Tonkolili (SCS-Rosint). In the ¨sentinel site¨ districts data obtained in this study were compared with baseline data, while among the ¨spot check site" districts, the results of this survey were compared with baseline results obtained in the original sentinel sites in these districts. See Table 7 below for details of the survey sites used during the midterm evaluation.

Table 7: Survey site selection for midterm LF evaluation carried out in 12 districts in 2011

Groups of districts	Districts	Sentinel sites	Spot check sites
1	Bonthe	Moboya	
	Moyamba	-	Taninahun Kapuima
2	Koinadugu	Kumala	-
	Bombali	-	Makoba Yelima
3	Bo	Gelehun	-
	Pujehun	-	Kundorwahun
4	Port Loko	Gbabai	-
	Kambia -	-	Kamasasa
5	Kailahun	Manowa	-
	Kenema	-	Joru
6	Kono	Tombodu	-
	Tonkolili	-	Rosint

Sampling and diagnosis

The survey teams met with community leaders upon arrival in communities and explained the nature of their work, after which, meetings were held with the general community to explain the study and its significance and respond to questions from community members before the study was conducted. Some 300-500 participants of five years of age or above were recruited per site according to WHO guidelines (WHO 2011a). In sites with less than 300 participants, more participants were recruited in neighbouring villages. To ensure standardisation of activities and data, two-day practical training was conducted for all technicians before the

study started. Fingertip blood was collected between ten pm and two am. A 60 µl blood sample was collected from each participant, smeared gently and uniformly in a circular shape and allowed to air dry at room temperature for 12–24 hours.

The next day, the dried smear was dehaemoglobinized through flooding with distilled water for three–five minutes, air dried again, fixed with methanol for 30–60 seconds, stained with GIEMSA for 10 minutes, and examined for MF under a light microscope by experienced examiners. Positive findings of MF were recorded, and individual MF density of infection was calculated and expressed as the number of MF per ml of blood (mf/ml). A total of 6,023 "midnight" blood samples were collected and examined for MF as shown in Table 8, male 3,170 (52.6%) and female 2,853 (47.4%). The mean age (± standard deviation) of the subjects examined was 28.91±18.92 years (males: 27.65±18.77, females: 30.32±18.92). For quality control, all positive slides and 10% of the negative slides were preserved and examined by an experienced researcher. There were no false positives and no false negatives. The coordinates of each sample site were recorded using hand-held units of global positioning system.

Statistical analysis

Results were entered into MS Excel and analysed in SPSS (IBM, Version 19). Prevalence and density of mf were calculated for all 12 districts and compared with the baseline data. The 95% CIs for prevalence were calculated using the Wilson score method without continuity correction (Newcommbe 1998). The arithmetic mean MF density of infection with 95% CI was calculated using the total population examined and the positive samples only (Koroma *et al.* 2012; WHO 2005). The Chi-squared test was used to compare the differences in prevalence, and the Kruskal-Wallis test was used to compare the differences in MF density. Treatment coverage was calculated according to the WHO guidelines (WHO 2011a). Programme coverage was the percentage of people ingesting the drugs among the total targeted population in the endemic districts. Epidemiological coverage was the percentage of people ingesting the drugs among the total population in the endemic districts. The total population used in rural areas was the total number of people registered during the pre-MDA census, while the total population used in urban/non-rural areas was the projected figure according to the 2004 national census (Koroma, Turay, Moihua 2006), with an annual growth rate of 2.5%. Spatial

analysis of the LF MF prevalence was conducted using the kriging method in the Geostatistical Analyst Extension of ArcGIS version 10 (ESRI, Redlands, USA). Spatially smoothed contour maps of the interpolated prevalence of MF at baseline and after three MDAs were produced as described previously (Zoure *et al.* 2011; Koroma *et al.* 2012).

RESULTS

MDA results 2008-2010

A total of 14,253 villages and urban areas were treated each year during the three years in the 12 districts. This represents 100% geographic coverage for endemic villages and urban areas in all 12 districts during each of these three rounds of MDA, as shown in Table 9. Over four million people were targeted for treatment each year during the three years. Overall epidemiological coverage[7] was 70.1%, 74.1% and 75.2% in 2008, 2009 and 2010 respectively at the national level, and was ≥65.0% in each district in each round, except in Bonthe, where it was 59.5% in 2008. Epidemiological coverage also improved between 2008 and 2010. Five districts had <70.0% in 2008 (Bo: 66.3%, Bonthe: 59.5%, Kono: 69.0%, Port Loko: 66.6% and Tonkolili: 68.6%); while in 2009 and 2010, all districts had >70.0% epidemiological coverage, as shown in Table 9. The overall programme coverage was 82.5%, 87.1% and 88.5% in 2008, 2009 and 2010, respectively. The programme coverage is a measure of how well MDA was conducted and is considered adequate when ≥80.0% (15). Programme coverage by the district in each round was ≥80.0%, except in Bo, Bonthe and Port Loko, which had 78.0%, 70.0% and 78.3% respectively in 2008, as shown in Table 9.

Microfilaraemia prevalence

Five districts (Bo, Kenema, Kono, Moyamba and Pujehun) had 0.0% MF prevalence. One district (Pujehun) had baseline MF prevalence of 0.0%, which was maintained. Another six districts had MF prevalence between 0.0 and 1.0%: Bonthe (0.20%), Kailahun (0.20%), Kambia (0.40%),

[7] The indicators used for coverage in this study is different from what is in the publication because WHO made some changes in the latest monitoring and evaluation guidelines for LF. What was referred to as epidemiological drug coverage (EDC) in the publication is now simply epidemiological coverage in the study, while drug coverage (DC) that is in the publication is now replaced by programme coverage in the study (WHO 2011; Koroma *et al.* 2013).

Koinadugu (0.80%), Port Loko (0.20%) and Tonkolili (0.19%). Only one district had MF prevalence of over 1%: Bombali (1.58%). Overall MF prevalence among males was 0.35% and among females 0.25%. Prevalence by age group, 5-14 years (N=1947), 15-20 years (N=858), 21-30 years (N=858), 31-40 years (N=849) and 41-50 years (N=640), was 0.21%, 0.12%, 0.58%, 0.59% and 0.47% respectively, while prevalence in the age group >50 years (N=871) was 0.0%. In total, 18 persons (0.30%, 95% CI: 0.19-0.47%) had a positive blood smear, and there was no significant difference in MF prevalence in males 0.35% (95% CI: 0.19-0.62%) as compared to females 0.25% (95% CI: 0.12-0.51%) (p=0.47). There were also no significant differences in prevalence among age groups.

Compared with the baseline, overall MF prevalence decreased by 87.5%, from 2.40% to 0.30%, after three rounds of MDA. As shown in Table 8, among the 11 districts with baseline MF prevalence ≥1%, seven districts showed MF prevalence reduction of over 90% after three rounds of MDA, three districts by over 80%, and only one district by below 80%. Spatial prediction suggested a sweeping reduction in MF prevalence from the baseline level after three MDAs across the country. There was an 88.3% decrease in MF prevalence among males: 3.00% to 0.35%; and an 86.1% decrease in MF prevalence among females: 1.80% to 0.25%. There was 0.21% prevalence among the age group 5-14 years, but this could not be compared, as the baseline study did not include participants <15 years. Decreases in MF prevalence among the age groups 15-20, 21-30, 31-40, 41-50 and >50 years ranged between 75.4% and 100.0%. Figures 13, 14 and 15 show graphs of the reduction of LF MF prevalence, MF density for the entire population studied and MF density for positive-only. Figure 16 shows predicted MF prevalence at baseline (A) and predicted MF prevalence after three rounds of MDA (B).

MF density

The overall arithmetic mean MF density was 0.05 mf/ml (95% CI: 0.03-0.08 mf/ml) in the total participants examined and 17.59 mf/ml (95% CI: 15.64-19.55 mf/ml) among MF-positive individuals. The mean MF density by district was well below one mf/ml for the population examined and below 21 mf/ml among those who were MF positive. There was no significant difference in MF density in males versus females (p>0.05). There was also no significant difference in MF density among age groups in the total population examined (p>0.05). Overall

mean MF density among MF positive individuals decreased by 65.0%, from 50.3 mf/ml at baseline to 17.63 mf/ml; and in the total population examined, there was a 95.5% decrease, from 1.19 mf/ml at baseline to 0.05 mf/ml. In Bo, Kenema, Kono and Moyamba, there was 100.0% decrease in MF density among both MF positive participants and the entire population. Six districts, Bonthe, Kailahun, Kambia, Koinadugu, Port Loko and Tonkolili, had a >90.0% decrease in MF density for the entire population, and a >36.0% decrease in MF density among positive participants. Bombali had the lowest decreases in MF density, 86.3% for the entire population and 40.6% among positive individuals. Table 8 shows the reduction of MF density in the 12 districts after 3 MDAs. There was a 96.2% decrease in MF density among all males and a 66.6% decrease in MF density among males that are MF positive, and there was a 94.7% decrease in MF density among all females and a 62.2% decrease in MF density among females that are MF positive. The age groups 15-20, 21-30, 31-40 and 41-50 years had >90.0% decrease in MF density for the entire population and >60.0% decrease in MF density among MF positive individuals. The age group >50 years had a 100.0% decrease in MF density for the entire population and among MF positive individuals.

DISCUSSION

LF is widely endemic across Sierra Leone, transmitted by *Anopheles* mosquitoes. All districts qualified for MDA intervention in accordance with WHO guidelines because they had baseline LF prevalence by ICT cards ≥1.0% (Koroma *et al.* 2012; WHO 2005). Remarkable progress in LF elimination has been achieved since the start of co-administration of ivermectin and albendazole in 2007. The results from the 12 rural districts showed that over the three years, geographic coverage was 100% in all 12 districts, epidemiological coverage was ≥65.0% in all districts except for Bonthe in 2008 (59.5%), and programme coverage was ≥80.0% in all districts except for Bo (78.0%), Bonthe (70.0%) and Port Loko (78.3%) in 2008. The treatment coverage was verified through independent monitoring activities, as described previously (Hodges *et al.* 2011; Hodges *et al.* 2012b). The current assessment showed that the average MF prevalence in the country was only 0.30% and the average population MF density was only 0.05 mf/ml after three rounds of MDA, with no microfilaria detected in six of the 12 districts, including all the districts in the Southern Province and only one district showing MF prevalence

of >1% (Bombali, 1.58%). This represents an overall reduction of 87.5% in MF prevalence and 95.5% in population MF density.

The number of MDA rounds needed to eliminate LF depends on baseline infection rates, vectoral capacity, the efficacy of the MDA regimen used, and community adherence with treatment. It is possible to eliminate LF in some IUs with low baseline infection rates using less than five rounds of MDA, while more than six MDA rounds may be needed for IUs with relatively high baseline LF prevalence (El-Setouhyet al. 2007; Grady *et al.* 2007; Huppatz *et al.* 2009). The high level of reduction in MF prevalence and intensity after three rounds of MDA in Sierra Leone may have been partly due to the relatively low baseline MF level (Koroma *et al.* 2012).

Pre-baseline prevalence of LF was high in southeastern Sierra Leone. Blacklock in 1922 examined 240 men in Mabang village and found 20% to be microfilaraemic, with the prevalence of elephantiasis and hydrocoele of 4.6% and 3.8%, respectively ((Blacklock 1926; Hawking 1957). Surveys in the early 1990s showed an average MF prevalence of 34.8% in three villages in the Moyamba district (Gbakima, Pessima, Sahr 1996). Similarly, high prevalence rates were recorded in neighbouring Liberia prior to the 1980s (Brinkmann 1977; Zielke and Chlebowsky 1979). In 2007-2008, the pre-treatment MF prevalence for the 12 districts outside the Western Area ranged from 0 – 6.9%, although prevalence was below 3% in the southeastern districts (Koroma *et al.* 2012). This significant reduction of MF prevalence from earlier high levels prior to the start of the LF MDA coincides with the commencement of CDTI for onchocerciasis control in the 1980s (Hodges *et al.* 2011). The significant impact of CDTI on LF infection has been reported in some countries (Kyelem *et al.* 2003; Kyelem et al. 2005). Therefore, it is likely that annual nationwide CDTI has impacted significantly on LF infections in Sierra Leone, resulting in a relatively low level of MF prevalence at baseline.

Three rounds of MDA with adherence ≥65.0% in Papua New Guinea reduced MF prevalence from 18.6% to 1.3%, a 94.0% reduction (Weil *et al.* 2008). The authors believed that the large decrease in prevalence occurred in part because the vector transmitting LF in the study area was the *Anopheles* mosquito, which is less efficient than *Culex* on the transmission of filariasis

(Weil *et al.* 2008). This may have also been the case in Sierra Leone. Similar successes in reducing MF prevalence after annual MDA rounds have been reported by many authors. In Kenya, there were similar reductions in MF prevalence (from 20.9% to 0.9%, a 95.7% reduction of MF prevalence) even when there were missed rounds of MDA (Njenga *et al.* 2011). Prevalence was reduced by 93.0%, from 12.0% to 0.8%, after just two rounds of MDA in Vanuatu (Fraser *et al.* 2005). In Northern Uganda, a reduction of MF prevalence from 3.7% to 0.4% (an 89.2% decrease) was reported after 3 MDAs (Ashton *et al.* 2011). Therefore, it is not surprising that three effective rounds of MDA would reduce the MF prevalence to below 1% in 11 out of 12 districts in the current LF elimination programme, given the relatively low MF prevalence at baseline.

The successful implementation of the LF programme benefited from the existing onchocerciasis control programme by using the CDTI as the platform (Hodges *et al.* 2011). Health workers had already been trained and were available to provide technical support in additional training, supervision and surveys. Treatment has been given between September and December each year, as this is the period that was found to be convenient for the communities (*i.e.* harvest and post-harvest period). All the lessons learnt from CDTI during the years of the onchocerciasis control programme were used to improve the LF elimination programme.

There is reason for optimism with the results of this survey because some research suggests that residual infections of filariasis disappear when prevalence is below 1.0% (Mitja *et al.* 2011). However, it is prudent to consider experiences and lessons learnt from other countries. In Tanzania, it was demonstrated that MDA using ivermectin and albendazole reduced MF prevalence by 21.2% and 40.4% after the first and second MDA respectively, but in subsequent MDAs, the effect levelled off and transmission, albeit low-level, was still noted after the third MDA (Simonsen *et al.* 2010). In Leogane, Haiti, there was a significant reduction in MF rates after several rounds of MDA for LF, but transmission was not interrupted (Grady *et al.* 2007). MF prevalence detected after three MDAs does not demonstrate a change in filariasis transmission (Weil *et al.* 2008; Ashton *et al.* 2011). The drug combination destroys the microfilaria over the four-six year it takes for the adult worm to die a natural death (Weil *et al.*

2008; Ashton *et al.* 2011; Ottesen 2000). Therefore, MDA must continue each year for four-six years, which is equivalent to the lifespan of the adult worm. It is noted that two health districts in the Western Area have not reached three effective rounds of MDA, and Bombali still had MF prevalence of 1.58%. Therefore, the NTDP needs to continue with MDA in all health districts, even though MF prevalence is already <1.0% in 11 out of 12 districts.

CONCLUSION

There was a significant reduction in MF prevalence and density across the 12 rural districts in Sierra Leone after three annual MDAs. This was coupled with good MDA adherence and relatively low baseline endemicity. The results show that the LF elimination programme in Sierra Leone is on course to reach the objective of eliminating LF by the year 2020. However, experiences and lessons must be learnt from other countries, and MDA should continue in all health districts to reach the recommended number of rounds.

Figure 13 Reduction of MF prevalence after three annual MDAs for LF in 12 districts of Sierra Leone 2008–2010

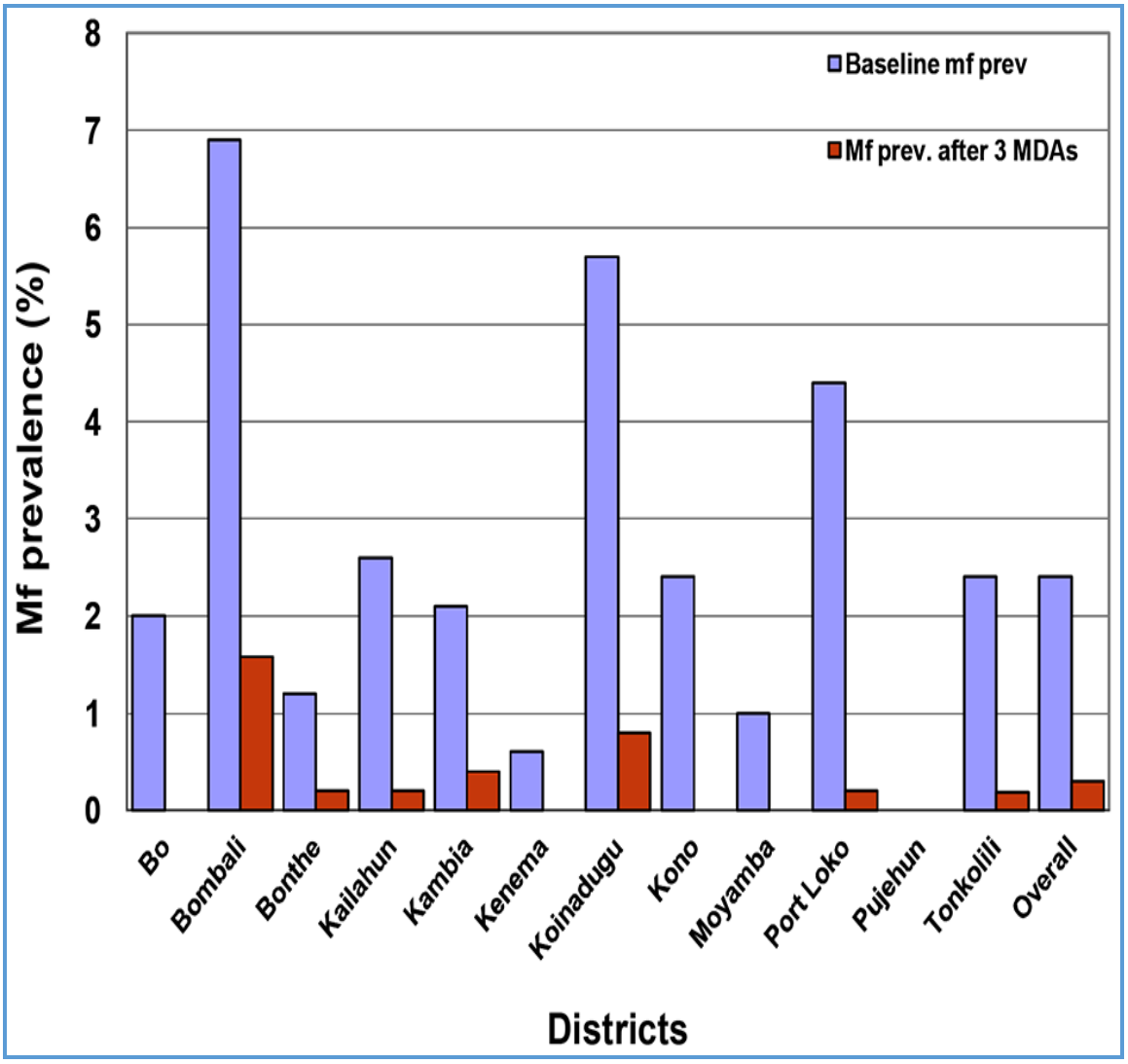


Figure 14. Reduction of entire-population mf density after three annual LF MDAs in 12 districts of Sierra Leone 2008–2010

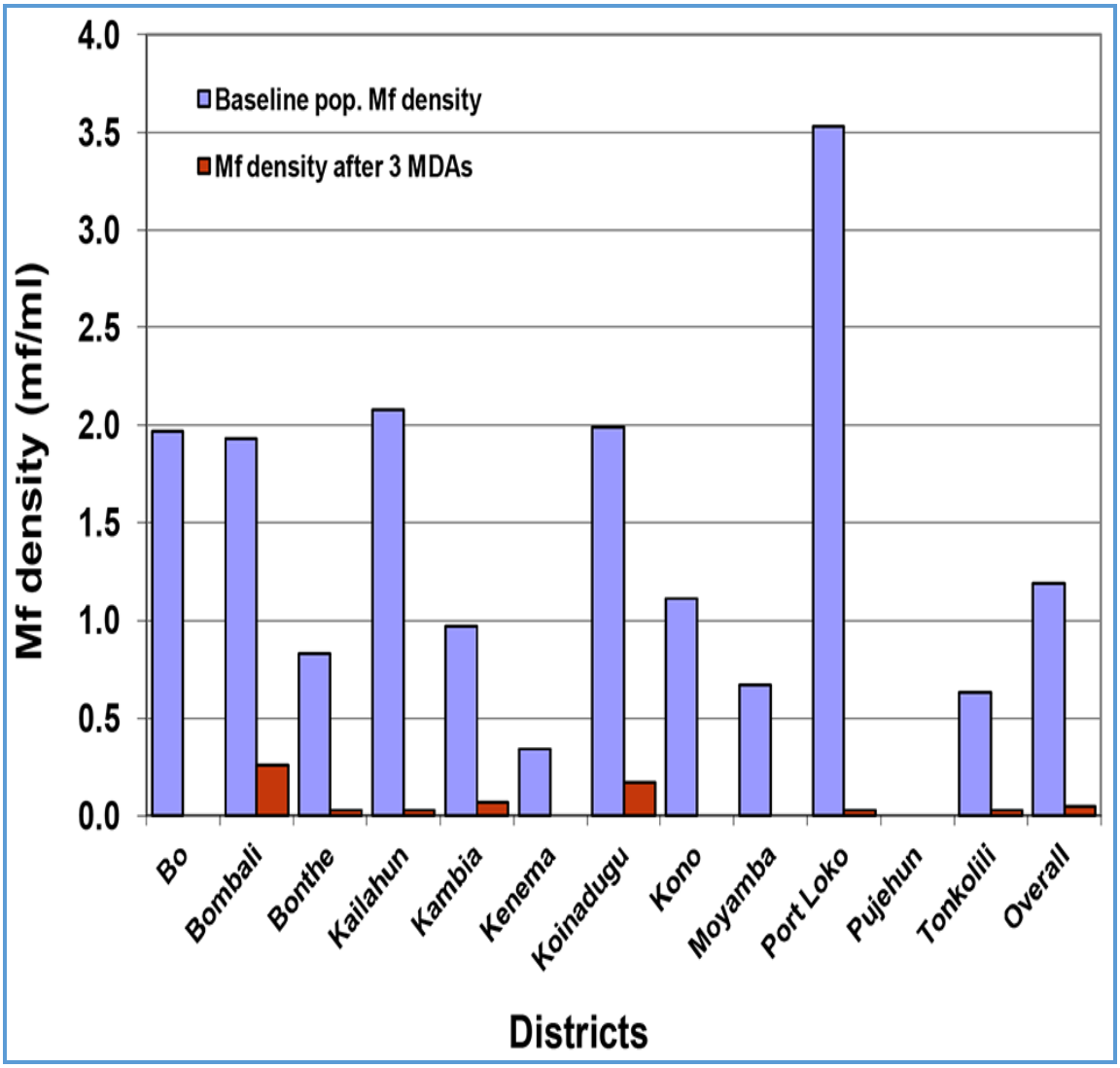


Figure 15. Reduction of positive-only mf density after three annual LF MDAs in 12 districts of Sierra Leone 2008–2010

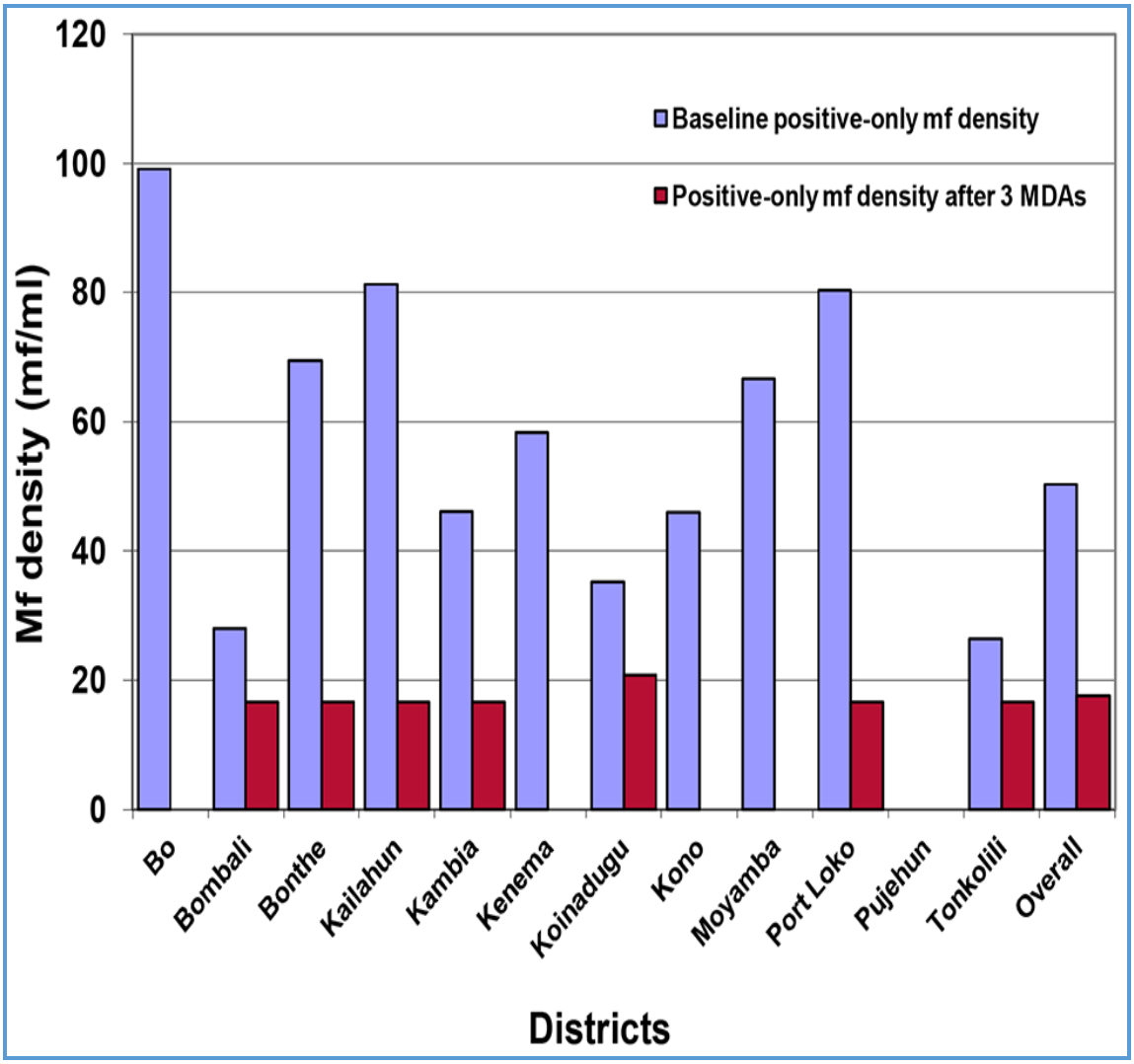
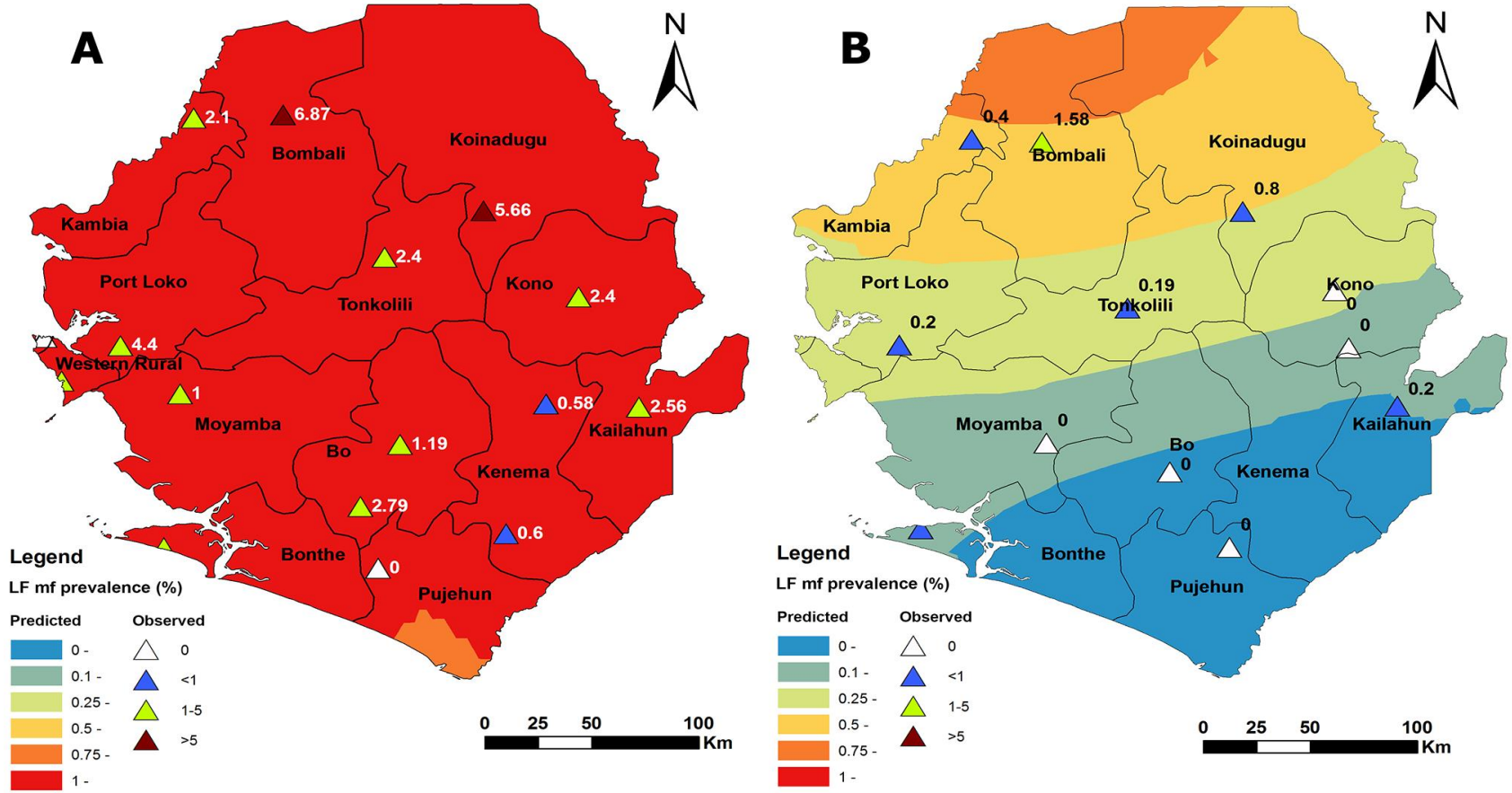


Figure 16. Survey sites and spatially smoothed contour maps of predicted LF MF prevalence in Sierra Leone*. A. Predicted MF prevalence at baseline; B. Predicted MF prevalence after three rounds of MDA.



*The same legend scale was used for the contour map of both A and B for easy comparison. Triangles and labels show the survey locations and the observed MF prevalence in each location.

Table 8: Crude microfilaraemia prevalence and mf density by district, sex and age group in Sierra Leone after three rounds of MDA														
		Baseline survey			Mid-term assessment				Percentage reduction from baseline			Significance test for reduction (p values)		
	No of persons examined for MF	MF prevalence (%)	Population MF density (mf/ml)	Positive-only MF density (mf/ml)	No of persons examined for MF	Percentage MF prevalence (95% CI)	Population MF density (mf/ml) (95% CI)	Positive-only MF density (mf/ml) (95% CI)	MF prevalence	Population MF density	Positive-only mf density	MF prevalence	Population MF density	Positive-only MF density
Overall	8233	2.4	1.19	50.3	6023	0.30 (0.19 – 0.47)	0.05 (0.03 – 0.08)	17.59 (15.64 – 19.55)	87.5	95.5	65.0	0.000	0.000	0.001
By district														
Bo	1005	2.0	1.97	99.17	500	0	0	0	100	100	100	0.001	0.002-	-
Bombali**	830	6.9	1.93	28.07	506	1.58 (0.80 – 3.09)	0.26 (0.08 – 0.45)	16.67 (-)	77.1	86.3	40.6	0.000	0.000	0.068
Bonthe	504	1.2	0.83	69.44	499	0.20 (0.04 – 1.13)	0.03 (0 – 0.10)	16.67 (-)	83.3	96.0	76.0	0.060	0.059	0.295
Kailahun**	624	2.6	2.08	81.25	499	0.20 (0.04 – 1.13)	0.03 (0 – 0.10)	16.67 (-)	92.3	98.4	79.5	0.001	0.001	0.472
Kambia**	619	2.1	0.97	46.15	500	0.40 (0.11 – 1.45)	0.07 (0 – 0.16)	16.67 (-)	81.0	93.1	63.9	0.014	0.014	0.311
Kenema	1016	0.6	0.34	58.33	500	0	0	0	100	100	100	0.085	0.085	-

Koinadugu**	636	5.7	1.99	35.19	498	0.80 (0.31 – 2.05)	0.17 (0 – 0.34)	20.83 (7.57 – 34.09)	86.0	91.6	40.8	0.000	0.000	0.454
Kono**	875	2.4	1.11	46.03	499	0	0	0	100	100	100	0.000	0.000	-
Moyamba	500	1.0	0.67	66.67	500	0	0	0	100	100	100	0.025	0.025	-
Port Loko	500	4.4	3.53	80.30	499	0.20 (0.04 – 1.13)	0.03 (0 - 0.10)	16.67 (-)	95.5	99.1	79.2	0.000	0.000	0.219
Pujehun**	624	0	-	-	500	0	-	-	-	-	-	-	-	-
Tonkolili	500	2.4	0.63	26.39	523	0.19 (0.03 – 1.08)	0.03 (0 – 0.10)	16.67 (-)	92.1	94.9	36.8	0.002	0.002	0.442
By sex														
Male	3863	3.0	1.66	54.42	3170	0.35 (0.19 – 0.62)	0.06 (0.03 - 0.10)	18.18 (14.80 - 21.56)	88.3	96.2	66.6	0.000	0.000	0.013
Female	4370	1.8	0.78	44.13	2853	0.25 (0.12 – 0.51)	0.04 (0.01 - 0.07)	16.67 (-)	86.1	94.7	62.2	0.000	0.000	0.023
By age groups														
5--14	-	-	-	-	1947	0.21 (0.08 – 0.53)	0.04 (0 - 0.09)	20.83 (7.57 – 34.09)	-	-	-	-	-	-
15-20	1614	1.8	0.78	44.44	858	0.12 (0.02 – 0.66)	0.02 (0 - 0.06)	16.67 (-)	93.3	97.6	62.5	0.000	0.000	0.341
21-30	1750	2.6	1.77	68.59	858	0.58 (0.25 – 1.36)	0.10 (0.01 - 0.18)	16.67 (-)	77.7	94.5	75.7	0.000	0.000	0.042

31-40	1623	2.4	1.01	43.02	849	0.59 (0.25 – 1.37)	0.10 (0.01 - 0.18)	16.67 (-)	75.4	90.3	61.3	0.000	0.000	0.059
41-50	1271	3.4	1.60	47.87	640	0.47 (0.16 – 1.37)	0.08 (0 - 0.17)	16.67 (-)	86.2	95.1	65.2	0.000	0.000	0.159
>50	1975	2.1	0.89	42.96	871	0	0	0	100	100	100	0.000	0.000	-

*The table shows crude MF prevalence and MF density by district, sex and age group, their percentage reductions and significance test for reductions in MF prevalence and density after three rounds of MDA in Sierra Leone.

**Districts that piloted MDA in 2007.

Table 9: Summary results of annual MDA carried out for LF elimination in Sierra Leone 2008–2010

Districts	Villages/ Urban areas targeted*	Villages/ Urban areas treated	2008					2009					2010				
			Total pop. of IUs	Eligible pop. of IUs	Total treated in IUs	Epid. Cov. by IUs	Prog. cov. by IUs	Total pop. of IUs	Eligible pop. of IUs	Total treated in IUs	Prog. Cov. by IUs	Drug cov. by IUs	Total pop. of IUs	Eligible pop. of IUs	Total treated in IUs	Prog. Cov. by IUs	Drug cov by IUs
Bo	1367	1367	574053	487945	380676		78.0	595318	506020	420968	70.7	83.2	613178	521201	445996	72.7	85.6
Bombali**	1596	1596	440932	374792	316672	71.8	84.5	454604	386413	350278	77.1	90.6	498115	423398	363078	72.9	85.8
Bonthe	550	550	166140	141219	98856	59.5	70.0	150718	128110	110834	73.5	86.5	154860	131631	117201	75.7	89.0
Kailahun**	977	977	392819	333896	287536	73.2	86.1	401215	341033	313367	78.1	91.9	410509	348933	322206	78.5	92.3
Kambia**	837	837	269673	229222	202999	75.3	88.6	289136	245766	211926	73.3	86.2	310705	264099	234910	75.6	88.9
Kenema	1380	1380	551797	469027	391778	71.0	83.5	601661	511412	439136	73.0	85.9	583278	495786	449763	77.1	90.7
Koinadugu**	1041	1041	207995	176796	151395	72.8	85.6	216472	184001	157339	72.7	85.5	222966	189521	162059	72.7	85.5
Kono**	1360	1360	466223	396290	321833	69.0	81.2	442235	375900	323907	73.2	86.2	461562	392328	346719	75.1	88.4
Moyamba	1539	1539	309436	263021	232327	75.1	88.3	304416	258754	232859	76.5	90.0	350779	298162	268876	76.7	90.2
Port Loko	1769	1769	376212	319780	250457	66.6	78.3	547672	465521	386929	70.6	83.1	480920	408782	363026	75.5	88.8
Pujehun**	813	813	261509	222283	188872	72.2	85.0	272436	231571	210954	77.4	91.1	250280	212738	193485	77.3	90.9
Tonkolili	1024	1024	368678	313376	252785	68.6	80.7	418828	356004	318229	76.0	89.4	412404	350543	304195	73.8	86.8
	14253	**14253**	**4385467**	**3727647**	**3076186**	**70.1**	**82.5**	**4694711**	**3990504**	**3476726**	**74.1**	**87.1**	**4749556**	**4037123**	**3571514**	**75.2**	**88.5**

*Geographic coverage of villages and urban areas was 100% in all 12 districts over the three years (2008-2010).

**Districts that piloted MDA in 2007.

CHAPTER 6: PRE-TRANSMISSION ASSESSMENT SURVEY FOR LYMPHATIC FILARIASIS AFTER FIVE EFFECTIVE ANNUAL ROUNDS OF MASS DRUG ADMINISTRATION IN SIERRA LEONE

ABSTRACT

Background

Previous studies on LF in Sierra Leone have shown a significant reduction in LF MF prevalence and MF density. A pre-TAS was conducted in the 12 districts that have completed five effective rounds of MDA in accordance with WHO guidelines and recommendations.

Methodology

The LF MF prevalence and intensity in the 12 districts were determined using the TBF method and results compared with baseline data from 2007–2008 and midterm data of 2011.

Results

The overall MF prevalence was 0.54% (95% CI: 0.36-0.81%); 0.7% (95% CI: 0.43-0.14%) for males and 0.36% (95% CI: 0.17-0.74%) for females. Males had higher MF prevalence although the prevalence for males and females was below 1% and the difference was not statistically significant (P=0.128970). Four districts are considered to have failed the pre-TAS: Koinadugu with 0.98% MF prevalence (close to 1%), Bombali with 2.67%; Kailahun with 1.56%, and Kenema district with 0% MF prevalence. Kenema is considered to have failed the pre-TAS even though the MF prevalence was 0% because the districts was paired with Kailahun district that failed the TAS to form a unit with a population of close to a million with Kailahun having the sentinel site and Kenema the spot check site. Both districts are considered to have failed due to the pairing.

Conclusion

There was a significant reduction in MF prevalence and density across the 12 provincial districts after five annual MDAs. Eight of 12 districts have passed the pre-TAS with <1% MF prevalence and now qualify for a TAS. The other four districts need to conduct two additional rounds of MDA and repeat the pre-TAS (re-pre-TAS).

BACKGROUND

LF and onchocerciasis are two PC NTDs currently targeted for elimination (Molyneux *et al.* 2003; Ottesen *et al.* 2008; WHO 2011a). Mapping and baseline studies conducted for LF and onchocerciasis in Sierra Leone have demonstrated that all 14 districts of Sierra Leone are endemic for LF while 12 are coendemic for onchocerciasis and LF (Hodges *et al.* 2011; Koroma *et al.* 2012; Koroma *et al.* 2013). Integrated LF/onchocerciasis treatment with albendazole and ivermectin was piloted in six of the 12 coendemic districts in 2007 and upscaled to all 12 coendemic districts in 2008 (Koroma *et al.* 2013). MDA results reported by the NTDP between 2008 and 2012 indicate good community adherence with treatment: epidemiological coverage was, in general, ≥65%, programme coverage was ≥80%, and geographic coverage was maintained at 100%. This success has partly been attributed to the use of CDTI as a platform for introducing LF treatment in the country (Koroma *et al.* 2013). The NOCP was transformed into the NTD program in 2007 and with the experience already acquired in the control of onchocerciasis the NTDP was able to reach all targeted communities in all 12 districts using the CDTI plus albendazole strategy: albendazole was added to ivermectin and CDDs were selected in all villages to conduct mass drug distribution in villages targeted for treatment with supervisory support from district health workers (Bockarie, Kelly-Hope, Haskew 2010).

The CDTI plus albendazole strategy, which was based on CDDs volunteering and not being paid for their services, could not work in district headquarter towns as they were highly urbanised. People in headquarter towns also refused to accept medication from volunteers who had not been trained officially as health workers. Therefore, students in health and nursing institutions were trained to conduct treatment in headquarter towns and other urban areas within districts (Hodges *et al.* 2010). By early 2013, all 12 provincial health districts had received at least five rounds of MDA. In accordance with WHO guidelines, a pre-TAS for LF was conducted in October/November 2013 after five rounds of MDA in sentinel and spot check sites of the 12 rural health districts to assess progress towards LF elimination and identify districts that have reached the phase of conducting a TAS (WHO 2005, WHO 2011a). The aim of this study is to determine whether the criteria for initiating TAS has been met. In this chapter, the impact of five rounds of MDA (2008-2012) on LF prevalence and MF density in the 12 districts is discussed to assess indicators for initiating TAS.

METHODS

Ethics statement

This study was conducted by the NTDP of the MOHS, Sierra Leone as part of the routine monitoring and evaluation activities of the NTDP. Ethical approval for the study was obtained from the MOHS Research and Ethics Committee. Informed oral consent was obtained from each participant before samples were collected and their acceptance was recorded on a form by the leader of the study team, as literacy rates are low in the country. All participants aged five years and above in each site were eligible for inclusion without discrimination on gender, social status, religion or ethnicity. Participants' identities were protected by collecting, recording and analysing data such that participants remained anonymous.

Mass drug administration

Integrated onchocerciasis/LF annual MDA with ivermectin and albendazole continued in all 12 onchocerciasis/LF coendemic districts between 2008 and 2013. Mass drug distribution is district-wide covering all villages, towns and district headquarter towns. The CDTI strategy used for onchocerciasis treatment was expanded to include albendazole and used to treat all 12 districts for onchocerciasis and LF. Within rural communities, Ivermectin plus albendazole were distributed by CDDs who are literate members of different communities that are selected by their communities and trained by health workers to conduct MDAs and report all incidences of adverse events following treatment to district health workers. The CDDs are trained to use dose poles to determine the number of ivermectin tablets to be administered depending on the height of the person treated and between one and four tablets of 3mg ivermectin is administered to all those treated. Only one tablet of albendazole is administered to all those eligible for treatment (*i.e.* all those five years and above or with a height greater than 90cm, women who are not pregnant or not in the two first weeks after delivering a baby, and all those who are not seriously ill). District health workers conducted training of CDDs and supported them to carry out the MDA within their communities. NTDP staff and members of the DHMTs also supported training and supervision for MDAs. MDA was performed once a year between September and December, which is the post-harvest period that communities have accepted for MDAs. The addition of albendazole to the already existing treatment with

ivermectin for onchocerciasis control did not create problems for the CDDs because only one tablet of albendazole is given to those treated.

Community registers that were previously used for onchocerciasis treatment were modified to include treatment with albendazole and provided to all targeted villages. The register is designed to capture all members of each community targeted for treatment, including those eligible for treatment and those not eligible for treatment, and is, therefore, a good source of demographic information for the communities that use them. Before each MDA in rural areas, CDDs conduct a pre-MDA census and update the community register to reflect those that leave the community, those that join the community and the newly born. MDA details are also captured in the registers. Simple tally sheets are used in urban areas by health and nursing students for recording treatment data. Each level has a summary form for ease of reporting: CDDs and health/nursing students summarize treatment data in a community summary form and submit to the PHU; PHUs complete PHU summary forms and submit to the DHMT; and DHMTs compile all data from the PHUs into a district summary form that is submitted to the NTDP at central level.

Survey site selection

Sampling was conducted in accordance with WHO guidelines in one sentinel site and one spot check site per population of one million people. The 12 rural districts had all carried out at least five rounds of MDA and so were involved in the pre-TAS. As the populations of districts in Sierra Leone are small, two districts had to be put together to have a population that is close to one million. The 12 districts were put in six groups of two districts depending on geographical proximity and epidemiological characteristics so that the total population for each group was about a million (WHO 2005, WHO 2011a). For the baseline study in 2007 and 2008, SSs were randomly selected for all 14 health districts according to WHO guidelines (WHO 2011a; Koroma *et al.* 2012). In each of the six groups, a SS was selected in one district for this study, and a SCS was chosen in the other district. While the SSs selected were those from the LF mapping/baseline study, SCSs have been selected in consultation with DHMTs. DHMTs suggested the selection of villages from areas where a high number of hydrocoele and lymphedema is reported. The groups included the following pairs of districts: Bonthe (SS) and

Moyamba (SCS); Koinadugu (SS) and Bombali (SCS); Bo (SS) and Pujehun (SCS); Port Loko (SS) and Kambia (SCS); Kailahun (SS) and Kenema (SCS); Kono (SS) and Tonkolili (SCS). Since Bombali was the only district with greater than 1% MF prevalence at mid-term, 2 SCs were selected in the district. Koinadugu had close to 1% MF prevalence but had to be paired with Bombali because of proximity and so the SS in Koinadugu was maintained. See table 10 below for more details on study sites. Survey teams had to move to neighbouring villages when the number of participants in an SS or SCS is less than the 300 minimum required by WHO (2011a). All data obtained in the ¨sentinel site¨ districts and the ¨spot check site" districts were compared with mid-term and baseline results obtained in the original sentinel sites of these districts.

Table 10: Survey site selection for LF Pre-TAS carried out in 12 districts in 2013

S. No.	District	Sentinel site	Spot-check site
1	Bonthe	Moboya	
	Moyamba		Mosenesie & Wubangay)
2	Koinadugu	Kumala & Yataya	
	Bombali		Kagberay
			Makaprr, Mayoba& Matak
3	Bo	Gelehun & Gborgborbu	
	Pujehun		Moala & Njaluahun
4	Port loko	Gbabai and Mamamah	
	Kambia		Yebaya
5	Kailahun	Manowa, Bunumbu & Madina	
	Kenema		Ngolahun
6	Kono	Tombodu & Penduma	
	Tonkolili		Massagble

Sampling and diagnosis

The survey teams met with community leaders upon arrival in communities and explained the nature of their work, after which, meetings were held with the general community to explain the study and its significance and respond to questions from community members before the study was conducted. At least 300 participants of five years of age or above were recruited per

site according to WHO guidelines (WHO 2011a). In sites with less than 300 participants, more participants were recruited in neighbouring villages. To ensure standardisation of activities and data, two-day practical training was conducted for all technicians before the study started. Fingertip blood was collected between ten pm and two am. A 60 µl blood sample was collected from each participant, smeared gently and uniformly in a circular shape and allowed to air dry at room temperature for 12–24 hours. The next day, the dried smear was dehaemoglobinized through flooding with distilled water for three–five minutes, air dried again, fixed with methanol for 30–60 seconds, stained with GIEMSA for ten minutes, and examined for MF under a light microscope by experienced examiners. Positive findings of MF were recorded, and individual MF density of infection was calculated and expressed as the number of MF per ml of blood (mf/ml). A total of 4,230 "midnight" blood samples were collected and examined for MF as shown in tables 11 and 12, male 2,275 (53.8%) and female 1,955 (46.2%). For quality control, all positive slides and 10% of the negative slides were preserved and examined by an experienced researcher. There were no false positives and no false negatives. The coordinates of each sample site were recorded using hand-held units of global positioning system.

Statistical analysis

Results were entered into MS Excel and analysed in SPSS (IBM, Version 23). Prevalence and density of MF were calculated for all 12 districts and compared with the midterm and baseline data. The 95% CIs for prevalence were calculated using the Wilson score method without continuity correction (Newcombe 1998). The arithmetic mean MF density of infection with 95% CI was calculated using the total population examined and the positive samples only (WHO 2005; Koroma *et al.* 2012). Treatment coverage was calculated according to the WHO guidelines (WHO 2011a). Epidemiological coverage was the percentage of people ingesting the drugs among the total population in the endemic districts. Programme coverage was the proportion of people ingesting the drugs among the total population targeted (or eligible for treatment) in the endemic districts. The total population used in rural areas was the total number of people registered during the pre-MDA census, while the total population used in urban/non-rural areas was the figure projected from the 2004 national census (Koroma, Turay, Moihua 2006), with an annual growth rate of 2.5% . A spatially smoothed contour map

showing summary results of the pre-TAS conducted after five rounds of MDA was produced (Zoure *et al.* 2011; Koroma *et al.* 2012).

RESULTS

Table 11 and 12 show LF MF prevalence, MF density for positives-only and MF density for the entire population studied at baseline, midterm (after 3 MDA rounds) and during the pre-TAS (after 5 MDA rounds).

MDA results 2011-2014

Annual MDA results for treatment with ivermectin and albendazole has been reported for the period 2011-2014 with 100% geographic coverage, ≥65% epidemiological coverage and ≥80% programme coverage[8]. See table 13 for details of treatment coverage for each district between 2011 and 2014. A total of 14,253 villages and urban areas were treated each year during the four years in the 12 districts. This represents 100% geographic coverage for endemic villages and urban areas in all 12 districts during each of these four rounds of MDA, as shown in Table 13. Over four million people were targeted for treatment each year during the four years. Overall epidemiological coverage was 75.9%, 79.6%, 80.3% and 78.2% in 2011, 2012, 2013 and 2014 respectively at the national level, and was ≥65.0% in each district in each round. The overall programme coverage was 94.9%, 93.6%, 94.5% and 91.8% in 2011, 2012, 2013 and 2014, respectively, and was ≥80% in each district in each round. The programme coverage is a measure of how well MDA was conducted and is considered adequate when ≥80.0% (WHO 2011a).

Microfilaraemia prevalence

In total 23 persons (0.54%, 95% CI: 0.36-0.81%) had a positive blood smear. Males had 0.7% (95% CI: 0.43-0.14%) MF prevalence and females had 0.36% (95% CI: 0.17-0.74%) MF prevalence. Males had higher MF prevalence although both were below 1% and the difference was not statistically significant (P=0.128970). Five districts (Bonthe, Kambia, Kenema,

[8] MDA results for the period 2008-2010 is discussed in the previous chapter (Koroma *et al.* 2013).

Moyamba and Tonkolili) had 0.0% MF prevalence; four districts had <0.7% prevalence (Bo-0.29%; Kono- 0.63%; Port Loko -0.28%; and Pujehun- 0.33%). Koinadugu district had 0.98% MF prevalence (close to 1%), and two districts had >1% MF prevalence: Bombali- 2.67%; and Kailahun- 1.56%. Thus, Koinadugu, Bombali and Kailahun are considered to have failed the pre-TAS because Bombali and Kailahun had MF prevalence ≥1% and Koinadugu had MF prevalence close to 1%. Two SCs were selected for Bombali district and one SCS had the 2.6% MF prevalence while the other had 0% MF prevalence. The district is considered to have failed when one site had more than 1% MF prevalence. Kenema district had 0% MF prevalence but was paired with Kailahun district with Kailahun having the SS and Kenema the SCS. Both districts are considered to have failed due to the pairing. Prevalence by age group, 5-14 years (N=1621), 15-20 years (N=515), 21-30 years (N=572), 31-40 years (N=547),41-50 years (N=414), and >50 years (N=561) was 0.19%, 0.1.75%, 1.22%, 0.18%, 0.48% and 0.18% respectively. The age groups 15-20 and 21-30 had the highest MF prevalence. The difference between the MF prevalence of the two age groups (15-20 and 21-30) and the MF prevalence of the other groups is statistically significant (P=<0.05).

Compared to the mid-term survey results, the overall MF prevalence increased from 0.3% to 0.54%. The MF prevalence among males increased from 0.35% to 0.70% (almost twice), while the MF prevalence among females increased from 0.25% to 0.36%. The three districts with MF prevalence close to or greater than 1% have recorded increase in MF prevalence: Bombali from 1.58% to 2.67%; Koinadugu from 0.80% to 0.98%; and Kailahun from 0.20% to 1.56%.

Compared with the baseline, overall MF prevalence decreased by 77.5%, from 2.40% to 0.54%, after five rounds of MDA. As shown in Tables 11 and 12, among the 11 districts with baseline MF prevalence ≥1%, five districts showed MF prevalence reduction of 100%; five showed MF prevalence reduction of >60% and only one district (Kailahun) had MF prevalence reduction of less than 50% (40%). There was 76.67% decrease in MF prevalence among males: 3.00% to 0.70%; and an 80.0% decrease in MF prevalence among females: 1.80% to 0.36%. There was 0.19% prevalence among the age group five-14 years, but this could not be compared, as the baseline study did not include participants <15 years. Decreases in MF prevalence among the age groups 31-40, 41-50 and >50 years ranged between 85.4% and 92.5%. However, the

reduction in prevalence among the age groups 15-20 and 21-30 were 2.78% and 53.08% respectively. Figure 17 shows predicted MF prevalence for each of the 12 districts after five annual rounds of MDA.

MF density

The overall arithmetic mean MF density was 0.15 mf/ml (95% CI: 0.08-0.21 mf/ml) in the total participants examined and 26.87 mf/ml (95% CI: 22.66-31.08 mf/ml) among MF-positive individuals. The mean MF density for all categories (district, sex and age groups) was well below one mf/ml for the population examined and below 42 mf/ml among those who were MF positive. There was no significant difference in MF density in males versus females ($p>0.05$). However, four districts had significantly higher density for the population studied: Bombali-0.69 mf/ml, 95% CI: 0.22-1.17 mf/ml; Kailahun-0.35 mf/ml, 95% CI: 0.05-0.64 mf/ml; Koinadugu-0.27 mf/ml, 95% CI: -0.05-0.60 mf/ml; and Kono-0.26 mf/ml, 95% CI: -0.11-0.63. The arithmetic mean MF density for the entire population studied was significantly higher within the age groups 15-20 years (0.49 mf/ml, 95% CI: 0.16-0.82) and 21-30 years (0.38 mf/ml, 95% CI: 0.08-0.68 mf/ml) compared to the other age groups.

Compared to results of the mid-term survey (see table 11 for details), the mean arithmetic MF density has increased significantly. The overall mean arithmetic MF density for the entire population studied increased from 0.05 mf/ml to 0.15 mf/ml and the overall arithmetic mean MF density for positives-only increased from 17.59 mf/ml to 26.87 mf/ml. The arithmetic mean MF density for the entire population studied for Bombali, Kailahun, Koinadugu and Kono and the age groups 15-20 years and 21-30 years also increased. At mid-term, the arithmetic mean MF density for the entire population studied was 0.26 mf/ml for Bombali, 0.03 mf/ml for Kailahun, 0.17 mf/ml for Koinadugu, and 0 mf/ml for Kono; and was 0.02 mf/ml and 0.10 mf/ml for the age groups 15-20 years and 21-30 years respectively.

Compared to baseline (see table 11 and 12 for details), the overall arithmetic mean MF density for the entire population studied dropped by 87.39% from 1.19 mf/ml to 0.15 mf/ml; and the overall arithmetic mean MF density for positives-only decreased by 46.58% from 50.30 mf/ml to 26.87 mf/ml. Among districts, the reduction of the arithmetic mean MF density for the

entire population studied ranges from 64.25% to 97.46%; and for positives-only ranges from 7.45% to 83.16%. Bombali district had the lowest drop in arithmetic mean MF density for the entire population studied (64.25%), and the lowest drop in arithmetic mean MF density for positives-only (7.45%). The reduction in arithmetic mean MF density for positives-only was also low for Kono district (9.30%) and Koinadugu district (20.92%). Reduction in arithmetic mean MF density for the entire population studied ranges from 37.18% for the age group 15-20 years to 96.63% for the age group >50 years. The reduction of the arithmetic mean MF density for positives-only ranges from 22.36% for the age group 31-40 years to 61.13% for the age group >50%. Thus, in general, the lowest reduction of MF density was in the age group 15-20 years and the highest was in the age group >50 years.

DISCUSSION

Our results show that the criteria for initiating TAS were achieved in eight districts after five effective rounds of MDA. This indicates that the NTDP has made remarkable progress towards LF elimination since integrated onchocerciasis/LF MDA using ivermectin and albendazole was piloted in 2007 (Koroma *et al.* 2013). Effective epidemiological (≥65%) and programme coverage (≥80%) and 100% geographic coverage were achieved for the 12 districts in 2008 (Koroma *et al.* 2013). The treatment coverage was verified through independent monitoring activities, as described previously (Hodges et al. 2011; Hodges et al. 2012). The epidemiological and programme coverage has been maintained at ≥65% and ≥80% respectively after the last assessment in 2010.

Prior to MDA, the endemicity of LF in Sierra Leone was one of the highest in Africa (Michael and Bundy 1997). Blacklock in 1922 examined 240 men in Mabang village and found 20% to be microfilaraemic, with the prevalence of elephantiasis and hydrocoele of 4.6% and 3.8%, respectively ((Blacklock 1926; Hawking 1957). Surveys in the early 1990s also showed an average MF prevalence of 34.8% in three villages in the Moyamba district (Gbakima, Pessima, Sahr 1996). In 2007-2008, the pre-treatment MF prevalence for the 12 districts outside the Western Area ranged from 0 – 6.9%, although prevalence was below 3% in the southeastern districts (Koroma *et al.* 2012). This significant reduction of MF prevalence from earlier high

levels prior to the start of the LF MDA coincides with the onchocerciasis treatment efforts of the 1950s, 1960s, 1980s, 1990s, and up to 2006 as described in previous chapters (Hodges *et al.* 2011). The significant impact of onchocerciasis treatment with ivermectin on LF infection has been reported in a number of countries (Kyelem *et al.* 2003; Kyelem *et al.* 2005). Therefore, it is likely that annual nationwide CDTI may have impacted significantly on LF infections in Sierra Leone, resulting in a relatively low level of MF prevalence at baseline. The successful implementation of the LF programme also benefited from the existing onchocerciasis control programme by using the CDTI as the platform (Bockarie, Kelly-Hope, Haskew 2010; Hodges *et al.* 2011). Health workers had already been trained and were available to provide technical support in additional training, supervision and surveys. Treatment was provided between September and December each year as this is the period that was found to be convenient for the communities (*i.e.* harvest and post-harvest period). All the lessons learnt from CDTI during the years of the NOCP were used to establish and improve the LF elimination programme within a short period (Bockarie, Kelly-Hope, Haskew 2010).

Five districts had 0.0% MF prevalence while 4 districts had <0.7% prevalence. Three districts have MF prevalence close to or above 1%. Thus, Koinadugu, Bombali and Kailahun are considered to have failed the pre-TAS because Bombali and Kailahun had MF prevalence ≥1% and Koinadugu had MF prevalence close to 1% (WHO 2011a). Since Kenema was paired with Kailahun district, it is also considered to have failed the pre-TAS even though the MF prevalence was 0% in an SCS. Compared to the mid-term survey results, there was an increase in overall MF prevalence and overall MF intensity. The three districts with MF prevalence close to or greater than 1% recorded an increase in MF prevalence after the mid-term evaluation. However, it is worth noting that MF prevalence detected after three MDAs does not demonstrate a change in filariasis transmission (Weil *et al.* 2008; Ashton *et al.* 2011). The drug combination destroys the microfilariae with each round of MDA, but treatment should be continued for up to the four-six year it takes for the adult worm to die a natural death (Ottesen 2000; Weil *et al.* 2008; Ashton *et al.* 2011). Therefore, MDA must continue each year for four-six years, which is equivalent to the lifespan of the adult worm.

The observation made with male/female MF prevalence during the pre-TAS could be explained by transmission dynamics as males may be more active and located outside during the biting periods of the mosquitos. It has been suggested that females may be more resistant to LF infection due to hormonal activity (Lammie *et al.* 1994). The age-related observation that has more active age groups (15-20 years and 21-30 years) being more infected could also be explained by the same transmission dynamics. As described previously, the MF prevalence and MF density increases with age, peaks between 15 and 25 years, and then declines gradually in higher age groups. It is also suggested that vector biting rates is higher in these age groups (Lammie *et al.* 1994). Four districts were considered to have failed the pre-TAS: two because MF prevalence was >1%; one because MF prevalence was close to 1%; and the fourth district because it was paired with one of the districts that had >1% MF prevalence. The controversy of the fourth district was discussed, and it has been decided that during the re-pre-TAS all four districts will each have one SS and one SCS so decisions can easily be made for each district. The NTDP had organised special social mobilisation and health education meetings in the four districts before MDAs were conducted in 2013, 2014 and 2015 that involved district council members, paramount chiefs, community leaders and community members. These were the same community meetings that were organised before MDAs between 2005 and 2008 to bring treatment coverage to what they are now after the poor performance of 2003 and 2004. The communities of the four districts that were considered to have failed the pre-TAS need to know the negative implication of the failure and the importance of better adherence although treatment coverage reported for the districts have been good.

It has also been suggested that the number of MDA rounds needed to eliminate LF depends on baseline infection rates, vectoral capacity, the efficacy of the MDA regimen used, and community adherence with treatment. It is possible to eliminate LF in some IUs with low baseline infection rates using less than five rounds of MDA, while more than six MDA rounds may be needed for IUs with relatively high baseline LF prevalence (El-Setouhy *et al.* 2007; Grady *et al.* 2007; Huppatz *et al.* 2009). The high level of reduction in MF prevalence and intensity in most of the districts after five rounds of MDA in Sierra Leone may have been partly due to the relatively low baseline MF level (Koroma *et al.* 2012). The relatively high baseline and pre-TAS MF prevalence and density for Bombali and Kailahun may be explained by this

theory. Three additional MDA rounds have been conducted by the NTD program after the pre-TAS in 2013, 2014 and 2015 that were preceded by good social mobilisation. The social mobilisation also involved district health workers so they are also aware that all villages should receive the same attention during MDAs because the selection of the SCS can lead to another failure that can create an "embarrassment" for the DHMT. Another suggestion made within the NTDP was that cross-border factors may be responsible for the persistent high MF prevalence and density in the four districts considered to have failed the pre-TAS because all four are located along the border (Bombali, Koinadugu and Kailahun with Guinea; and Kailahun and Kenema with Liberia). Both countries have not yet succeeded in establishing an LF programme that covers the entire country. High prevalence rates were recorded in neighbouring Liberia prior to the 1980s (Brinkmann 1977; Zielke and Chlebowsky 1979).

Some authors believe that *Anopheles* mosquitos are less efficient as LF vectors than *Culex* and so the large decrease in prevalence that has occurred in most of the LF-endemic districts after just five rounds of MDA may be due to this phenomenon (Weil *et al.* 2008). Many similar studies have been conducted in different countries to determine the impact of MDA on the prevalence and intensity of LF. It was demonstrated in Kenya that MF prevalence of 8 villages dropped from 20.9% to 0.9% after eight years of treatment even though MDA with diethylcarbamazine and albendazole was conducted only for four of the eight-year period. It was suggested by the authors that this results could be due more to high use of insecticide treated nets within these villages (Njenga *et al.* 2011). The impact of MDA with diethylcarbamazine and albendazole was measured after five rounds of MDA in four sentinel sites in Egypt with adherence rate >80%. In Giza, microfilaraemia rate fell from 11.5% to 1.2%, while in Qalubyia microfilaraemia rate reduced from 3.1% to 0% (Ramzy *et al.* 2006). Studies on LF conducted in Egypt showed that while residual infection rates were highest in those who reported never taking treatment, two doses were better than one dose and as effective as five doses for clearing MF (El-Setouhy *et al.* 2007).

Overall success of the NTDP in Sierra Leone has been due also to other factors such as the effect of LF treatment (ivermectin and albendazole) on soil transmitted helminthiasis (Ottesen *et al.* 2008; WHO 2015), effect on scabies and lice (Meinking *et al.* 1995; David, Flinders, De

Schweinitz 2004; Burkhart and Burkhart 2006; Moncayo *et al.* 2008), and the anecdotal so-called effect on 'male sexuality' as it is reported that older men become more virile when they take ivermectin. People have come to know the 'onchocerciasis' and lately the 'big fut' (or enlarged foot in English) treatment through earlier intensified social mobilisation within communities such that even after the EVD outbreak treatment coverage was still high within all communities targeted. Initial social mobilisation and health education had included talks on possible side effects relating to ivermectin. It was explained that the side effects are due to deaths of the worms (onchocerciasis or LF) due to the treatment and side effects reduce as treatment continues and the worm load reduces. Therefore, due to initial treatment for onchocerciasis with ivermectin within these districts, the number of adverse events reported has been few, and no severe adverse event has been reported during treatment for LF (unpublished NOCP/NTDP Reports 2005-2015).

This study has also shown the importance of having SCSs for monitoring the impact of MDAs for any control programme. The SCSs are randomly selected usually in consultation with DHMTs, and they are changed with each study. The SCSs to be chosen for the re-pre-TAS will be different from those selected before midterm and pre-TAS and the same SSs used at baseline will be chosen for districts where only SCSs have been selected at mid-term and pre-TAS. The SCSs and the way they are selected ensure that district health authorities and PHU staff give the same attention to all sub-district areas to ensure that coverage is good in every village and that future assessments end up with a 'pass' for their district.

There are several possible limitations of the study. Districts were paired to meet the WHO recommendation of having one SS and one SCS per one million populations such that one district had an SS while the other had an SCS. This appears to have created a problem in the interpretation of the pre-TAS results. Furthermore, the districts that were paired based on proximity and topographic features may not be so similar in relation to transmission dynamics as shown by the pre-TAS results of Kailahun and Kenema; Kailahun had >1% MF prevalence while MF prevalence was 0% for Kenema. The re-pre-TAS will be conducted with one SS and one SCS for each district to avoid a repeat of this situation. Having one SS and one SCS per district may also not be enough to ensure that all areas of a district are 'free' from the disease.

The number of sites currently selected for pre-TAS as recommended by WHO may be too small to be sure that the entire district is 'clean' from the disease. To address this, the village selected as SCS for the re-pre-TAS will be different from those used as SCS in the midterm and pre-TAS and will be selected in consultation with the DHMTs based on rumours and registration of signs and symptoms of the disease in the registers of the PHUs within districts. The night blood method used to determine MFs may not be the ideal method at this stage when prevalence and density are so low in all communities. It has been suggested that other methods that identify LF antigenaemia and/or antibodies may be better at this stage (Braga *et al.* 2003; Weil and Ramzy 2007). WHO currently recommends the use of a new tool (the FTS) that has replaced ICT cards for pre-TAS (WHO 2016c). The FTS will be used for the pre-TAS and TAS. The key difference between MF detection and use of FTS in terms of interpreting results is that the threshold for FTS will be 2% and not the 1% used for NBS/TBF. Another possible limitation is that it is impossible to compare baseline data for the ages five-14 years because this age was not studied at baseline based on previous WHO guidelines (WHO 2005; WHO 2011a). However, it is good to note that the ages five-9 years and 10-14 years had 0.14% and 0.22% MF prevalence during the pre-TAS. The age group five-14 years had 0.21% and 0.19% MF prevalence at mid-term and pre-TAS, respectively. This indicates low infection among children and indirectly shows that LF transmission has significantly reduced in the country.

CONCLUSION

There was a significant reduction of LF MF prevalence and density across the 12 rural districts in Sierra Leone that are coendemic for LF and onchocerciasis after five annual MDAs. Eight of 12 districts have passed the pre-TAS with <1% MF prevalence and now qualify for a TAS that has not yet been implemented due to the recent EVD outbreak. The other four districts need to conduct two additional rounds of MDA and repeat the pre-TAS (re-pre-TAS) (WHO 2011a). These relatively promising results were possible because of good MDA adherence and relatively low baseline endemicity. The results also show the importance of using SCSs for

monitoring programme implementation and that the LF elimination programme in Sierra Leone is on course to reach the objective of eliminating[9] LF by the year 2020.

[9] Elimination here is considered to be availability of evidence through the TAS that justifies stopping MDA in the whole country.

Figure 17: Map showing predicted LF MF prevalence for each of the 12 districts of Sierra Leone after five annual rounds of MDA

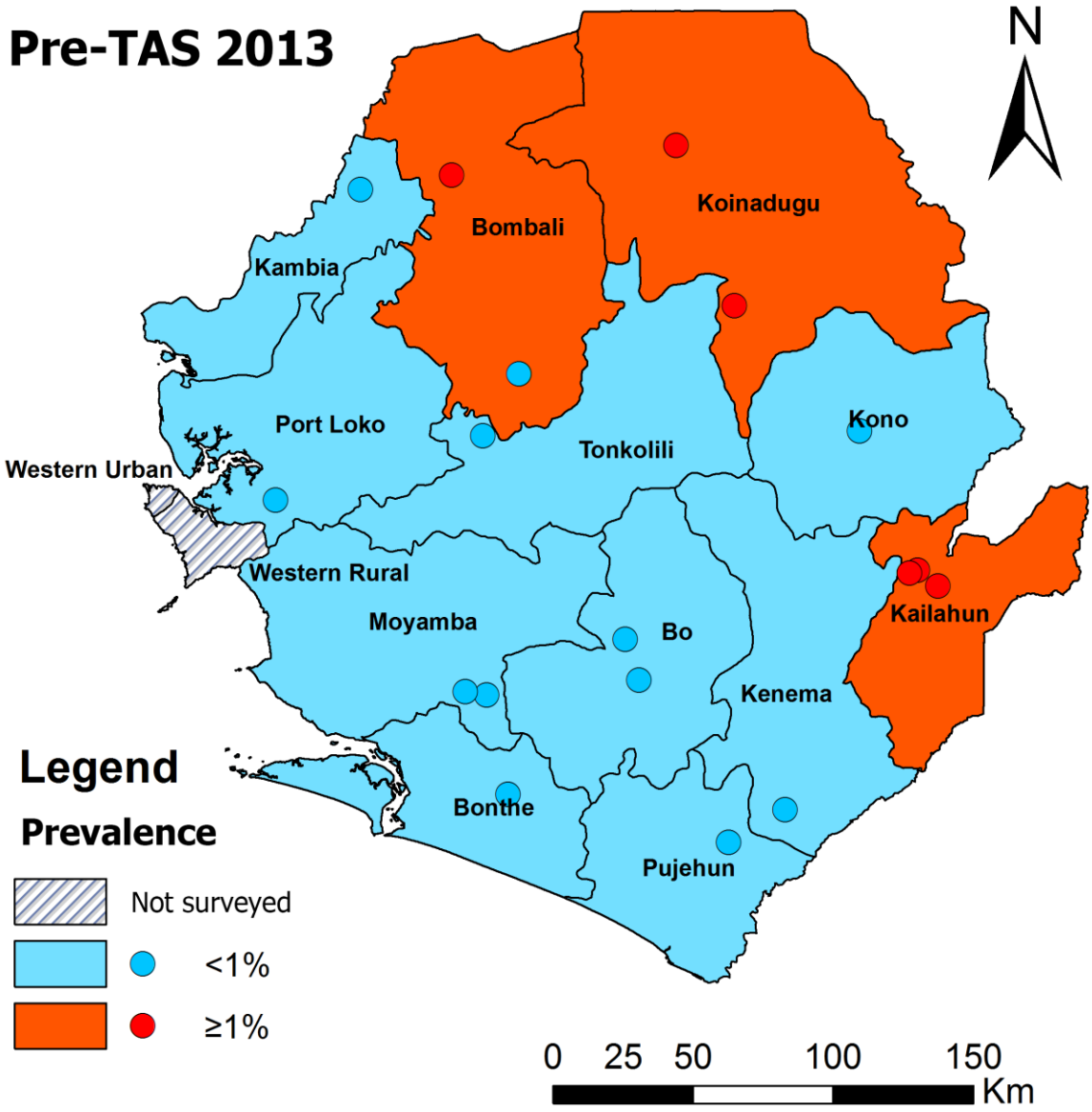


Table 11: Summary results for all LF studies in Sierra Leone from 2005 to 2013 in 12 districts

	Baseline survey				Mid-term				Pre-TAS			
	No of persons examined for MF	Percentage prevalence of MF positives (95% CI)	Population MF density (mf/ml) (95% CI)	Positive-only MF density (mf/ml) (95% CI)	No of persons examined for MF	Percentage prevalence of MF positives (95% CI)	Population MF density (mf/ml) (95% CI)	Positive-only MF density (mf/ml) (95% CI)	No of persons examined for MF	Percentage prevalence of MF positives (95% CI)	Population MF density (mf/ml) (95% CI)	Positive-only MF density (mf/ml) (95% CI)
Overall	9288	2.4 (2.1 - 2.7)	1.19 (0.90 - 1.48)	50.3 (39.89 - 60.71)	6023	0.30 (0.19 – 0.47)	0.05 (0.03 – 0.08)	17.59 (15.64 – 19.55)	4230	0.54 (0.36-0.81)	0.15 (0.08-0.21)	26.87 (22.66-31.08)
By district												
Bo	1005	2.0 (1.3 - 3.1)	1.97 (0.84 -3.11)	99.17 (58.32 - 140.01)	500	0	0	0	350	0.29 (0.05-1.60)	0.05 (-0.05-0.14)	16.7 (-)
Bombali1	830	6.9 (5.3 - 8.8)	1.93 (1.28 - 2.57)	28.07 (21.70 - 34.44)	506	1.58 (0.80 – 3.09)	0.26 (0.08 – 0.45)	16.67 (-)	337	2.67 (1.41-5.00)	0.69 (0.22-1.17)	25.98 (19.21-32.74)
Bombali2	-	-	-	-	-	-	-	-	303	0.00 (0.00-1.25)	-	-
Bonthe	504	1.2 (0.6 - 2.6)	0.83 (0.02 - 1.63)	69.44 (13.68 - 125.21)	499	0.20 (0.04 – 1.13)	0.03 (0 – 0.10)	16.67 (-)	309	0.00 (0.00-1.23)	-	-
Kailahun	624	2.6 (1.6 - 4.1)	2.08 (0.00 - 4.89)	81.25 (0.00 - 195.58)	499	0.20 (0.04 – 1.13)	0.03 (0 – 0.10)	16.67 (-)	385	1.56 (0.72-3.36)	0.35 (0.05-0.64)	22.27 (13.22-31.32)
Kambia	619	2.1 (1.2 - 3.6)	0.97 (0.23 - 1.71)	46.15 (17.04 - 75.27)	500	0.40 (0.11 – 1.45)	0.07 (0 – 0.16)	16.67 (-)	300	0.00 (0.00-1.26)	-	-
Kenema	1016	0.6 (0.3 - 1.3)	0.34 (0.00 - 0.70)	58.33 (4.42 - 112.24)	500	0	0	0	313	0.00 (0.00-1.21)	-	-
Koinadugu	636	5.7 (4.1 - 7.7)	1.99 (0.95 - 3.04)	35.19 (19.83 - 50.54)	498	0.80 (0.31 – 2.05)	0.17 (0 – 0.34)	20.83 (7.57 – 34.09)	305	0.98 (0.34-2.85)	0.27 (-0.05-0.60)	27.83 (3.88-51.79)
Kono	875	2.4 (1.6 - 3.6)	1.11 (0.37 - 1.84)	46.03 (20.09 - 71.97)	499	0	0	0	320	0.63 (0.17-2.25)	0.26 (-0.11-0.63)	41.75 (-64.35-147.85)
Moyamba	500	1 (0.4 - 2.3)	0.67 (0.00 - 1.36)	66.67 (6.33 - 127.00)	500	0	0	0	330	0.00 (0.00-1.15)	-	-
Port Loko	500	4.4 (2.9 - 6.6)	3.53 (1.48 - 5.59)	80.30 (44.49 - 116.12)	499	0.20 (0.04 – 1.13)	0.03 (0 -0.10)	16.67 (-)	357	0.28 (0.05-1.57)	0.09 (-0.09-0.28)	33.40 (-)
Pujehun	624	0 (0 - 0.6)	-	-	500	0	-	-	305	0.33 (0.06-1.83)	0.11 (-0.11-0.33)	33.40 (-)
Tonkolili	500	2.4 (1.4 - 4.2)	0.63 (0.24 - 1.03)	26.39 (17.99 - 34.79)	523	0.19 (0.03 – 1.08)	0.03 (0 – 0.10)	16.67 (-)	316	0.00 (0.00-1.20)	-	-

By sex												
Male	4335	3.0 (2.6 - 3.6)	1.66 (1.11 - 2.20)	54.42 (38.81 - 70.02)	3170	0.35 (0.19 – 0.62)	0.06 (0.03 - 0.10)	18.18 (14.80 - 21.56)	2275	0.70 (0.43-1.14)	0.19 (0.09-0.29)	27.14 (21.63-32.65)
Female	4953	1.8 (1.4 - 2.2)	0.78 (0.52 - 1.04))	44.13 (32.50 - 55.76)	2853	0.25 (0.12 – 0.51)	0.04 (0.01 - 0.07)	16.67 (-)	1955	0.36 (0.17-0.74)	0.09 (0.02-0.17)	26.24 (17.99-34.50)
By age groups												
5--9	-	-	-	-	-	-	-	-	716	0.14 (0.02-0.79)	0.02 (-0.02-0.07)	16.7 (-)
10--14	-	-	-	-	-	-	-	-	905	0.22 (0.06-0.80)	0.04 (-0.02-0.07)	16.7 (-)
5--14	-	-	-	-	1947	0.21 (0.08 – 0.53)	0.04 (0 - 0.09)	20.83 (7.57 – 34.09)	1621	0.19 (0.06-0.54)	0.03 (-0.00-0.07)	16.7 (-)
15-20	1873	1.8 (1.3 - 2.5)	0.78 (0.38 - 1.19)	44.44 (26.37 -62.52)	858	0.12 (0.02 – 0.66)	0.02 (0 - 0.06)	16.67 (-)	515	1.75 (0.92-3.29)	0.49 (0.16.-0.82)	27.83 (21.42-34.25)
21-30	2019	2.6 (2.0 - 3.4)	1.77 (0.73 - 2.80)	68.59 (31.79 - 105.39)	858	0.58 (0.25 – 1.36)	0.10 (0.01 - 0.18)	16.67 (-)	572	1.22 (0.59-2.50)	0.38 (0.08-0.68)	31.01 (20.36-41.67)
31-40	1830	2.4 (1.8 - 3.2)	1.01 (0.55 - 1.47)	43.02 (27.55 -58.50)	849	0.59 (0.25 – 1.37)	0.10 (0.01 - 0.18)	16.67 (-)	547	0.18 (0.03-1.03)	0.06 (-0.06-0.18)	33.40 (-)
41-50	1404	3.4 (2.5 - 4.4)	1.60 (0.94 - 2.27)	47.87 (32.75 - 62.99)	640	0.47 (0.16 – 1.37)	0.08 (0 - 0.17)	16.67 (-)	414	0.48 (0.13-1.74)	0.12 (-0.06-0.30)	25.05 (-81.05-131.15)
>50	2162	2.1 (1.6 - 2.8)	0.89 (0.49 - 1.30)	42.96 (27.40 - 58.53)	871	0	0	0	561	0.18 (0.03-1.00)	0.03 (-0.029-0.09)	16.7 (-)

Table 12: Comparison of results of baseline survey and Pre-TAS for LF in Sierra Leone

	Baseline survey			Pre-TAS			Percentage reduction from Baseline		
	Percentage prevalence of MF positives (95% CI)	Population MF density (mf/ml) (95% CI)	Positive-only MF density (mf/ml) (95% CI)	Percentage prevalence of MF positives (95% CI)	Population MF density (mf/ml) (95% CI)	Positive-only MF density (mf/ml) (95% CI)	MF prevalence (%)	Population MF density (%)	Positive-only MF density (%)
Overall	2.4 (2.1 - 2.7)	1.19 (0.90 - 1.48)	50.3 (39.89 - 60.71)	0.54 (0.36-0.81)	0.15 (0.08-0.21)	26.87 (22.66-31.08)	77.50	87.39	46.58
By district									
Bo	2.0 (1.3 - 3.1)	1.97 (0.84 -3.11)	99.17 (58.32 - 140.01)	0.29 (0.05-1.60)	0.05 (-0.05-0.14)	16.7 (-)	85.50	97.46	83.16
Bombali1	6.9 (5.3 - 8.8)	1.93 (1.28 - 2.57)	28.07 (21.70 - 34.44)	2.67 (1.41-5.00)	0.69 (0.22-1.17)	25.98 (19.21-32.74)	61.30	64.25	7.45
Bombali2	-	-	-	0.00 (0.00-1.25)	-	-	-	-	-
Bonthe	1.2 (0.6 - 2.6)	0.83 (0.02 - 1.63)	69.44 (13.68 - 125.21)	0.00 (0.00-1.23)	-	-	100.00	-	-
Kailahun	2.6 (1.6 - 4.1)	2.08 (0.00 - 4.89)	81.25 (0.00 - 195.58)	1.56 (0.72-3.36)	0.35 (0.05-0.64)	22.27 (13.22-31.32)	40.00	83.17	72.59
Kambia	2.1 (1.2 - 3.6)	0.97 (0.23 - 1.71)	46.15 (17.04 - 75.27)	0.00 (0.00-1.26)	-	-	100.00	-	-
Kenema	0.6 (0.3 - 1.3)	0.34 (0.00 - 0.70)	58.33 (4.42 - 112.24)	0.00 (0.00-1.21)	-	-	100.00	-	-
Koinadugu	5.7 (4.1 - 7.7)	1.99 (0.95 - 3.04)	35.19 (19.83 - 50.54)	0.98 (0.34-2.85)	0.27 (-0.05-0.60)	27.83 (3.88-51.79)	82.81	86.43	20.92
Kono	2.4 (1.6 - 3.6)	1.11 (0.37 - 1.84)	46.03 (20.09 - 71.97)	0.63 (0.17-2.25)	0.26 (-0.11-0.63)	41.75 (-64.35-147.85)	73.75	76.58	9.30
Moyamba	1 (0.4 - 2.3)	0.67 (0.00 - 1.36)	66.67 (6.33 - 127.00)	0.00 (0.00-1.15)	-	-	100.00		
Port Loko	4.4 (2.9 - 6.6)	3.53 (1.48 - 5.59)	80.30 (44.49 - 116.12)	0.28 (0.05-1.57)	0.09 (-0.09-0.28)	33.40 (-)	93.64	97.45	58.41
Pujehun	0 (0 - 0.6)	-	-	0.33 (0.06-1.83)	0.11 (-0.11-0.33)	33.40 (-)	-	-	-
Tonkolili	2.4 (1.4 - 4.2)	0.63 (0.24 - 1.03)	26.39 (17.99 - 34.79)	0.00 (0.00-1.20)	-	-	100.00	-	-
By sex									
Male	3.0 (2.6 - 3.6)	1.66 (1.11 - 2.20)	54.42 (38.81 - 70.02)	0.70 (0.43-1.14)	0.19 (0.09-0.29)	27.14 (21.63-32.65)	76.67	88.55	50.13
Female	1.8 (1.4 - 2.2)	0.78 (0.52 - 1.04))	44.13 (32.50 - 55.76)	0.36 (0.17-0.74)	0.09 (0.02-0.17)	26.24 (17.99-34.50)	80.00	88.46	40.54

By age groups									
5--9	-	-	-	0.14 (0.02-0.79)	0.02 (-0.02-0.07)	16.7 (-)	-	-	-
10--14	-	-	-	0.22 (0.06-0.80)	0.04 (-0.02-0.07)	16.7 (-)	-	-	-
5--14	-	-	-	0.19 (0.06-0.54)	0.03 (-0.00-0.07)	16.7 (-)	-	-	-
15-20	1.8 (1.3 - 2.5)	0.78 (0.38 - 1.19)	44.44 (26.37 -62.52)	1.75 (0.92-3.29)	0.49 (0.16.-0.82)	27.83 (21.42-34.25)	2.78	37.18	37.38
21-30	2.6 (2.0 - 3.4)	1.77 (0.73 - 2.80)	68.59 (31.79 -105.39)	1.22 (0.59-2.50)	0.38 (0.08-0.68)	31.01 (20.36-41.67)	53.08	78.53	54.79
31-40	2.4 (1.8 - 3.2)	1.01 (0.55 - 1.47)	43.02 (27.55 -58.50)	0.18 (0.03-1.03)	0.06 (-0.06-0.18)	33.40 (-)	92.50	94.06	22.36
41-50	3.4 (2.5 - 4.4)	1.60 (0.94 - 2.27)	47.87 (32.75 - 62.99)	0.48 (0.13-1.74)	0.12 (-0.06-0.30)	25.05 (-81.05-131.15)	85.88	92.50	47.67
>50	2.1 (1.6 - 2.8)	0.89 (0.49 - 1.30)	42.96 (27.40 - 58.53)	0.18 (0.03-1.00)	0.03 (-0.029-0.09)	16.7 (-)	91.43	96.63	61.13

Table 13: Summary of coverage for LF treatment conducted in 12 districts of Sierra Leone 2011 – 2014

	2011					2012					2013					2014				
	Population		Treatment Coverage			Population		Treatment Coverage			Population		Treatment coverage			Population		Treatment coverage		
Districts	Elig pop	Total pop	Total treated	Epid cov	Prog Cov	Elig pop	Total pop	Total treated	Epid cov	Prog Cov	Elig pop	Total pop	Total treated	Epid cov	Prog Cov	Elig pop	Total pop	Total treated	Epid cov	Prog Cov
Bo	444317	555397	427682	77.0	96.3	483417	568727	449508	79.0	93.0	494507	581774	459785	79.0	93.0	505875	595148	461300	77.5	91.2
Bombali	390424	488030	366980	75.2	94.0	424781	499743	399794	80.0	94.1	434550	511236	419077	82.0	96.4	444542	522991	406188	77.7	91.4
Bonthe	118597	148246	112424	75.8	94.8	128703	151416	120640	79.7	93.7	131676	154915	124719	80.5	94.7	134704	158476	126223	79.6	93.7
Kailahun	343508	429386	335567	78.2	97.7	373737	439691	349889	79.6	93.6	382142	449580	364629	81.1	95.4	390925	459912	359677	78.2	92.0
Kambia	258571	323214	244376	75.6	94.5	281326	330972	263822	79.7	93.8	287795	338583	270923	80.0	94.1	294409	346364	271964	78.5	92.4
Kenema	488245	610307	463162	75.9	94.9	531550	625354	501280	80.2	94.3	543408	639305	512759	80.2	94.4	555904	654005	509953	78.0	91.7
Koinadugu	300392	375491	282735	75.3	94.1	326826	384502	307878	80.1	94.2	334343	393346	318488	81.0	95.3	342027	402385	314522	78.2	92.0
Kono	358286	447858	342241	76.4	95.5	389816	458608	364975	79.6	93.6	398730	469095	382121	81.5	95.8	407896	479878	378940	79.0	92.9
Moyamba	261017	326272	238818	73.2	91.5	283987	334103	264863	79.3	93.3	290518	341787	270205	79.1	93.0	297197	349644	274331	78.5	92.3
Port Loko	399995	499994	378976	75.8	94.7	434034	510629	403508	79.0	93.0	444016	522373	415108	79.5	93.5	454223	534380	411029	76.9	90.5
Pujehun	188875	236094	176924	74.9	93.7	205496	241760	192140	79.5	93.5	210276	247385	198626	80.3	94.5	215110	237529	198516	83.6	92.3
Tonkolili	341039	426299	325639	76.4	95.5	370702	436121	345643	79.3	93.2	379193	446111	355057	79.6	93.6	387911	456366	353296	77.4	91.1
	3893266	4866588	3695524	75.9	94.9	4234375	4981626	3963940	79.6	93.6	4331154	5095490	4091497	80.3	94.5	4430723	5197078	4065939	78.2	91.8

*Geographic coverage of villages/urban areas was 100% in all 12 districts over the four years (2011-2014)

CHAPTER 7: IMPACT OF THE EBOLA OUTBREAK ON THE NTD PROGRAM IN SIERRA LEONE

ABSTRACT

Background

A qualitative study was designed to determine the effect of the EVD outbreak on the treatment for NTDs in Sierra Leone as part of the effort to understand the effect of the outbreak on NTD control. The findings of the study were used to advise the NTDP on the way forward for NTD control in the country after the EVD outbreak ends.

Methodology

The study was conducted through interviews using a simple questionnaire with open-ended questions and focus group discussion (FGD). Interviews using open-ended questions were used when high-level officials were interviewed and focus group discussions were used for PHU staff and CDDs.

Principal Findings

The EVD outbreak in May 2014 led to many deaths including the death of many health workers. The outbreak was controlled and declared over in November 2015 after a lot of improvement in treatment and diagnosis of the diseases. Although there was a delay of about a year in implementing MDAs, the NTDP has successfully completed two rounds of MDA since the outbreak, one of the two conducted while the outbreak was still ongoing in May/June 2015. However, all disease-specific assessments for LF and onchocerciasis were suspended till early 2017 for fear that the communities targeted will reject an intervention that involves blood and the skin. The importance of using CDDs, who are members of their communities, to treat their own people and intensified health education/social mobilisation for maintaining effective treatment coverage was highlighted.

Conclusions/Significance

Through the use of CDDs and intensified health education/social mobilisation the NTDP has conducted two MDAs with effective coverage including one that was conducted while the outbreak was ending. Intensive social mobilisation and health education must be continued for the MDAs and disease-specific assessments to maintain good community acceptance and adherence to the NTDP treatment and disease-specific assessments.

INTRODUCTION

Sierra Leone is a poor West African country that belongs to what MacKinnon and MacLaren (2012) describe as "fragile and conflict-affected states". The country's socio-economic and health indicators are among the worst in the world (UNDP 2015; African Health Observatory, WHO AFRO 2016). After going through a civil war between 1991 and 2002 that devastated the economy and almost brought the entire health care delivery system to a standstill, there has been significant progress since 2005 in controlling the PC NTDs in the country (LSTM 2014). Many partners of the MOHS, including partners of the NTDP such as the USAID NTDP, FHI 360, HKI, CNTD (now Known as FPSU) and Sightsavers, have been at the forefront of assisting Sierra Leone rebuild its health system since 2007 and significant achievements were being made in controlling the PC NTDs (LSTM 2014). Unfortunately, an EVD outbreak, which started in Guinea in December 2013 and had spread to neighbouring Liberia by March 2014 and Sierra Leone by May 2014, appeared to be a threat to all the achievements made in the fight against NTDs in the country (Bociaga-Jasik *et al.* 2014; Dixon *et al.* 2014; LSTM 2014; Greiner *et al.* 2015; Boisen *et al.* 2015; Hersey *et al.* 2015; Lu *et al.* 2015; Gleason *et al.* 2015; Lokuge *et al.* 2016).

The outbreak appeared to be having negative impact on the human resources for health and the negative effect on the socio-economic situation in the country (Helleringer and Noymer 2015; Brolin-Ribacke *et al.* 2016; Fitzgerald *et al.* 2016). The NTDP has had to address the weak human resources for health in the country by using the community directed treatment with Ivermectin plus albendazole strategy in its efforts to eliminate onchocerciasis and LF in the country (Bockarie, Kelly-Hope, Haskew 2010; MacKinnon and MacLaren 2012; Koroma *et al.* 2013). It appeared at the height of the outbreak that health workers were more at risk of dying from the disease (Kilmarx *et al.* 2014). All NTD and other public health program activities were suspended in the country for about a year as the outbreak spread to all 14 districts. The situation improved significantly early in 2015, and the outbreak was declared over on 7th November 2015 albeit with warnings from WHO of possible flare-ups after the declaration (GoSL 2015).

The author made several visits to the country between May 2015 and November 2015 to support the NTDP in understanding the effect of the outbreak on the NTD program and determine the way forward for NTD control/elimination in the country including planning the restart of the programme. A qualitative study was designed to determine the effect of the EVD outbreak on the treatment for NTDs in Sierra Leone as part of the effort to understand the impact of the outbreak on NTD control. The findings of the study were used to advise the NTDP on the way forward for NTD control in the country. The visits were organised against the background that some authors were referring to the EVD as an NTD (Troncoso 2015) and there were also calls to simultaneously deal with EVD and NTDs within the affected countries (Hotez *et al.* 2015).

Two visits were organised in early May 2015 and September 2015. The objectives of the interviews were:

a. To determine when and how NTDP activities can be restarted in the country.
b. To determine the effect of the EVD outbreak on the NTD capacity in terms of staff loss and staff morale towards the NTDP.
c. To determine attitude changes towards the NTD program within affected communities in terms of adherence to treatment.
d. To document positive changes that may have taken place within the health system while addressing the outbreak that can strengthen the health system in general and therefore the NTDP.

METHODS

Ethics statement

The interviews were conducted by the author with administrative support from the NTDP at national and district levels. All meetings were pre-arranged through the NTDP at the different levels. Ethical approval for the study was obtained from the Ethics Committee of the MOHS. The information obtained was filtered and only information relevant to the NTDP is reported in this chapter. The author first explained the objectives of the study and obtained the consent of those interviewed and the participants of the FGDs before interviews/discussions were

conducted. All those interviewed were adults. The analysis of the information obtained is conducted such that no individual's identity can be revealed upon publication of the results.

Interviews and FGDs

The study was conducted through qualitative research methods - interviews using a simple questionnaire with open-ended questions, and FGD. Interviews with open-ended questions were used for senior personnel of the GoSL (a representative of the Office of the President, a representative of the National Ebola Response Centre (NERC), senior officials of the MOHS, NTD partners- HKI, Sightsavers, WHO Country Office, and the DMOs. This first part was accomplished in early May 2015 over a year after the last MDA was completed in March 2014. The FGDs were conducted in September 2015 among PHU staff and CDDs. CDDs as members of their communities gave an insight into the community aspects of what was required in the study. All interviews and FGDs were recorded mostly in the vernacular (Krio) to allow people to express themselves freely.

Interviews were conducted on six levels:

(1) National level interviews with representatives from the Departments/agencies that were coordinating the Ebola response within the GoSL (the Office of the President and the NERC);

(2) Interviews with representatives of NTD partner organisations- WHO Country Office in Freetown, Sightsavers and HKI Sierra Leone;

(3) National level interviews within the MOHS- senior officials including the Director of PHC, the DPC Director that supervises the NTDP, and the NTD Program Manager;

(4) Interviews with the DHMTs (DMOs and selected members of the DHMTs);

(5) FGDs with PHU personnel who serve as coordinators of the NTD program within chiefdoms and villages); and

(6) FGDs with CDDs.

The first three interviews above were conducted in the capital Freetown while the district level interviews and FGDs were conducted in only four of the 12 LF/onchocerciasis coendemic districts: Port Loko and Bombali district in the north; Bo district in the south and Kenema district in the east. It was assumed that the districts selected will be representative of the other

districts within their regions. While the same set of questions were used in all interviews, the questions were adjusted depending on the person being interviewed: interviewing health workers was different from interviewing non-health workers, and so questions were modified accordingly.

Analysis of information

No specific method was used to analyse the results. The results discussed in this chapter are obtained after listening to the recording of the interviews and the FGDs. The interpretation of the results is based on what was recorded during the interviews and have been filtered to show general EVD-related issues and issues that directly or indirectly relate to NTDP in Sierra Leone.

RESULTS

May 2015-Interview with a representative of the Office of the President: the main objective of this interview was to know the position of the GoSL on allowing the restart of public health programmes while the outbreak was still ongoing albeit on a small scale. By May 2015 only a few cases were still being detected in a district that borders with neighbouring Guinea (the Kambia district). The ban on travelling and curfew starting at nine pm daily was still being maintained, but the Government was aware of the non-Ebola morbidity and deaths occurring because of the restrictions and suspension of public health interventions. The Government had already started engaging the public health programmes, DHMTs and NGOs to see how interventions can be started without any negative impact on the achievements made to control the outbreak. The President himself had led the social mobilisation campaign and had visited all the districts multiple times to get the communities to adhere to the restrictions on movement imposed and also for people to collaborate with the Ebola Response Team. As Malaria is the leading cause of mortality in the country, the Malaria Control Programme was prioritised and allowed to conduct mass treatment in the entire country in March 2015 and the campaign appeared successful. The GoSL was prepared to allow other community-based programmes such as treatment for onchocerciasis and LF conducted by CDDs to be implemented since community members do most of the work. The second argument put

forward to the GoSL representative was that the tablets that will be given to the people would not pose any danger to them.

May 2015-Interview with a Representative of the National Ebola Response Centre (NERC): This visit was with the same objective as above, and similar sentiments were expressed: the restrictions on movement and the 9 pm curfew had to be maintained because they were yielding the right results in controlling the outbreak, but after the successful malaria campaign, other community-based campaigns can be considered. It was suggested that the NTDP coordinate directly with the district Ebola response centres (DERCs) for successful implementation of the MDA campaign.

Interviews with Representatives of NTD Partner Organizations- HKI, Sightsavers and the WHO Country Office: The most negative aspect of the outbreak was that the masses had lost all their trust in the health system. Health workers to some extent were seen as carriers of the disease. The need for intensive health education and social mobilisation was noted. HKI, as the subgrantee in Sierra Leone for the USAID-supported END in Africa project, had already put a team together to develop messages on NTDs that reminds people of the onchocerciasis/LF treatment and explain that NTD is not linked with EVD. It was decided that the first MDA to be conducted should be preceded by a month of social mobilisation and CDDs must be at the forefront of this campaign. Posters, banners, brochures and jingles had already been developed and ready for use. It was reported that all NTD Partners were involved in the Ebola response. HKI worked on educating commercial bike riders about the disease and how they can avoid being infected. Sightsavers supported activities in a few treatment centres. The Disease Prevention and Control Advisor of the WHO Country Office in Sierra Leone blames the delayed response by the MOHS and WHO on bureaucracy because the MOHS and WHO still wanted to adhere to financial rules and regulations during the outbreak. This was however addressed when the government declared a State-of-Emergency and WHO declared the outbreak a public health emergency of international concern. Access to funds and therefore logistics became better (Bociaga-Jasik *et al.* 2014; Dixon *et al.* 2014; Hersey *et al.* 2015; Bogoch *et al.* 2015).

Interviews with Senior Officials of the MOHS: "We were caught with our pants down" was the statement from a MOHS official. There was almost zero knowledge on the management of an EVD outbreak among health workers, and when messages on EVD were disseminated nationwide, the communities refused to accept what was passed on. This led to many 'conspiracy theories' about the origin of the disease. Initially, the MOHS was accused of exaggerating the seriousness of the disease to get donor funds until the high death rate became the convincing factor for the communities. Community response and collaboration with the Ebola Response improved only when the death rate became high. The MOHS had set up an Emergency Operation Center (EOC) with a Task Force that was jointly chaired by the CMO and the WHO Representative in the country. The role of the Task Force and the EOC became minimal as the masses lost confidence in the health services. There were reports of health workers being chased out of villages. The situation had to be controlled through the forces, and the MOHS was relegated to playing the role of advisors. During the visit, it was noted that the MOHS had seconded two senior officers to the NERC: The Director of PHC and the National Surveillance Manager, in addition to other cadres. In May 2015, the outbreak was still ongoing in the capital Freetown and a few northern districts. The reason for that was that the outbreak had initially started in the eastern district of Kailahun and people in the other regions tended to think that the disease would stay in the east. Health education messages on how to avoid the infection were disseminated nationwide, but it appeared that the eastern and southern districts adhered better to them than people in the north. The figures on death among health workers was not available with the MOHS officials but the media reported EVD-related death of an estimated 200 health care workers. However, the number of medical doctors that had died was given as 11 in May 2015.

Interview with the NTDP manager: When the outbreak was declared in May 2015 all public health programme activities stopped, the personnel of the public health programmes were posted to Ebola treatment Centres (ETCs) and the NTDP manager was in charge of the of the ETC on the outskirts of Freetown (in Hastings). Other NTDP staff were also involved in the outbreak response. All MOHS personnel were posted and obligated to play a role in the outbreak response. Vehicles belonging to the NTDP were also 'borrowed' and use for outbreak response. It was reported that the vehicles became worn out and were not replaced by the

GoSL. This meant that vehicles had to be rented for implementation of future NTDP activities. The NTDP was prepared and ready to work with partners to restart NTD interventions. All NTDP vehicles were part of the outbreak response. In the districts, PHU staff and CDDs were either in ETCs or served as contact tracers and specimen collectors. The NTD partner organisations were all involved in the outbreak response by either supporting ETCs or working with specific social groups to improve knowledge on EVD.

Interviews with 4 DMOs: The interviews with the DMOs was more to advocate for their support to have MDAs for NTDs restarted. All the four DMOs interviewed recognised that the suspension of other health interventions was leading to many unreported deaths within communities, possibly higher than that reported for the EVD. The DMOs readily accepted the need for restarting public health programmes such as the LF/onchocerciasis MDA and were ready to use the Ebola Response System within districts to conduct the MDA. The reason for this is that human resources for health are limited especially in the rural areas and in general the same staff are used for all health-related interventions including those for the EVD. CDDs are currently accepted as part of the district health workforce due to the CDTI strategy. For the Ebola response, CDDs were being used mostly as contact tracers while health workers managed EVD treatment centres or served as specimen collectors.

FGDs with PHU Staff and CDD: During the discussion, the PHU staff showed good knowledge of the disease and indicated that they have been trained on the disease and were also well equipped with enough medication and logistics to prevent themselves and patients from the disease. Initially, most of the PHU staff had heard of the diseases but linked the disease with East Africa. So when the disease was announced, the announcement was met with scepticism until many people started dying. In the Kailahun district, many health workers died in the first three months of the outbreak, and most health workers abandoned their PHUs. They returned because NGOs partners came in with necessary logistics and financial incentives for health workers. Health workers served as specimen collectors from suspected cases, and some were responsible for EVD treatment units. Most of the PHUs were used as EVD treatment units. Contact tracers were selected from each community/village, and most of the people selected as contact tracers were CDDs. They had the responsibility of investigating

to find out all those who had contacted anyone who was suspected of the disease so they can be isolated and observed for 21 days. The most obvious negative effect was that NTDP interventions were suspended during the outbreak. They believed that there were no other negative effects because the use of CDDs for treatment served well to allay the fears of communities. They trusted their own more than the health workers so complied well with the last MDA in May-July 2015.

At the onset of the outbreak there was also a complete breakdown of the health services for various reasons: the health system was unprepared for the outbreak (health facilities did not have PPEs, medications for treating cases, and a large part of the health service personnel did not know how to handle the infection, and so lost the respect of the general population. At some point, people who fall ill were kept away from the health workers because there was a fear they (the sick) were 'being killed' by health workers. Health workers themselves at some point realised that treating people could lead to contact with those infected and deserted the health facilities. Diagnosis of EVD was late in the initial part of the outbreak and those infected were kept together with those not infected in health facilities. Poor triaging meant that those who were not infected with the EVD were kept together with those infected with the disease and this led to the nosocomial spread of the disease. Consequently, many people with other diseases that had symptoms similar to the EVD symptoms lost their lives by seeking help in health facilities. At the peak of the infection, when there were many deaths, it appeared to people that all those taken from their houses ended up dying. Being picked up by the response team signalled death to many people during the peak of the outbreak. A few people believed that Ebola patients were being killed deliberately instead of being treated to stop the spread of the infection. It was also thought that health workers were trying to make the situation looked worse than it was to attract donor funding. There were other allegations of corruption within the MOHS. At the peak of the infection around September 2014, there was a complete mistrust of the health system and the government in general. The government had to use the forces to take control of the situation, and the Minister of Defence was appointed the head of the NERC to enforce all decisions. It was noted that tablets are seen as not so dangerous especially when given by CDDs who are members of communities. However, it was advised

that any intervention such as surveys for LF and onchocerciasis that involve blood and touching of the skin should be avoided.

The current surveillance system for EVD is that community members mostly CDDs now called 'community health workers' are trained to report any unusual occurrences within their communities to the DHMT who will immediately alert the surveillance programme within the MOHS and action is supposed to be taken within 48 hours. Action should include the visit of a team including surveillance officers from the national level and surveillance officers from the DHMT to the village and examination of the person with the unusual symptoms/signs. Action to be taken afterwards depends on the findings. The MOHS officially took over this responsibility from the NERC when the outbreak was declared over in November 2015.

The positive aspect of the EVD in relation to NTDs is that there is significantly more laboratory in the country with more people trained on laboratory methods that can be invited to support NTD-related evaluations within districts. It was noted that the delay of one year in implementing the MDAs meant that communities were eager to receive the treatment. The use of CDDs who are members of their respective communities for drug distribution has a positive impact on adherence to treatment. It was believed that during the EVD outbreak transmission of onchocerciasis and LF had to be minimal because of the many years of MDA and because there was minimal movement between districts due to the ban on movement between districts and the curfew imposed. The belief is that the epidemiological situation should not have changed much since people were forced to remain within their immediate environs during the outbreak. This is different from the civil war when mass movement took place, and the two diseases were spread nationwide.

Because of the initial findings in May 2015, a meeting was held with HKI, Sightsavers and the DPC Advisor for WHO and a date was set for the start of integrated MDA for LF and onchocerciasis. This visit was used to convince the donor USAID that it was possible and not a waste of money to conduct MDA at that moment. MDA was started at the end of May and was allowed to continue till mid-July 2015 so that coverage can be as high as possible. Even though it appeared as if MDA can be conducted within communities, the findings indicated that any

attempt to conduct diseases specific assessments that involve blood and skin (assessments for LF and onchocerciasis respectively) will be rejected and so all DSAs relating to LF and onchocerciasis were postponed for at least 12 months and intensive social mobilization will be needed to help improve acceptance and participation within communities.

DISCUSSION

It is interesting to note that EVD has been called an NTD (Troncoso 2015). The LSTM (2014) highlighted the possible negative effect that the outbreak could have on NTDs. Hotez (2015) advised simultaneous interventions to address the EVD and NTD problems. The first question that needed an answer for the NTDP in Sierra Leone was when and how to restart MDAs for the NTDs after such deadly outbreak that had forced a whole country to shut down? Discussions with different people at the highest level revealed that it was already known that people were also dying from other causes besides EVD and public health programmes had to be started (Helleringer and Noymer 2015). Through negotiations, the LF/onchocerciasis MDA became the second large-scale public health intervention in May 2015 after the Malaria campaign in March 2015. The treatment period was extended so that as many people as possible could be treated. The MDA results for the onchocerciasis/LF MDA was better than expected mainly because of the use of CDDs for community drug distribution as they are also members of their respective communities (Bockarie, Kelly-Hope, Haskew 2010; Hodges *et al.* 2011; Koroma *et al.* 2012). Two effective rounds of MDA have since been conducted in 2015 and 2016. However, it was decided that disease-specific assessment for onchocerciasis and LF will be conducted one whole year after the end of the outbreak. The TAS in 8 districts and pre-TAS in 6 districts are now planned for early 2017 over a year after the outbreak was declared over.

The media announced that an estimated 200 health workers died from EVD, but this could be an underestimation because the information of EVD among health care workers (Olu *et al.* 2015) provides a completely different picture from what was previously reported. Kilmarx *et al.* (2014) reported that about 5.2% of EVD positive cases were health workers and in the Kenema district up to 12.9% of the positive EVD cases were health workers. The numbers reported by

the media on EVD-related deaths among health workers do not add up because the final figures from WHO are a total of 14,123 people infected and 3,956 deaths from EVD (WHO 2016e). However, given the already poor human resource situation in the country, any number of deaths among health care workers creates an extra burden for the health services (Fitzgerald *et al.* 2016). The numbers announced did not report for CDDs that died, and to date, there is no detailed report on the number of CDDs that died. It was, however, easier to know that 11 doctors died because the death of doctors received more media coverage. The magnitude of the outbreak, especially in Sierra Leone, showed the fragility and weakness of the health system and the country succeeded in controlling the outbreak only through the help of NGDOs (Gursky 2015; Fitzgerald *et al.* 2016). With the death of over 200 health workers (this does not include CDDs), the already bad human resource for health situation has deteriorated further (Kilmarx *et al.* 2014, Fitzgerald *et al.* 2016). During the outbreak access to essential health services was almost zero (Brolin Ribacke *et al.* 2016). Therefore, the non-EVD related deaths could have been high although difficult to determine. Some experts have suggested that life expectancy in the country dropped due to the EVD outbreak and could be the same as the immediate post-war period (Helleringer and Noymer 2015).

Boyles (2015) and Gleason *et al.* (2015) also reported that there was a delay in diagnosing EVD cases initially that had led to nosocomial transmission and many avoidable deaths. However, significant progress was made towards the end of the outbreak that led to the control of the outbreak that was declared over in November 2015 (Bogoch *et al.* 2015).

The positive aspect of the EVD in relation to NTDs is that there are significantly more laboratories in the country with more laboratory trained personnel who can participate in NTD evaluation studies. It was reported that the delay of one year in implementing the MDAs made communities even ‘eager’ to receive the onchocerciasis/LF treatment probably because of the additional benefits communities get from the treatment such as deworming of children and adults (Ottesen *et al.* 2008; WHO 2015), and the effect on scabies and lice (Meinking *et al.* 1995; Burkhart, Burkhart 2006). The CDDs who are members of their respective communities served as a bridge between the NTDP and communities and thus contributed to improving community adherence to treatment. The district health workers believed that transmission of

both LF and onchocerciasis was limited during the outbreak firstly because the situation was already good for both diseases (low prevalence and density) before the outbreak, and also because of the restriction of movement between districts, several 'lock downs', and curfew imposed during the outbreak. They expect results to be good because the NTDP would have conducted two rounds of MDAs before the next diseases specific assessment early in 2017.

A similar review of the situation in Liberia concluded that there is a high degree of community trust in the MDAs conducted for NTDs, but concerns were expressed that the coverage may be relatively worse that before because there is fear within communities that EVD and MDAs for NTDs may be linked. These were the same fears expressed in Sierra Leone and are being addressed currently with the help of CCDs and intensified social mobilisation with positive results (Bogus *et al.* 2016).

CONCLUSION

The EVD outbreak that started in the country in May 2014 led to many deaths including the death of many health workers. The outbreak was controlled and declared over in November 2015 after a lot of improvement in treatment and diagnosis of the diseases. The PHUs in the entire country are prepared for any resurgence of the EVD as they have received adequate training and logistics to manage and report EVD cases. There was an ongoing surveillance within communities lead by community health workers to detect any strange health-related occurrences within communities. Although there was a delay of about a year in implementing MDAs, the NTDP has successfully completed two rounds of MDA since the outbreak. However, disease-specific assessments were suspended till early 2017 for fear that the communities targeted will reject an intervention that involves blood and the skin. Intensive social mobilisation and health education must be continued for the MDAs and disease assessments to maintain good community acceptance of the NTDP and adherence to treatment and assessments.

QUESTIONNAIRE (Open ended questions used for the interviews and FGDs)

1. What do you know about the Ebola Virus Disease (EVD)?
2. Did you know anything about the disease when it was announced?
3. Did you believe that it was real when announced?
4. If no, why did you not believe it was real?
5. What changed your perception of the disease?
6. How did you learn about Ebola- cause, prevention, what to do and how not to get the disease?
7. Were you affected by the disease? How? Please explain.
8. What have you done to help combat the disease? Have you been involved in any Ebola response?
9. What did you have to go through during this outbreak? What were the challenges encountered? How did you overcome them?
10. How is the surveillance system set up to detect EVD currently?
11. In what way is the EVD experience affecting the NTD program currently?
12. We need to understand peoples' beliefs to bring change. What were/are the fears within communities in relation to NTD treatment and research studies?
13. Do you think communities are prepared to accept onchocerciasis/LF treatment?
14. How can we get people to trust the health system again and the NTDP?
15. Can you think of any positive change that has taken place within the MOHS?

CHAPTER 8: WAY FORWARD FOR ELIMINATION OF ONCHOCERCIASIS AND LF

INTRODUCTION

While the NTDP has reached the 'end game' for LF, there is still some work needed for the elimination of onchocerciasis. In this chapter what has to be done between now and the WHO verification of elimination of both diseases in the country is discussed.

It should be noted that both diseases (onchocerciasis and LF) have a lot in common. Diagnosis of both diseases is done at an individual level to define the population at risk and population eligible for MDA, and also to monitor the impact of MDA (Taylor, Hoerauf and Bockarie 2010). LF and onchocerciasis are parasitic diseases that constitute a serious public health problem in tropical regions of the world (including Sierra Leone), the filarial nematodes that cause these diseases are transmitted by blood-feeding insects, and both diseases produce chronic and long-term infection by suppressing the immunity of the host (Taylor, Hoerauf and Bockarie 2010). The pathogenesis of both diseases is linked to inflammatory processes within the host that are triggered by the death of the parasites thus causing hydrocoele, lymphoedema, and elephantiasis for LF, and skin disease and eye disease (including total blindness) for onchocerciasis (Taylor, Hoerauf and Bockarie 2010). Among the eight filarial nematode species that have a human host, three produce disease-causing infections among which two are responsible for LF (*W. bancrofti* and *B. malayi*); and the third disease-causing species is *O. volvulus*. LF affects an estimated 120 million people globally while *O. volvulus* affects more than 37 million people globally in 34 countries and is most prevalent in Africa (Taylor, Hoerauf and Bockarie 2010).

Policies for implementation of programs for the two diseases present challenges and opportunities as not all elements of mapping, monitoring and surveillance can be integrated during programme implementation. New opportunities for integration besides integrated MDAs for the two diseases are many although research is still needed to advance the integration of interventions for the two diseases (Baker *et al.* 2010). Programmes for control and elimination of both diseases have been developed and established in Sierra Leone to provide sustained delivery of drugs to affected communities for the interruption of transmission of the diseases and ultimately to eliminate their burden on public health. Drugs

for integrated filariasis treatment in Sierra Leone include ivermectin, and albendazole, which are used in combination to reduce microfilariae in blood for LF, and the skin for onchocerciasis (Taylor, Hoerauf and Bockarie 2010).

WAY FORWARD FOR ELIMINATION OF ONCHOCERCIASIS IN SIERRA LEONE

The WHO has set the goal of eliminating onchocerciasis in selected African countries by 2020 (WHO 2016b). Six annual rounds of integrated onchocerciasis/LF treatment have been conducted since the last onchocerciasis evaluation in 2010 (2010-2015) with effective treatment coverage (100% geographic coverage, ≥65% epidemiological coverage and ≥80% programme coverage). An onchocerciasis evaluation is planned for early 2017 in the same 39 sentinel sites that were evaluated in 2010 to determine the MF prevalence and MF density after 13 years of treatment (2003-2015). Effective treatment coverage has so far been reported for only nine of the 13 years: 2003 and 2004 treatments had poor coverage, 2005 treatment could not reach the effective coverage for all districts, and 2015 treatment results are yet to be released by the NTDP. The study will be done 11 months after the last treatment for 2015 before the 2016 treatment is conducted in the first half of 2017 (Katabarwa *et al.* 2008; Katabarwa *et al.* 2012; Katabarwa *et al.* 2013). These MDAs are usually conducted in October-December each year, but in the past three-four years, the NTDP has had to conduct MDAs later than planned in the first quarter of the following year. This delay was exacerbated by the EVD outbreak, and MDAs continue to be delayed and conducted in April-June of the following year. The NTDP is committed to pushing the MDA period backwards so they can be completed latest in the first quarter of the following year. The NTDP is contemplating using a newly developed tool (OV16 rapid diagnostic tests (RDTs)) for future onchocerciasis evaluations. Details of this tool are discussed below (Weil *et al.* 2000; Lipner *et al.* 2006; Golden *et al.* 2016). The sampling and registration of participants will be the same as described in chapters 3 unless new guidelines on monitoring the impact of MDA on onchocerciasis is developed and the survey methodology will be adjusted accordingly.

Assuming results of the 2015 treatment will be good, the results of the next onchocerciasis evaluation in 2017 will determine the impact of ten effective annual rounds of MDAs. It is recommended that one site per district be selected as spot check site in addition to the 39 sentinel sites for future onchocerciasis evaluations to ensure that reductions in MF prevalence occur evenly in all areas treated. A decision on the way forward will be made based on the results of the evaluation. However, it is speculated and projected that at least another five years of effective MDA will be needed to bring the number of effective rounds of MDA to 15 and reduce the onchocerciasis MF prevalence to 0% or close to 0% in all sentinel sites so that stop-MDA evaluations can be conducted (WHO 2016d). Current WHO guidelines indicate that 15-17 years of treatment is needed for onchocerciasis to reduce the MF prevalence to 0% or close to 0%. The years of treatment considered here are those for which effective epidemiological and programme coverage was achieved and geographic coverage was 100% (2006-2013, 2015, 2016). It is assumed that 15 years of treatment will be enough for the NTDP in Sierra Leone to reach 0% or close to 0% for onchocerciasis based on the results of the study after five effective rounds and also because it is believed that treatment before 2006 will also have an impact even though coverage was not effective. The additional five MDAs after 2016 will be carried out between 2017 and 2021 and during this treatment period surveys will be conducted to determine the impact of MDAs (WHO 2016d). However, the question that is still outstanding in relation to impact assessment for onchocerciasis is that the threshold for deciding when to move to stop-MDA evaluation has still not been determined for onchocerciasis as it is for LF (<1% MF prevalence or <2% antigenaemia prevalence) (WHO 2011a). The threshold must be different for skin snip method that detects MFs and the OV16 RDTs that detects antibodies to the onchocerciasis OV16 antigen (Weil *et al.* 2000, Lipner *et al.* 2006). Assuming the right results are attained with these studies conducted, stop MDA onchocerciasis evaluation will be conducted as described below in 2022. The results of the stop-MDA evaluations will be reviewed by an onchocerciasis elimination committee (OEC) that will also advise the NTDP on whether to stop MDA or not based on the stop-MDA evaluation results. A post-MDA surveillance for onchocerciasis will be conducted after MDA is stopped nationwide and on the advice of the OEC a dossier will be prepared and submitted to WHO that will announce the elimination of transmission of OV in the country. The dossier will be reviewed by a committee that will be set up by WHO. The Committee will visit the country to

ascertain that all that has been reported in the dossier on the disease is correct. The committee then advises WHO to accept the claim of elimination or reject it based on the review of the dossier and the findings of the country visit. The WHO Director-General will provide a letter of acknowledgement of elimination based on the advice of the WHO committee. It is projected that verification of elimination of onchocerciasis in Sierra Leone by the WHO Director-General will take place between 2027 and 2030 if the situation continues to be stable and MDAs are not disrupted. Post-elimination surveillance must be conducted after the letter of acknowledgement is received from the WHO Director-General to monitor and ensure that there is no resurgence or reintroduction of the infection from neighbouring countries. For onchocerciasis, the same entomological and serological methodologies are used for stopping MDA, post-MDA surveillance and post-elimination surveillance (WHO 2016d).

WAY FORWARD FOR ELIMINATION OF LF IN SIERRA LEONE

The LF programme in Sierra Leone is currently in the 'end-game' and if not for the EVD outbreak should already have reached the phase of stopping MDA for LF in all districts by 2016. LF TAS was planned in 2014 for the eight districts that passed the pre-TAS in 2013. The four districts coendemic for LF and onchocerciasis that failed the pre-TAS in 2013 needed to conduct two additional rounds of MDA (2013 and 2014 MDAs) and then repeat the pre-TAS in 2015 (WHO 2011a). The two districts in the Western Area started MDA two years later (in 2010) but would also have qualified for pre-TAS in 2015. If successful, the last TAS would have been conducted in 2016 so MDA can be stopped in all 12 districts. The eight districts that passed the pre-TAS could not conduct the TAS due to the EVD outbreak, but at least three annual rounds of MDA have been conducted since the pre-TAS in these districts (in 2013, 2015 and 2016). It hoped that these additional three rounds of MDA would ensure a pass in the TAS for these eight districts. The three additional rounds of MDA also conducted in the other districts means that the required number of additional treatment rounds for the four districts that failed the pre-TAS in 2013 were reached in 2014 (2013 and 2015 MDAs) and the two Western Area districts that completed five annual rounds of MDA in 2015 also now qualify for a pre-TAS. Therefore, currently, TAS will be conducted in eight districts and pre-TAS in six districts early in 2017. FTS will be used for the pre-TAS and the TAS as described previously

(WHO 2011a; Chu *et al.* 2013). Although the diagnostic tool to be used will be changed (from NBS/thick blood film to FTS, the sample size remains the same and selection of sites will be as already discussed (one SS and one SCS per district to avoid the confusion noted in the last pre-TAS of 2013). For the pre-TAS, the threshold for a pass is 2% for antigenaemia detection (using FTS) instead of the 1% used with the night blood survey/thick blood film method that detects MF. All six districts will go on to conduct a TAS the following year (2018) if the LF antigenaemia is below 2% using FTS. It is projected that MDA can be stopped in all 14 districts of Sierra Leone by 2018 after which post-MDA or post-treatment surveillance will commence. Post-MDA surveillance currently involves two additional TAS conducted two-three and then five-six years after MDA is stopped. With a pass in both additional TAS (TAS2 and TAS3), the country is considered to have interrupted LF transmission and can move towards the preparation of a dossier based on the advice of an LF elimination committee. The process is repeated for LF as described for onchocerciasis above and ends with a letter of acknowledgement of LF elimination from the WHO Director General. If MDA is stopped in all districts by 2018, followed by five-six years of post-MDA surveillance, the letter of acknowledgement can be obtained by 2026 (WHO 2011a; WHO 2016a). The methodology and sampling for the TAS before stopping MDA and after stopping MDA remains the same as described previously (WHO 2011a; Chu *et al.* 2013; WHO 2013).

GLOBAL INNOVATIONS FOR NTD ELIMINATION

There are currently over 40 ongoing studies to identify or develop new treatments for NTDs by different research institutions. Many gaps remain in developing new diagnostic tools that will improve the evaluation of NTDs. New tools are being developed for easy detection of NTDs including onchocerciasis and LF that have been demonstrated to be highly sensitive and specific (Uniting to Combat NTDs 2015). A public-private partnership between the Program for Appropriate Technology in Health (PATH), the National Institutes of Allergy and Infectious Diseases, part of the US National Institutes of Health, Standard Diagnostics Inc., and the global onchocerciasis community through funding from the BMGF was able to develop several new tools for NTD surveillance that are cheap and easily affordable, easy to use, field friendly, and provide results within a short time in field conditions. They include the OV16 RDTs that detect

antibodies to the onchocerciasis OV16 antigen, the Biplex test or SD Bioline Onchocerciasis and LF IgG4 RDT that at the same time detects antibodies to the onchocerciasis OV16 antigen and the Wb123 LF antigen, and the Wb123 RDT or SD Bioline LF IgG4 RDT that detects antibodies to the Wb123 LF antigen alone (PATH 2012; PATH 2013; PATH 2014; PATH 2016). The WHO recently also announced the availability of FTS for use for LF impact assessment to replace the ICT cards used previously (WHO 2016c). Significant progress has also been made to replace the 'human capture" method with use of traps to collect black flies during entomology studies for onchocerciasis (Rodríguez-Pérez *et al.* 2013; Rodríguez-Pérez *et al.* 2014; Toe *et al.* 2014).

Many studies have been conducted on the proposed tools to validate their use. Weil *et al.* (2000), Lipner *et al.* (2006) and Golden *et al.* (2015) reports results of studies conducted to validate the use of the OV16 RDTs; OV16 ELISA, and development of positive control for the serology test. The OV16 RDT and OV16 ELISA tests are proven to be good serology tests for detecting the presence of antibodies to the OV16 onchocerciasis antigen in human blood and therefore exposure to onchocerciasis infection. They detect latent infection in the absence of MF in the skin and thus indicate exposure to the onchocerciasis infection. This means that they become useful in the final phase of the onchocerciasis elimination programme and are recommended for use in the stop-MDA evaluations, post-MDA evaluation and post-elimination evaluation. Testing of children <ten years of a programme that lasts for over ten years means these children should be less exposed to the onchocerciasis infection and so should not test positive in high numbers. The OV16 RDTs are also being recommended for use to study the impact of MDAs on onchocerciasis as they detect the antibodies to the OV16 onchocerciasis antigen and therefore exposure to the onchocerciasis infection. They could be a good replacement for skin snip that is invasive (painful and scary to many children and adult). However, since the antibodies reduce more slowly in the body than onchocerciasis MFs, adults could remain positive even when the infection is already absent due to control measures. Therefore, the appropriate threshold needs to be defined when using this tool during surveys for assessing the impact of MDAs while MDAs are being conducted. Threshold also needs to be defined when using this tool to decide when to conduct stop-MDA evaluations. While the decision to use OV16 in place of skin snip methodology for assessments during treatment still remains unclear (as adults can test positive for the antibodies to the OV16 antigen even when

they do not have the disease), threshold also need to be determined for cases when programmes decide to use skin snip methodology to detect onchocerciasis MFs. The threshold should be established that will guide the decision by programmes while treatment is ongoing to conduct stop-MDA evaluations. It has been noted that antibodies to the OV16 antigen reduce more slowly than onchocerciasis MFs during control measures, and so the threshold for skin snip will be different from the threshold for OV16 (Weil *et al.* 2000; Lipner *et al.* 2006).

Many authors have also reported studies conducted to compare the FTS and ICT cards and have validated its use for LF surveillance and also its replacement of the BinaxNOW Filariasis ICT cards (Weil *et al.* 2013; Rebollo and Bockarie 2013; Yahathugoda *et al.* 2015). The FTS detects antigen of *W. bancrofti* in human blood and was developed by Alere (Scarborough, ME, United States) the company that was producing the BinaxNOW Filariasis ICT cards. The development of this new tool was made possible through funding from the BMGF (WHO 2016c). A similar study was also reported for the Biplex with positive results showing high specificity and sensitivity of the tool (Steel *et al.* 2015).

POSSIBLE USE OF BIANNUAL TREATMENT TO REDUCE ADDITIONAL YEARS NEEDED FOR TREATMENT OF ONCHOCERCIASIS

The author's analysis has indicated that MDA cannot be stopped nationwide for onchocerciasis before 2020 and LF MDA can be stopped nationwide in 2018 provided all the districts pass the pre-TAS/TAS. The additional five rounds of MDA needed for onchocerciasis can be conducted in less than five years if the NTDP can change from annual MDAs to biannual MDAs (Cupp *et al.* 2004; Cupp *et al.* 2005; Molyneux et al. 2014). This will demand more coordination at all levels, more health education and social mobilization within targeted communities, extra financial and logistics support. However, all these extra requirements will be balanced by a reduced number of years of treatment needed. It is projected that with biannual treatment, only three additional years of treatment will be needed (2017, 2018 and 2019) and the NTDP can meet the 2020 target to stop MDA nationwide by 2020 (WHO 2011a).

The current LF situation appears straightforward- TAS in 8 districts and pre-TAS in 6 districts in 2017, and then TAS in the 6 districts in 2018. It is expected that all the districts will pass the pre-TAS and the TAS. However, biannual treatment can be implemented during the two additional years of treatment that will be needed if any districts fails the pre-TAS or TAS (WHO 2011a).

POSSIBLE USE OF DOXYCYCLINE FOR LF AND ONCHOCERCIASIS ELIMINATION IN AREAS OF PERSISTENT HIGH INFECTION

As discussed previously, most of the filarial species that infects humans co-exist in mutualistic symbiosis with Wolbachia bacteria that are essential for growth, development, and survival of their nematode hosts (Hoerauf 2008; Wanji et al. 2009; Tamarozzi et al. 2012; Molyneux et al. 2014). These endosymbionts contribute to inflammatory disease pathogenesis and are a target for doxycycline therapy, which delivers macrofilaricidal activity, improves pathological outcomes, and is effective as monotherapy (Taylor, Hoerauf and Bockarie 2010; Molyneux et al. 2014). Use of doxycycline, therefore, is a possible solution for areas where there will be persistently high prevalence of the two diseases after many years of treatment. This is especially possible for countries like Sierra Leone where both diseases are coendemic in 12 of the 14 health districts. Treatment of some districts can be done using the proposed community-directed treatment with doxycycline although the treatment has to be conducted for six weeks with multiple daily doses to be administered (Hoerauf 2008; Wanji et al. 2009; Tamarozzi et al. 2012; Molyneux et al. 2014).

CONCLUSION

The path towards the elimination of the two diseases in Sierra Leone appears clear. However, it should be noted that many questions still exist especially for onchocerciasis surveillance that need to be addressed by the NTD community in collaboration with research institutions. Another fact that should be noted is that due to conflicts and most recently outbreaks of other more virulent infection (the EVD), Sierra Leone will not be among the countries meeting the

WHO 2020 targets for elimination of LF (WHO 2015; WHO 2016a) and will also not meet the onchocerciasis 2020 target (Uniting to Combat NTDs 2015).

CHAPTER 9: GENERAL DISCUSSIONS, SUMMARY AND CONCLUSIONS

GENERAL DISCUSSIONS

Sierra Leone is highly endemic for the neglected tropical diseases that are amenable to preventive chemotherapy. Among these, LF and onchocerciasis have been targeted for elimination. The goal of this study was to determine the impact of preventive chemotherapy on the transmission intensity of LF and onchocerciasis measured through changes in the human infection status using standard epidemiological indicators as described in the WHO guidelines for monitoring national programmes. This was achieved through the following specific objectives: i) evaluate the impact of vertical treatment of onchocerciasis (2005-2006) plus integrated onchocerciasis/LF treatment (2007-2009) on transmission of onchocerciasis in Sierra Leone; ii) determine the impact of vertical treatment of onchocerciasis in Sierra Leone (before 2007) on the LF transmission and endemicity; iii) evaluate the impact of integrated onchocerciasis/LF treatment in Sierra Leone at mid-term (*i.e.* after three effective MDA rounds) on the LF transmission intensity; iv) evaluate the impact of integrated onchocerciasis/LF treatment in Sierra Leone after five effective rounds of MDA on the LF transmission intensity; and v) determine the way forward to achieve elimination of both diseases as public health problems using the latest available WHO guidelines and diagnostic tools.

The targeted outcomes for the quantitative research studies reported in this study are all WHO requirements for successful completion of the onchocerciasis and LF programs. The studies were designed and conducted strictly in line with WHO recommendations for the two diseases. Data collection and archiving in resource poor settings in Sierra Leone and through this project the studies conducted relating to onchocerciasis and LF elimination are documented. According to WHO recommendations and requirements, the NTDP will need to put together a dossier of survey and treatment data that will be used in the near future by the Elimination Committees that will be set up to verify elimination of onchocerciasis and LF in Sierra Leone. This study and its content will serve as a good collection of all data needed by the NTDP for verification of elimination of onchocerciasis and LF. Data reported and information available in this project will be used by the NTDP for decision making as the onchocerciasis and LF programmes continue to be implemented. The international scientific community, especially the NTD community, will benefit from the documented onchocerciasis/LF elimination

experiences obtained from co-implementation of activities for the two diseases and integration of onchocerciasis and LF programme coordination within the MOHS service delivery system in Sierra Leone. It is also hoped that countries with similar challenges (post-conflict background, co-endemicity of onchocerciasis and LF, and maintaining the NTDP during and after the outbreak of a far deadlier disease), especially in Africa, can learn from the experience in Sierra Leone.

The NTDP, including the NOCP that existed alone before the establishment of an integrated programme for all NTDs, has had and continues to receive good support, either technical or financial, direct or indirect, from many international and national NTD partners: the WHO HQ, AFRO, APOC, USAID, HKI, CNTD Liverpool (now known as FPSU), Johnson & Johnson, the World Food Program, the World Bank, TOMS Shoes, the school and adolescent health programme of the Ministry of Health (Baker *et al.* 2010). Mebendazole/albendazole for soil transmitted helminthiasis treatment has been donated from the Saint Andrews Clinic for Children in Sierra Leone, De-worm the World, Feed the Children, and World Vision Sierra Leone. One of the important aspects of the NTDP globally is the donation of the drugs needed for treatment. In 1987 Merck and Co. Inc. offered to donate ivermectin free of cost for treatment of onchocerciasis, and in 1998 also for treatment of LF, for as long as it is needed. This support has been coordinated through the MDP (Alleman, Twum-Danso, Thylefors 2006; Boatin 2008; Colatrella 2008; Thylefors, Alleman, Twum-Danso 2008; Thylefors 2008; Yameogo 2008; Baker *et al.* 2010; Hopkins and Boatin 2011; Hodges *et al.* 2011; Meredith, Cross, Amazigo 2012). Similarly, GlaxoSmithKline also donates albendazole for LF control globally (Hodges *et al.* 2011). This contribution by the drug companies comes down to billions of US Dollars, without which the global LF and onchocerciasis elimination programmes cannot continue (Alleman, Twum-Danso and Thylefors 2006; Boatin 2008; Colatrella 2008; Thylefors, Alleman, Twum-Danso 2008; Thylefors 2008; Yameogo 2008; Baker *et al.* 2010; Hopkins and Boatin 2011; Hodges *et al.* 2011; Meredith, Cross, Amazigo 2012). The contribution of the BMGF in supporting research for the development of new tools and drugs for NTD control and the contribution by research institutions such as PATH, the TASK for Global Health and CDC has to be acknowledged because they shape the strategies used for NTD control and they help the development of

better tools for disease assessment (PATH 2012; PATH 2013; PATH 2014; PATH 2016; Uniting to Combat NTDs 2015; WHO 2016c).

However, the NTDP has been and is still being implemented under challenging circumstances. Sierra Leone is a poor West African country with a weak and fragile economy with poor socio-economic and health indicators (MacKinnon and MacLaren 2012; Fitzgerald *et al.* 2016). Many health reports present different health indicators for Sierra Leone, but there is a consensus that the country is among the poorest in the world with one of the lowest life expectancy. The socio-economic and health situation in Sierra Leone is critical compared even to other sub-Saharan African countries. About 70% of Sierra Leoneans lived below the poverty level in 2007 (*i.e.* earn less than one US$ per day). (GoSL, MOHS 2009; UNDP 2014a,b; UNDP 2015; African Health Observatory WHO AFRO 2016; Focus 1000 2016). The country is currently ranked 181 out of 188 in terms of human development index (UNDP 2015; Focus 1000 2016). A greater part of the country's population is involved in agriculture, mostly subsistence farming. Yet a high proportion (about 70%) of total health expenditure is out-of-pocket spending because of the low government expenditure on health (GoSL, MOHS 2009; UNDP 2009).

Within the MOHS the NTDP to a large extent remains 'neglected' because of the other competing priorities that the MOHS has to deal with including one of the highest infant and maternal mortality rates in the world, and other killer diseases such as Malaria, TB, HIV/AIDS, nutritional deficiencies, pneumonia, anemia, respiratory tract infection and diarrhoeal diseases. Maternal mortality and infant mortality rates still remain among the highest in the world. High infant mortality is linked to high prevalence of malaria, diarrhoea, and pneumonia. High maternal mortality is due to obstructed labour, haemorrhage, anaemia, and toxaemia in pregnancy (GoSL, MOHS 2010; WHO Sierra Leone 2009; GoSL, MOHS 2012a).

The 'neglect' of NTDs is compounded by a weak HRH situation (MacKinnon and MacLaren 2012; Fitzgerald *et al.* 2016). In 2008, the country had a sixth of the minimum number of health personnel recommended by WHO. Accessibility to health care services (and in this case to health personnel) is poor especially in rural areas due to an acute shortage of trained health professionals, the significant dichotomy of staff between rural and urban health facilities,

unequal distribution of health cadres, and poor access to good quality health care. The scarcity of physicians and registered nurses is even more pronounced in rural areas where two-thirds of the population live. The total health workforce was estimated at 6,000, and there were 95 physicians practising in the country in 2008 (MacKinnon and MacLaren 2012; Fitzgerald *et al.* 2016). More recent data on human resources for health report that the overall health workforce in the country is slightly above 8000 personnel. However, about half of all health personnel are in the Western Area alone. The limited human resource for health is a concern of the GoSL (GoSL, MOHS 2012a; Fitzgerald *et al.* 2016).

The NTDP has used the health services provided at the different levels well. District hospitals manage serious adverse events cases following treatment that are referred to them and also are responsible for a large part of the morbidity management for LF (hydrocoele surgery and lymphoedema/elephantiasis management) and onchocerciasis (eye care). The NTDP is coordinated within districts by DHMTs in collaboration with central level NTDP staff, and each of the 14 districts has a district NTD focal point. The health system personnel that work within the PHUs (CHCs, CHPs and MCHPs) provide direct support to the community volunteers or CDDs that implement MDAs within their respective communities and report treatment results. Since accessibility to health care services is poor especially in rural areas due to an acute shortage of trained health professionals, the NTDP implements activities within communities using community volunteers or CDDs who are supervised, trained and monitored by PHU staff. These CDDs have gradually become the backbone of all the NTDP activities in the rural setting. While in the rural setting CDDs serve as volunteers within the NTDP, in the district headquarter towns and the Western Urban district and Western Rural district there are no volunteer CDDs and NTD drugs are distributed by paid health workers for a fixed number of days (Hodges *et al.* 2011; MacKinnon and MacLaren 2012; Fitzgerald *et al.* 2016).

The EVD outbreak that started in Guinea in late 2013 and spread to Sierra Leone is believed to have caused almost the same devastating socio-economic effect as the civil war of 1991-2002 and appeared to have derailed the NTDP (Boisen *et al.* 2015; Hersey *et al.* 2015).

The study has used baseline data for onchocerciasis obtained using the skin snip method for the period 1988 – 2005; baseline data for LF including mapping results obtained using ICT cards in 2005 and baseline survey results obtained using the NBS/TBF method in 2007/2008; results of onchocerciasis evaluation conducted in 2010; results of mid-term evaluation conducted for LF in 2011 after three years (2008-2010); results of pre-TAS conducted in 2013 for LF after five years of treatment (2008-2012) in sentinel and spot-check sites; results of MDA for onchocerciasis (2005-2015) and LF (2008-2015); annual Implementation plans for the period 2005-2015; annual NTDP Reports for the period 2005-2015 and publications on NTDs focusing on onchocerciasis and LF. All treatment results for the period 2005-2015 (for onchocerciasis and LF), and all research studies conducted at baseline (1988-2008) and during universal treatment (2008-2013) for monitoring the impact of treatment were reviewed. Apart from NTDP data and information, an extensive literature search was conducted using the appropriate search words and information obtained was used to review the data obtained from treatment and research studies. Some of the data obtained from the research studies have been published already in international peer-reviewed journals (please see attached in the appendices). This study and all the data it contains will also be made available to the MOHS for use in the future as part of the dossier to be prepared for verification of elimination of onchocerciasis and LF in Sierra Leone.

The fight to combat NTDs reached an unprecedented peak for public health programmes with the formation of a coalition of partners including donors, international health-oriented NGDOs, and pharmaceutical companies that are prepared to support endemic countries globally with their efforts to eliminate NTDs. This big development started in 2012 with the London Declaration on NTDs during which key donors pledged their support for this development and committed to continue either donating drugs or providing the funds needed for the interventions. The highest level of financial and other support was attained around the London Declaration in 2012. This coalition offers countries like Sierra Leone the opportunity to improve the socio-economic status of its people by reducing the prevalence and density of the two diseases that are known to be poverty-promoting parasitic diseases (Uniting to combat NTDs 2015). The two diseases also result in often stigmatising conditions such as total blindness, hydrocoele, lymphoedema and elephantiasis (Taylor, Hoerauf and Bockarie 2010). Apart from

affecting mainly the poor and exacerbating their poverty, there is strong evidence that when infected with NTDs one becomes increasingly susceptible to or there is worsening of the progression of morbidity from HIV/AIDS, TB, and Malaria. Therefore, NTD control/elimination is an indirect effective, low-cost means of reducing morbidity and mortality associated with these three global health problems (Gloeckner *et al.* 2010). Ocular diseases, total blindness and skin diseases relating to onchocerciasis, and hydrocoele, lymphoedema and elephantiasis due to LF can all be reduced within the population and prevented from affecting future generations (Taylor, Hoerauf and Bockarie 2010).

Onchocerciasis is caused by the filarial worm *O. volvulus* and transmitted in Sierra Leone by the black fly *Simulium damnosum* (Gbakima and Sahr 1996). Sierra Leone has always been known to be endemic for onchocerciasis since 1926 when Blacklock first described the disease transmission in the Kono district (Blacklock 1926). There have been efforts to control onchocerciasis in the country albeit haphazard between the 1950s and the establishment of the NOCP in 1988-1989. Many studies were conducted on onchocerciasis by the NOCP and other researchers to determine areas of the country that should be treated for onchocerciasis. Thus, it was determined that only the 12 provincial districts of Sierra Leone are endemic for onchocerciasis. Each of the 12 onchocerciasis-endemic districts has hyper-endemic, meso-endemic and hypo-endemic areas and so onchocerciasis treatment was not conducted in entire districts. Treatment was conducted between 1989 and 1996 only in some areas of the country mainly due to insecurity related to a civil conflict between 1991 and 2002 and the then onchocerciasis policy of treating only meso-endemic and hyper-endemic areas. Before the introduction of CDTI in 1997-1998, treatment for onchocerciasis control was done in meso-endemic and hyper-endemic communities using mobile teams. Treatment was completely stopped in 1997 and restarted in 2003 under the SIZ that was coordinated by APOC. Therefore, the CDTI strategy could only be established in Sierra Leone in 2003. Challenges with restarting the onchocerciasis programme after a five-year absence of interventions resulted in relatively poor treatment coverage for onchocerciasis in 2003 and 2004 (Hodges *et al.* 2010; Hodges *et al.* 2011).

There has been a paradigm shift from onchocerciasis control to elimination after it was demonstrated in many south American countries and some countries in Africa that elimination of onchocerciasis is possible after 15-17 years of treatment (Diawara *et al.* 2009; APOC 2010; Tekle *et al.* 2012; Crump *et al.* 2012; Traore *et al.* 2012; Uniting to Combat NTDs 2015). The NTDP is also towing this line and has targeted onchocerciasis elimination in Sierra Leone. Results of the onchocerciasis evaluation conducted in 2010 demonstrated that there has been a significant reduction in MF prevalence and density. It should be noted that the situation will be even better now after additional six annual rounds of treatment conducted between 2010 and 2016. The remarkable observation made is that women and children who usually bear the brunt of diseases in the country are reaping the best benefits from this programme. The results of 2010 show that women are less affected by onchocerciasis and children are also less likely to be infected with onchocerciasis than adults. This means that onchocerciasis transmission is generally low in the country as those born after initiation of programme activities are less exposed to the disease. The vegetation ranges from mangrove along the coasts to forest covered hills and savannah as one moves further inland and this has created regional variations of onchocerciasis distribution (McMahon *et al.* 1988c; Gbakima and Sahr 1996). Baseline onchocerciasis results show that northern districts had relatively higher prevalence, followed by southern and then eastern having the lowest relative prevalence. This variation appears to have changed slightly in 2010, as by then the southern districts had relatively the highest average prevalence, followed by the average prevalence of eastern districts, and northern districts have relatively the lowest average MF prevalence.

LF is endemic in all 14 districts of Sierra Leone, transmitted by *Anopheles* mosquitoes, and all districts qualified for MDA intervention in 2005 in accordance with WHO guidelines because they had baseline LF antigenaemia prevalence by ICT cards ≥1.0%. Baseline studies were also conducted in 2007/2008 using the night blood survey/thick blood film method to obtain data that can be used to monitor decline in LF MF prevalence and density in the country. The NTDP has made remarkable progress towards LF elimination since integrated onchocerciasis/LF MDA using ivermectin and albendazole was piloted in 2007. The results of the mid-term assessment and pre-TAS show significant reductions in MF prevalence and MF density. Pre-TAS results show that eight of the 12 districts coendemic for onchocerciasis and LF passed the pre-TAS and

will conduct TAS in 2017. The four that failed the pre-TAS in 2013 have since conducted three additional rounds of treatment as required by WHO (in 2013, 2015 and 2016). The two Western Area districts that had not qualified for the pre-TAS in 2013, now also qualify for pre-TAS after completing five effective rounds of MDA and all six districts will conduct pre-TAS in 2017 (re-pre-TAS for the four that failed in 2013). Another remarkable observation with LF is that transmission has reduced significantly because fewer children are now being infected with the disease. Women are also less infected that men. This means that the same pattern is noted for women and children for the two diseases.

The study suggests that LF prevalence may have reduced significantly at baseline because of the effect of onchocerciasis treatment on LF before LF treatment proper was started in 2007 (Kyelem *et al.* 2003; Kyelem et al. 2005). The study shows that the rapid reduction of MF LF prevalence and density could also be due to many factors including low baseline MF prevalence (Ottesen 2000), the LF vector (the *Anopheles* mosquitos) being less efficient as LF vectors than *Culex* (Weil *et al.* 2008), and high community adherence to treatment because communities appreciate the effect of LF/onchocerciasis treatment on soil transmitted helminthiasis, scabies and lice (Meinking *et al.* 1995; Burkhart, Burkhart 2006; Ottesen *et al.* 2008; WHO 2015). The study also shows the importance of having SCS in addition to SS for monitoring the impact of MDAs for LF that are randomly selected usually in consultation with DHMTs and changed with each study (WHO 2011a). This same policy can be applied to assessments conducted for onchocerciasis.

The EVD outbreak that started in Sierra Leone in 2014 was first detected in the eastern Kailahun district but had spread to the entire country before it was controlled (Gleason *et al.* 2015; Lokuge *et al.* 2016). Initially, the response to the outbreak was uncoordinated and was compounded by the weak health system in the country. With the support of international organisations, the MOHS succeeded in stopping the outbreak by November 2015 (MOHS 2015; Fitzgerald *et al.* 2016). All public health interventions including NTD interventions were suspended nationwide so the entire health service can be used to control the EVD outbreak. After successful implementation of a nation-wide Malaria treatment campaign in March 2015, the NTDP became the second public health programme post-EVD to conduct an MDA for

onchocerciasis and LF in June 2015. Although there have been challenges in restarting onchocerciasis/LF MDAs, they were overcome through concerted efforts and the support of CDDs who served as a bridge between the NTDP and communities. There was a delay of about a year in implementing MDAs, but the NTDP has successfully completed two rounds of MDA since the outbreak. Based on findings of the qualitative study in 2015, a decision was made to suspend disease-specific assessments for onchocerciasis and LF till early 2017 for fear that the communities targeted will reject an intervention that involves blood and the skin. Intensive social mobilisation and health education had to be conducted to maintain the usual effective treatment coverage and should be continued before and during MDAs to maintain good community acceptance and adherence to treatment. The disease-specific assessments should be preceded by the same intensive social mobilisation and health education to have good community participation in the assessments.

Cross-border transmission of infectious diseases including NTDs is cited as a major problem for many infectious disease and NTD control efforts (Kaferstein, Motarjemi, Bettcher 1997; Bhumiratana *et al.* 2005; Asian Development Bank 2010; Bhumiratana *et al.* 2010; HKI 2010; International Coalition for Trachoma Control 2011; NNN 2011; Centers for Disease Control and Prevention 2011; The Carter Center and MOH Uganda 2011; Bhumiratana *et al.* 2012; Hodges *et al.* 2012a; Hodges *et al.* 2012b; WHO 2012; Gustavsen, Sodahlon, Bush 2016). Resurgence or importation of the NTDs targeted presently for elimination in Africa from neighbouring endemic countries remains a concern due to possible cross-border disease transmission, which must be addressed to sustain achievements in these countries because neighbouring countries may not have achieved similar results (Gustavsen, Sodahlon, Bush 2016). The NTDs that are currently targeted for elimination in Sierra Leone (onchocerciasis and LF) can be reintroduced into the country from neighbours Liberia and Guinea that have not achieved similar results in controlling the two diseases. The threat of cross-border transmission of NTDs has been expressed by the NTDP in Sierra Leone and other NTDPs in countries that the author has worked with. It is the opinion of the author that the cross-border issue must be addressed and talk should be translated into action at this stage of the global NTDP when endemic countries are making remarkable achievements in controlling NTDs, and many countries are reaching the ‘end game’.

The cross-border problem for NTDs can be addressed if countries can provide technical support and services to each other, share experiences and knowledge through cross-border meetings, establish common surveillance and reporting systems, and use similar indicators and forms for reporting NTDs. Experiences from successful cross-border initiatives established for other diseases such as malaria and HIV/AIDS in Africa and elsewhere can be used to inform decisions on addressing possible cross-border issues in West Africa. It has been reported that countries make recommendations for addressing cross-border issues during cross-border meetings but appear to have many challenges in implementing the recommendations they make. There has recently been positive progress in this direction as a few organisations are implementing interventions that will improve country collaboration for addressing cross-border problems. The END in Africa project is introducing aspects of cross-border collaboration in agreements with countries supported to encourage synchronisation of treatments along borders, and the World Bank has introduced a project in Niger, Burkina Faso and Mali to help address cross-border issues (World Bank 2015; FHI360 2016).

While the NTDP has reached the 'end game' for LF, there is still some work needed for the elimination of onchocerciasis. After reviewing the necessary interventions and procedures needed for eliminating the two diseases in the country, it is projected that both LF and onchocerciasis can only be eliminated in the country between 2025 and 2030, later than the 2020 targets set by international NTD community. This is mainly because of the many challenges highlighted above. Although policies for implementing NTDPs present challenges and opportunities as not all elements of mapping, monitoring and surveillance can be integrated for onchocerciasis and LF during programme implementation, it is demonstrated in this study that the NTDP in Sierra Leone has been successful in integrating the treatment of the two diseases.

There are currently many ongoing studies by different research institutions with the support of many donors to identify or develop new treatments for NTDs, to address the many gaps in knowledge for NTDs, and also to develop better tools for disease assessment. The availability of the options of conducting biannual treatment (Cupp *et al.* 2004; Cupp *et al.* 2005) and using

doxycycline to treat for both diseases in the country has been noted although this will require long-duration treatment (up to 6-weeks) (Hoerauf 2008; Wanji *et al.* 2009; Tamarozzi *et al.* 2012; Molyneux et al. 2014). These strategies will require more coordination, intensive health education and social mobilization with targeted communities, more logistical and financial support. This treatment option can be reserved for areas of persistent high onchocerciasis and LF prevalence to speed up the elimination process. The decision can be made based on results of the onchocerciasis and LF assessments that are planned for 2017. This way elimination of both diseases can be achieved earlier than the period projected above. Furthermore, new tools have been developed and put in the market for the assessment of onchocerciasis and LF that can be used by the NTDP in Sierra Leone for future diseases assessments (PATH 2012; PATH 2013; PATH 2014; PATH 2016; WHO 2016c).

Although many gaps remain in developing new diagnostic tools that will improve the evaluation of NTDs, several new tools have been developed for easy detection of onchocerciasis and LF through public-private partnerships that have been demonstrated to be highly sensitive and specific (Uniting to Combat NTDs 2015). For onchocerciasis, there is the OV16 rapid diagnostic tests and OV16 ELISA, serology tests that detect antibodies to the onchocerciasis OV16 antigen. For LF the ICT cards have been replaced by the FTS that were modified to be easier to use in the field in terms of the temperature at which they can be stored (refrigeration is not needed when they are used in areas with temperature up to a 30 degree centigrade) and also the Wb123 RDT or SD Bioline LF IgG4 RDT that detects antibodies to the Wb123 LF antigen alone is now available for use by programmes. The Biplex test or SD Bioline Onchocerciasis and LF IgG4 RDT that at the same time detects antibodies to the onchocerciasis OV16 antigen and the Wb123 LF antigen is also available for use by programmes (PATH 2012; PATH 2013; PATH 2014; PATH 2016; WHO 2016c).

Many studies have been conducted on some of the proposed tools to validate their use. Available evidence shows that programmes can use the OV16 RDTs and FTS for monitoring the impact of MDA on onchocerciasis and LF respectively (Weil *et al.* 2000; Lipner *et al.* 2006; Rebollo and Bockarie 2013; Weil *et al.* 2013; Golden *et al.* 2015; Yahathugoda *et al.* 2015). The OV16 RDT and OV16 ELISA tests are proven to be good serology tests for detecting the

presence of antibodies to the OV16 onchocerciasis antigen in human blood and therefore exposure to onchocerciasis infection. They detect latent infection in the absence of MF in the skin and thus indicate exposure to the onchocerciasis infection. This means that they become useful in the final phase of the onchocerciasis elimination programme and are recommended for use in the stop-MDA evaluations, post-MDA evaluation and post-elimination evaluation. Testing of children <ten years of a programme that lasts for over ten years means these children should be less exposed to the onchocerciasis infection and so should not test positive in high numbers. These tests (especially the OV16 RDTs) are also being recommended for studying the impact of MDAs on onchocerciasis as they detect the antibodies to the OV16 onchocerciasis antigen and therefore exposure to the onchocerciasis infection and could be a good replacement for skin snip that is considered invasive (painful and scary to many children and adult). However, since the antibodies reduce more slowly in the body than onchocerciasis MFs, adults could remain positive even when the infection is already absent due to control measures. Therefore, the appropriate threshold needs to be defined when using this tool during surveys for monitoring impact of MDAs. Threshold also needs to be defined when using this tool to decide when to conduct stop-MDA evaluations. Furthermore, while the decision to use OV16 in place of skin snip methodology for assessments during treatment still remains unclear (there is still no WHO guideline on this), the threshold also need to be determined for cases when programmes decide to continue using the skin snip methodology that detects onchocerciasis MFs to monitor the impact of MDAs. Threshold also should be defined for making the decision to move to stop-MDA evaluations for onchocerciasis when using the skin snip methodology to measure the impact of MDAs. It has been noted that antibodies to the OV16 antigen reduce more slowly than onchocerciasis MFs during control measures, and so the threshold for skin snip will be different from the threshold for OV16 (Weil *et al.* 2000; Lipner *et al.* 2006). The NTDP in Sierra Leone is considering using the OV16 RDTs for the next surveys to monitor the impact of MDAs on onchocerciasis. However, it is important that an appropriate threshold is defined for this tool to guide programmes in making programme decisions based on survey results.

Available evidence also shows that the FTS is better than the ICT cards for field use, has better sensitivity and specificity and can be used by programmes for monitoring impact of MDA and

endgame evaluations (stop-MDA evaluation, post-MDA surveillance and post-elimination surveillance) (Weil *et al.* 2013; Rebollo and Bockarie 2013; Yahathugoda *et al.* 2015). Studies have also been conducted to demonstrate the high specificity and sensitivity of the Biplex (Steel *et al.* 2015) but more studies are needed to demonstrate their suitability for field use. Further research is also needed to demonstrate field use of the Wb123 RDT or SD Bioline LF IgG4 RDT that detects antibodies to the Wb123 LF antigen alone.

The disadvantages of using the night blood method for monitoring MDA have been highlighted by many authors. MF testing (through microscopy of thick blood films) is determined to be insensitive for active infections and misses people with low MF density and people with amicrofilaraemic LF infection that can lead to irreversible major lymphatic damages in these patients and they (the patients) can still contribute to transmission in the future within their communities. Thus, MF testing can lead to underdiagnosis and exclusion of areas with active LF transmission (Braga *et al.* 2003; Weil and Ramzy 2007). Other challenges of MF testing are the unsociable hours that the tests are conducted (before and after midnight) with high refusal and the extensive microscopy needed that requires extensive training (Bockarie et al. 2013). The recommendation to use antigenaemia detection with ICT cards and now FTS for monitoring the impact of MDAs on LF instead of the night blood method is considered here a good development for the LF programme in Sierra Leone. FTS are therefore recommended for use in the next pre-TAS to be conducted in 2017 instead of the NBS/TBF method.

This project has demonstrated how onchocerciasis control activities can be co-implemented with LF control activities in areas where both diseases exist and the effectiveness of co-implementation for control of both diseases. The project also shows how the onchocerciasis and LF control programmes can be integrated into a country's health care delivery system. Similar countries with weak health systems can learn how an integrated control program can be conducted in a post-conflict country with a weak health system and weak human resources for health.

SUMMARY OF KEY FINDINGS

The findings are summarised as follows:

LF and onchocerciasis are highly endemic in Sierra Leone. Using WHO guidelines for monitoring national programmes where both infections are co-endemic, this study aimed to determine the impact of preventive chemotherapy on transmission intensity by measuring changes in human infection status using standard epidemiological indicators.

Separate longitudinal studies designed to deliver WHO outcomes for programmes targeting the elimination of both diseases were conducted.

1. Studies to map onchocerciasis using skin snip method in 1988-2005 across Sierra Leone showed that 12 of the 14 health districts were onchocerciasis-endemic. The baseline average MF prevalence was 53.1%, and MF densities in positive-only or entire populations were 28.87 and 15.33 mf/snip, respectively. MF prevalence and density increased with age and was higher in males than females.
2. Mapping and baseline prevalence and intensity surveys showed that LF was endemic in all 14 districts (*Wuchereria bancrofti* antigenaemia prevalence > 1%) and MDA was necessary nationwide for elimination to be achieved. LF prevalence by ICT cards was 21% (males 28%; females 15%) with higher prevalence in the northeast (Bombali 52%; Koinadugu 46%; Tonkolili 37%; Kono 30%) and lower in the south-west (Bonthe 3%; Pujehun 4%). MF prevalence by night blood method was 2.4% (males 3.0%; females 1.8%). MF prevalence was also relatively higher in the northeast (Bombali 6.7%; Koinadugu 5.7%; Port Loko 4.4%; Kono 2.4%) and higher in the over 20 years' age-group (2.5%) than younger (1.7%). Arithmetic mean MF density was 50.30 mf/ml among MF-positive individuals and 1.19 mf/ml in the population examined.
3. Relatively better treatment coverage for onchocerciasis was achieved between 2005 and 2009 after the end of an 11-year civil conflict in the country in 2002 using the CDTI strategy although treatment coverage was effective nationwide only in four of the five districts. Assessments conducted in 2010 showed that five rounds of MDA had significantly reduced the MF prevalence and intensity. MF prevalence was reduced by 60.22% from 53.09% at baseline to 21.12%. Overall MF intensity reduced by 71.29% among MF-positive individuals from 28.87 mf/snip at baseline to 8.29 mf/snip, and 88.58% among the entire population

from 15.33 mf/snip at baseline to 1.75 mf/snip. MF prevalence and density were higher in males, lowest in the 1-9 and highest in the 40-49 year age groups. MF prevalence was reduced by >50% in 10/12 districts, and reduction in skin MF density ≥50% among positives-only in 11 out of 12 districts.

4. After MDAs with effective treatment coverage in 2008-2010, LF MF prevalence decreased to less than 1% in 11 of the 12 provincial districts. MF prevalence fell by 88.5% from 2.4% at baseline to 0.3%, with decreases of 70-95% in seven districts and 100% (0 prevalence) in four districts, respectively. Overall arithmetic mean MF density after three MDAs was 17.59 mf/ml among MF positive individuals and 0.05 mf/ml for the entire population examined.
5. Previous studies on LF in Sierra Leone have shown a significant reduction in LF MF prevalence and MF density. A pre-TAS was conducted in the 12 districts that have completed five effective rounds of MDA in accordance with WHO guidelines and recommendations. After five MDAs, eight of the 12 districts had <1% MF prevalence and so passed the pre-TAS and therefore qualified for a TAS to determine whether MDA could be stopped. The overall MF prevalence was 0.54% and was higher in males (0.7%) than females (0.36%). Four districts failed the pre-TAS: Koinadugu with 0.98% MF prevalence (close to 1%), Bombali with 2.67%; Kailahun with 1.56%, and Kenema district with 0% MF prevalence. In accordance with WHO recommendations of selecting one sentinel site and one spot check site per million population, Kenema district was paired with Kailahun district to form a unit with a total population close to one million. Kailahun had the sentinel site and Kenema the spot check site. Kenema is considered to have failed the pre-TAS even though the MF prevalence is 0% because Kailahun district failed.
6. A qualitative study designed to determine the effect of the EVD outbreak on the treatment for NTDs in Sierra Leone was conducted to inform post EVD disease prevention strategies. The EVD outbreak in May 2014 led to many deaths including the death of many health workers. The outbreak was controlled and declared over in November 2015 after a lot of improvement in treatment and diagnosis of the diseases. Although there was a delay of about a year in implementing MDAs, the NTDP has successfully completed two rounds of MDA, one of them while the outbreak was still ongoing in May/June 2015. However, disease-specific assessments were suspended till early 2017 for fear that the communities

targeted will reject interventions that involve blood and the skin surveys. Intensive social mobilisation and health education should be continued for the MDAs and disease assessments to maintain good community acceptance of the NTDP and adherence to treatment and assessments.

In conclusion, while the NTDP has reached the 'end game' for LF, there is still some work needed for the elimination of onchocerciasis. The path towards the elimination of the two diseases in Sierra Leone appears clear. However, it should be noted that many questions still exist, especially for onchocerciasis surveillance, that should be addressed by the NTD community in collaboration with research institutions. Another fact that should be noted is that challenges for effective MDA implementation in the country during the EVD outbreak will affect progress towards achieving the 2020 target for the elimination of LF and control of onchocerciasis.

RELEVANCE OF WHO GUIDELINES TO CONCLUSIONS OF STUDY

Countries generally look up to WHO for guidelines on how to control or eliminate PC NTDs including interventions that should be conducted such as MDAs, the assessment/evaluations of the impact of MDAs, strategies including methodologies for MDA campaigns and evaluations, the tools to be used and guidance on 'who, what, where, when, how and why' for these interventions. In Sierra Leone WHO guidelines were used to conduct mapping, MDAs, and assessment of the impact of MDAs on the two diseases.

The study shows that while the NTDP has reached the 'end game' for LF, there is still some work needed for the elimination of onchocerciasis. Although the path towards the elimination of the two diseases in Sierra Leone appears clear, WHO guidelines are still needed on the way forward for the country to achieve elimination of onchocerciasis and LF in addition to those guidelines already available and mentioned above. Many questions still exist, especially for onchocerciasis surveillance, that should be addressed by WHO in collaboration with the NTD community and research institutions.

Gaps still exist on the tools and types of surveys that should be conducted for monitoring the impact of MDAs on onchocerciasis. Should spot check or control sites be used in addition to sentinel sites as is done for LF so that reductions in MF prevalence and density can be monitored better in endemic districts? How should spot check or control sites be selected for surveys to monitor the impact of treatment?

Recent WHO guidelines on stop MDA evaluations and verification of onchocerciasis elimination (WHO 2016d) have addressed many questions that countries have on the endgame for onchocerciasis. However, there are questions that should be answered such as the level at which stop MDA evaluations should be conducted. Countries want to use the district level for stop MDA evaluations (author's personal experience dealing with some onchocerciasis-endemic countries in West Africa) while the guidelines recommend the use of transmission zones. The concept of transmission zones remains unclear to countries and WHO guidelines are needed on the subject so that countries can easily make decisions for stop MDA evaluations.

Cross-border transmission of NTDs could become a major challenge for achieving elimination of onchocerciasis and LF in endemic countries with the possibility of resurgence or importation from neighbouring endemic countries (The Carter Center and MOH Uganda 2011; Bhumiratana *et al.* 2012; Hodges *et al.* 2012a; Hodges *et al.* 2012b; WHO 2012; Gustavsen, Sodahlon, Bush 2016). WHO should be involved in the efforts being made by some NTD partners to address this challenge especially so when the implementation of recommendations made during cross-border meetings are hardly implemented by countries (Gustavsen, Sodahlon, Bush 2016).

New tools are being developed and put in the market for the assessment of onchocerciasis and LF that can be used by the NTDP in Sierra Leone for future diseases assessments (PATH 2012; PATH 2013; PATH 2014; PATH 2016; WHO 2016c).

Should serology (OV16 RDTs or OV16 ELISA) be used to monitor the impact of MDAs for onchocerciasis before stop-MDA evaluations are conducted? What should be the threshold for the OV16 RDTs or OV16 ELISA when they are used for monitoring the impact of MDAs on onchocerciasis for deciding to conduct stop-MDA evaluations? If OV16 RDTs are not useful for monitoring impact of MDAs on onchocerciasis given that the antibodies they detect reduce more slowly in the body than onchocerciasis MFs, and adults could remain positive even when

the infection is already absent due to control measures, can countries continue with the skin snip method? What should be the threshold for deciding to conduct the stop MDA evaluations when the skin snip method is used? Some countries want to use microfilaredermia prevalence of 5% while others go for 1% copying from the LF programme.

For LF there is the Wb123 RDT or SD Bioline LF IgG4 RDT that is now available for use by programmes that detects antibodies to the Wb123 LF antigen alone. There is also the Biplex test or SD Bioline Onchocerciasis and LF IgG4 RDT that at the same time detects antibodies to the onchocerciasis OV16 antigen and the Wb123 LF antigen available for use by programmes (PATH 2012; PATH 2013; PATH 2014; PATH 2016; WHO 2016c). These tools could make integrated assessments for onchocerciasis and LF possible but WHO should develop guidelines on how national programmes can use these new tools.

LIMITATIONS OF THE STUDY

The main limitation of this study is the absence of entomological investigations and morbidity surveys to establish the role of MMDP in relating to both diseases. The relevance of both issues in Sierra Leone was, however, discussed in the in the literature review. While there is no WHO MMDP requirement for elimination of onchocerciasis (WHO 2016d), the WHO MMDP requirement for LF is data supporting availability and provision of the basic recommended package of care for LF patients (WHO 2016a). While stop-MDA evaluation for onchocerciasis prioritises entomology and entomology results are needed for verification of onchocerciasis elimination (WHO 2016b,d), there is no entomology requirement for verification of LF elimination (WHO 2016a).

RECOMMENDATIONS

While the study has highlighted the progress and achievements made in addressing onchocerciasis and LF in the country, the following recommendations are made for effective and efficient elimination of both diseases:

1. Surveys for monitoring the impact of MDAs on onchocerciasis should be conducted in spot check or control sites as well as sentinel sites as is done for LF so that reductions in MF

prevalence and density can be monitored better in endemic districts. The sites selected as control sites should be changed with each study.

2. The threshold should be defined for the OV16 RDTs when they are used for monitoring the impact of MDAs on onchocerciasis.
3. Guidelines should be developed to guide national programmes on deciding whether to use serology method (OV16 RDTs) or skin snip method for monitoring the impact of MDAs on onchocerciasis.
4. The threshold should, in general, be defined for making the decision to move towards stop-MDA evaluations for onchocerciasis.
5. Intensive social mobilisation and health education should be continued before and during MDAs and disease-specific assessments to maintain good community acceptance of the NTDP and maintain high adherence to treatment and assessments. The social mobilisation should involve district health workers as well as communities so that district health workers are also aware that all villages should receive the same attention during MDAs because the selection of the SCS can lead to another failure that can create an "embarrassment" for the DHMT.
6. NTD partners should continue to support cross-border meetings to encourage collaboration between NTD endemic countries. Countries should be encouraged to participate more in cross-border initiatives, and NTD partners and donors should consider supporting initiatives for addressing possible cross-border transmission that go beyond the usual cross-border meetings.
7. More research is needed to investigate the suitability for field use of some of the new tools developed for assessment of NTDs such as the Biplex.
8. Experts should conduct a review of the proposed inclusion of cross-border component in agreements between NTD partners and programmes in countries and the recently established World Bank Sahel project to inform future decisions on cross-border collaboration.
9. The NTDP in Sierra Leone should consider biannual MDA or the use of community-directed distribution of doxycycline after 2016 for areas that will still require MDA for onchocerciasis and LF based on results of onchocerciasis and LF assessments that will be conducted early in 2017. The NTDP and NTD partners supporting the NTDP in Sierra Leone

will need to advocate for the additional logistics and financial resources that will be needed for these new treatment strategies. The NTD partners will need to work together with the NTDP in coordinating biannual MDAs and/or community-directed treatment with doxycycline to ensure successful implementation.

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APPENDICES

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Thursday, 10 February 2011

Dear Joseph Brima Koroma

Re: Research Protocol (10.86) Studies on the Impact of Community Directed Treatment with Ivermection (CDTI) plus on Lymphatic Filariasis and other Neglected Tropical Diseases in Sierra Leone

Thank you for your letter dated 8 February 2011 responding to the points raised by the Research Ethics Committee. The protocol now has formal ethical approval from the Chair of LSTM Research Ethics Committee.

The approval is for a fixed period of three years, renewable annually thereafter. The committee may suspend or withdraw ethical approval at any time if appropriate.

Approval is conditional upon:

- Submission of ethical approval from other ethics committees.
- Notification of all amendments to the protocol for approval before implementation.
- Notification of when the project actually starts.
- Provision of an annual update to the Committee. Failure to do so could result in suspension of the study without further notice.
- Reporting of all severe unexpected Adverse Events to the Committee
- Reporting of new information relevant to patient safety to the Committee
- Provision of Data Monitoring Committee reports (if applicable) to the Committee

Failure to comply with these requirements will result in withdrawal of approval. The Committee would also like to receive copies of the final report once the study is completed.

Yours sincerely

Prof David Lalloo
Chair, Research Ethics Committee

Parasites & Vectors

RESEARCH Open Access

Lymphatic filariasis mapping by Immunochromatographic Test cards and baseline microfilaria survey prior to mass drug administration in Sierra Leone

Joseph B Koroma[1,2*], Momodu M Bangura[1], Mary H Hodges[3], Mohamed S Bah[3], Yaobi Zhang[4] and Moses J Bockarie[2]

Abstract

Background: National mapping of lymphatic filariasis (LF) was conducted using Immunochromatographic tests (ICT) in 2005 to determine endemicity and geographic spread of the disease. A baseline microfilaria survey was then conducted to determine LF prevalence and microfilaria intensity.

Methods: In 2005 1,982 persons of 15 years and over from 14 health districts were selected and fingertip blood samples were tested with ICT cards. In 2007-8 blood samples were taken between 10 p.m. and 2 a.m. and examined for microfilaria (mf) from 9,288 persons from 16 sentinel sites representing each district and 2 additional sites for districts with populations over 500,000 (Bo and Kenema).

Results: The overall LF prevalence by ICT cards was 21% (males 28%, females 15%). All districts had a prevalence of *Wuchereria bancrofti* antigen > 1%. Distribution of LF prevalence showed a strong spatial correlation pattern with high prevalence in a large area in the northeast gradually decreasing to a relatively low prevalence in the southwest coast. High prevalence was found in the northeast, Bombali (52%), Koinadugu (46%), Tonkolili (37%) and Kono (30%). Low prevalence was found in the southwest, Bonthe (3%) and Pujehun (4%). The mf prevalence was higher in the northeast: Bombali, 6.7%, Koinadugu 5.7%, Port Loko 4.4% and Kono 2.4%. Overall there was a significant difference in mf prevalence by gender: males 2.9%, females 1.8% ($p = 0.0002$) and within districts in Kailahun, Kono, Port Loko, Moyamba and Koinadugu (all $p < 0.05$). The mf prevalence was higher in people > 20 years (2.5%) than in people ≤ 20 years (1.7%) ($p = 0.043$). The overall arithmetic mean mf density was 50.30 mf/ml among mf-positive individuals and 1.19 mf/ml in the population examined which varied significantly between districts.

Conclusions: The ICT results showed that LF was endemic nationwide and that preventive chemotherapy (PCT) was justified across the country. Both the ICT and microfilaraemia surveys found that prevalence was greater in males than females. The increase in microfilaraemia prevalence by age was evident when grouped as ≤ 20 versus > 20 years demonstrating early exposure. Baseline LF microfilaria load will be used to monitor PCT program progress.

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Background

Lymphatic filariasis (LF) is a chronic, debilitating disease that affects people in tropical and subtropical areas of Asia, Africa, the Western Pacific and some areas of the Americas caused by the parasites *Wuchereria bancrofti* or *Brugia malayi* and *B. timori*, transmitted by *Culex, Anopheles* and other mosquitoes [1-4]. An estimated 90% of all LF cases worldwide and all cases in Africa are infections with the parasite *W. bancrofti*. The main vectors in West Africa are the *Anopheles* mosquitoes [5]. Over 120 million people in over 80 countries worldwide in the tropics and subtropics and over 40 million people in Africa are infected with the parasite [6,7]. Bancroftian filariasis, which is prevalent in Africa, is endemic in rural as well as urban communities thriving within poor communities [5,8,9].

LF has a wide range of clinical manifestation from acute attacks of filarial fever, chronic conditions such as hydroceles, lymphoedema, elephantiasis of limbs, and enlarged breasts, to kidney damage, thus causing great morbidity and disability for those affected [10]. Filariasis is one of the most common causes of permanent disability worldwide creating the highest disease burden in terms of DALYs among tropical diseases [7]. Those affected also suffer psychosocial stigmatization and economic suffering as it can lead to job loss or inability to work. The disease is therefore a major cause of poverty as it creates economic burden for those affected, their dependants, their communities and the country as a whole [8,9,11-13]. In 1993 the International Task Force on Disease Eradication identified LF as one of six diseases that could be eradicated, which led the World Health Assembly in 1997 to pass resolution WHA 50.29 calling for the elimination of LF as a public health problem in the world by 2020. In 1998, the Global Alliance to Eliminate LF was formed to support LF elimination programmes in endemic countries and World Health Organization (WHO) launched a Global Programme for the Elimination of LF as a result [2,3,13-15].

Circulating microfilariae (mf) are responsible for transmission, therefore transmission can be broken/interrupted by reducing the number of people with microfilaraemia within affected communities through annual mass drug administration (MDA) for 4-6 years to ≥ 80% of the entire at-risk population which can reduce mf to zero or close to zero [16,17]. Before MDA is started in a country, implementation units to be targeted should be determined through a rapid assessment study and also baseline data on LF mf level should be obtained to monitor effectiveness of MDA. There are already countries that have succeeded in eliminating the disease (Cape Verde, China, Costa Rica, Solomon Islands, South Korea, Suriname, and Trinidad and Tobago) using a combination of strategies that include vector control and single annual doses of 2-drug treatments (albendazole together with ivermectin or diethylcarbamazine) [16,17]. The current preferred strategy for LF elimination recommended by WHO is the preventive chemotherapy using the available drugs [18,19]. The global LF elimination programme has been strengthened by donation of albendazole by GlaxoSmithKline and continued donation of ivermectin by Merck & Co [20].

In Sierra Leone, reports from health facilities indicated endemicity of LF in all districts, and in 1996, a study in Moyamba district using the thick blood film method showed mf prevalence: 10.2% with 36.5% clinical manifestation (26.6% hydroceles and 9.4% lymphoedema/elephantiasis of the lower extremities) [21]. In 2004, a country profile of communicable diseases in Sierra Leone developed by WHO, quoting an anonymous 1999 study in 55 sites including the capital Freetown, showed that 14.5% of people tested for circulating filarial antigen of *W. bancrofti* were positive [22]. The Northern Province had the highest prevalence (19.6%), followed by Western Area (12.8%), Eastern Province (12.7%) and Southern Province (10.9%) [22]. Infection was noted in children, and this indicated ongoing transmission and infections acquired early in life.

In preparation for the national LF elimination programme, national mapping was conducted in 2005 using immunochromatographic test (ICT) cards. The national LF elimination programme started when the Ministry of Health and Sanitation (MoHS), Sierra Leone in consultation with WHO decided to conduct the integrated management of onchocerciasis, LF, schistosomiasis, soil-transmitted helminthes and trachoma, and the existing National Onchocerciasis Control Programme became National Neglected Tropical Disease Control Programme (NTDCP) in 2006 [23]. Based on the mapping results, the implementation units (districts) for LF MDA were determined and national baseline data on mf level were collected pre-MDA. The current paper presents the distribution and the level of infection of LF in Sierra Leone which formed the base for the national LF elimination programme.

Methods

Ethics statement

The studies were conducted by the National NTDCP of the MoHS, Sierra Leone. Ethical approval for data collection was obtained from the Ethics Committee of the MoHS and upon arrival at the randomly selected communities the investigating team met with the community leaders and explained the nature of their work. All participants aged 15 years or above in each site were eligible for inclusion without discrimination on gender,

social status, religion or ethnicity. People participated in the studies after informed consent was verbally obtained and recorded by the team leader, as literacy rates are low in Sierra Leone. Data collection was conducted such that participants remained anonymous during data entry and analysis. No individual identity can be revealed upon publication.

National mapping of LF with ICT cards in 2005

Although previous studies and clinical records indicated that LF was prevalent particularly in the north, detailed data on distribution and level of risk throughout the country was not available, and all districts including the Rural Western Area both Rural (RWA) and Urban Western Area (UWA) were included in the mapping. Thirty-four (34) communities were randomly selected from all districts in consultation with WHO/AFRO with each district having at least one community selected. Participants who were 15 years of age or above were selected for the antigenaemia study using ICT cards [24]. During the survey ICT cards were kept overnight at 8°C in district cold rooms for the expanded programme on immunization and during the day the cards were transported in cold boxes and vaccine carriers with ice packs. The left index finger was pricked with a sterile lancet after cleaning with cotton wool soaked with spirit and 100 μl blood collected and applied straight to the ICT cards. The survey teams were trained to read the results of the ICT cards at exactly 10 minutes after application, according to the manufacturer's instructions. No late reading of ICT cards was reported by the survey teams. Due to limited resources and the high sensitivity and specificity of the ICT [25,26], fifty (50) persons were sampled in each randomly selected community and if a positive case was identified the sampling was complete and the teams moved on to the next site. If in the first 50 samples there was no positive case found, a further 50 persons were sampled bringing the total to 100 per site [26]. Training of technicians in the use of the ICT cards to detect *W. bancrofti* antigen and data recording took place in Makeni and York Village, RWA. Three teams of three technicians (2 for specimen collection and 1 for reading and recording of results) worked with a village volunteer (usually a school teacher) who served as registrar. Data included name, sex, village, chiefdom and district. A total of 1,982 people were tested; males 904 (45.6%) and females 1,078 (54.4%).

Baseline microfilaraemia data collection before MDA

Sampling was conducted in accordance with WHO guidelines [26] of two sentinel sites per implementation unit (district for Sierra Leone) with a population of one million people. Ten of the fourteen health districts of Sierra Leone have a population below 500,000 and one sentinel site per district was selected representing a population ≤ 500,000. One sentinel site each was selected for RWA (232,294) and UWA (901,953). Bo district (Bo Town: Bo District, 222,561: 347,610) and Kenema district (Kenema Town: Kenema District, 188,869: 377,067) had population above 500,000 and two sentinel sites were selected in these two districts, making a total of 16 sites. Communities/villages that showed the highest ICT prevalence in each district in 2005 were selected as mf sentinel sites [26]. The survey was performed in two phases according to funding availability: Bombali, Koinadugu, Kambia, Kono, Kailahun and Pujehun in 2007 and Tonkolili, Port Loko, Kenema, Bonthe, Moyamba, Bo, RWA and UWA in 2008. Pre-sensitization was carried out before the survey in each site. Five hundred participants of 15 years of age or above were recruited per site. In sites with less than 500 people selected, extra participants were recruited in neighbouring villages. To ensure the standardization of activities and data, two day practical training was performed before the study started for all technicians. Fingertip blood was collected between 10 p.m. and 2 a.m. from each volunteer. A 60 μl blood sample was collected, smeared gently and uniformly in a circular shape and allowed to air dry at room temperature for 12-24 hours. The following day the dried smear was dehaemoglobinized by flooding with distilled water for 3-5 minutes, air dried again, fixed with methanol for 30-60 seconds, stained with Giemsa for 10 minutes then examined for mf under a light microscope by experienced examiners. Positive findings of mf were recorded and individual mf density of infection was calculated and expressed as the number of mf per ml of blood (mf/ml) [26-29]. A total of 9,288 night blood samples were examined. The mean age (± standard deviation) of the subjects examined was 37.7 ± 17.04 years (males: 37.27 ± 17.6, females: 38.12 ± 16.5). For quality control, all positive slides and 10% of the negative slides were preserved and examined by an experienced researcher.

Statistical analysis

Results were entered into Epi-Info version 3.5.2 and analyzed in SPSS (IBM, Version 19). Prevalence of positive circulating LF antigen or microfilaraemia was calculated. The 95% confidence intervals (CIs) for prevalence were calculated using the Wilson score method without continuity correction [30]. The arithmetic mean mf density of infection with 95% CIs was calculated using the total population examined and the positive samples only [26]. Chi-square test was used to compare the differences in prevalence and Kruskal-Wallis test was used to compare the differences in mf density. Correlation analysis was conducted for the two sets of data (ICT and microfilaraemia prevalences) and the significance of the

correlation tested [31]. The coordinates of each sample site were recorded using hand-held units of global positioning system (site coordinates available upon request). Spatial analysis of the LF antigenaemia prevalence (ICT card data) was conducted using the kriging method in the Geostatistical Analyst Extension of ArcGIS version 10 (ESRI, Redlands, USA). Spatially smoothed contour maps of the interpolated prevalence of antigenaemia and the predictive probability for the ICT prevalence of greater than 1% were produced [32].

Results

Distribution of lymphatic filariasis in Sierra Leone

Table 1 summarizes the results of the survey using ICT cards for each district. All the districts of Sierra Leone were found to be endemic for LF with a prevalence of ICT positive tests ≥ 1%. Point prevalence for each survey site was shown in Figure 1. Among 34 sites surveyed, only one site in Bonthe district was shown to be negative. The median prevalence across the 34 sites was 20% ranging from 0% to 68% (inter-quantile range: 11.7-31%). Overall ICT positive prevalence was 20.8%. High

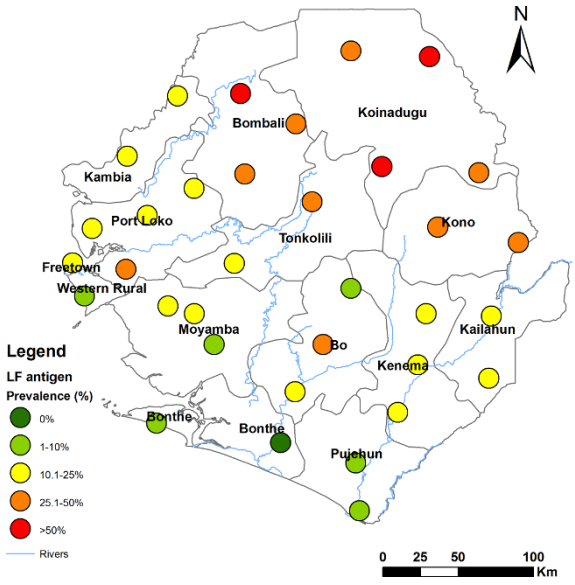

Figure 1 Geographical distribution of lymphatic filariasis point prevalence by circulating antigen detection with ICT cards according to survey locations in Sierra Leone.

Table 1 Crude LF prevalence with antigen detection and microfilaraemia tests by district, sex and age group in Sierra Leone

	No of persons tested by ICT cards	Percentage prevalence of antigen positives (95% CI)	No of persons examined for Mf	Percentage prevalence of Mf positives (95% CI)	Population Mf density (mf/ml) (95% CI)	Positive-only Mf density (mf/ml) (95% CI)
Overall	1982	20.8 (19.1 - 22.7)	9288	2.4 (2.1 - 2.7)	1.19 (0.90 - 1.48)	50.3 (39.89 - 60.71)
By district						
Bo	173	15.0 (10.5 - 21.1)	1005	2.0 (1.3 - 3.1)	1.97 (0.84 - 3.11)	99.17 (58.32 - 140.01)
Bombali	150	52 (44.1 - 59.8)	830	6.9 (5.3 - 8.8)	1.93 (1.28 - 2.57)	28.07 (21.70 - 34.44)
Bonthe	160	3.1 (1.3 - 7.1)	504	1.2 (0.6 - 2.6)	0.83 (0.02 - 1.63)	69.44 (13.68 - 125.21)
Kailahun	110	19.1 (12.8 - 27.4)	624	2.6 (1.6 - 4.1)	2.08 (0.00 - 4.89)	81.25 (0.00 - 195.58)
Kambia	110	15.5 (9.9 - 23.4)	619	2.1 (1.2 - 3.6)	0.97 (0.23 - 1.71)	46.15 (17.04 - 75.27)
Kenema	180	13.3 (9.1 - 19.1)	1016	0.6 (0.3 - 1.3)	0.34 (0.00 - 0.70)	58.33 (4.42 - 112.24)
Koinadugu	200	46 (39.2 - 52.9)	636	5.7 (4.1 - 7.7)	1.99 (0.95 - 3.04)	35.19 (19.83 - 50.54)
Kono	100	30 (21.9 - 39.6)	875	2.4 (1.6 - 3.6)	1.11 (0.37 - 1.84)	46.03 (20.09 - 71.97)
Moyamba	200	10.5 (7.0 - 15.5)	500	1 (0.4 - 2.3)	0.67 (0.00 - 1.36)	66.67 (6.33 - 127.00)
Port Loko	210	20.5 (15.6 - 26.4)	500	4.4 (2.9 - 6.6)	3.53 (1.48 - 5.59)	80.30 (44.49 - 116.12)
Pujehun	160	4.4 (2.1 - 8.8)	624	0 (0 - 0.6)	-	-
Tonkolili	100	37 (28.2 - 46.8)	500	2.4 (1.4 - 4.2)	0.63 (0.24 - 1.03)	26.39 (17.99 - 34.79)
WA Rural	69	7.3 (3.1 - 15.9)	500	1.2 (0.6 - 2.6)	0.33 (0.01 - 0.65)	27.78 (6.60 - 48.96)
WA Urban	60	11.7 (5.8 - 22.2)	555	0 (0 - 0.7)	-	-
By sex						
Male	904	27.5 (24.7 - 30.6)	4335	3.0 (2.6 - 3.6)	1.66 (1.11 - 2.20)	54.42 (38.81 - 70.02)
Female	1078	15.2 (13.2 - 17.5)	4953	1.8 (1.4 - 2.2)	0.78 (0.52 - 1.04))	44.13 (32.50 - 55.76)
By age group (yrs)						
15-20	-	-	1873	1.8 (1.3 - 2.5)	0.78 (0.38 - 1.19)	44.44 (26.37 - 62.52)
21-30	-	-	2019	2.6 (2.0 - 3.4)	1.77 (0.73 - 2.80)	68.59 (31.79 - 105.39)
31-40	-	-	1830	2.4 (1.8 - 3.2)	1.01 (0.55 - 1.47)	43.02 (27.55 - 58.50)
41-50	-	-	1404	3.4 (2.5 - 4.4)	1.60 (0.94 - 2.27)	47.87 (32.75 - 62.99)
> 50	-	-	2162	2.1 (1.6 - 2.8)	0.89 (0.49 - 1.30)	42.96 (27.40 - 58.53)

prevalence was found in the northeast part of the country (Bombali 52%, Koinadugu 46%, Tonkolili 37% and Kono 30%). Relatively low prevalence was found in the southwest coastal districts (Bonthe 3.1% and Pujehun 4.4%).

There were significantly more positive ICT tests in males (27.54%, 95% confidence interval (CI): 24.7-30.6%) than in females (15.2%, 95% CI: 13.2-17.5%) ($p < 0.00001$). Detailed analysis of prevalence among different age groups was not carried out as detailed age information was not recorded for the ICT card survey.

Microfilaraemia prevalence and density

Overall 9,288 night blood samples, male 4,335 (46.7%) and female 4,953 (53.3%), were examined for mf as shown in Table 1. There were less than 5% false positives and no false negative slides. All positive slides were reexamined and 3 were redefined as artifacts. No mf of *Mansonella perstans* was detected.

In total, 220 persons (2.4%, 95% CI: 2.1-2.7%) had a positive blood smear and there was significantly higher mf prevalence in males 3.0% (95% CI: 2.6-3.6%) versus females 1.8% (95% CI: 1.4-2.2%) (p = 0.0002). Age distribution of the mf prevalence is also shown in Table 1. There was a significant difference in mf prevalence among age groups with higher prevalence in persons of 41-50 years (p = 0.041).

The point prevalence of microfilaraemia for each site is shown in Figure 2. There was a significant correlation between the mf prevalence and the ICT card prevalence (r = 0.86, p < 0.05). In line with the ICT results, the mf prevalence (95% CI) was higher in the northeast part of the country: Bombali, 6.9% (5.3-8.8%), Koinadugu 5.7% (4.1-7.7%), Port Loko 4.4% (2.9-6.6%), Kailahun 2.6% (1.6-4.1%) and Kono 2.4% (1.6-3.6%). No mf was found in persons examined in the UWA and Pujehun.

The overall arithmetic mean mf density was 50.30 mf/ml (95% CI: 39.89-60.71 mf/ml) among mf-positive individuals, and 1.19 mf/ml (95% CI: 0.90-1.48 mf/ml) in the population examined (Table 1). There was significantly higher mf density in the male population than in the female population (p < 0.0001). There was also a significant difference in mf density among age groups in the total population examined (p = 0.041). There was no significant difference in mf density by sex or age groups of infected persons (p > 0.1).

Spatial prediction of LF distribution

The spatial analysis of the ICT card data showed a strong spatial correlation pattern as the semi-variance in prevalence data in relation to the distance between survey sites (Figure not shown). The predicted spatial distribution of LF by kriging is shown in Figure 3. This shows a widespread distribution of LF prevalence with a clear geographical distribution pattern in Sierra Leone: high (> 40%) in a large area spanning the northeast of the country with two clusters of predicted prevalence of over 50%, gradually decreasing towards the southwest, and ending low (< 5%) in the coastal part of Bonthe and Pujehun districts. Figure 4 shows the predicted probability of the LF prevalence being over 1%, which shows

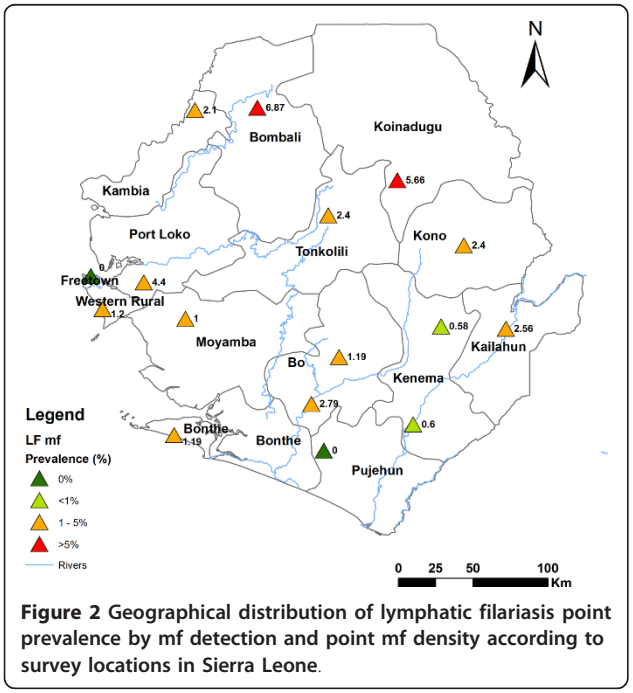

Figure 2 Geographical distribution of lymphatic filariasis point prevalence by mf detection and point mf density according to survey locations in Sierra Leone.

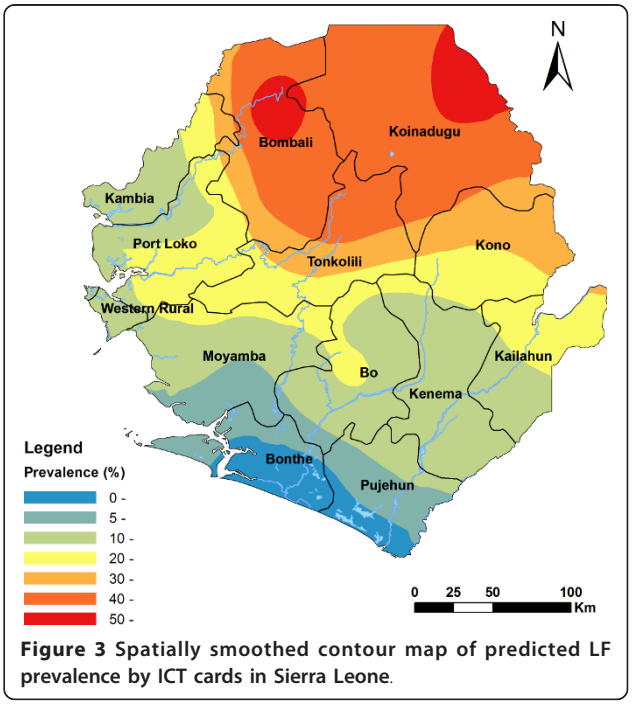

Figure 3 Spatially smoothed contour map of predicted LF prevalence by ICT cards in Sierra Leone.

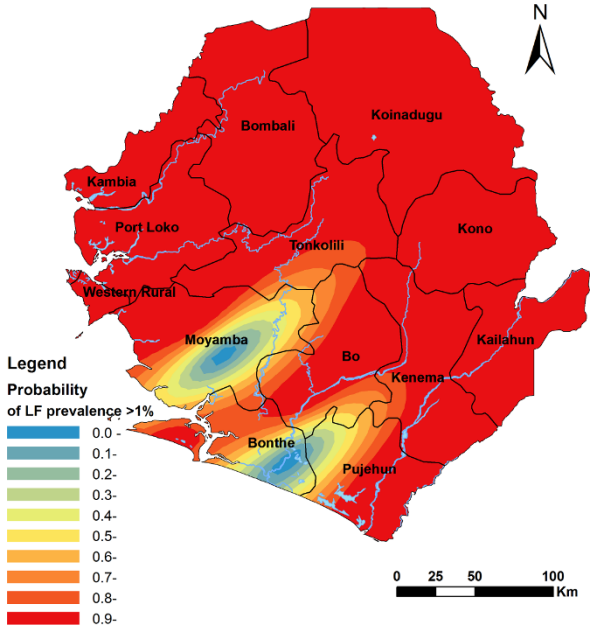

Figure 4 Spatially smoothed contour map of the predicted probability that the prevalence of LF antigenaemia exceeds 1%.

high probability throughout the country with only two small clusters of relatively low probability (< 50%) in Bonthe and Moyamba.

Discussion

All districts in Sierra Leone were endemic with LF and qualified for MDA. Distribution of LF prevalence showed a strong spatial correlation pattern with high prevalence in a large area in the northeast gradually decreasing to relatively low prevalence in the southwest coast. ICT results showed two distinct patterns: males were more infected than females and districts in the northeast part of the country had a higher prevalence than other districts. The ICT results obtained in this study were higher than in 2004 but the same pattern of a higher prevalence for circulating filarial antigen in the north than all other regions was repeated [22]. Three distinct patterns were also noted in the microfilaraemia survey: microfilaraemia was higher in males (3.0%) versus females (1.8%), increased with age in the population peaking at 41-50 years, and showed higher prevalence in the northeast than in other parts of the country. In two districts (UWA and Pujehun), microfilaraemia was not identified among the subjects examined, even though ICT prevalence was 11.7% and 4.4% respectively.

The mf prevalence was lower than that reported in 1996 but that study was conducted in an area with clearly visible signs of the disease to highlight the seriousness of the problem [21]. There were many such areas in the districts where LF signs were clearly visible among the population but in this study the sites were randomly selected to avoid bias, therefore the results of this study were more representative of the mf prevalence in the district population. The results acquired in this study on mf prevalence and mf density/intensity will form the basis for monitoring and evaluation of the effectiveness of MDA in interrupting LF transmission in each district.

Similar patterns are noted for both studies in geographical and sex distribution of the disease, which further strengthens the notion that these results are representative of the actual national picture. The ICT positive prevalence was nine times greater than the mf prevalence. Several authors have reported that ICT positive prevalence, which detects antigen released by adult *W. bancrofti*, can be 3-5 times higher than mf prevalence. People can be infected with the disease and still be amicrofilaraemic, which may explain the zero mf prevalence in UWA and Pujehun district in these studies [27,33,34].

Previous studies demonstrated the impact of long-term treatment with ivermectin alone for onchocerciasis control on LF prevalence and transmission, which showed that in villages treated for many years with ivermectin, LF microfilaraemia prevalence and intensity were significantly lower than in untreated villages [35,36]. Antigenaemia rates were significantly higher than microfilaraemia rates generally [35,36]. Onchocerciasis was endemic in 12 out of the 14 health districts in Sierra Leone [23]. Community based treatment with ivermectin for the control of onchocerciasis in Sierra Leone started in the late 1980s but did not reach full geographical coverage due to insecurity at the beginning of the civil war in 1991 and were subsequently suspended in 1994. In 2003 community-directed treatment with ivermectin (CDTI) was introduced but therapeutic coverage was low in the post conflict setting. In 2005 the National Onchocerciasis Control Program (NOCP) was reorganized and therapeutic coverage reached the prerequisite ≥ 65% and has been maintained in all endemic districts since [23]. The relatively low microfilaraemia rates in our study and the difference between antigenaemia rates and microfilaraemia rates may have been due to the ivermectin treatment for onchocerciasis control in Sierra Leone before the surveys were conducted.

The current results are in line with other studies that males have higher prevalence than females for circulating filarial antigen as well as for microfilaraemia [12,37,38]. The most probable reason for this is that males spend more time exposed to the bites of mosquitoes. The distribution of mf prevalence increasing with age shown in this study is in line with results of many other studies [9,12,33,37,38]. This emphasizes the

socioeconomic impact of the disease as the age groups affected most are the major workforce in the villages. In Sierra Leone an estimated 70% of adults are farmers [39], and disability from LF incapacitates those affected and increases poverty, which is a cause for concern as the country is among the poorest in the world and demands appropriate attention for elimination of the disease. It has been suggested that adults could be more exposed to mosquito bites because of higher relative heat, more carbon dioxide output or simply because they have relatively greater surface area that can be bitten by mosquitoes [38]. Similar studies on antigenaemia and microfilaraemia for *W. bancrofti* have been conducted in other countries that reflected similar gender and age pattern as our studies [40-42].

There are certain limitations for the current studies. Firstly, children below 15 years were not selected for circulating filarial antigen and for microfilaria according to the WHO guidelines [24]. The WHO profile for LF in Sierra Leone in 2004 indicated that children were infected and that the infection could be acquired early in life [22]. It has been suggested that excluding children below 15 years could bias the studies towards older people and since it is common knowledge that filariasis infection increases with age, the prevalence might have been overestimated for the general population compared to other studies that used population based sampling methodology [33]. While this may have been true in this study, considering the overall global objective is LF elimination, such slight overestimation of LF prevalence due to the age bias should not have made much difference in terms of MDA decision in Sierra Leone. Secondly, it is recommended that ICT cards be stored at or around 8°C [13]. Although efforts were made to keep the cards in cold box during the field work, the relatively poor field conditions in the remote villages may have made it difficult to keep the box cold at all time. In such field conditions, reading every card within the time limit may not have been guaranteed. This may in part explain the higher ICT positive prevalence (nine times greater than the mf prevalence) in the current studies than in other studies [27,33,34]. However, taking both ICT and mf positive prevalence together, there is a strong correlation between the results of the two surveys for the 14 health districts as shown through correlation analysis. Therefore, the results can be considered to be representative of the true LF endemic situation in Sierra Leone.

Based on the information provided by these studies, the national NTDCP started LF MDA in 2007 [23]. Four rounds of MDA with albendazole and ivermectin have been delivered in 6 districts, three rounds in 7 districts RWA and two rounds in the UWA [43]. The mid-term impact assessment is now being conducted at the sentinel sites plus several hot spots with local knowledge of high occurrence of LF morbidity using blood smears for mf detection. It is hoped that the assessment results will provide tools to evaluate the impact of the MDA and to adjust the course of MDA if necessary.

Conclusion

LF mapping using ICT cards was successfully conducted in 2005 in all districts of Sierra Leone which showed that all districts were endemic for LF and qualified for MDA. Baseline data collection with night blood smear was conducted in 2007-08 before MDA, which provided baseline values for mf prevalence and mf density and confirmed LF endemic status determined by ICT card survey across the country. These surveys provided tools for the NTDCP to design and implement MDA and provided the basis for future monitoring and evaluation of the national LF elimination programme.

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Authors' contributions

JBK was the NTDCP national programme manager, designed the studies and initial reports. MMB led and conducted the field work. MSB and MHH conducted the data entry and initial analysis. JBK and MHH drafted and revised the paper, conducted correlation analysis. MJB provided support during revision of the paper and revised the paper. YZ conducted the final data analysis, spatial analysis and revised the paper. All authors reviewed and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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PLOS | NEGLECTED TROPICAL DISEASES

Impact of Three Rounds of Mass Drug Administration on Lymphatic Filariasis in Areas Previously Treated for Onchocerciasis in Sierra Leone

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Abstract

Background: 1974–2005 studies across Sierra Leone showed onchocerciasis endemicity in 12 of 14 health districts (HDs) and baseline studies 2005–2008 showed lymphatic filariasis (LF) endemicity in all 14 HDs. Three integrated annual mass drug administration (MDA) were conducted in the 12 co-endemic districts 2008–2010 with good geographic, programme and drug coverage. Midterm assessment was conducted 2011 to determine impact of these MDAs on LF in these districts.

Methodology/Principal Findings: The mf prevalence and intensity in the 12 districts were determined using the thick blood film method and results compared with baseline data from 2007–2008. Overall mf prevalence fell from 2.6% (95% CI: 2.3%–3.0%) to 0.3% (95% CI: 0.19%–0.47%), a decrease of 88.5% ($p = 0.000$); prevalence was 0.0% (100.0% decrease) in four districts: Bo, Moyamba, Kenema and Kono ($p = 0.001$, 0.025, 0.085 and 0.000 respectively); and seven districts had reductions in mf prevalence of between 70.0% and 95.0% ($p = 0.000$, 0.060, 0.001, 0.014, 0.000, 0.000 and 0.002 for Bombali, Bonthe, Kailahun, Kambia, Koinadugu, Port Loko and Tonkolili districts respectively). Pujehun had baseline mf prevalence of 0.0%, which was maintained. Only Bombali still had an mf prevalence $\geq$1.0% (1.58%, 95% CI: 0.80%–3.09%)), and this is the district that had the highest baseline mf prevalence: 6.9% (95% CI: 5.3%–8.8%). Overall arithmetic mean mf density after three MDAs was 17.59 mf/ml (95% CI: 15.64 mf/ml–19.55 mf/ml) among mf positive individuals (65.4% decrease from baseline of 50.9 mf/ml (95% CI: 40.25 mf/ml–61.62 mf/ml; $p = 0.001$) and 0.05 mf/ml (95% CI: 0.03 mf/ml–0.08 mf/ml) for the entire population examined (96.2% decrease from baseline of 1.32 mf/ml (95% CI: 1.00 mf/ml–1.65 mf/ml; $p = 0.000$)).

Conclusions/Significance: The results show that mf prevalence decreased to $<$1.0% in all but one of the 12 districts after three MDAs. Overall mf density reduced by 65.0% among mf-positive individuals, and 95.8% for the entire population.

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Introduction

Lymphatic filariasis (LF) and onchocerciasis are two of the major neglected tropical diseases (NTDs), presently targeted for elimination using the World Health Organization (WHO) recommended strategy of preventive chemotherapy and transmission control (PCT) [1,2,3]. LF is a disease caused by the lymphatic filarial roundworms *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*, and transmitted by mosquitos. It is highly endemic in the tropics and subtropics (Africa, Asia, South Pacific and some parts of South America). The elimination strategy is through annual mass drug administration (MDA) with albendazole and ivermectin/diethylcarbamazine [1,2]. LF elimination is implemented through the Global Programme to Eliminate Lymphatic Filariasis (GPELF) which has expanded MDA coverage from three million people treated in 12 countries in 2000, to more than 450 million in 53 countries in 2010 [4,5]. During that period, the disease was eliminated in China and Korea. Nine countries no longer require MDA because of a natural decline in transmission intensity in areas of low disease endemicity. Globally, a total of 73 countries (including the recently independent Republic of South Sudan) are presently endemic for LF. Onchocerciasis, caused by *Onchocerca volvulus*, is transmitted by blackflies belonging to the *Simulium damnosum* complex. It is mainly endemic in Africa, Yemen and the Americas [6]. Control of the disease in Africa is through the African Programme for Onchocerciasis Control (APOC) using the

Author Summary

Onchocerciasis studies across Sierra Leone between 1974 and 2005 showed that 12 of the 14 health districts (HDs) are endemic for onchocerciasis. Baseline lymphatic filariasis (LF) studies 2005–2008 showed that all 14 HDs of Sierra Leone are LF endemic. Three annual rounds of integrated mass drug administration (MDA) with ivermectin and albendazole 2008–2010 were conducted in the 12 HDs that are co-endemic for onchocerciasis and LF with good geographic, epidemiological drug (or programme) and drug coverage. A midterm evaluation study of mf prevalence and density was conducted in the 12 HDs in 2011. The hypothesis proposed for this study is that areas previously exposed to ivermectin treatment for onchocerciasis control may require less rounds of annual MDA to eliminate LF (i.e. reduce microfilaremia (mf) prevalence to <1%). Results of the midterm evaluation study showed very significant and rapid reduction of mf prevalence and density with 11 out of the 12 districts having mf prevalence <1%. Relatively low LF baseline prevalence and effective integrated MDA for onchocerciasis and LF have led to rapid reduction in LF prevalence.

annual community-directed treatment with ivermectin (CDTI) strategy [7]. In 2008 alone, 56.7 million people received treatment in 19 endemic African countries [7].

In Sierra Leone, both diseases are widely distributed across the country and co-endemic in 12 of the 14 health districts. The early distribution and clinical manifestations of both diseases in Sierra Leone were described in previous publications [8,9,10,11,12]. When Sierra Leone was included as part of the Onchocerciasis Control Programme (OCP) of WHO in 1989, treatment strategy for onchocerciasis control included aerial larviciding using helicopters and aircrafts targeting the breeding sites of the blackflies and ivermectin treatment as Merck & Co. Inc. had started donation of Mectizan (ivermectin) in 1987. National Onchocerciasis Control Programme (NOCP) records show that by 1994 annual biting rates of the savannah blackfly population dropped from the 1988 pre-treatment level of 60 bites/person/day to 1 bite/person/day and the community microfilaria load decreased by over 90%. However, by 1996 onchocerciasis control activities were stopped in all areas of the country when the civil conflict that started 1991 engulfed the entire country. The civil conflict ended in 2002, the same year that OCP was closed. NOCP activities recommenced in 2003 under the Special Intervention Zones (SIZ) established by APOC for some ex-OCP countries, including Sierra Leone. Surveys on onchocerciasis conducted in Sierra Leone after 2002 (unpublished NOCP data) showed that vector biting rates and community microfilaria load had reverted to pre-treatment levels in many communities. Since 2003 annual MDAs have been conducted for onchocerciasis control using the CDTI strategy with technical and financial support from APOC. The CDTI strategy, which promotes community participation as the key aspect of ivermectin distribution to improve access to ivermectin and ensure community ownership of the process, was adopted by APOC in the mid-1990s after a multi-country study. At first the local health workers and NGDO representatives introduce CDTI to the community in a participatory manner. Through a series of community meetings they explain the roles and responsibilities of communities in the CDTI process. The communities themselves then direct the planning and implementation of the interventions. The community collectively selects the community drug distributors (CDDs) and then plan the distribution process by deciding the method used (house to house or central location), the place where the distribution is conducted if fixed location is accepted, when the distribution is conducted, by whom activities will be implemented, how all activities will be monitored, and the support, if any, that CDDs will receive (financial or otherwise) from the community. With CDTI communities manage ivermectin by collecting their supply from a central point agreed upon with the health services and storing it within the community until the distribution period. The health workers and NGDO representatives train, supervise and monitor the CDDs while the community directs the process. It has been observed that when the community takes charge of onchocerciasis control MDAs can be sustained for up to 20 years. Furthermore, programme costs are reduced significantly because the community plays the leading role in all aspects of programme implementation [13,14]. Apart from training of communities to assume leadership of the CDTI process, NGDOs have also made significant contribution to the CDTI process through operational research, provision of resources to complement national programmes by supporting health staff in remote communities, and provision of technical and financial support. An NDGO Coalition was created in 1991 for onchocerciasis control that meets regularly to coordinate collaboration at international and national levels [15]. Annual MDAs using the CDTI strategy has significantly reduced parasite prevalence and intensity in many communities of Sierra Leone since control operations resumed in 2003 [16]. Reports from health facilities had always indicated high endemicity of LF in all districts. Pre-baseline prevalence of LF was very high in south-eastern Sierra Leone. Blacklock (1922) examined 240 men in Mabang village and found 20% to be microfilaraemic, with prevalence of elephantiasis and hydrocoele of 4.6% and 3.8%, respectively [17]. Surveys in the early 1990s showed an average mf prevalence of 34.8% in three villages in the Moyamba district [18]. Similarly high prevalence rates were recorded in neighboring Liberia prior to the 1980s [19,20]. In 2007–2008, the pre-treatment mf prevalence for the 12 districts outside the Western Area ranged from 0–6.9%, although prevalence was below 3% in the south-eastern districts [21] with Moyamba district showing pre-treatment mf prevalence of 1% (95%CI 0.4%–2.3%) [21]. This significant reduction of mf prevalence from earlier high levels prior to the start of the LF MDAs coincides with the commencement of mass administration of ivermectin for onchocerciasis control in the 1980s [16]. After national mapping of LF in 2005 and baseline data collection on microfilaria (mf) prevalence and density in 2007–2008 [21], CDTI was expanded to include albendazole distribution to control LF in six co-endemic districts in 2007 [16]. With support from the United States Agency for International Development (USAID) NTD Control Program, managed at the time by RTI International, the NOCP was transformed into the National Neglected Tropical Diseases Control Programme (NTDCP) in 2008 to upscale treatment for LF from 6 districts to all 14 endemic districts and integrate other NTDs such as schistosomiasis and soil transmitted helminthiasis into the control effort [16]. After the civil war in Sierra Leone, during which almost all health programmes had stopped, the Ministry of Health and Sanitation (MOHS) had decided to put the control of all NTDs under the existing onchocerciasis control programme with 1(one) programme manager responsible for all NTDs and working in close collaboration with strong district health management teams (DHMTs). It was decided that running vertical programmes for NTDs will be inefficient given the post war situation and the limited number of health workers and so the national coordination for NTDs had to work in close collaboration with the DHMTs and the existing district health structure.

Annual MDA with ivermectin and albendazole has been implemented since then. By early 2011, all 12 rural health districts (except Urban Western Area and Rural Western Area) had received at least three rounds of MDA. LF antigenemia prevalence (ICT) in 2005 was 11.7% (95% CI: 5.8%–22.2%) and 7.3% (95% CI: 3.1%–15.9%) for Urban Western Area and Rural Western Area respectively and baseline microfilaremia prevalence in 2008 was 0% (95% CI: 0%–0.7%) and 1.2% (95% CI: 0.6%–2.6%) for Urban Western Area and Rural Western Area respectively. The study presented in this manuscript is the midterm evaluation of the LF programme in Sierra Leone as part of the national NTD Control Programme and was conducted following guidelines provided by WHO, which recommends midterm programme review before the 4th round of MDA. The 2 LF-only districts were not included in this study because effective MDA in these 2 districts started in 2010, while effective MDA in the other districts started in 2007/2008. These 2 districts have been treated through MDAs since 2010 but post-MDA microfilaremia studies have not yet been done. According to WHO guidelines [22], a mid-term survey was conducted in July/August 2011 in sentinel and spot check sites in the 12 rural health districts. The hypothesis of the study is that areas previously exposed to ivermectin treatment for onchocerciasis control may require fewer rounds of MDA to interrupt transmission of LF. Study objectives are to assess midterm progress towards LF elimination by measuring the microfilaremia prevalence for LF in districts that had conducted 3 good round of MDA and identify any implementation units (districts) that may require additional effort to reach the target of LF elimination. In this paper we describe the impact of three rounds of MDA on LF prevalence and mf density in areas of low LF endemicity which may be related to previous treatment with ivermectin for onchocerciasis control.

Methods

Ethics Statement

This study was conducted by the National NTDCP of the MOHS, Sierra Leone as part of the routine monitoring and evaluation activities of the national control programme. Ethical approval for the study was obtained from the MOHS Research and Ethics Committee. Informed oral consent was obtained from each participant before samples were collected. Parents and guardians provided informed consent for child participants to participate in the study before samples were collected. The acceptance of all participants/parents and guardians (for children) was recorded on a form by the team leader, as literacy rates are low in the country. All participants aged 5 years and above in each site were eligible for inclusion without discrimination on gender, social status, religion or ethnicity. Participants' identities were protected by collecting, recording and analyzing data such that participants remained anonymous.

Mass Drug Administration

Annual MDA with ivermectin and albendazole was piloted in 2007 in six rural districts located in border areas with neighboring Guinea and Liberia: Bombali, Kailahun, Kambia, Koinadugu, Kono, and Pujehun. This was scaled up to cover 12 rural districts in 2008 with six additional districts added to the previous six: Bo, Bonthe, Kenema, Moyamba, Port Loko and Tonkolili. Geographic coverage for the endemic districts targeted reached 100% in 2010 when MDA was scaled up to cover the remaining two health districts: Urban Western area and Rural Western area [23]. Within rural communities ivermectin and albendazole were distributed by CDDs who are literate members of the respective communities selected by their communities and trained by health workers. CDDs are trained by district health workers to conduct pre-MDA census, house-to-house visits in the village, treat all eligible members of the community by observing them while they take the doses, conduct follow up visits to treat absentees and complete the relevant reporting tools used at community level. 1 CDD is trained to cover approximately 100 people and for Sierra Leone where the average population per community is about 200, each community has on average 2 CDDs. In urban areas the programme tried but could not succeed in getting community volunteers (CDDs) to distribute the ivermectin and albendazole without getting any financial payment as in rural areas and so students in medical and nursing institutions were trained and paid to conduct MDAs. District health workers conduct trainings for MDA and provide supervision during MDAs. NTDCP staff and members of the DHMTs also supported training and supervision for MDAs. MDA is conducted once a year between September and December, which is the post-harvest period that communities have accepted for MDAs.

Before each MDA, CDDs conduct a pre-MDA census. Details on all community members are recorded in the community registers and updated each year prior to subsequent MDA. MDA details are also captured in the registers. After each MDA, details are summarized in the reporting forms by drug distributors and submitted to the supervising health workers. The supervising health workers prepare summary reports for all villages/urban areas targeted and submit the reporting forms to the DHMTs. Each DHMT then submits the district MDA report to the NTDCP, which collates MDA results from all districts. It should be noted that all activities were co-implemented for both onchocerciasis and LF control starting from trainings of district health workers and CDDs, community sensitization and mobilization, advocacy and mass distribution of ivermectin and albendazole. The NTD control programme is also strongly integrated in the national and district health system and has benefitted from a well-structured health system at district level that has a focal person responsible for NTD control within each district, which ensures high treatment and geographic coverage.

MDA in the 6 districts that piloted MDA for LF in 2007 took place in rural areas (villages) only as the main aim of this pilot MDA was to see how the CDDs and the district health workers can manage integrated MDA for onchocerciasis and LF (i.e. distribution of both ivermectin and albendazole). The onchocerciasis control programme is not implemented in urban areas with large populations or populations greater than 2000 people. Therefore, the integrated MDA in 2007 was done only in areas previously treated for onchocerciasis. As the 6 districts that piloted MDA for LF in 2007 did not cover the urban areas (i.e. district headquarter towns and other large towns with population >2000 people) with relatively poor treatment coverage (well below 65%), the 2007 MDA results were considered inadequate. It was only in 2008 that urban areas of the 12 districts were treated using health workers as distributors. 2008 is therefore considered year 1 when MDA results were "adequate" as treatment coverage was above 65% and geographic coverage was 100%. Please see tables 1 and 2 for districts that conducted pilot MDA in 2007.

Survey Site Selection

34 Villages were randomly selected by AFRO in Brazzaville using the available database for villages in Sierra Leone in 2005 with at least 2 villages selected per district depending on the population and sent to the programme. After the mapping in 2005, villages with relatively very high antigenemia prevalence were selected for all 14 health districts as sentinel sites for the

Table 1. LF microfilaraemia prevalence/density at baseline and midterm, their percentage reductions and p-values.*

	Baseline survey				Mid-term assessment				Percentage reduction			Significance test for reduction (p values)		
	No of persons examined for Mf	Mf prevalence (%) (95% CI)	Population mf density (mf/ml) (95% CI)	Positive-only mf density (mf/ml) (95% CI)	No of persons examined for Mf	Percentage mf prevalence (95% CI)	Population mf density (mf/ml) (95% CI)	Positive-only mf density (mf/ml) (95% CI)	Mf prevalence	Population mf density	Positive-only mf density	Mf prevalence	Population mf density	Positive-only mf density
Overall	8233	2.6 (2.3–3.0)	1.32 (1.00–1.65)	50.9 (40.25–61.62)	6023	0.30 (0.19–0.47)	0.05 (0.03–0.08)	17.59 (15.64–19.55)	88.5	96.2	65.4	0.000	0.000	0.001
By district														
Bo	1005	2.0 (1.3–3.1)	1.97 (0.84–3.11)	99.17 (58.32–140.01)	500	0	0	0	100	100	100	0.001	0.002	-
** Bombali	830	6.9 (5.3–8.8)	1.93 (1.28–2.57)	28.07 (21.70–34.44)	506	1.58 (0.80–3.09)	0.26 (0.08–0.45)	16.67 (-)	77.1	86.3	40.6	0.000	0.000	0.068
Bonthe	504	1.2 (0.6–2.6)	0.83 (0.02–1.63)	69.44 (13.68–125.21)	499	0.20 (0.04–1.13)	0.03 (0–0.10)	16.67 (-)	83.3	96.0	76.0	0.060	0.059	0.295
**Kailahun	624	2.6 (1.6–4.1)	2.08 (0.00–4.89)	81.25 (0.00–195.58)	499	0.20 (0.04–1.13)	0.03 (0–0.10)	16.67 (-)	92.3	98.4	79.5	0.001	0.001	0.472
**Kambia	619	2.1 (1.2–3.6)	0.97 (0.23–1.71)	46.15 (17.04–75.27)	500	0.40 (0.11–1.45)	0.07 (0–0.16)	16.67 (-)	81.0	93.1	63.9	0.014	0.014	0.311
Kenema	1016	0.6 (0.3–1.3)	0.34 (0.00–0.70)	58.33 (4.42–112.24)	500	0	0	0	100	100	100	0.085	0.085	-
**Koinadugu	636	5.7 (4.1–7.7)	1.99 (0.95–3.04)	35.19 (19.83–50.54)	498	0.80 (0.31–2.05)	0.17 (0–0.34)	20.83 (7.57–34.09)	86.0	91.6	40.8	0.000	0.000	0.454
**Kono	875	2.4 (1.6–3.6)	1.11 (0.37–1.84)	46.03 (20.09–71.97)	499	0	0	0	100	100	100	0.000	0.000	-
Moyamba	500	1 (0.4–2.3)	0.67 (0.00–1.36)	66.67 (6.33–127.00)	500	0	0	0	100	100	100	0.025	0.025	-
Port Loko	500	4.4 (2.9–6.6)	3.53 (1.48–5.59)	80.30 (44.49–116.12)	499	0.20 (0.04–1.13)	0.03 (0–0.10)	16.67 (-)	95.5	99.1	79.2	0.000	0.000	0.219
**Pujehun	624	0 (0–0.6)	1.19 (0.90–1.48)	-	500	0	-	-	-	-	-	-	-	-
Tonkolili	500	2.4 (1.4–4.2)	0.63 (0.24–1.03)	26.39 (17.99–34.79)	523	0.19 (0.03–1.08)	0.03 (0–0.10)	16.67 (-)	92.1	94.9	36.8	0.002	0.002	0.442
By sex														
Male	3863	3.3 (2.8–3.9)	1.83 (1.21–2.44)	55.08 (39.00–71.15)	3170	0.35 (0.19–0.62)	0.06 (0.03–0.10)	18.18 (14.80–21.56)	89.4	96.7	67.0	0.000	0.000	0.013
Female	4370	2.0 (1.6–2.4)	0.88 (0.59–1.18))	44.76 (32.89–56.64)	2853	0.25 (0.12–0.51)	0.04 (0.01–0.07)	16.67 (-)	87.5	95.4	62.8	0.000	0.000	0.023
By age groups														
5–14	-	-	-	-	1947	0.21 (0.08–0.53)	0.04 (0–0.09)	20.83 (7.57–34.09)	-	-	-	-	-	-
15–20	1614	2.0 (1.4–2.8)	0.90 (0.43–1.37)	45.31 (26.73–63.89)	858	0.12 (0.02–0.66)	0.02 (0–0.06)	16.67 (-)	94.0	97.8	63.2	0.000	0.000	0.341

Table 1. Cont.

Baseline survey					Mid-term assessment				Percentage reduction			Significance test for reduction (p values)		
	No of persons examined for Mf	Mf prevalence (%) (95% CI)	Population mf density (mf/ml) (95% CI)	Positive-only mf density (mf/ml) (95% CI)	No of persons examined for Mf	Percentage mf prevalence (95% CI)	Population mf density (mf/ml) (95% CI)	Positive-only mf density (mf/ml) (95% CI)	Mf prevalence	Population mf density	Positive-only mf density	Mf prevalence	Population mf density	Positive-only mf density
21–30	1750	2.8 (2.1–3.7)	2.00 (0.81–3.19)	71.43 (32.45–110.41)	858	0.58 (0.25–1.36)	0.10 (0.01–0.18)	16.67 (-)	79.3	95.0	76.7	0.000	0.000	0.042
31–40	1623	2.6 (2.0–3.6)	1.14 (0.62–1.66)	43.02 (27.54–58.50)	849	0.59 (0.25–1.37)	0.10 (0.01–0.18)	16.67 (-)	77.3	91.2	61.3	0.000	0.000	0.059
41–50	1271	3.6 (2.7–4.8)	1.72 (0.99–2.44)	47.46 (32.02–62.90)	640	0.47 (0.16–1.37)	0.08 (0–0.17)	16.67 (-)	86.9	95.3	64.9	0.000	0.000	0.159
>50	1975	2.2 (1.7–3.0)	0.97 (0.53–1.41)	43.56 (27.68–59.44)	871	0	0	0	100	100	100	0.000	0.000	-

*The table shows crude mf prevalence and mf density by district, sex and age group, their percentage reductions and significance test for reductions of mf prevalence and density after 3 rounds of MDA in Sierra Leone.
**Districts that piloted MDA in 2007.
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baseline mf survey in 2007/2008. The number of sentinel sites selected per district depended on the population of the district. The then WHO guidelines recommended 1 sentinel site per 500,000 population and 1 sentinel site was selected for districts with population less than 500,000 and 2 for districts with population more than 500,000 [21,24].

Sampling for the midterm survey July/August 2011 was conducted in accordance with new WHO guidelines in one sentinel site and one spot check site per population of one million people [22]. The 12 rural districts that had conducted at least three rounds of MDA were involved in this study. As the populations of the districts were small, the 12 districts were put in six groups of two districts depending on geographical proximity and epidemiological characteristics so that the total population for each group was about a million [22]. In each of the six groups (table 3), a sentinel site was selected in one district for this study, and a spot check site was selected in the other district, in consultation with the DHMTs. The groups included the following pairs of districts: Bonthe (sentinel site (SS)- Moboya) and Moyamba (spot check site (SCS)- Taninahun Kapuima); Koinadugu (SS-Kumala) and Bombali (SCS-Makoba Yelima); Bo (SS-Gelehun) and Pujehun (SCS- Kundorwahun); Port Loko (SS-Gbabai) and Kambia (SCS- Kamasasa); Kailahun (SS-Manowa) and Kenema (SCS- Joru); Kono (SS- Tombodu) and Tonkolili (SCS-Rosint). In the "sentinel site" districts data obtained in this study were compared with baseline data, while among the "spot check site" districts, the results of this survey were compared with baseline results obtained in the original sentinel sites in these districts.

The spot check sites were selected in consultation with DHMTs because according to WHO guidelines of 2011 spot check sites are to be selected according to the local knowledge where LF is most likely to be found as the objective of LF control is elimination [22]. By consulting with DHMTs and selecting areas where LF prevalence could be high the possibility of selecting spot check sites that will have zero prevalence while there were areas with high prevalence within the same districts might have been avoided [22].

Recent WHO guidelines [22] recommend study of a minimum of 300 participants per sentinel/spot check site but villages in Sierra Leone generally have small populations (average of 250) and so in most cases all those 5 years and above that volunteered in the sentinel/spot check villages were simply selected while others in neighboring villages were randomly selected to have a number greater than 300 participants. WHO recommends convenience sampling for any group selected for LF survey because they are seen to be at high risk [22].

Sampling and Diagnosis

The survey teams met with community leaders upon arrival in communities and explained the nature of their work, after which, meetings were held with the general community to explain the study and its significance and respond to questions from community members before the study was conducted. Some 300–500 participants of 5 years of age or above were recruited per site according to WHO guidelines [22]. In sites with less than 300 participants, more participants were recruited in neighboring villages. To ensure standardization of activities and data, two-day practical training was conducted for all technicians before the study started. Fingertip blood was collected between 10 pm and 2 am. A 60 µl blood sample was collected from each participant, smeared gently and uniformly in a circular shape and allowed to air dry at room temperature for 12–24 hours. The next day, the dried smear was dehaemoglobinized through flooding with

Table 2. Summary results of annual MDA*** for LF**** elimination in Sierra Leone 2008–2010.

			2008					2009					2010				
Districts	**Villages/ Urban areas targeted***	**Villages/ Urban areas treated**	**Total pop. of IUs**	**Eligible pop. of IUs**	**Total treated in IUs**	**Prog. Cov. by IUs**	**Drug cov. by IUs**	**Total pop. of IUs**	**Eligible pop. of IUs**	**Total treated in IUs**	**Prog. Cov. by IUs**	**Drug cov. by IUs**	**Total pop. of IUs**	**Eligible pop. of IUs**	**Total treated in IUs**	**Prog. cov. by IUs**	**Drug cov. by IUs**
Bo	1367	1367	574053	487945	380676		78.0	595318	506020	420968	70.7	83.2	613178	521201	445996	72.7	85.6
** Bombali	1596	1596	440932	374792	316672	71.8	84.5	454604	386413	350278	77.1	90.6	498115	423398	363078	72.9	85.8
Bonthe	550	550	166140	141219	98856	59.5	70.0	150718	128110	110834	73.5	86.5	154860	131631	117201	75.7	89.0
**Kailahun	977	977	392819	333896	287536	73.2	86.1	401215	341033	313367	78.1	91.9	410509	348933	322206	78.5	92.3
**Kambia	837	837	269673	229222	202999	75.3	88.6	289136	245766	211926	73.3	86.2	310705	264099	234910	75.6	88.9
Kenema	1380	1380	551797	469027	391778	71.0	83.5	601661	511412	439136	73.0	85.9	583278	495786	449763	77.1	90.7
**Koinadugu	1041	1041	207995	176796	151395	72.8	85.6	216472	184001	157339	72.7	85.5	222966	189521	162059	72.7	85.5
**Kono	1360	1360	466223	396290	321833	69.0	81.2	442235	375900	323907	73.2	86.2	461562	392328	346719	75.1	88.4
Moyamba	1539	1539	309436	263021	232327	75.1	88.3	304416	258754	232859	76.5	90.0	350779	298162	268876	76.7	90.2
Port Loko	1769	1769	376212	319780	250457	66.6	78.3	547672	465521	386929	70.6	83.1	480920	408782	363026	75.5	88.8
**Pujehun	813	813	261509	222283	188872	72.2	85.0	272436	231571	210954	77.4	91.1	250280	212738	193485	77.3	90.9
Tonkolili	1024	1024	368678	313376	252785	68.6	80.7	418828	356004	318229	76.0	89.4	412404	350543	304195	73.8	86.8
	14253	**14253**	**4385467**	**3727647**	**3076186**	**70.1**	**82.5**	**4694711**	**3990504**	**3476726**	**74.1**	**87.1**	**4749556**	**4037123**	**3571514**	**75.2**	**88.5**

*Geographic coverage of villages and urban areas was 100% in all 12 districts over the 3 years (2008–2010).
**Districts that piloted MDA in 2007.
***MDA = mass drug administration.
****LF = lymphatic filariasis.
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distilled water for 3–5 minutes, air dried again, fixed with methanol for 30–60 seconds, stained with GIEMSA for 10 minutes, and examined for mf under a light microscope by experienced examiners. The ×40 objective was used to first locate the mf by moving patiently from left to right or right to left starting at the extreme top end of the thick blood film and moving through all available fields; then moving slightly downwards and repeating the same process of moving from left to right or right to left until all areas of the thick blood film are covered. When mf is located the filarial species was identified using ×100 objective [22]. A minimum of 50 microscopic fields were examined before a specimen was considered negative. The research team included laboratory technicians from the national reference laboratory and the University of Sierra Leone who have adequate experience in diagnostic detection of filarial parasites. The team leader was also supported in 2007 by WHO and the NTD Support Center in Ghana to receive further training on detection of filarial parasites at the Noguchi Memorial Institute for Medical Research in Accra, Ghana. Positive findings of mf were recorded and individual mf density of infection was calculated and expressed as the number of mf per ml of blood (mf/ml). A total of 6,023 "midnight" blood samples were collected and examined for mf as shown in table 1, male 3,170 (52.6%) and female 2,853 (47.4%). The mean age (± standard deviation) of the subjects examined was 28.91±18.92 years (males: 27.65±18.77, females: 30.32±18.92). For quality control, all positive slides and 10% of the negative slides were preserved and examined by a researcher, who was invited during the design of the study to help in designing the study and to conduct the quality control because he has been involved in the study and detection of filarial parasites since 1995–1996 [18]. There were only 18 positive slides and these were submitted for quality control together with 600 randomly selected negative slides. Results of the quality control showed that all 18 positive slides were true positives while the negative slides were all true negatives. The coordinates of each sample site were recorded using hand-held units of global positioning system (site coordinates available upon request).

Statistical Analysis

Results were entered into MS Excel and analyzed in SPSS (IBM, Version 19). Prevalence and density of mf were calculated for all 12 districts and compared with the baseline data. The 95% confidence intervals (CIs) for prevalence were calculated using the Wilson score method without continuity correction [25]. The arithmetic mean mf density of infection with 95% CI was calculated using the total population examined and the positive samples only [21,24]. The Chi-squared test was used to compare the differences in prevalence and the Kruskal-Wallis test was used to compare the differences in mf density. Treatment coverage was calculated according to the WHO guidelines [22]. Epidemiological drug coverage (EDC), otherwise known as Programme coverage, is the treatment coverage reported using total population of IU as denominator and is calculated as the number of people who were reported to have ingested the medicines for LF divided by total population in IU multiplied by 100. The epidemiological drug coverage calculated using the total population of the IU is a reflection of what proportion of the at-risk population is being covered by MDA. Drug coverage (DC) is the treatment coverage reported using individuals targeted or eligible for treatment in the IU as denominator and is calculated as the number of people who were reported to have ingested the medicines for LF divided by all individuals targeted or eligible for treatment in the IU multiplied by 100. The drug coverage in the targeted or eligible population is considered the best measure of how well MDAs are implemented. An adequate level of EDC is estimated to be 80% and the DC should be close to 100%. These indicators enable IU authorities to assess the status of the elimination programme. WHO recommends that programme managers use the reported coverage to identify areas with low coverage, investigate the causes and find solutions that will improve programme implementation as the programme continues [22]. The total population for rural areas used as denominator for analyzing MDA results was the total number of people registered during the pre-MDA census, while the total population used in urban/non-rural areas was the projected figure according to the 2004 national census [26], with an annual growth rate of 2.5%. Spatial analysis of the LF mf prevalence was conducted using the kriging method in the Geostatistical Analyst Extension of ArcGIS version 10 (ESRI, Redlands, USA). Spatially smoothed contour maps of the interpolated prevalence of mf at baseline and after three MDAs were produced as described previously [21,27].

Table 3. Survey site selection.

Groups of districts	Districts	Sentinel sites	Spot check sites
1	Bonthe	Moboya	-
	Moyamba	-	Taninahun Kapuima
2	Koinadugu	Kumala	-
	Bombali	-	Makoba Yelima
3	Bo	Gelehun	-
	Pujehun	-	Kundorwahun
4	Port Loko	Gbabai	-
	Kambia	-	Kamasasa
5	Kailahun	Manowa	-
	Kenema	-	Joru
6	Kono	Tombodu	-
	Tonkolili	-	Rosint

doi:10.1371/journal.pntd.0002273.t003

Results

Mass Drug Administration Results 2008–2010

A total of 14,253 villages and urban areas were treated for LF each year during the 3 years in the 12 districts. As all the villages and urban areas were treated in each of the 12 districts, this represents 100% geographic coverage for endemic villages and urban areas in all 12 districts during each of these 3 rounds of MDA, as shown in table 2. Over 4 million people were targeted for treatment each year during the 3 years. Overall EDC was 70.1%, 74.1% and 75.2% in 2008, 2009 and 2010 respectively at the national level, and was ≥65.0% in each district in each round, except in Bonthe, where it was 59.5% in 2008. EDC also improved between 2008 and 2010. Five districts had <70.0% in 2008 (Bo: 66.3%, Bonthe: 59.5%, Kono: 69.0%, Port Loko: 66.6% and Tonkolili: 68.6%); while in 2009 and 2010, all districts had >70.0% EDC, as shown in table 2. The overall DC was 82.5%, 87.1% and 88.5% in 2008, 2009 and 2010, respectively. The DC is a measure of how well MDA was conducted and is considered adequate when ≥80.0% [22]. DC by district in each round was ≥80.0%, except in Bo, Bonthe and Port Loko, which had 78.0%, 70.0% and 78.3% respectively in 2008, as shown in table 2.

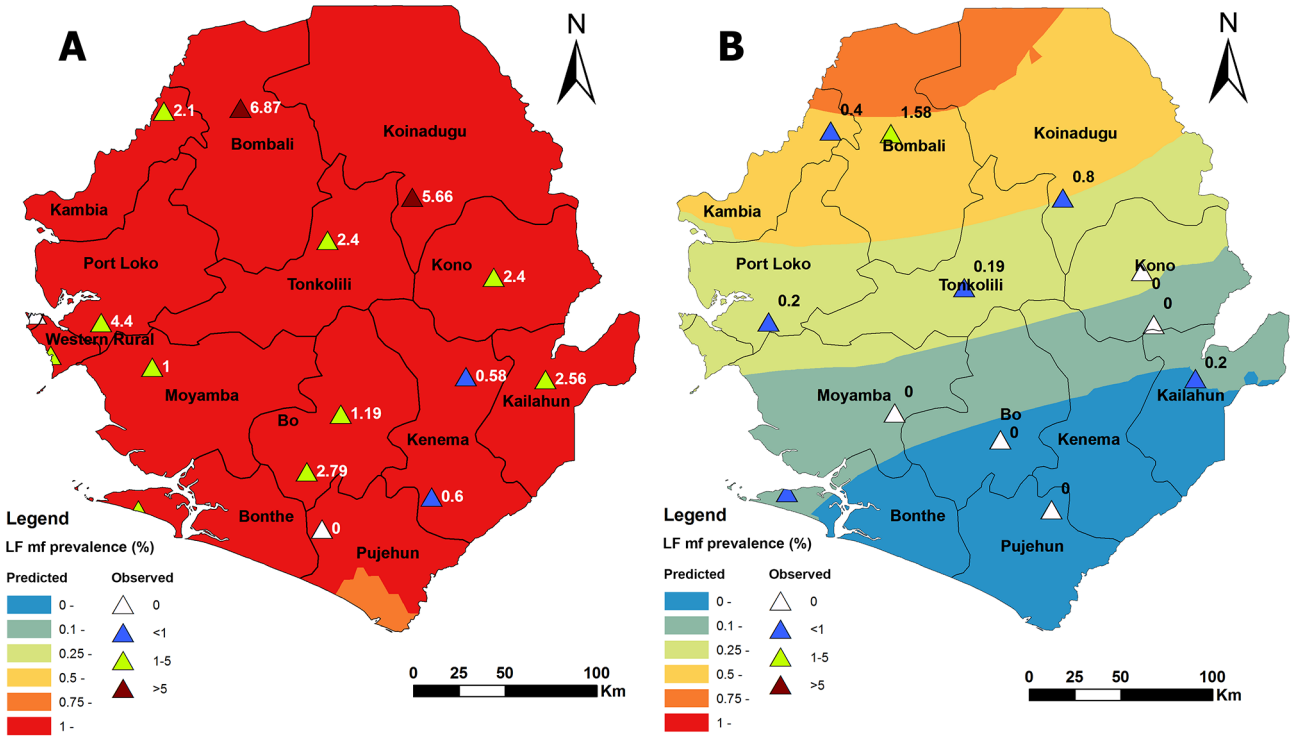

Figure 1. Survey sites and spatially smoothed contour maps of predicted LF mf prevalence in Sierra Leone. A. Predicted mf prevalence at baseline; **B**. Predicted mf prevalence after three rounds of MDA. The same legend scale was used for the contour map of both A and B for easy comparison. Triangles and labels show the survey locations and the observed mf prevalence in each location.
doi:10.1371/journal.pntd.0002273.g001

Microfilaraemia Prevalence

Five districts (Bo, Kenema, Kono, Moyamba and Pujehun) had 0.0% mf prevalence. One district (Pujehun) had baseline mf prevalence of 0.0%, which was maintained. Another six districts had mf prevalence between 0.0 and 1.0%: Bonthe (0.20%; 95% CI: 0.04%–1.13%), Kailahun (0.20%; 95% CI: 04%–1.13%), Kambia (0.40%; 95% CI: 0.11%–1.45%), Koinadugu (0.80%; 95% CI: 0.31%–2.05%), Port Loko (0.20%; 95% CI: 0.04%–1.13%) and Tonkolili (0.19%; 95% CI: 0.03%–1.08%). Only one district had mf prevalence of over 1%: Bombali (1.58%; 95% CI: 0.80%–3.09%). Overall mf prevalence among males was 0.35% (95% CI: 0.19%–0.62%), and among females 0.25% (95% CI: 0.12%–0.51%). Prevalence by age group, 5–14 years (N = 1947), 15–20 years (N = 858), 21–30 years (N = 858), 31–40 years (N = 849) and 41–50 years (N = 640), was 0.21% (95% CI: 0.08%–0.53%), 0.12% (95% CI: 0.02%–0.66%), 0.58% (95% CI: 0.25%–1.36%), 0.59% (95% CI: 0.25%–1.37%) and 0.47% (95% CI: 0.16%–1.37%) respectively, while prevalence in the age group >50 years (N = 871) was 0.0%. In total, 18 persons (0.30%, 95% CI: 0.19–0.47%) had a positive blood smear, and there was

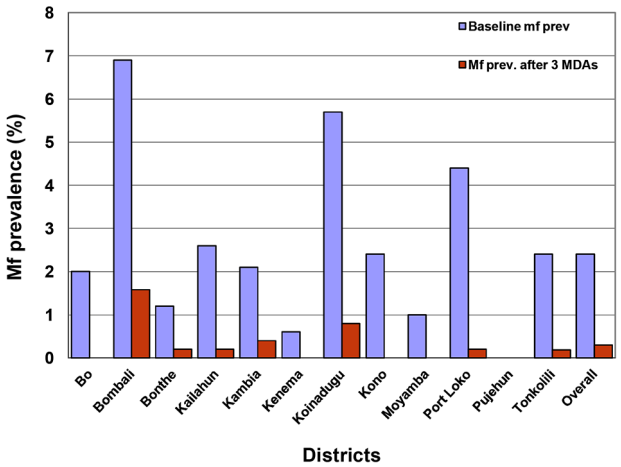

Figure 2. Reduction of MF prevalence after 3 annual MDAs for LF in Sierra Leone 2008–2010.
doi:10.1371/journal.pntd.0002273.g002

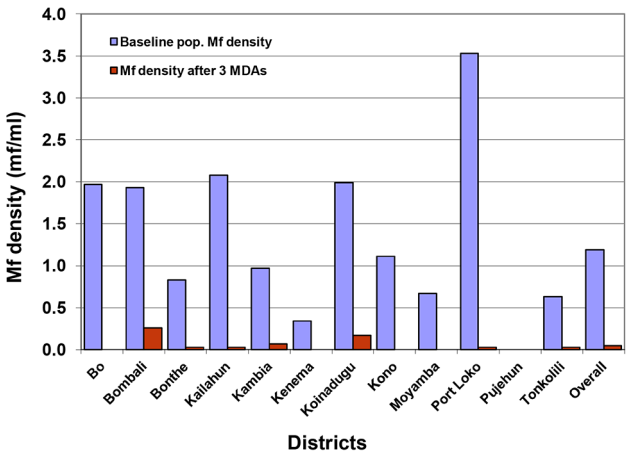

Figure 3. Reduction of entire-population mf density after 3 annual LF MDAs in Sierra Leone 2008–2010.
doi:10.1371/journal.pntd.0002273.g003

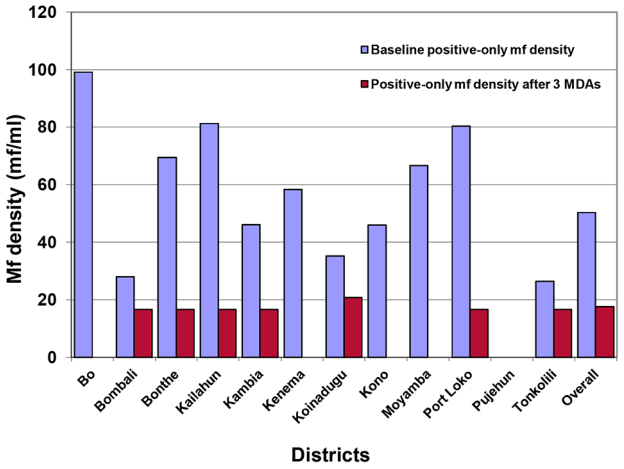

Figure 4. Reduction of positive-only mf density after 3 annual LF MDAs in Sierra Leone 2008–2010.
doi:10.1371/journal.pntd.0002273.g004

no significant difference in mf prevalence in males as compared to females (p = 0.47). There were also no significant differences in prevalence among age groups.

Compared with the baseline, overall mf prevalence decreased by 88.5% (p = 0.000), from 2.6% (95% CI: 2.3%–3.0%) to 0.30% (95% CI: 0.19%–0.47%), after 3 rounds of MDA. As shown in table 1, among the 11 districts with baseline mf prevalence ≥1%, seven districts showed mf prevalence reduction of over 90% after three rounds of MDA, three districts by over 80%, and only one district by below 80%. Spatial prediction suggested a sweeping reduction in mf prevalence from the baseline level after three MDAs across the country. There was an 89.4% decrease (p = 0.000) in mf prevalence among males: 3.3% (95% CI: 2.8%–3.9%) to 0.35% (95% CI: 0.19%–0.62%); and an 87.5% decrease (p = 0.000) in mf prevalence among females: 2.0% (95% CI: 1.6%–2.4%) to 0.25% (95% CI: 0.12%–0.51%). There was 0.21% (95% CI: 0.08%–0.53%) prevalence among the age group 5–14 years, but this could not be compared, as the baseline study did not include participants <15 years. Decreases in mf prevalence among the age groups 15–20, 21–30, 31–40, 41–50 and >50 years ranged between 77.3% and 100.0% (p = 0.000, 0.000, 0.000, 0.000 and 0.000 respectively). Figure 1 shows predicted mf prevalence at baseline (A) and predicted mf prevalence after three rounds of MDA (B). Figure 2 shows the overall decrease in mf prevalence and the decrease for each district. A statistical comparison between the 6 districts that piloted MDA for LF in 2007 and the other 6 showed no statistical difference between the decreases in microfilaremia prevalence of the 2 groups of districts. 3 out of the 4 districts that had 100% decreases in mf prevalence had conducted only 3 MDAs.

Microfilaraemia Density

The overall arithmetic mean mf density was 0.05 mf/ml (95% CI: 0.03 mf/ml–0.08 mf/ml) in the total participants examined and 17.59 mf/ml (95% CI: 15.64 mf/ml–19.55 mf/ml) among mf-positive individuals. The mean mf density by district was well below 1 mf/ml for the population examined and below 21 mf/ml among those who were mf positive. There was no significant difference in mf density in males versus females (p>0.05). There was also no significant difference in mf density among age groups in the total population examined (p>0.05). Overall mean mf density among mf positive individuals decreased by 65.4% (p = 0.001), from 50.9 mf/ml (95% CI: 40.25 mf/ml–61.62 mf/ml) at baseline to 17.59 mf/ml (95% CI: 15.64 mf/ml–19.55 mf/ml); and in the total population examined, there was a 96.2% decrease (p = 0.000), from 1.32 mf/ml (95% CI: 1.00 mf/ml–1.65 mf/ml) at baseline to 0.05 mf/ml (95% CI: 0.03 mf/ml–0.08 mf/ml). In Bo, Kenema, Kono and Moyamba, there was 100.0% decrease in mf density among both mf positive participants and the entire population. Six districts, Bonthe, Kailahun, Kambia, Koinadugu, Port Loko and Tonkolili, had a >90.0% decrease in mf density for the entire population (p = 0.059, 0.001, 0.014, 0.000, 0.000 and 0.002 respectively), and a >36.0% decrease in mf density among positive participants (p = 0.295, 0.472, 0.311, 0.454, 0.219 and 0.442 respectively). Bombali had the lowest decreases in mf density, 86.3% for the entire population (p = 0.000) and 40.6% among positive individuals (p = 0.068). Table 1 shows the reduction of mf density in the 12 districts after 3 MDAs. There was a 96.7% decrease in mf density among all males (p = 0.000) and a 67.0% decrease in mf density among males that are mf positive (p = 0.013); and there was a 95.4% decrease in mf density among all females (p = 0.000) and a 62.8% decrease in mf density among females that are mf positive (p = 0.023). The age groups 15–20, 21–30, 31–40 and 41–50 years had >90.0% decrease in mf density for the entire population (p = 0.000, 0.000, 0.000 and 0.000 respectively) and >60.0% decrease in mf density among mf positive individuals (p = 0.341, 0.042, 0.059 and 0.159 respectively). The age group >50 years had a 100.0% decrease in mf density for the entire population and among mf positive individuals. For details of mf prevalence and density at baseline and after 3 MDAs, reductions in mf prevalence and density after 3 MDAs and p values for the reductions in prevalence and density please see table 1. Figures 3 and 4 show overall and district decreases in mf density for the entire population and for those who were mf positive respectively.

Discussion

LF is widely endemic across Sierra Leone, transmitted by *Anopheles* mosquitoes. All 14 health districts qualified for MDA intervention in accordance with WHO guidelines because they had baseline LF prevalence by ICT cards ≥1.0% [21,24]. Although MDA was piloted in rural areas of 6 health districts in 2007, the 2007 MDA results were relatively poor and considered "inadequate" and so 2008 is considered year 1 for LF MDA when treatment and geographic coverage was ≥65% and 100% respectively. The results from the 12 rural districts showed that over the three years (2008–2010), geographic coverage was 100% in all 12 districts, EDC was ≥65.0% in all districts except for Bonthe in 2008 (59.5%), and DC was ≥80.0% in all districts except for Bo (78.0%), Bonthe (70.0%) and Port Loko (78.3%) in 2008. The treatment coverage was verified through independent monitoring activities, as described previously [23]. The current assessment showed that the average mf prevalence in the country was only 0.30% and the average population mf density was only 0.05 mf/ml after three rounds of MDA, with no microfilaria detected in six of the 12 districts, including all the districts in the Southern Province and only one district showing mf prevalence of >1% (Bombali, 1.58%). This represents an overall reduction of 87.5% in mf prevalence and 95.5% in population mf density. The zero mf prevalence recorded for Pujehun district at baseline may have been as a result of the randomness of the selection of the sentinel sites. Consequently, a spot check site was selected in Pujehun for the midterm study in consultation with the DHMT of Pujehun district based on results of reported hydroceles and

lymphedema, which increased the chances of finding mf positive cases. Since the mf prevalence is again zero it is recommended that another spot check site be selected for the next survey in the district (the pre-transmission assessment survey). The use of pre-MDA census data as denominator in rural settings versus use of projected census population as denominator in urban or non-rural settings for the calculation of MDA results may have created bias in terms of interpretation and comparability of MDA results. However, it should be noted that the issue of what denominator to use for MDAs in urban settings still has to be resolved by the international NTD community as this poses a big challenge for national control programmes. Pre-MDA census in urban settings could be cumbersome, very expensive and results reported cannot be easily validated. The NTDCP therefore decided to use projected census figures as denominator in the analysis of MDA results for non-rural or urban areas of the districts.

The number of MDA rounds needed to eliminate LF depends on baseline infection rates, vectoral capacity, efficacy of the MDA regimen used, and community compliance with treatment. It is possible to eliminate LF in some implementation units (IUs) with low baseline infection rates using less than five rounds of MDA, while more than six MDA rounds may be needed for IUs with relatively high baseline LF prevalence [28,29,30]. The high level of reduction in mf prevalence and intensity after three rounds of MDA in Sierra Leone may have been partly due to the relatively low baseline mf level [21].

Several studies on LF conducted before the baseline studies in 2007/2008 in Sierra Leone and neighboring Liberia show mf prevalence $\geq$20% but the LF prevalence at baseline (2007/2008) ranged from 0%–6.9% for all districts with prevalence of the southeastern districts that were studied previously $<$3% at baseline [21]. Many studies have shown that there are 3 drugs that have microfilaricidal effect on the lymphatic filarial roundworms and are available for LF treatment: diethylcarbamazine (DEC), ivermectin and albendazole. Treatment with DEC or ivermectin alone significantly reduces blood mf levels (up to 90% mf clearance is reported) but combination of both drugs is more effective than using one drug. The marked filaricidal effect of these drugs makes them suitable for annual treatment designed to control transmission immediately and in the long term to control morbidity [31]. In Burkina Faso and India it was demonstrated that 5–14 years of ivermectin treatment (i.e. treating with ivermectin alone) reduced mf prevalence and intensities of W. bancrofti but transmission was not interrupted. The treatment rounds with ivermectin alone can significantly reduce prevalence and intensity of W. bancrofti microfilaremia, which provides an opportunity for synergy where onchocerciasis and LF are coendemic [32,33,34]. It is reported that there is a strong relationship between mf prevalence and intensity in humans and mf intake and development in the mosquito vector which means that lower intensity can lead to reduced transmission [34,35]. The mass administration of ivermectin for onchocerciasis control using the CDTI strategy, which has been demonstrated to be very effective in reaching the target communities and populations, could have been responsible for the reduction in mf prevalence and density at baseline as indicated in previous studies mentioned above. The reduction in mf prevalence as a result of ivermectin treatment could have resulted in reduced transmission among the populations of the 12 districts because mf intake and development within the vector depends on the level of mf prevalence and density. Low mf prevalence and density could have resulted in reduced mf intake and development in the mosquito vector, reduced mf transmission and therefore even further reduction of mf prevalence and density in the populations with time.

By studying infection and infectivity prevalence in the vector mosquitos it was demonstrated in Nigeria that 5 years of semi-annual MDAs with ivermectin alone targeted at onchocerciasis control reduced but did not interrupt transmission of W. bancrofti [36,37]. Adding albendazole provided better mf clearance (up to 99%) and clearance of soil transmitted helminths in communities treated [34,35]. Addition of albendazole to ivermectin significantly reduced mf prevalence in mosquitos in the sentinel villages studied, which was an entomological confirmation of the importance of albendazole for LF control [36,37]. This observation is related to our proposed hypothesis for the study (“areas previously exposed to ivermectin treatment for onchocerciasis control may require less rounds of annual MDA to eliminate LF”). Since the populations of the 12 districts had been exposed to ivermectin treatment for onchocerciasis control, this could have resulted in massive lowering of mf prevalence and density because ivermectin can reduce mf prevalence by up to 90%. The mf population was already under a selective pressure (based on the massive use of ivermectin), and this selective pressure was enhanced with the addition of a second drug (albendazole) to the MDA that has been occurring for years.

The successful implementation of the LF programme benefited from the existing onchocerciasis control programme by using CDTI as the platform [16]. The Onchocerciasis control programme was already well established using the CDTI strategy which allows communities to be in charge of all programme activities that are implemented within communities thus ensuring good sense of ownership and good compliance within communities. Health workers had already been trained and were available to provide technical support in additional training, supervision and surveys. Treatment has been given between September and December each year, as this is the period that was found to be convenient for the communities (i.e. harvest and post-harvest period). With integration of Onchocerciasis control and LF control CDTI plus (CDTI+) was adopted with the same principles as CDTI and Albendazole added to Ivermectin [16,24,35]. All the lessons learnt from CDTI during the years of the onchocerciasis control programme were used to improve the LF elimination programme, such as the use of the good health infrastructure in the districts that had focal persons for coordinating onchocerciasis control within districts to ensure a high treatment and geographic coverage by the national programme. These district onchocerciasis coordinators became district NTD coordinators. After the civil war in Sierra Leone in 2002, during which almost all health programmes had stopped, the MOHS had decided that running the onchocerciasis control programme as a vertical programmes would have been inefficient given the post war situation and the limited number of health workers and so the national coordination had to work in close collaboration with the DHMTs and within the existing district health structure. Furthermore, community directed interventions were continued for control of onchocerciasis and LF with which communities plan activities with health workers, decide treatment periods and select volunteers who are trained to distribute ivermectin and albendazole in their own communities.

Three rounds of MDA with compliance $\geq$65.0% in Papua New Guinea reduced mf prevalence from 18.6% to 1.3%, a 94.0% reduction [38]. The authors believed that the large decrease in prevalence occurred in part because the vector transmitting LF in the study area was the *Anopheles* mosquito, which is less efficient than *Culex* in the transmission of filariasis [38]. This may have also been the case in Sierra Leone. Similar successes in reducing mf prevalence after annual MDA rounds have been reported by many authors. In Kenya, there were similar reductions in mf prevalence

(from 20.9% to 0.9%, a 95.7% reduction of mf prevalence) even when there were missed rounds of MDA [39]. Prevalence was reduced by 93.0%, from 12.0% to 0.8%, after just 2 rounds of MDA in Vanuatu [40]. In Northern Uganda, a reduction of mf prevalence from 3.7% to 0.4% (a 89.2% decrease) was reported after 3 MDAs [41]. Therefore, it is not surprising that three effective rounds of MDA would reduce the mf prevalence to below 1% in 11 out of 12 districts in the current LF elimination programme, given the relatively low mf prevalence at baseline.

The NTDCP in Sierra Leone has succeeded in building on an existing and effective CDTI programme for integrated management of onchocerciasis and LF and had the unique opportunity of using the integrated approach of managing both onchocerciasis and LF for LF elimination. As a result of the effectiveness of ivermectin alone in reducing LF in endemic communities baseline LF prevalence was relatively low. The NTDCP was able to use the good health infrastructure in the districts that had focal persons for coordinating NTD control within districts to ensure a high treatment and geographic coverage. Other countries embarking on LF elimination can learn the following lessons: in countries where the onchocerciasis control programme already exists and is successfully implemented, NTD control programmes can build on the existing CDTI structure for elimination of LF; integrated approach can be used for management of onchocerciasis and LF in areas co-endemic for onchocerciasis and LF (all activities can be co-implemented for the 2 diseases from training, community sensitization and mobilization to the MDA itself); in areas where CDTI has been implemented for many years programmes should expect to have relatively low baseline prevalence; integration of NTD control activities into strong existing national and district health system can ensure good programme implementation and improve programme sustainability especially for post MDA surveillance. Most African countries have problems providing adequate number of staff for public health programmes and integrating NTD programme into the national and district health system and co-implementation of activities for control of multiple NTDs can improve programme effectiveness and sustainability. It should be noted also that use of CDDs who do not get financial payments for the services they render may not work for MDAs in urban areas. The main difference noted in the NTDCP in Sierra Leone is that after the civil war 1991–2002, during which almost all health programmes had stopped, the MOHS had decided to put the control of all NTDs under the existing onchocerciasis control programme with 1(one) programme manager responsible for all NTDs and working in close collaboration with strong DHMTs. It was decided that running vertical programmes for NTDs will be disastrous given the post war situation and the limited number of health workers. This decision was easy to implement because before 2005–2008 when studies were conducted to map the other NTDs only the Onchocerciasis Control Programme was existing in the country.

The use of different sites for comparison (sentinel sites in 6 districts versus spot check sites for the other 6 districts) might be a limitation of the study considering the comparability of the impact assessment done in the districts where the same site was used relative to the districts where different sites were used. However, this depends on how you look at the study. In terms of the programme implementation it is not a limitation because recent WHO guidelines (WHO 2011) recommend 1 sentinel site per 1 million people. Only 1 district in Sierra Leone (the Urban Western Area, which is not in this group of 12 districts) has more than 1 million people and should have 1 sentinel site and 1 spot check site (total of 2 sites). The rest have far less than 1 million people per district and so have been grouped as recommended by WHO [22] depending on geographical proximity and epidemiological characteristics so that each pair has a total population of about 1 million people. Bonthe and Moyamba for example are geographically neighboring districts and have low baseline antigenemia and microfilaremia prevalence. The pair should have 1 sentinel site and 1 spot check site, so the sentinel site (selected and used for the baseline microfilaremia study) was used as sentinel site for the pair (in the case of Bonthe/Moyamba, Moboya in Bonthe was selected as a sentinel site) and a spot check site was selected in the other district as explained above (Taninahun Kapuima was recommended by the district health management team as good spot check site). The possible limitation for our paper is that we use the results obtained in the spot check sites and compare with baseline results in villages previously considered sentinel sites. Given the overall relatively low baseline microfilaremia prevalence and the pattern that emerges of a huge decrease noted in this mid-term evaluation, we believe that the impact assessment done in the districts where the same site was used relative to the districts where different sites were used are comparable if only to assess impact of MDA. In the case of Pujehun that had baseline mf prevalence of zero with the possibility that due to random selection the endemic areas (communities) might have been missed during the random selection of the sentinel sites at baseline, we think it is prudent to select and study another site/village that is indicated to be more LF endemic. In the pre-6th MDA survey (pre-TAS), it will be recommended that another spot check site be selected, which is even more likely to be LF endemic in Pujehun to avoid risk of overlooking villages that could possibly still be a source of LF transmission within the district.

There is reason for optimism with the results of this survey because some research suggests that residual infections of filariasis disappear when prevalence is below 1.0% [42]. However, it is prudent to consider experiences and lessons learnt from other countries. In Tanzania, it was demonstrated that MDA using ivermectin and albendazole reduced mf prevalence by 21.2% and 40.4% after the first and second MDA respectively, but in subsequent MDAs, the effect leveled off and transmission, albeit low-level, was still noted after the third MDA [43]. In Leogane, Haiti, there was a significant reduction in mf rates after several rounds of MDA for LF, but transmission was not interrupted [44]. Mf prevalence detected after 3 MDAs does not demonstrate a change in filariasis transmission [38,41]. The drug combination destroys the microfilaria over the 4–6 year it takes for the adult worm to die a natural death [38,41,45]. Therefore, MDA has to continue each year for 4–6 years, which is equivalent to the lifespan of the adult worm.

In conclusion, there was significant reduction of mf prevalence and density across the 12 rural districts in Sierra Leone after three annual MDAs. This was coupled with good MDA compliance and relatively low baseline endemicity. The results show that the proposed hypothesis is highly probable and that the LF elimination programme in Sierra Leone is on course to reach the objective of eliminating LF by the year 2020. Eliminating diseases such as LF has to follow models that use rigorous scientific data as is being demonstrated in this case. The next logical steps after the midterm evaluation include the following: continuation of annual MDAs for another 3 years (4th, 5th and 6th MDA rounds); a pre-transmission assessment survey (pre-TAS) before the 6th MDA rounds; a TAS after the 6th MDA rounds if district mf prevalence continue to be below 1%; and then 2 more TAS at intervals of 2–3 years before a request is made for certification of elimination. Manifestations of LF such as lymphoedema and hydroceles have to be included within the national surveillance system and monitored closely by the NTDCP.

Supporting Information

Checklist S1 STROBE Checklist. Information/checkmarks were put against the sections of the STROBE checklist, used for reporting of observational studies, to indicate areas of the checklist covered in the manuscript.
(DOC)

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Author Contributions

Conceived and designed the experiments: JBK SS MS MHH FS YZ MJB. Performed the experiments: JBK SS FS YZ. Analyzed the data: JBK MHH YZ. Wrote the paper: JBK MJB. Coordinated the study: JBK SS MS. Revised the paper: JBK SS MS MHH FS YZ MJB. Reviewed and approved the final manuscript: JBK SS MS MHH FS YZ MJB. Conducted quality control: FS.

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