Neglected Tropical Diseases

John Gyapong
Boakye Boatin *Editors*

Neglected Tropical Diseases - Sub-Saharan Africa

Springer

Neglected Tropical Diseases

Series editor
Peter J. Hotez, MD, PhD
Dean, National School of Tropical Medicine,
Texas Children's Hospital Endowed Chair of Tropical Pediatrics,
Professor of Pediatrics and Molecular Virology and Microbiology,
Baylor College of Medicine,
Houston, Texas, USA

President, Sabin Vaccine Institute,
Washington, District of Columbia, USA,
Houston, Texas, USA

University Professor of Biology, Baylor University,
Waco, Texas, USA

Baker Institute Fellow in Disease and Poverty, Rice University,
Houston, Texas, USA

More information about this series at
http://www.springer.com/series/11165

John Gyapong • Boakye Boatin
Editors

Neglected Tropical Diseases - Sub-Saharan Africa

Springer

Editors
John Gyapong
Research, Innovation and Development
University of Ghana
Accra
Ghana

Boakye Boatin
Lymphatic Filariasis Support Centre
University of Ghana
Accra
Ghana

ISSN 2194-8275 ISSN 2194-8283 (electronic)
Neglected Tropical Diseases
ISBN 978-3-319-25469-2 ISBN 978-3-319-25471-5 (eBook)
DOI 10.1007/978-3-319-25471-5

Library of Congress Control Number: 2015958883

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Foreword

Today, Sub-Saharan Africa represents one of the most important global "hotspots" for highly endemic neglected tropical diseases (NTDs). First and foremost, NTDs are the major afflictions of profound poverty, and such levels of poverty are pervasive on the African continent. According to the World Bank, more than 900 million people live in Sub-Saharan Africa with approximately one-half living on less than $1.25 per day.

NTDs thrive under these circumstances. The World Health Organization (WHO) has now determined the numbers of people who require mass drug administration for their NTDs, and indeed these numbers are disturbing. Overall 658.7 million people in WHO's African region require mass drug administration for NTDs, including 468.4 million people for lymphatic filariasis, 324.2 million for soil-transmitted helminth infections, 240.7 million for schistosomiasis, and 168.8 million for onchocerciasis. Overall, the WHO African region accounts for less than 15 % of the world's population, but almost 40 % of the people requiring treatment for their NTDs.

Another feature of Sub-Saharan Africa is its (unwelcome) exclusivity for some specific NTDs. Today, the region accounts for all of the world's cases of loiasis and human African trypanosomiasis (HAT), and (again according to the WHO) 92 and 99 % of the world's population that requires mass treatment for schistosomiasis and onchocerciasis, respectively. Most of the planet's podoconiosis and Buruli ulcer, and possibly trachoma and yaws, are also found in Sub-Saharan Africa.

The impact of this massive load of NTDs is felt at different levels. These diseases produce deleterious and direct negative consequences for public health through their long-term effects on disability, or in some cases by causing death (especially for HAT and leishmaniasis). In addition there are important indirect effects. For example, urogenital schistosomiasis (which is responsible for roughly two-thirds of the schistosomiasis) has now been shown to be a major co-factor in Africa's HIV/AIDS epidemic, while malaria, together with hookworm infection and schistosomiasis, greatly exacerbate anemia. Both of these indirect effects represent important causes of ill health for Africa's girls and women.

In addition to their health impact, Africa's NTDs also exhibit important links to social forces. They promote poverty, as they make people too sick to work and impair child development. They are also inextricably linked to Africa's civil and international wars. During the 1970s, 1980s, and 1990s in Angola, Democratic Republic of Congo, and Sudan, HAT may have killed annually ten times more people than those who died in the 2014–2015 West African Ebola virus infection outbreak. Just as the NTDs help promote poverty, diseases such as HAT may also cause destabilization and further promote conflict on the African continent.

Solving Africa's NTD problem will require a multi-pronged approach including social scientists to design culturally sensitive interventions. We must expand mass treatments, especially for diseases such as schistosomiasis, a disease for which only about 10–15 % of children have access to praziquantel, together with case detection and treatment for NTDs such as HAT and leishmaniasis. Mass treatment needs to be accompanied by intersectoral approaches that embrace sanitation, clean water, and other environmental measures. In parallel, vector control will be needed for leishmaniasis, HAT, and other NTDs. The good news is that through these approaches we are beginning to see declines in the number of cases of lymphatic filariasis, onchocerciasis, and HAT, such that it is now possible to realistically discuss the potential for eliminating these NTDs. For others, we are going to need to enlarge programs of research and development, which must include capacity enhancement for African scientists.

I am very excited about this new volume. Dr. John Owusu Gyapong and Dr. Boakye Boatin have assembled a top-flight team of African authors and scientists with direct first-hand knowledge about these diseases. In this respect, this volume is practically unique – a book about disease and poverty in Africa written by scientists and public health experts from Africa. I would like to congratulate Drs. Gyapong and Boatin and the authors of each of the important book chapters, and Springer for creating this important series on NTDs!

Houston, TX, USA Peter J. Hotez, MD, PhD

Preface

This book sets out the neglected tropical diseases (NTDs) through the lens of sub-Saharan Africa (SSA). Twelve of the major NTDs are presented. They include Buruli ulcer, Guinea worm, human African trypanosomiasis, leishmaniasis, leprosy, Loa loa, and lymphatic filariasis. Others are onchocerciasis, podoconiosis, schistosomiasis, soil-transmitted helminths, trachoma, and yaws. Additional areas which transcend all the NTDs such as health systems and their role in NTDs, the social and economic impact as well as vector control, an often less talked about area in recent times in the control of NTDs are also discussed.

The disease specific chapters are written following a theme which is common to all, but there are important variations on the theme within the structured sections. Each chapter therefore can be read independently on its own but read together with the chapters on health systems and social and economic implications will make them even more complete. Areas that have received detailed attention include diagnostics especially for those diseases that are targeted for elimination, future control tools including drugs as well as critical research needed to help overcome the challenges that have been identified for each disease.

As expected most the challenges that have been identified for the diseases cut across many of them, but some challenges are very disease specific. With this in mind, a section on the expected situation for each disease in the next decade is highlighted for each of the chapters.

The authors were drawn almost entirely from African research scientists and individuals who have either worked in their respective ministries of health, have come face to face with the realities of the ravages of NTDs in their countries, or have experience in the control of the diseases.

In taking on this assignment it was clear that there would be difficulties in trying to work with so many contributors; however, the task was made less arduous by the willingness of the authors to work as a team and in close collaboration with each other. Many people who are not listed in the chapters helped in many ways to get the manuscripts together. Their contributions are well acknowledged.

It is our wish that this book, apart from providing some basic information on the specific NTDs and the special ways that NTDs present in SSA, will also be a good

source of a wide range of references on NTDs to readers. In a word, this book will be a useful read for all who are interested in doing something about NTDs in SSA.

Accra, Ghana

John O. Gyapong, MD, MPH, PhD
Boakye A. Boatin, MD, MPH

Acknowledgments

The editorial team is grateful to Ms Grace Annan, a Senior Research and Administrative Assistant of the Office of Research Innovation and Development of the University of Ghana, for her secretarial support.

The work was partly supported by a grant (Grant Number: G1001337) from the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement, through the Liverpool School of Tropical Medicine Council and managed by the School of Public Health, University of Ghana.

Contents

About the Editors

Professor John Gyapong is the Pro-Vice Chancellor for Research Innovation and Development of the University of Ghana. He is a Public Health Physician and an Epidemiologist. He studied Medicine in Ghana and later studied Public Health (MSc) and Epidemiology (PhD) at the London School of Hygiene and Tropical Medicine of the University of London. His main area of research is infectious diseases epidemiology, especially lymphatic filariasis and other neglected tropical diseases and malaria. He established and managed the Ghana Filariasis Elimination Programme for 8 years where he was also in-charge of the Onchocerciasis Control. For 12 years, he was Director for Research and Development of the Ghana Health Service where he was responsible for health systems and implementation research.

Before assuming responsibility as Pro-Vice Chancellor, he was the Vice-Dean and Professor of Epidemiology and Disease Control at the School of Public Health of the University of Ghana, and an Adjunct Professor of International Health at the Georgetown University in Washington. He serves on several international research review committees and boards and has over 120 publications in peer-reviewed journals.

Dr. Boakye A Boatin holds degrees in Medicine, International Public Health, and Epidemiology. His research focuses on infectious diseases, particularly filariasis, schistosomiasis, and human African trypanosomiasis. Until recently he led research in integrated community-based interventions and lymphatic filariasis at the Special Programme for Tropical Diseases at WHO. He worked at the Onchocerciasis Control Programme in West Africa for 15 years, first as its epidemiologist, then as head of Planning Evaluation and Transfer and later as Director. He is currently an Adjunct Professor at the Institute of Parasitology, McGill University, Canada, and Senior Scientific Advisor to the Lymphatic Filariasis Support Centre for Africa, Ghana.

An Overview of Neglected Tropical Diseases in Sub-Saharan Africa

John Owusu Gyapong

Contents

Abstract Neglected tropical diseases (NTDs) affect many neglected and marginalised populations worldwide, but the burden in sub-Saharan Africa is rather overwhelming. Many of the endemic communities are of very low socioeconomic status with very limited access to health services. Investing to overcome the global impact of NTDs will yield a very high economic rate of return and impact significantly on the quality of life of these populations. In order to scale up interventions to achieve control, elimination or eradication of NTDs, programmes must be integrated into the regular health system of endemic countries. Efforts to expand global coverage and targeting of NTDs must therefore involve national and international harmonisation with coordination of the activities of partnerships devoted to control of these diseases. The continued support of major donors beyond the initial commitments announced during the London Declaration meetings remains crucial to funding the implementation of programmes. Ultimately, we need to address the social structures in which NTDs flourish and invest in research and development for new diagnostics and drugs.

J.O. Gyapong
School of Public Health, University of Ghana, Accra, Ghana
e-mail: jgyapong@ug.edu.gh

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_1

Introduction

Neglected tropical diseases (NTDs) are a diverse group of diseases with distinct characteristics that thrive mainly among the poorest and deprived populations. Most NTDs are found primarily in low- and middle-income countries of Africa, Asia and Latin America. Within these countries, the affected populations are in themselves very neglected in many ways and are usually in the lowest socioeconomic status. Populations, where people have little access to clean water, improper ways of disposing human waste and therefore live in unsanitary environments, tend to have a high burden of NTDs (Hotez et al 2006, WHO 2013).

The World Health Organization has prioritised 17 of these NTDs in 149 endemic countries for focused global attention (Table 1). These affect more than 1.4 billion people, costing developing economies billions of dollars every year. This list is by no means exhaustive since there are some other diseases in neglected populations that are not on this list; however, this list represents the biggest disease burden they face (WHO 2010).

The burden of these diseases is extremely high in sub-Saharan Africa (SSA). For example, approximately 40 % of the global burden of lymphatic filariasis (LF) is found in SSA, while all the remaining cases of guinea worm disease (GWD) are also found in the same region (WHO 2010).

The German government under GTZ (now GIZ) played an important role in the NTD movement by cosponsoring with the World Health Organization (WHO) two key meetings of leading stakeholders in 2003 and 2005 in Berlin. These meetings achieved two important outcomes: (i) a unified support for an integrated approach in addressing NTD control and elimination efforts and (ii) the brand "neglected tropical diseases" was coined and has since become part of the global health nomenclature (WHO 2004, 2006).

Prior to the Berlin meetings, several global directives in the form of World Health Assembly resolutions had been passed to mobilise political and social capital to address these diseases individually, and many more have been passed since then (Table 2) (WHO 2015).

Table 1 WHO prioritised neglected tropical diseases for control

Helminth	Protozoa
Cysticercosis/taeniasis	Chagas disease
Dracunculiasis (guinea worm disease)	Human African trypanosomiasis (sleeping sickness)
Echinococcosis	Leishmaniases
Food-borne trematodiases	Bacteria
Lymphatic filariasis	Buruli ulcer
Onchocerciasis (river blindness)	Leprosy (Hansen's disease)
Schistosomiasis	Trachoma
Soil-transmitted helminthiases	Yaws
Virus	
Dengue and chikungunya	
Rabies	

Table 2 Selected resolutions of the World Health Assembly concerning neglected tropical diseases

Subject area	Resolution	Title	Year
Neglected tropical diseases	WHA66.12	Neglected tropical diseases	2013
Schistosomiasis	WHA65.21	Elimination of schistosomiasis	2012
Chagas disease	WHA63.20	Chagas disease: control and elimination	2010
Leishmaniases	WHA60.13	Control of leishmaniasis	2007
Buruli ulcer	WHA57.1	Surveillance and control of *Mycobacterium ulcerans* disease	2004
Dracunculiasis	WHA57.9	Eradication of dracunculiasis	2004
Human African trypanosomiasis	WHA56.7	Pan-African tsetse and trypanosomiasis eradication campaign	2003
Dengue and dengue haemorrhagic fever	WHA55.17	Prevention and control of dengue fever and dengue haemorrhagic fever	2002
Schistosomiasis and soil-transmitted helminthiases	WHA54.19	Schistosomiasis and soil-transmitted helminth infections	2001
Trachoma	WHA51.11	Global elimination of blinding trachoma	1998
Chagas disease	WHA51.14	Elimination of transmission of Chagas disease	1998
Leprosy	WHA51.15	Elimination of leprosy as a public health problem	1998
Lymphatic filariasis	WHA50.29	Elimination of lymphatic filariasis as a public health problem	1997
Human African trypanosomiasis	WHA50.36	African trypanosomiasis	1997
Onchocerciasis	WHA47.32	Onchocerciasis control through ivermectin distribution	1994
Dengue and dengue haemorrhagic fever	WHA46.31	Dengue prevention and control	1993
Endemic treponematoses	WHA31.58	Control of endemic treponematoses	1978
Leprosy	WHA30.36	Leprosy control	1977

These resolutions were all very comprehensive, for example, the 50th World Health Assembly held in Geneva in May 1997 called on Member States to take advantage of recent advances in the understanding of lymphatic filariasis and the new opportunities for its elimination by developing national plans leading to its elimination, as well as for the monitoring and evaluation of programme activities; to strengthen local programmes and their integration with the control of other diseases, particularly at the community level, in order to implement simple, affordable, acceptable and sustainable activities based on community-wide treatment strategies, but supplemented where feasible by vector control and improved sanitation; to strengthen capabilities for training, research, laboratory diagnostic, disease management and data management in order to improve clinical, epidemiological and operational activities directed towards eliminating lymphatic filariasis as a public health

problem; and to mobilise support of all relevant sectors, affected communities and non-governmental organisations for the elimination of the disease (WHA50.29).

The Assembly also invited other specialised agencies of the United Nations system, bilateral development agencies, non-governmental organisations and other groups concerned, to increase cooperation in the elimination of lymphatic filariasis through support of national and international programmes relevant to the prevention and elimination of lymphatic filariasis. Finally, they requested the Director General of WHO to bring to the attention of the other specialised agencies and organisations of the United Nations system, bilateral development agencies, non-governmental organisations and other groups concerned the need for closer collaboration in the elimination of lymphatic filariasis as a public health problem, to mobilise support for global and national elimination activities (WHA50.29).

This is probably the most comprehensive global commitment one could get for a disease elimination programme. However, by the year 2005, only 8 out of the 38 endemic countries in Africa had active lymphatic filariasis elimination programmes, and of these only Burkina Faso, Ghana, Togo and Zanzibar were treating their entire national populations at risk. Clearly, targeting the individual diseases was not the most efficient way of dealing with the huge burden of NTDs; hence, in 2013, a more encompassing resolution WHA66.12 called for monitoring progress in achieving the targets for NTDs set in WHO's road map for accelerating work to overcome the global impact of NTDs and intensified, integrated measures and planned investments to improve the health and social well-being of the affected populations (WHA66.12).

There are many factors that have contributed to the belief that something can really be done about these diseases which hitherto were perceived to have no remedies. As a result, these World Health Assembly resolutions have managed to draw attention by mobilising resources and political capital to support these initiatives. These factors include among others:

- Better understanding of the diseases
- Improved delivery mechanisms including opportunities for integration
- Investment case including cost-benefit evaluation, funding and economic considerations
- Moral, political and social determinants
- Drug donations

Better Understanding of the Diseases

Research over many years has played a critical role in providing the necessary information to understand these diseases and the subsequent development of interventions and programme creation. As a result, we have a better understanding of the:

- Epidemiology of these diseases
- Transmission dynamics and vector biology
- Socioeconomic factors

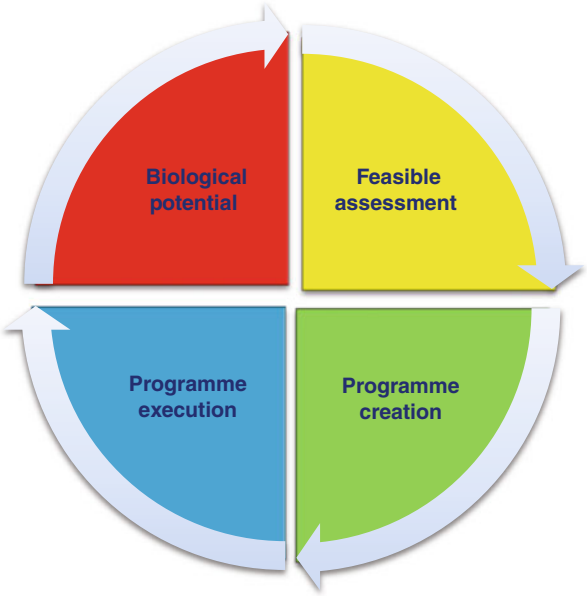


Fig. 1 Control programme planning process

These have also led to:

- Development of drugs and diagnostics
- Testing of new interventions
- Operational delivery of interventions
- Development of monitoring and evaluation tools to assess the impact of these interventions
- The development of better surveillance tools

Thus, knowledge generated in recent years has demonstrated aptly that the biological potential of controlling, eliminating and even eradicating these NTDs does exist, and ample diagnostic tools and strategies are available to assess the burden and distribution of these diseases and that it is possible to create and execute control programmes effectively if we can mobilise the necessary economic, social and political capital (Fig. 1).

Improved Delivery Mechanisms and Opportunities for Integration

Various mapping studies and other available anecdotal information suggest that most countries in SSA have more than three of these diseases (Fig. 2). Strategies, tools and interventions available for combating these diseases can be used for more than one disease. Therefore, the integration and co-implementation of these

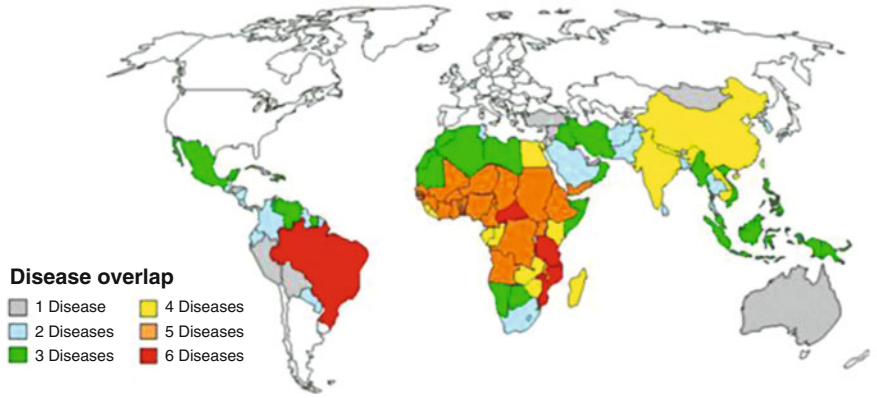


Fig. 2 Extent of disease overlap

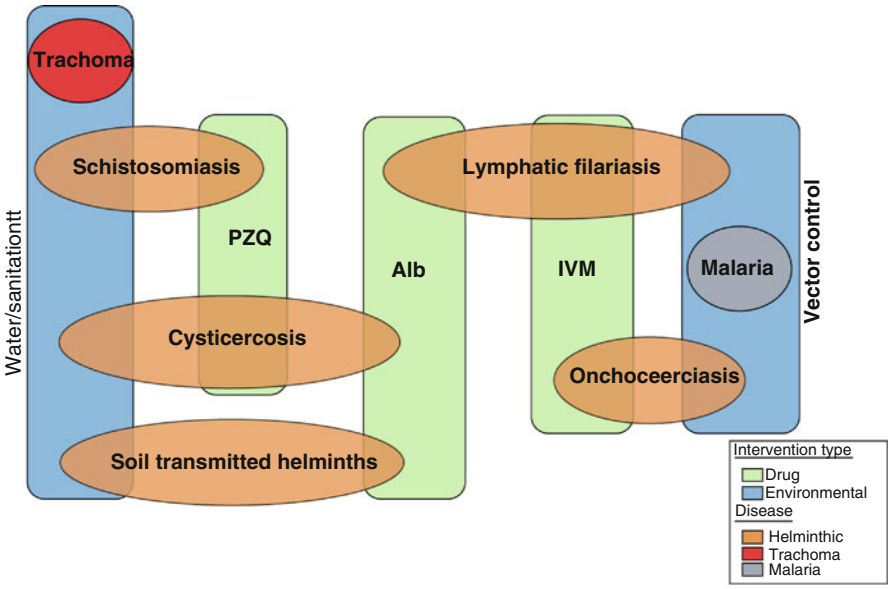


Fig. 3 Some strategies, tools and interventions for NTD control

strategies, tools and interventions is the key to the control/elimination of the diseases (Gyapong et al. 2010; Molyneux et al. 2005).

Figure 3 illustrates how improved water and sanitation, drugs (praziquantel, albendazole and ivermectin) and vector control could be delivered as an intervention package to fight several NTDs and malaria. As a result, the World Health Organization (WHO) recommends two main strategies for NTD control: preventive chemotherapy and transmission control (PCT) and innovative intensified disease management (IDM) (WHO 2010, 2015).

PCT focuses on diseases for which a strategy exists as well as on tools and the availability of safe and effective drugs that make it feasible to implement large-scale preventive chemotherapy. The diseases amenable to the PCT strategy include cysticercosis, dracunculiasis (guinea worm disease), food-borne trematode infections, lymphatic filariasis, onchocerciasis, schistosomiasis and soil-transmitted helminthiasis. Blinding trachoma control through the SAFE strategy – combining drug treatment with hygiene and environmental management – can be linked to helminth control interventions to improve the overall health of affected communities (WHO 2010, 2015).

IDM focuses on diseases for which cost-effective control tools do not exist and where large-scale use of existing tools is limited. The diseases include Buruli ulcer, Chagas disease, human African trypanosomiasis and leishmaniasis and share the following characteristics:

- Difficult and costly to manage in terms of diagnosis, treatment and follow-up.
- Burden is poorly understood.
- Lack of appropriate control tools.
- Relatively lower investment in research and development.
- People affected often live in remote rural areas with limited access to diagnosis and treatment (WHO 2010, 2015).

Having prioritised NTDs for control, having mapped their distribution and being armed with interventions that work, the biggest challenge has been to deliver these interventions through a health system in the midst of severe human resource constraints and other health system challenges (Gyapong et al. 2010). The health worker/population ratio is extremely high in Africa with some areas not served at all. In order to improve access, there is the need to engage other cadre of staff for the delivery of these interventions and explore other delivery mechanisms such as school-based and community-based distribution. The community-directed treatment approach, which provides opportunities for health services to work closely with, and the community to deliver interventions have been shown to be highly feasible (Amazigo et al. 2007; Gyapong et al. 2000; WHO 2008). These studies have found community volunteers to be capable, motivated and reliable; however, they need to be provided with incentives. With this approach, the community decides the timing of the distribution and selects distributors to be trained by health workers. The distribution is done at the convenience of community, and the health worker helps with monitoring and supervision.

Such large-scale community-based treatments could be associated with inadvertent exposure of some population even when standard operating procedures are adhered to. This requires putting in place an efficient community education, monitoring and evaluation systems. The challenge of dealing with serious adverse events in any mass drug distribution exercise can be daunting particularly if an adverse reaction like Stevens-Johnson syndrome occurs. How strong is our pharmacovigilance infrastructure to pick up these occasional mishaps? (Gyapong et al. 2003)

Efforts to expand global coverage and targeting of NTDs must involve national and international harmonisation. We need coordination of the activities of partnerships devoted to the control or elimination of these diseases. Programmes with similar delivery strategies and interventions such as those for lymphatic filariasis,

onchocerciasis and soil-transmitted helminthiasis could be managed on the same platform and together. In order to scale up neglected tropical disease (NTD) interventions to achieve complete eradication, programmes must be integrated into the regular health system of countries with the principles of:

- Where things fit well, do them together.
- Where things do not, do them separately.
- Look for ways of coordinating efforts to deliver a more cost-effective way.
- Make integration an "attitude", not a strategy.

Investment Case

Investment case (IC) for the control, elimination or eradication of these diseases has been done in various forms including the traditional cost-benefit evaluation of proposed interventions. The "critical elements" of an IC include the proposed investment, the rationale for the investment, the management and the governance. The final product is practical in nature, going beyond a description of what to do, by describing how to do it with respect to some core methodological issues. A reasonable projected cost based on an investment case have garnered political and social support especially when there is indication that these interventions will not jeopardise existing health systems but rather offer opportunities for synergies with health system activities (Molyneux 2008, Cochi and Dowdle 2011).

Investing to overcome the global impact of neglected tropical diseases makes the case that the elimination and control of NTDs will be a "litmus test" for universal health coverage. Endemic countries can contribute by increasing domestic investments and scaling up interventions. Large middle-income economies can also play an important role in developing new diagnostics and medicines and in influencing market dynamics. The recent report of the Uniting to Combat NTDs coalition estimates cash and in kind aid at about US$ 300 million in 2014, excluding donated medicines. Investing to overcome the global impact of neglected tropical diseases sets investment targets for universal coverage against NTDs that are more than double current levels of foreign aid – as much as ten times when including investments in vector control. It is unlikely that an increase in aid of this magnitude can be achieved in the current global health financing climate. NTD control must become an integral part of national health plans and budgets if it is to achieve the scale of universal coverage (Cochi and Dowdle 2011, WHO 2015).

Moral, Political and Social Determinants

The "duty to rescue" is a moral one! The potential of getting rid of a disease forever or controlling it to insignificant levels will protect future generations from its scourge, but beyond all, the notion of disease control/eradication as a public good is one that cannot be overlooked. Firstly, an ethical analysis presents a dimension of the

investment case for control/eradication. This can be called the "moral investment" that is seldom discussed in the literature. This is an important dimension to emphasise since it has long been recognised that social and political commitment is essential for the successful control/eradication of a disease. Social and political commitment involves moral motivation, or the ethical reasons to act. It is thus important to understand those reasons and how they are relevant in decisions involving large-scale public health interventions. Secondly, as moral beings, members of the global community have a fundamental interest in identifying what ethical obligations they have to one another. In the context of disease control/eradication, such obligations can impact the lives of millions of people and reflect choices about the kind of world in which we want to live: one where all are free from the burden of disease or one where inequity exists and only some have that luxury of good health (Hotez et al. 2006).

Political and societal support is therefore crucial for initiating and delivering these programmes and must be mobilised at all costs. Broad social perception of the importance of the disease is essential, and without it, there is no programme! Polio, guinea worm disease and lymphatic filariasis elimination/eradication was launched with the high-level political and technical consensus inherent in World Health Assembly resolutions. Polio eradication from the onset had tremendous societal and political support because of the awareness of the disease in developed and endemic countries. Resource mobilisation by Rotary International, their network of volunteers and the overwhelming support of civil society groups have been the lifeblood of the programme. Chinese President Zemin, South African President Mandela and US President Clinton have heightened the programme's visibility and through that raised lots of resources for the programme. The guinea worm eradication initiative has also relied heavily on political advocacy, benefiting tremendously from the support of former heads of state such as US President Carter.

Neglected tropical diseases (NTDs) as a brand on the other hand had not had that much visibility with heads of states until recently when President Bush committed USD 350 million to their control. The recent NTD forum in London and the follow-up in Paris convened by the Gates foundation have raised the profile of NTD elimination even the more. Total commitments at these fora were way in excess of USD 800 million. The challenge is to maintain the commitment of central-level authorities for a campaign that targets a very small proportion of the national morbidity burden in the poorest communities. Sustaining societal-level support is complicated by the logistic difficulties of routinely supplying, supervising and ensuring surveillance in remote rural areas and the fatigue of multiple years of national immunisation days. A lot more advocacy is therefore required especially at the local level to maintain the required steam (Hotez et al. 2006; Molyneux et al. 2005; Gyapong et al. 2010).

Drug Donations

Investing in drug/vaccine development for interventions targeted for elimination is a critical part of the equation. This is where big pharmaceutical industry comes in. Once these products are developed, they need to be tested for their applicability in the field. When they are proven to be efficacious, access to these medicines at

reasonable costs becomes an issue. Given that these diseases occur mainly in the poorest communities, most affected individuals would be unable to afford these essential drugs. The decision by many of the pharmaceutical companies to donate or supply at production cost to the programmes is therefore highly commendable and a good example of appropriate corporate social responsibility. In the case of LF elimination GlaxoSmithKline and Merck decided to donate Albendazole and Ivermectin to the global programme for as long as they are needed as part of the corporate social responsibility. Diethylcarbamazine (DEC), for instance, is not a donated product in Southeast Asia, so it has to be procured at production cost. Table 3 shows a list of pharmaceutical companies that contribute to the NTD portfolio of medicines.

The pharmaceutical industry donated nearly 1.35 billion treatments in 2013, representing a 35 % increase since 2011. A set of forms is available to facilitate application, review and reporting and to improve programme coordination and integration. This puts the Ministry of Health in control by centralising all country requests for medicines and providing oversight for progressive ownership of control programmes (WHO 2015).

Beyond the drug donation, some of the pharmaceutical companies such as GlaxoSmithKline and Merck have in addition made substantial investments in support for programme delivery at the global and country level, operational research and capacity building in endemic areas and in many other areas. These investments have been critical and timely for success of the programme.

Control, Eliminate or Eradicate?

Disease control, elimination and subsequent eradication are a desirable goal that many health systems hope to achieve. It represents the ultimate in global equity and the definitive outcome of good public health practice. The elimination of smallpox over three decades ago demonstrated that disease eradication could bring lasting benefits to society. As a result today, several diseases have been identified as potentially eradicable with massive investments by several stakeholders. In 1997, the Dahlem conference on eradication of infectious diseases provided some working definition for disease elimination and eradication. These definitions have since been revised based on better understanding of epidemiology and control of infectious diseases. The recent Ernst Strüngmann Forum helped to build consensus around these working definitions (Cochi and Dowdle 2011; Dowdle 1999).

Control refers to “reduction of disease incidence, prevalence, morbidity, and/or mortality to a locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction”.

Elimination of transmission (interruption of transmission) means “reduction to zero of the incidence of infection caused by a specific pathogen in a defined geographical area, with minimal risk of reintroduction, as a result of deliberate efforts; continued actions to prevent re-establishment of transmission may be required”. The process of documenting elimination of transmission is called “verification”.

Table 3 Medicines for controlling neglected tropical diseases donated by the pharmaceutical industry

Pharmaceutical company	Medicine	Donation
Bayer	Nifurtimox	Up to 300,000 tablets of 120 mg and 20,000 tablets of 30 mg per year during 2014–2019 for human African trypanosomiasis; donation made through WHO
	Nifurtimox	Up to 1 million tablets of 120 mg including paediatric formulations in 30 mg tablets during 2012–2017 for second-line treatment of Chagas disease; donation made through WHO
	Suramin	Up to 10,000 1 g vials per year until November 2017 for human African trypanosomiasis; donation made through WHO
Eisai	Diethylcarbamazine	Up to 2.2 billion tablets until 2020 for lymphatic filariasis; donation made through WHO
Gilead sciences	AmBisome	Up to 445,000 vials during 2012–2016 for visceral leishmaniasis in South East Asia and East Africa; donation made through WHO
GlaxoSmithKline	Albendazole	Unlimited supply for as long as needed for lymphatic filariasis and up to 400 million tablets during 2012–2016 for soil-transmitted helminthiases; donation made through WHO
Johnson & Johnson	Mebendazole	Up to 200 million tablets per year during 2012–2016 for soil-transmitted helminthiases control programmes for school-age children; donation made through WHO
Merck & Co., Inc	Ivermectin	Unlimited supply for as long as needed; donation made directly to countries for lymphatic filariasis and onchocerciasis
Merck KGaA	Praziquantel	Up to 250 million tablets per year for an unlimited period for schistosomiasis; donation made through WHO
Novartis	Multidrug therapy (rifampicin, clofazimine and dapsone in blister packs) and loose capsules of clofazimine	Unlimited supply for as long as needed for leprosy and its complications; donation made through WHO
	Triclabendazole	Unlimited supply for fascioliasis and paragonimiasis; donation made through WHO
Pfizer	Azithromycin	Unlimited quantity for blinding trachoma until at least 2020
Sanofi	Eflornithine	Unlimited quantity until 2020 for human African trypanosomiasis; donation made through WHO
	Melarsoprol	Unlimited quantity until 2020 for human African trypanosomiasis; donation made through WHO
	Pentamidine	Unlimited quantity until 2020 for human African trypanosomiasis; donation made through WHO

Source: WHO (2015)

Eradication means "permanent reduction to zero of a specific pathogen, as a result of deliberate efforts, with no more risk of reintroduction". The process of documenting eradication is called "certification".

Current global eradication initiatives are poliomyelitis and guinea worm. In the short term, measles and rubella could get onto the list. Potentially cysticercosis and lymphatic filariasis may be included in the list in the long term. Onchocerciasis and yaws are not on the list of International Task Force for Disease Eradication but have received considerable attention in recent times.

The Role of Research

Research has been very key to this whole process. Basic research to understand the biology and transmission dynamics of these diseases continues to open opportunities to the development of diagnostic tools and drugs. Several clinical trials are ongoing to help optimise these tools for field use. The importance of research in identifying solutions and options for overcoming implementation obstacles in health systems and programmes has been pursued vigorously. Such implementation research has helped to resolve many operational challenges in a multidisciplinary approach. This form of research addresses implementation bottlenecks, identifies optimal approaches for a particular setting and promotes the uptake of research findings: ultimately, it leads to improved health care and its delivery. There are however many disease-specific research questions that need answers, which are discussed in subsequent chapters.

Conclusion

The control of neglected tropical disease is definitely a good public health investment with potentially high economic return. The political platform provided by World Health Assembly resolutions coupled with drug donations by pharmaceutical companies and financial support from the international community sets the scene for success. The remaining chapters in this book address some of these NTDs that are prevalent in sub-Saharan Africa, focusing on:

1. *Epidemiology of the disease*: distribution, burden and public health impact of disease in sub-Saharan Africa
2. *Basic biology*: life cycle, mode of transmission, disease presentation and diagnosis of the infection/disease
3. *Diagnostic tools*: what is available? Are they adequate? Are their use supported by evidence? How cost-effective is their application? Are they operationally feasible?

4. *Treatment and control strategies*: what are the available options? Are currently available strategies effective? Are they evidence-based? Is their application sustainable/cost-effective?
5. *Chemotherapy-based strategies*: is the choice of first-line treatment evidence-based? What are the gaps in knowledge, for example, dose and regimen, geographic/regional variation in effect, their implications on treatment and control etc.? Was there any hosts' variation in efficacy, for example, between children and adults and implications for control? Were there opportunities for combination therapies and would they improve therapeutic efficacy and/or slow resistance development? How reliable are the data used over the years for policy recommendations?
6. *Challenges of programme implementation*
7. *Further research for policy and control*
8. *Outlook for the next decade*

References

Amazigo U, Okeibunor J, Matovu V, Zouré H, Bump J, Seketeli A (2007) Performance of predictors: evaluating sustainability in community-directed treatment projects of the African programme for onchocerciasis control. Soc Sci Med 64(10):2070–2082

Cochi SL, Dowdle WR (2011) Disease eradication in the 21st century- Implications for Global Health. The MIT Press, Cambridge MA. ISBN: 978-0-262-01673-5

Dowdle WR (1999) The principle of disease eradication and eradication. MMWR

Gyapong M, Gyapong JO, Owusu-Banahene G (2000) Community-directed treatment: the way forward to eliminating lymphatic filariasis as a public health problem in Ghana. Ann Trop Med Parasitol 95(1):77–86 (2001)

Gyapong JO, Chinbuah MA, Gyapong M (2003) Tropical medicine and international health 2003 inadvertent exposure of pregnant women to Ivermectin and Albendazole during Mass Drug Administration (MDA) for lymphatic filariasis. Trop Med Int Health 8(12):1093–1101

Gyapong JO, Gyapong M, Yellu N, Anakwah K, Amofah G, Bockarie M, Adjei S (2010) Integration of control of neglected tropical diseases into health-care systems: challenges and opportunities. Lancet 375(9709):160–165

Hotez PJ, Ottesen E, Fenwick A, Molyneux D (2006) The neglected tropical diseases: the ancient afflictions of stigma and poverty and the prospects for their control and elimination. Adv Exp Biol Med 582:22–33

Molyneux DH (2008) Combating the "other diseases" of MDG 6: changing the paradigm to achieve equity and poverty reduction? Trans R Soc Trop Med Hyg 102(6):509–519

Molyneux DH, Hotez PJ, Fenwick A (2005) "Rapid-impact interventions": how a policy of integrated control for Africa's neglected tropical diseases could benefit the poor. PLoS Med 2:e336

World Health Organisation (2008) Community directed interventions for major health problems in Africa. Multi-country Study Final Report. World Health Organisation, Geneva. doi:10.2174/TDR.07. ISBN ISBN 978 92 4 159660 2

World Health Organisation (2010) Working to overcome the global impact of neglected tropical diseases. First WHO report on Neglected Tropical Diseases. Geneva, Switzerland, WHO/HTM/NTD/2010.1

World Health Organisation (2015) Investing to overcome the global impact of neglected tropical diseases. Third WHO report on neglected tropical diseases. Geneva, Switzerland, WHO/HTM/NTD/2015.1

World Health Organisation (2004) Intensified control of the neglected diseases. World Health Organisation, Berlin, 10–12 December 2003. Report of an international workshop. WHO/CDS/CPE/2004.45

World Health Organisation (2006) Strategic and technical meeting on intensified control of neglected tropical diseases. World Health Organisation, Berlin, 18–20 April 2005. A renewed effort to combat entrenched communicable diseases of the poor - Report of an international workshop. WHO/CDS/NTD/2006.1

World Health Organisation (2013) Sustaining the drive to overcome the global impact of neglected tropical diseases. Second WHO report on neglected tropical diseases. World Health Organisation, Geneva, Switzerland, WHO/HTM/NTD/2013.1

Buruli Ulcer in Sub-Saharan Africa

Ghislain Sopoh and Kingsley Asiedu

Contents

G. Sopoh (✉)
Centre de Dépistage et de Traitement de l'Ulcère de Buruli d'Allada, Allada, Bénin
e-mail: ghislainsop@yahoo.fr

K. Asiedu
Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_2

Abstract Buruli ulcer is a chronic skin infection caused by an environmental *Mycobacterium ulcerans*. The disease has been documented in over 33 countries, but the bulk of the disease burden occurs in Sub-Saharan Africa. The majority of people affected are children below 15 years of age. The mode of transmission is still not known. However there have been significant advances in the pathogenesis, diagnosis, and treatment in the past decade. The public health strategy aimed at reducing the morbidity and disability is based on early detection of cases and antibiotic treatment. This requires intensive health education in the affected communities to encourage the population to report early to the health facilities. Research to develop rapid point-of-care diagnostic tests and to simplify antibiotic treatment are in progress and expected to be in practical application in the field within the next decade.

Keywords Neglected tropical disease • Buruli ulcer • Epidemiology • Treatment • Control

Introduction

Buruli ulcer (BU) is one of the 17 neglected tropical diseases cause by *Mycobacterium ulcerans*. It has been reported in 33 countries; however, the highest disease burden is in Sub-Saharan Africa. The disease was first described by Sir Albert Cook in Uganda in 1897. However, it was not until 1938 that a group of researchers in Australia were able to culture and characterize the causative organism (MacCallum et al. 1948). The organism grows at lower temperature 29–33° and produces a unique toxin called mycolactone which causes the destruction of the tissue (George et al. 1999). In 1998, WHO established the Global Buruli Ulcer Initiative to address the growing public health problem of the disease, especially in West Africa. In the same year, it organized the first international conference on Buruli ulcer control and research in Yamoussoukro, Côte d'Ivoire, which led to the Yamoussoukro declaration. This declaration contributed to the mobilization of national and international supports to advance the Buruli ulcer control and research. The WHO strategy for Buruli ulcer control is based on early detection and antibiotic treatment. The disease presents as a nodule, plaque, and edema. With time, all ulcerate with the typical undermining edges and white-yellowish necrotic base. The diagnosis is based on clinical criteria but requires training and experience. A number of other skin conditions can present like Bu ruli ulcer. In the laboratory, Buruli ulcer can be confirmed by four tests (direct microscopy, histopathology, culture, and polymerase chain reaction (PCR) (WHO 2014). However, because of sensitivity and specificity as well as the faster turnaround time, PCR analysis targeting the insertion sequence IS*2404* has become the standard laboratory diagnosis of BU. Many endemic countries have research laboratories able to perform this test, but it requires transport of samples from rural endemic communities to these laboratories which are based in the cities. The recommended antibiotic regimen is a combination of rifampicin and streptomycin given for 8 weeks (WHO 2012). In some cases, surgery (skin grafting) and physiotherapy may be necessary depending on the stage, location, and extent of

the disease. A clinical trial is in progress to evaluate the combination of rifampicin and clarithromycin in order to have a completely oral therapy. The development of point-of-care diagnostic test is a research priority now. In November 2013, WHO and FIND [the Foundation for Innovative New Diagnostics] convened a meeting of experts to review and prioritize diagnostic technologies under development (WHO 2014). Among the various tests, two are well advanced for field evaluations. These are direct detection of the toxin – mycolactone – by thin layer chromatography and antigen capture test. While efforts are being made to understand the mode of transmission, it is essential that national control programs intensify efforts to improve early detection of cases.

Definition

Buruli ulcer (BU) is an infectious disease caused by *Mycobacterium ulcerans*. The disease is characterized by extensive necrosis of the subcutaneous tissue that, if left untreated, results in disabling sequelae (WHO 2000).

Epidemiology

Geographical Distribution

BU is prevalent in countries with tropical and subtropical climates. It has been reported in over 33 countries with variable incidence. Although the foci are geographically circumscribed, they are always around aquatic ecosystems (rivers, lakes, artificial or natural wetlands, irrigation systems, etc.) (WHO 2000).

Table 1 presents a summary of the countries in which BU has been reported.

Figure 1 shows the global distribution of BU in 2012.

In 2012, cases were reported from 14 countries, most of which are in Africa, where efforts to control the disease have been focused during the past decade.

Table 1 Countries in which BU has been reported

Regions	Countries
Africa	Angola, Benin, Burkina Faso, Cameroon, Congo, Côte d'Ivoire, Democratic Republic of Congo, Gabon, Ghana, Guinea, Equatorial Guinea, Kenya, Liberia, Nigeria, Uganda, Sudan, Togo, and Central African Republic (Smith 1970; Bär et al. 1998; Meyers et al. 1996; Ouoba et al. 1998; WHO 2003; Janssens et al. 2005; Walsh et al. 2008, 2009, 2010, 2011; Minime-Lingoupou et al. 2010)
Latin America	French Guiana (De Gentile et al. 1992), Mexico (Walsh et al. 2011), Peru (Guerra et al. 2008), Suriname (WHO 2008b; Walsh et al. 2011)
Asia	China (Faber et al. 2000), Japan (Kondo et al. 2009; Watanabe et al. 2010)
South Pacific	Australia (Goutzamanis and Gilbert 1995; Johnson et al. 1996), Papua New Guinea (Lavender et al. 2007)

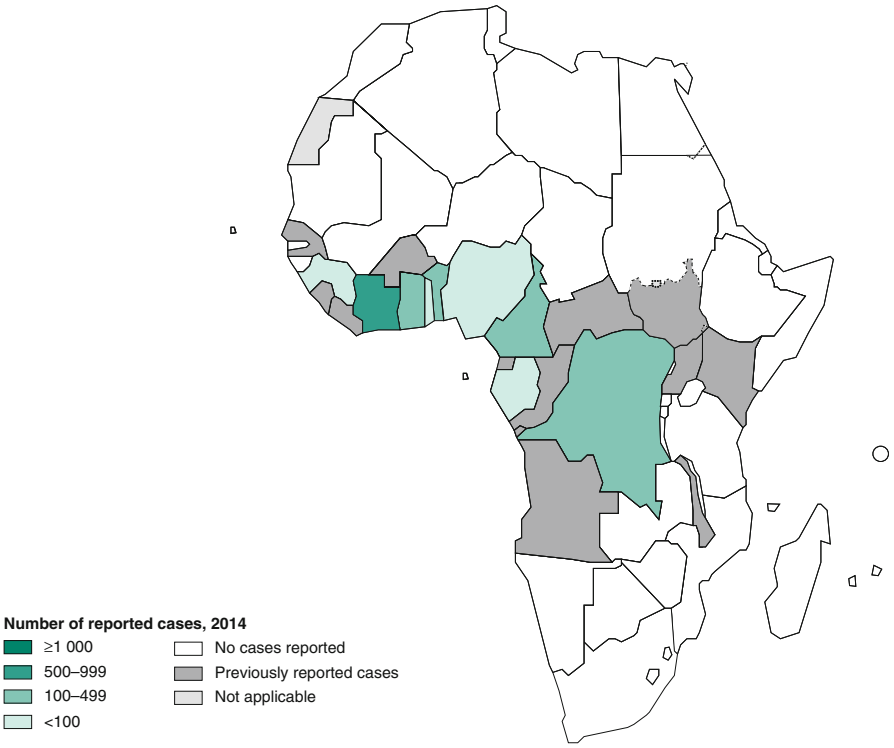


Fig. 1 The distribution of BU by country as of 2012. Relative endemicity is denoted as high (*red*), moderate (*pink*), or low (*light pink*) (Source: WHO Annual meeting on Buruli ulcer, 25–27 March 2013, Geneva)

Burden of the Disease in Sub-Saharan Africa

The true prevalence of BU in the various endemic countries is not known, and underreporting is suspected in some countries, such as Nigeria (Chukwuekezie et al. 2007). The annual number of reported new cases of BU, which had increased in the early and mid-1990s to about 10,000, has more recently stabilized to about 5000.

In 2012, 3215 new cases of Buruli ulcer were reported globally, 3104 of them from the African Region. The data available is limited for three reasons: (i) within endemic countries where cases are being reported regularly, control activities are limited in geographical scope, and the data may not therefore reflect the burden at the national level; (ii) there are large areas where limited or no activities are being carried out, and the extent of the disease is therefore relatively unknown; (iii) limited knowledge of the disease, its focal distribution, and the fact that it affects mainly poor rural communities all contribute to low reporting of cases. Only Côte d'Ivoire and Ghana have performed national surveys (Kanga and Kacou 2001; Amofah et al.

2002) from which la Côte d'Ivoire reported 32 cases per 100,000 inhabitants and Ghana a prevalence of 20.7 cases per 100,000 inhabitants. However, not all of these cases have been confirmed by laboratory tests.

Public Health Impact in Sub-Saharan Africa

The psychologic, social, and economic impacts of the disease on affected families and communities are important (Asiedu and Etuaful 1998; Aujoulat et al. 2003; Ackumey et al. 2012): These include (i) stigma of affected individuals perceived to be attributable in some affected communities' sorcery or witchcraft, (ii) anxiety about the progression of the disease, (iii) the debilitating consequences of pain and disabilities, and (iv) the disruption of school attendance. Others include high cost of treatment when this is not-subsidized, high indirect cost for affected individual and relatives in terms of lost productivity or depletion of income, and transport cost to centers for daily treatment.

Reservoir and Transmission Hypotheses

Epidemiological studies show that the disease appears in endemic foci often localized around aquatic niches (Merritt et al. 2005; Sizaire et al. 2006; Duker et al. 2006). In Uganda, Lunn et al. (1965) and Barker (1972) described cases primarily from the Nile Valley and bordering marshes. Bayley (1971) described the cases of three BU patients living around a river in Ghana. Ravisse (1977) described cases in Cameroon originating from the Nyong River and the surrounding swamps. Oluwasanmi et al. (1976) described cases in Nigeria located in an area near an artificial lake bordering the University of Ibadan. Johnson et al. (2005) showed that there was an inverse relationship between an area's prevalence of BU and its distance from the Couffo River in Benin. Kibadi et al. (2008) reported three patients originating from villages near the Cuango/Kwango River in Angola and the Democratic Republic of Congo.

Cultures of mycobacteria have been obtained from different grasses (*Hyparrhenia rufa*, *Imperata cylindrica*, *Panicum maximum*, *and Pennisetum catabasis*) (Barker et al. 1970). There is only one reported case of cultivation of *M. ulcerans* from an environmental niche – an aquatic insect (*Gerris* sp.) (Portaels et al. 2008b). However, the DNA of *M. ulcerans* has been detected, albeit not cultivated, in many aquatic insect and animal species (Portaels et al. 2001; Marsollier et al. 2002, 2004; Eddyani et al. 2004) as well as in mosquitoes (Johnson et al. 2007; Wallace et al. 2010). Therefore, a possible role of aquatic insects in the transmission of the disease from environment to human has been suggested (Portaels 1989, 2004; Portaels et al. 1999; Silva et al. 2007; Marsollier et al. 2007). Indeed, Portaels hypothesized that *M. ulcerans*, being concentrated by filtering water bodies, such as aquatic larvae,

mollusks, and small fishes, could be eaten by and then infect predatory insects such as water bugs. These bugs may transmit the bacteria to humans through a bite. Humans could also be contaminated directly from the environment through trauma. A study by Marsollier and colleagues subsequently demonstrated that aquatic bugs, such as *Naucoris cimicoides*, can transmit the disease to mice in a laboratory setting (Portaels et al. 1999, 2004; Marsollier et al. 2007).

M. ulcerans infection had been described in mammals (koalas, alpacas, possums, horses, and a cat) in Australia (Portaels et al. 2001; Elsner et al. 2008; van Zyl et al. 2010; Fyfe et al. 2010). However, the search for the bacteria in small terrestrial mammals in Benin has yielded no results (Durnez et al. 2010).

The transmission of the disease from man to man has never been demonstrated. However, the development of typical BU after a human bite has been reported (Debacker et al. 2002, 2003). The hypothesized explanation for this observation is that the introduction of *M. ulcerans*, previously present on the skin of the affected individual, was facilitated by the bite (Debacker et al. 2003).

Pathogenesis

The incubation period for BU is variable and relies heavily on the host's immune response (Andersen 1965). Some authors have estimated the incubation period to last between 1 and 3 months (Andersen 1965; Barker 1973). Others think that the incubation period may range from 2 weeks to 3 years (Meyers et al. 1974). In experimentally infected animals, the incubation period varied from 7 to 150 days and depended on the size of the inoculum (Fenner 1950; Marsollier 2002).

The course of the infection after the introduction of the bacteria into the skin is also poorly documented. Recently, Silva et al. (2009) developed a model based on the microbiological and immunological aspects of the disease, as shown in Fig. 2. This model implies that *M. ulcerans* behaves as an intracellular parasite that induces an inflammatory cellular response. During the active phase of the infection, *M. ulcerans* parasitizes macrophages and multiplies within them, continuously colonizing incoming monocytes or macrophages and progressively invading healthy tissues. The persistent influx of leukocytes to the site of active infection provides immune cells that interact with *M. ulcerans*, triggering leukocyte chemotaxis and cell-mediated immunity (CMI). The ability of this CMI to halt the progress of the infection, leading to mediated immunopathology or self-cure, depends upon factors that include the dose of infection, the virulence of the bacteria, and the immunocompetence of the host. The band of cellular infiltrate with *M. ulcerans* multiplying within macrophages therefore represents the front where crucial events in the development of the disease occur. As the front advances and invades healthy tissues, leukocyte lysis at the trailing edge of the infiltrate creates a continuously enlarging cellular necrotic area with freed bacilli that probably multiply extracellularly. In advanced disease, the necrotic lesion further expands, with extensive coagulation necrosis of the subcutaneous tissue, dermis, and epidermis, extensive vasculitis,

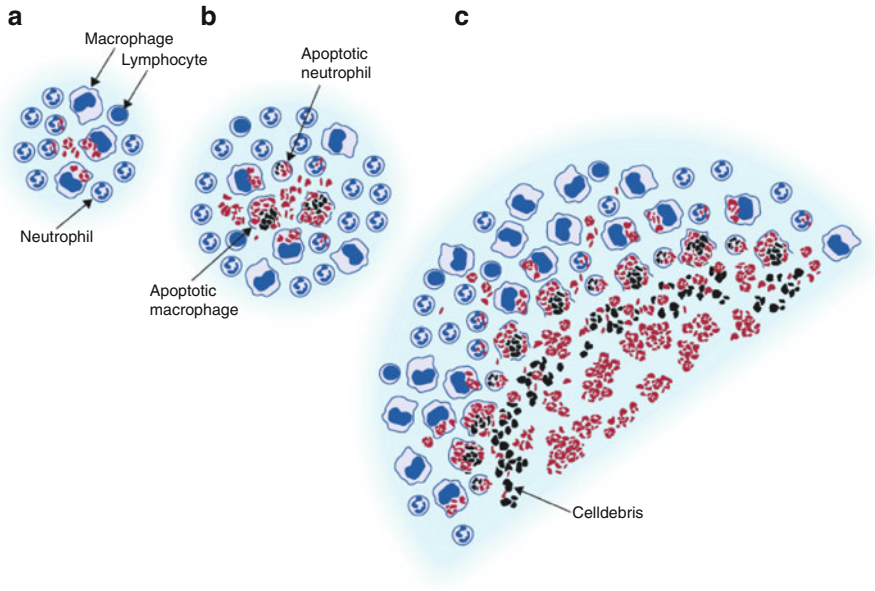


Fig. 2 Schematic representation of the initiation and establishment of a BU lesion (Source: Silva et al. 2009). (**a**) Early stage of infection with *M. ulcerans* (red bacilli) phagocytosed by neutrophils and macrophages in the acute inflammatory infiltrate. (**b**) A more advanced stage characterized by the presence of an area with an inflammatory cellular infiltrate with intraneutrophil and intramacrophage bacilli and apoptotic neutrophils and macrophages. (**c**) The advanced stage of the lesion, with extensive necrotic acellular areas containing abundant clumps of extracellular bacilli, cellular debris, neutrophils, and macrophages with intracellular bacilli at the edges of the necrotic areas

and, in some cases, ulceration. Over time, immunity becomes protective with the production of a granulomatous tissue reaction and healing.

According to this view of BU pathogenesis, inflammatory infiltrates in advanced lesions occupy a smaller area than the necrotic zones do because of the destruction of the continuously attracted infiltrates of immune cells by mycolactone rather than because of mycolactone-induced inhibition of cellular responses. That is, in advanced lesions of BU, the inflammatory cellular infiltrates are minor in spatial but not in immunological terms.

Another theory is based on the action of the mycolactone. *M. ulcerans* is unique in that the mycolactone it produces is necessary for its virulence (George et al. 1999). Indeed, after penetration into the dermis or subcutaneous tissue, the bacteria are latent for a variable duration and then proliferate and produce mycolactone. This cytotoxin has an affinity for fat cells (Dobos et al. 2001). Once secreted, mycolactone therefore causes the apoptosis of adipocytes and necrosis (George et al. 2000). This necrosis is a good environment for the proliferation of *M. ulcerans*. At this stage, the cutaneous manifestations appear as nodules, plaques, or ulcerations as the necrosis extends toward the surface (van der Werf et al. 2003). The mycolactone also induces the destruction of continuously produced inflammatory infiltrates,

resulting in a depressed or absent local immune response from the host (Adusumilli et al. 2005; Oliveira et al. 2005; Torrado et al. 2007a, b, 2010; Simmonds et al. 2009; Fraga et al. 2011). Gradually, following treatment, the host will develop a CMI response (Peduzzi et al. 2007; Silva et al. 2009). At this stage, a specific inflammatory reaction appears with the formation of granulomas that will isolate the bacteria, circumscribe the evolution of the disease, and lead to progressive scarring. The disease may then disappear, leaving a scar behind.

Clinical Characteristics

BU develops in three stages: the non-ulcerated stage, with four clinical forms (papule, nodule, edema, or plaque), the ulcerated stage, and the healing stage. In Africa, nonulcerative forms represent 26 % of the clinical presentation of the disease, when ulcerative forms are 74 % (WHO 2012).

The *papule* is defined as a painless, raised skin lesion less than 1 cm in diameter. The surrounding skin is reddened. This form is commonly seen in Australia.

The *nodule* is a lesion that extends from the skin into the subcutaneous tissue. It is 1–2 cm in diameter. It is usually painless but may be pruritic and the surrounding skin may be discolored compared to adjacent areas. This form is commonly seen in Africa (Fig. 3).

The *plaque* is a firm, painless, elevated, well-demarcated lesion more than 2 cm in diameter with irregular edges. The skin over the lesion is often reddened or otherwise discolored (Figs. 4 and 5).

The *edema* is a diffuse, extensive, usually nonpitting swelling. The affected area has ill-defined margins, is firm and painless, and involves part or all of a limb or other parts of the body. There may be color changes over the affected region (Fig. 6).

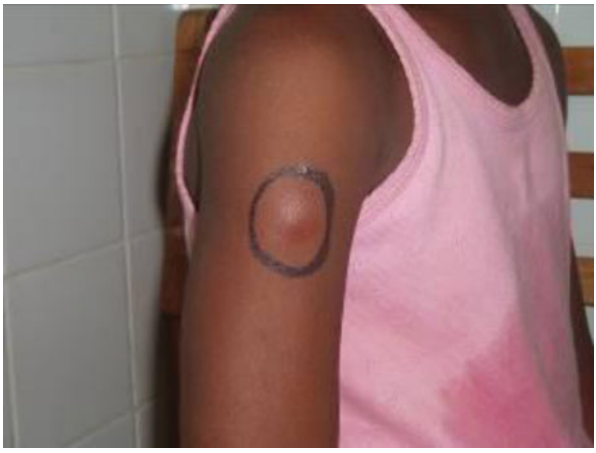


Fig. 3 Nodule on the upper limb

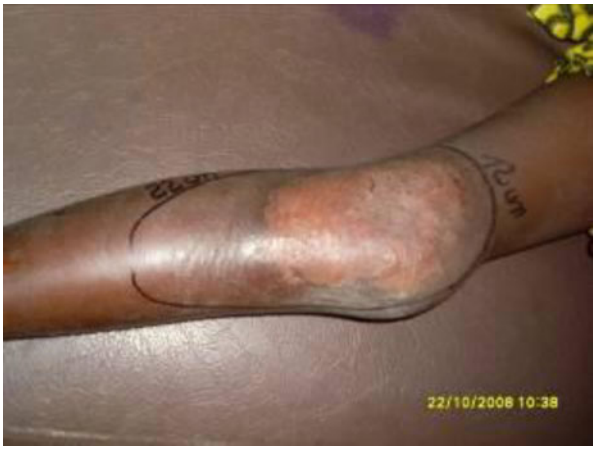


Fig. 4 Plaque on the lower limb

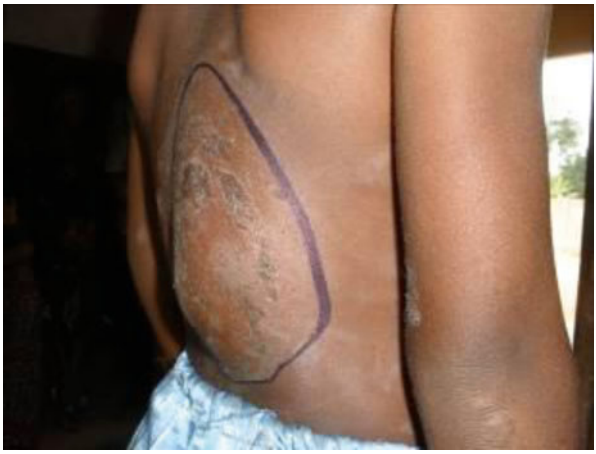


Fig. 5 Plaque on the back

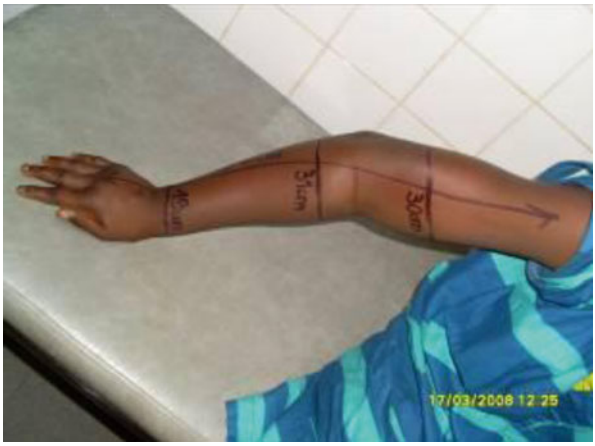


Fig. 6 Edema on the upper limb

The *ulcer* has undermined edges and is indurated peripherally. The floor of the ulcer may have a white cotton wool-like appearance from the necrotic slough. The ulcer is usually painless unless there is secondary bacterial infection. When there is more than one ulcer and the ulcers are close together, they often communicate beneath intact skin (WHO 2001a, b, 2004) (Fig. 7, 8, 9, and 10).

The *healing stages* are inactive forms characterized by a particular type of scar, with or without sequelae, that is hypopigmented, starry, retractile, and fibrous (Fig. 11).

Other clinical forms have been described:

- *Bone involvement* can be true osteomyelitis, focal or multifocal. The overlying skin is often intact with no obvious lesion. Osteomyelitis may occur as a primary condition or as a metastatic condition, sometimes at a distance from a cutaneous lesion or after a cutaneous lesion has healed. *M. ulcerans* osteomyelitis is initially painless but subsequently frankly painful and well localized. There is

Fig. 7 Multiple lesions

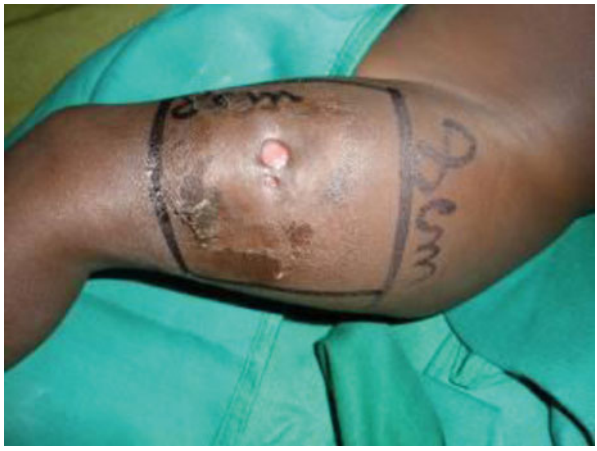


Fig. 8 Typical BU ulcer

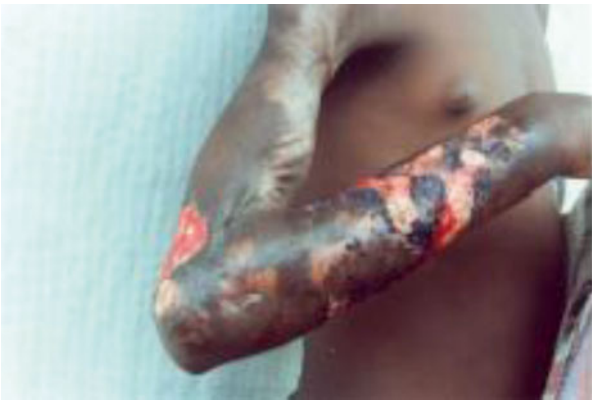


Fig. 9 Extensive ulcers

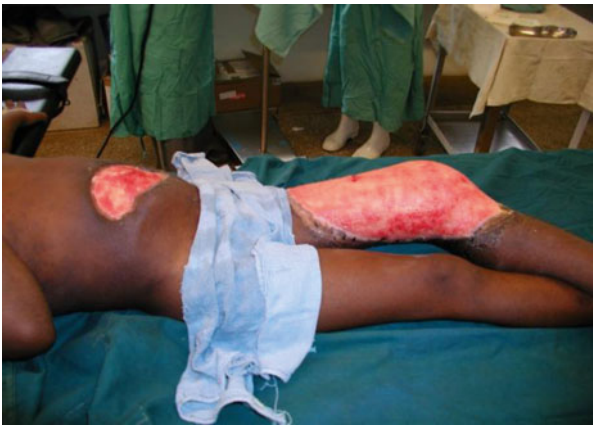


Fig. 10 Extensive ulcers

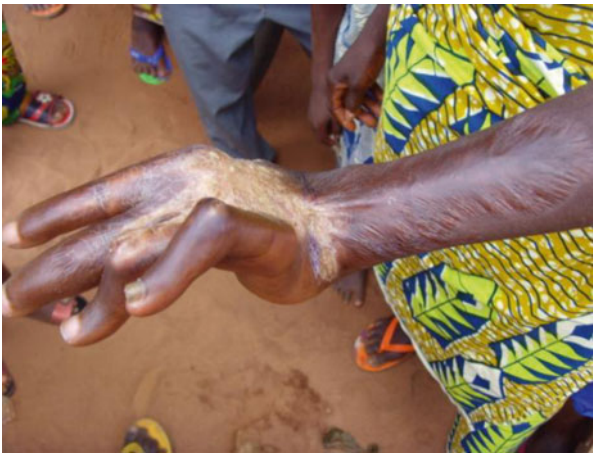


Fig. 11 Complication of healing

usually an identifiable area of increased warmth. A swelling then appears that may progress to a fistula that discharges necrotic material. Incision of the swelling reveals gelatinous tissue, and, beneath this, the bone has a moth-eaten appearance. Unlike open (contiguous) osteitis, the bone is the site of necrosis to a variable extent, similar to that seen in tuberculous osteomyelitis.

- Reactive (contiguous) osteitis occurs as a consequence of deep destruction of overlying soft tissues. Occasionally, the bone is exposed to the point of devascularization, necrosis of cortical bone, sequestration, and osteomyelitis. The macroscopic appearance is then that of white dead bone of almost normal appearance and texture (WHO 2001a, b).
- Portaels et al. first demonstrated the invasion of *M. ulcerans* into the bone (2003, 2008a).
- *Disseminated and mixed forms* are described as the simultaneous presence of different forms of the disease, including bone and joint involvement, in the same patient (WHO 2004).
- *HIV/AIDS coinfections*: Buruli ulcer and HIV coinfection is an emerging area and complicates clinical management. The first case of Buruli and HIV coinfection was reported from Democratic Republic of the Congo in 1992 (WHO 1997). A study conducted in Benin from 2002 to 2003 found that HIV prevalence among patients with Buruli ulcer was higher (2.6 %, 11/426) than among controls (0.3 %, 2/613) (Johnson et al. 2008). In Benin, 6 (3.6 %) out of 156 patients treated at Pobè Buruli Ulcer Treatment Center in 2006 were positive for HIV, and in 2010, 2 (1.5 %) out of 135 patients were HIV positive. In Cameroon, an HIV prevalence of 33 % has been reported among adult Buruli ulcer patients (compared to 5 % in the general population) (WHO 2010b).
- HIV weakens the immune system and tends to make Buruli ulcer progress more aggressive and could possibly affect the response to antibiotic treatment. Coinfected patients are often adults (>15 years old) who present with multifocal lesions and osteomyelitis (Johnson et al. 2002; Toll et al. 2005).
- *A recurrent case* is defined as a patient with previous surgical (and/or antibiotic) treatment for *M. ulcerans* who presents with another lesion or lesions at the same or a different site within 1 year of the completion of the last treatment (WHO 2004).
- *Paradoxical reaction* is a recently recognized phenomenon, and some cases previously classified as recurrent lesions may have been due to paradoxical reactions. Such reactions occur during or long after antibiotic treatment, with new inflammatory disease (presenting as a nodule/swelling, plaque, or edema) leading to extension of the existing ulcer or a new lesion on a different part of the body, usually with pus formation and pain. These are sometimes seen on parts of the body where there was no evidence of disease before antibiotic treatment, perhaps as a result of subclinical infection. Cultures of tissue or pus are usually sterile, although acid-fast bacilli can still be seen and polymerase chain reaction (PCR) for *M. ulcerans* IS2404 remains positive. Histopathological examination of the lesion demonstrates an intense immunological reaction within and around the lesion (WHO 2012).

In addition to the standard classification of the disease into non-ulcerated and ulcerated forms, an additional classification based on lesion size was introduced for two reasons: (i) small lesions are more likely to heal with antibiotic treatment, and (ii) small lesions reflect the impact of health education efforts promoting early diagnosis and therefore help to monitor the progress of different countries.

There are three *categories* of lesions:

- Category 1: single lesion less than 5 cm in diameter
- Category 2: single lesion between 5 and 15 cm in diameter
- Category 3: single lesion greater than 15 cm in diameter, multiple lesions, lesion(s) at critical sites (eye, breast, genitalia), and osteomyelitis (WHO 2012)

Complications and Sequelae

Contractures may result from scarring caused by lesions over or close to joints. Ankyloses may follow.

There may be continuous minor bleeding or a sudden major hemorrhage.

Secondary bacterial infection may be caused by organisms such as staphylococci, streptococci, *Pseudomonas* sp., and *Corynebacterium* sp. Secondary infection may progress to cellulitis and septicemia.

Infection may extend beneath the deep fascia to involve tendon sheaths, muscle, blood vessels, nerves, bone, and joints or may destroy periorbital tissue with loss of the eye.

Hypertrophic scars and keloids may develop at infection and surgical sites, including skin graft donor sites.

Squamous cell carcinoma (Marjolin's ulcer) may appear in an unstable scar or a persistent ulcer many years after the initial infection with *M. ulcerans* (WHO 2001a. b).

Clinical Diagnosis

The diagnosis of BU is based on epidemiological, clinical, and biological criteria. The following clinico-epidemiological features are important diagnostic clues:

- Most patients live in or have traveled to a known endemic area.
- Most patients are children under 15 years of age.
- About 85 % of lesions are on the limbs.
- Lower-limb lesions are twice as common as upper-limb lesions.
- Non-ulcerated lesions are almost painless or minimally painful (although ulcers may be painful in the presence of a secondary bacterial infection).
- In the absence of a secondary bacterial infection or other coinfections in ulcerated lesions, there are often no constitutional symptoms (such as fever).
- Enlarged lymph nodes are not a feature of *M. ulcerans* disease.

Biology

The biological diagnosis is based on a positive result of one or several of the following tests performed on samples collected from suspected lesions:

- Direct smear examination (DSE) showing acid-fast bacilli (AFB)
- Polymerase chain reaction (PCR)
- Culture of *M. ulcerans* on Löwenstein-Jensen medium
- Histopathology showing lesions consistent with BU and AFB on Ziehl-Neelsen stain (WHO 2004)

The advantages and limitations of these tests are summarized in Table 2.

Swabs, fine-needle aspiration, and biopsy (punch or surgical) are used to collect specimens. Fine-needle aspiration has recently been proposed as a minimally invasive technique for the diagnosis of non-ulcerated forms of BU. Its effectiveness has

Table 2 Summary of the advantages and disadvantages of confirmatory testing for BU

Method	Advantages	Disadvantages
Direct smear examination	Easy to perform at a local level	Low sensitivity (<60 %)
	Does not require expensive materials and equipment	Needs trained personnel
	Rapid results	Needs external quality assurance
	Uses swabs, fine-needle aspiration, and biopsy samples	
Polymerase chain reaction (PCR)	Results are fairly rapid	Requires a sophisticated laboratory
	Uses swabs, fine-needle aspiration, and biopsy samples	Expensive to perform
	High sensitivity (>95 %)	Needs trained personnel
		Requires strict quality control
Culture of *M. ulcerans*	Uses swabs, fine-needle aspiration, and biopsy samples	Requires a sophisticated laboratory
	Proves that the AFB are alive (viable)	Needs trained personnel
		Results take longer than 8 weeks
		Low sensitivity (20–60 %)
		Not useful for immediate patient management
Histopathology	Sensitivity is about 90 %	Requires a sophisticated laboratory
	Results are fairly rapid	Expensive to perform
	Useful in establishing a differential diagnosis and monitoring response to treatment	Needs trained personnel
		Requires an invasive procedure (i.e., biopsy)

Source: WHO (2010a)

been reported by several authors (Phillips et al. 2009; Eddyani et al. 2009; Cassisa et al. 2010; Herbinger et al. 2010), and a tutorial has been prepared on how to perform this technique (http://www.stopburuli.org/fna-e-tutorial/index_en.html).

Swabs and fine-needle aspiration are noninvasive procedures that can be undertaken at any level (community, health centers, hospitals) during routine management or for case finding in communities.

Specimens obtained by *swabs* should be taken from the undermined edges of a clinically diagnosed BU lesion. Physicians or experienced health workers can perform this technique.

Fine-needle aspiration (FNA) is mainly used to obtain samples from clinically diagnosed non-ulcerated lesions (nodules, plaques, and edema). This technique is necessary in up to 30 % of patients (depending on the setting) and is simple enough to be applied more widely in the field. FNA may also be used in some ulcerated lesions in which it is difficult to take swabs because of healing edges. Only physicians or experienced health workers should perform this technique; ongoing training and regular supervision should be provided to health workers to improve their skills. Extreme care should be taken when performing fine-needle aspiration around the head and neck area (especially around the eyes) and the genitalia. When necessary, an expert clinician should perform this technique to minimize any unintended damage to important organs or structures.

The WHO recommends that a maximum of two swabs or two fine-needle aspirations be taken from each lesion. Repeat sampling may be indicated if the results of the PCR of the initial samples are negative despite a strong clinical diagnosis. Samples obtained from swabs and fine-needle aspirations are sufficient in most cases.

Punch or surgical *biopsy* may be used when the diagnosis is in the direct interests of the patient (e.g., when swabs and fine-needle aspiration have been unsuccessfully attempted or abandoned). Surgical biopsy may be preferable when larger diagnostic sample specimens are required for histopathological analyses (WHO 2010a).

All samples collected for immediate analysis can be placed in a sterile container with no additives. Samples to be transported should be kept cool (ideally at 4 °C), such as in an insulated container with a frozen cooling block, if the analysis will be performed within 24 h. If the analysis will be performed after 24 h or more, the recommendation is to either keep the sample at 4 °C (not frozen) when refrigeration facilities are available or place it in a transport medium (Liquid Middlebrook 7H9 broth supplemented with polymyxin B, amphotericin B, nalidixic acid, trimethoprim, and azlocillin [PANTA]) when refrigeration facilities are not available. Supplementation with 0.5 % agar achieves a semisolid medium (WHO 2001a). Specimens kept in semisolid transport medium may still be culture positive after as long as 26 weeks (Eddyani et al. 2008).

The *direct smear examination* is generally performed after Ziehl-Neelsen staining. The bacteria appear red on a blue background. They are small acid-fast bacilli (AFB) of 2–3 μm in length and 0.3–0.5 μm in width, straight or curved, isolated or grouped.

The *culture* of *M. ulcerans* is performed on standard Löwenstein-Jensen medium at a low temperature (between 30 and 32 °C). However, *M. ulcerans* can survive at

37 °C for up to 13 days (Eddyani and Portaels 2007). The growth of the bacterium is very slow and the results are often available only after 6–8 weeks. The sensitivity of culture is low (<60 %) (Herbinger et al. 2009; Mensah-Quainoo et al. 2008).

PCR consists of amplifying small amounts of DNA to obtain easily detectable quantities in the laboratory. It targets an insertion sequence, *IS2404*, specific for *M. ulcerans* and presents at least 220 copies per genome. The use of the PCR technique for the detection of *M. ulcerans* was first suggested by Portaels et al. (1997). PCR targeting of *IS2404* was later developed in Australia (Ross et al. 1997; Stinear et al. 1999). The sensitivity of PCR remains high, even on punch biopsies (Stienstra et al. 2003; Rondini et al. 2003; Phillips et al. 2005) or FNA (Phillips et al. 2009; Eddyani et al. 2009; Cassisa et al. 2010; Herbinger et al. 2010). However, PCR is not suitable for the monitoring of treatment success, and currently, cultures are considered the only valid confirmatory test for the detection of viable bacilli (Beissner et al. 2010).

A *histopathological examination* is performed on biopsies fixed in 10 % formalin and after hematoxylin-eosin, Gram, Ziehl-Neelsen, and Grocott staining. The main histopathological lesion characteristic of BU is that of coagulative necrosis. The specific histopathological features have been described previously (Hayman and McQueen 1985; Hayman 1993; Guarner et al. 2003).

The histological examination of early lesions shows necrosis of dermal collagen, described as "fibrillary," resulting in an eosinophilic coagulum. In addition to involving the dermis, this necrosis may extend into the widened septa of the subcutaneous fat (Hayman and McQueen 1985). The collagen necrosis may be described as caseous. There is little cellular reaction despite the presence of large numbers of organisms. Although initially fibrillary, later there is complete loss of all cellular and structural detail, resulting in an amorphous eosinophilic coagulum in the affected dermis, histopathologically indistinguishable from that seen in tuberculous infection. Together with fat and collagen, there is also necrosis and degeneration of elastic fibers. Fragments of elastic fibers may also be seen within the cytoplasm of giant cells in the granulomas adjacent to the necrotic areas. In addition to elastolysis, there is also elastosis; an increase in elastic tissue occurs with the fibrosis in the widened septa prior to any degenerative changes. Duplication or irregular thickening of the internal elastic lamina also occurs in the arteries in the septa in association with the intimal proliferation described previously. Slight calcification, seen histopathologically, is noted in many cases in association with fat necrosis. The calcification appears to be confined to the proteinaceous areas between the lipid collections within the necrotic fat, developing around the foci of mycobacterial proliferation (Hayman 1993).

Recurrent or persistent infection produces a granulomatous reaction with epithelioid macrophages, variable numbers of giant cells of the Langerhans type, and relatively few organisms. This type of reaction is associated with more successful treatment of the disease and appears analogous to the tuberculoid form of leprosy (Hayman 1993).

Although the histopathological lesions usually seen in BU disease are well described, defining the histopathological criteria for a diagnosis of BU disease

remains of clinical and public health importance as it would allow earlier treatment, leading to less deforming sequelae.

Other useful exploration methods:

Radiography shows evidence of bone damage, which can occur even below apparently healthy skin or apparently early lesions, such as nodules (Portaels et al. 2008a). The images are not specific for BU. N'Zi et al. (1998) and Hans-Moevi et al. (2003) presented radiographic images of osteitis, demineralization, periosteal reaction, bone condensation, osteolysis, cortical thickening, and geodes.

Ultrasonography is an attractive, simple, and noninvasive method useful to assess the dermoepidermal damage caused by *M. ulcerans* and to follow the evolution of these lesions during treatment (Leigheb et al. 2008). Although the images are not specific, these can help distinguish for example, early-stage nodules (shown as hyperechoic imbibitions of the adipose tissue and hypoechoic areas due to adiponecrosis) from late-stage ones (shown as hypoechoic images with round or ragged forms, due to the presence of secondary granulomas).

Other techniques based on the detection of the toxin in tissue samples are currently under investigation. The World Health Organization, in collaboration with the Foundation for Innovative New Diagnostics, has started a thorough evaluation of an innovative diagnostic test developed by researchers at Harvard University that can lead to rapid confirmation of Buruli ulcer in a patient. Initial results from recent field trials in Benin and Ghana show that the test can detect mycolactone, a toxin produced by the bacteria that causes tissue damage and leads to Buruli ulcer (Converse et al. 2014). The most important aspect of this new test – which is more sensitive than microscopy – is that it can be carried out by technicians with minimal training in district hospital laboratories.

Differential Diagnosis

Many conditions can present like BU. Table 3 presents a summary of the diseases that can present like BU according to the clinical form.

Control Tools and Strategies

The mode of transmission and incubation period of BU are not fully known. Thus, primary prevention remains a challenge. However, prevention may rely on avoidance of contact with the causative agent. This, obviously, is not easy to implement, particularly for farmers, fishermen, and others who are in contact with the contaminated environment during their daily tasks. However, wearing protective clothing

Table 3 Summary of the diseases that can present like BU according to the clinical form

BU clinical form	Differential diagnosis	
Nodule	Painful nodule	Insect bite, furuncle, anthrax, abscess, infected sebaceous cyst, furunculoid myiasis, erythema nodosum, hidradenitis, chondrodermatitis nodularis
	Mildly or not painful nodule	Lipome, onchocercal nodule, nodular leishmaniasis
	Isolated noninflammatory nodules	Foreign-body granuloma, gummas, dermatofibroma
Edema	Inflammatory edema	Infectious cutaneous cellulitis, staphylococcal or salmonella osteomyelitis, necrotizing fasciitis, phlegmon, injuries
	Edema	Renal/cardiac insufficiency, anemia, protein-energy malnutrition, erysipelas
	Noninflammatory edema	Kaposi's sarcoma, elephantiasis, actinomycosis, onchocercoma
Plaque	Hematoma, psoriasis, mycosis, leprosy, phlegmon, erysipelas, lupus vulgaris, eczema, urticaria, sarcoidosis	
Ulcer	Tropical phagedenic ulcer, ulcer of venous or arterial origin, ulcerated cutaneous tuberculosis, necrotizing fasciitis, ulcerated carcinoma or melanoma, leishmaniasis, sickle cell disease ulcer, injection abscess, African histoplasmosis, sporotrichosis, tuberculosis, lymphadenitis	
Scar with or without sequelae	Dystrophic burn scar, ankylosis secondary to skin or bone tuberculosis	
Bone involvement	All other banal (staphylococcus, streptococcus, etc.) or specific (*Mycobacterium tuberculosis*) germs causing osteitis or osteomyelitis	

Sources: Guédénon and Portaels (2000), WHO (2000, 2001a)

when farming (Pouillot et al. 2007) and the use of soap for immediate cleansing of any skin injuries (Nackers et al. 2007) may reduce rates of infection. The use of protected sources of water for domestic purposes may reduce exposure to water contaminated by *M. ulcerans* and, consequently, may reduce the prevalence of BU (Debacker et al. 2006). Primary prevention activities should thus encourage health education on personal and environmental hygiene, the use of protective clothes when possible, the proper care of all injuries, and the avoidance of contact with natural water bodies.

Immunity can also be boosted by vaccination if a vaccine would be available. A vaccine against *M. ulcerans* will be useful to protect children in hyperendemic foci, but it may also play a role in therapy by shortening the duration of antibiotic treatment and preventing recurrences and severe forms of the disease. As of now, there is no specific vaccine against *M. ulcerans*, but there is some evidence for cross-reactive protection against BU by the *M. bovis* BCG vaccine used against tuberculosis. However, the BCG vaccine produces only short-term protection against BU disease. There is considerable evidence supporting the notion that the development of a vaccine is feasible. Studies have indicated that some household contacts of BU disease patients have been exposed to *M. ulcerans* without developing the disease. This may

be because they developed a protective immune response or because of different issues, such as an inadequate infective dose of the organism or the wrong conditions for bacterial proliferation in exposed skin. In addition, there is much anecdotal evidence that some people develop pathological lesions after infection with *M. ulcerans* that heal in a short time without treatment (Huygen et al. 2009).

Currently, health education focuses its efforts on identifying, reporting, and treating early forms of the disease.

The surveillance system in BU is based on the involvement of village volunteers and the use of the WHO's BU02 form containing information on registered BU cases (WHO 2000). The aim of the WHO's control strategy is to minimize the morbidity and disability associated with BU. To achieve this objective, the WHO recently made the following recommendations to endemic countries:

(i) Assess the actual magnitude of BU within each country.
(ii) Strengthen the case confirmation capacity of national laboratories in line with the WHO recommendations.
(iii) Intensify, at all levels, education on BU, especially in the affected communities, with a view to promoting early case detection.
(iv) Ensure that cases are detected at an early stage to reduce the frequency of disabilities.
(v) Provide access to specific antibiotic treatment and surgical and rehabilitation services free of charge or at reduced cost for people affected by BU
(vi) Improve BU mapping and surveillance in affected countries and promote cross-border exchange of information
(vii) Support research through active international cooperation on epidemiology; social and economic determinants and the impact, prevention, and development of new diagnostic tools; and simplification of treatment with orally administered medicines.
(viii) Mobilize additional resources for BU control.
(ix) Promote effective collaboration with other sectors to control the disease
(x) Promote the social and economic rehabilitation of people negatively affected by the disease
(xi) Strengthen further the primary health-care system in the affected areas to improve the integration and implementation of control and disability prevention activities (WHO 2009).

Chemotherapy-Based Strategies

The WHO recommends combination therapy using streptomycin and rifampin for the treatment of BU in doses of 10 mg/kg per day (for rifampin) and 15 mg/kg per day (for streptomycin) for a total of 8 weeks. The aim of the treatment is to cure *M. ulcerans* infection and to achieve a disability-free outcome with minimal scarring (WHO 2012). Thus, it is expected that most category 1 and some category 2 lesions

will completely heal with antibiotic treatment alone. However, most category 3 lesions will still require surgery (excision, skin grafting, or amputation in severe cases) in addition to antibiotics. Multiple small lesions and lesions located at critical sites may heal with antibiotics alone (WHO 2008b).

There is growing evidence of the efficacy of some rifampicin-based oral therapies. Although efficacy of oral treatment is still under evaluation, the 2012 WHO treatment guidance for health workers (WHO 2012) recommends, based on expert opinion, the use of oral therapy for the treatment of specific cases (e.g., pregnant women) as followed: rifampicin at 10 mg/kg, body weight by mouth daily for 8 weeks and clarithromycin at 7.5 mg/kg body weight by mouth, twice daily for 8 weeks. The extended-release formulation of clarithromycin may be used at 15 mg/kg body weight once daily.

When BU osteomyelitis is suspected, the first line of treatment should be with rifampicin and streptomycin for 8 weeks. Surgery is usually required to remove nonviable bone and to hasten healing. The response to treatment can be monitored radiologically.

Recurrence is rare after a full 8-week course of antibiotics has been completed. If antibiotics were given for fewer than 8 weeks in the first course or poor adherence is suspected, further antibiotic treatment or surgery should be considered. The duration of a second course of antibiotics depends on the situation, but care must be taken not to give streptomycin for more than 90 days in total.

Paradoxical reactions usually resolve without further antibiotic treatment. Clinicians should not therefore rush to restart or extend antibiotic treatment. Paradoxical reactions can be managed conservatively with drainage of pus and routine dressings. Samples should be taken for culture and histopathology. Underlying osteomyelitis should be eliminated. If the lesion due to a paradoxical reaction does not appeared to be improving within 6 weeks of conservative treatment, surgery should be considered and samples taken for microbiological and histopathological analyses to look for progressive active infection as an alternative diagnosis. If this reaction occurs during the course of antibiotic treatment, however, the full course of 8 weeks should be completed.

Although further studies are required to improve our understanding of BU/HIV coinfection, the WHO recommends that the management of such cases may follow the guidelines for managing TB/HIV coinfection. First, HIV counseling and testing should be offered for all patients presenting with BU. Second, coinfected patients should be screened for tuberculosis. Third, as for TB, coinfected patients may receive early antiretroviral treatment to ensure a better response to treatment irrespective of CD4 count. Due to the interaction between rifampicin and some ARVs, the NNRTI component of the ART regimen should be changed from NVP to EFV, and if protease inhibitors are being used, the TB/HIV guidelines should be consulted for suggested management. Combination antibiotic treatment for Bu should be commenced before initiating ART for HIV. Full guiding principles of management of BU/HIV co infected patients had been recently published by WHO (WHO 2015).

Other Treatment

Surgery

Until 2004, surgical intervention was the only therapeutic management technique recommended for BU. Surgical intervention typically requires large excisions of necrotic tissues with a rim of healthy tissue wider than 2 cm. Excision is usually followed by a thin-skin autograft (WHO 2001b), and in some instances, multiple surgical interventions are required. Unfortunately, surgical intervention frequently results in serious physical sequelae (Barogui et al. 2009) and may have a negative psychological impact on the patient (Aujoulat et al. 2003).

Currently, it have been demonstrated that all forms of Buruli ulcer – papules, nodules, plaques, edema, and ulcers – however extensive, respond well to antibiotic treatment. Thus, wide surgical removal of infected tissue is no longer necessary to achieve microbiological cure. Conservative surgery (debridement, skin grafting, and scar revision) may still be required only to speed healing of large lesions and to minimize scarring that might limit movement (WHO 2012).

The best time to undertake debridement and skin grafting, when indicated, is yet to be determined. Grafting should be late enough to allow all the *M. ulcerans* organisms to be killed by antibiotics but early enough to promote rapid recovery and a return to normal activities. Skin grafts should be applied to healthy vascular surfaces. It provides healthy new skin that is stronger and more flexible and is thus better able to withstand minor trauma. A sound conservative approach is to allow 8 weeks of antibiotic treatment before surgical intervention (WHO 2012).

Wound and Scar Management

Wound care is an important component of treatment but has received little attention so far. Various antiseptics and consumables are used for dressing in sub-Saharan Africa endemic areas. They are nonspecific and have no action on the mycobacteria. They are used to prevent secondary infection and necrosis and to prepare the wound for surgery (skin grafting). The most widely used antiseptics are povidone-iodine, Dakin, Mercryl, eosin, and hydrogen peroxide.

Since 2012, the WHO recommendations for wound management are as follows (WHO 2012):

- Manage systemic conditions appropriately.
- Protect the wound from trauma.
- Maintain a clean wound base and control infection.
- Maintain a moist wound environment.
- Control peri-wound lymphedema and edema.

Scar tissue resulting from slow normal healing may cause adhesions to and between underlying structures, which limit movement and are painful. Thick or tight scars resist injuries poorly, may limit movement, and detract from appearance and function. Their surface is usually dry, may crack or ulcerate, and is easily damaged by the sun. Such scars are easily injured during work or play. Note that scars that split frequently or ulcerate may, over many years, develop into squamous-cell carcinomas. Good scar management lessens complications. Management may involve moisturizing, massage, limb elevation, correct positioning of joints, and application of a pressure bandage for up to 1–2 years after natural healing or grafting (WHO 2012).

Prevention of Disabilities

This component of treatment has also received less attention since the beginning of the Global BU initiative (GBUI). However, within the past 4 years, the prevention of disability (POD) has gained greater attention as an important part of BU management. The WHO has published two important documents (WHO 2006, 2008a) to allow for the easy integration of POD activities into the primary health-care system (WHO 2008a).

Challenges of Program Implementation

During the 2013 WHO technical advisory group meeting, four programmatic objectives were set to be targeted by endemic control programs by the end of 2014 (WHO 2013):

1. At least 70 % of cases reported from any district or country should have been confirmed by a positive PCR.
2. The proportion of category III lesions reported from any district or country should have been reduced from the 2012 average of 33 % to below 25 %.
3. The proportion of ulcerative lesions at diagnosis reported from any district or country should have been reduced from the 2012 average of 84 % to a maximum of 60 %.
4. The proportion of patients presenting with limitation of movement at diagnosis reported from any district or country should have been reduced from the 2012 average of 25 % to a maximum of 15 % by the end of 2014.

These targets reflect the improvements in the accuracy of clinical diagnosis, correct sampling techniques, and the impact of early detection efforts (village education and active surveillance). To achieve the above mentioned targets, the WHO recommends to national BU programs:

- To develop or revise their national strategic plans, taking into consideration recent developments in Buruli ulcer control
- To document all case, using electronic and paper BU01 and BU02 forms
- To provide training to health workers on clinical diagnosis, sampling, laboratory confirmation, treatment guidelines, and prevention of disabilities

In order to improve the accuracy of clinical diagnosis of Buruli ulcer, a facility will be set for centers in which Internet access is available to upload clinical data and photographs of lesions for secondary remote confirmation. Laboratories should be strengthen for PCR confirmation and should participate to external quality assurance program and internal quality control programs for microscopy in collaboration with national tuberculosis control programs.

Further Research for Policy and Control

With regard to the epidemiological aspects, and in order to improve surveillance system, the distribution and dynamics of the evolution of the disease over the time should be better documented.

According to clinical aspects, better insights are needed on paradoxical reactions and BU/HIV coinfections.

According to the treatment aspects, efficacy of oral treatment should be assessed as well as the best time for surgery when indicated. Wound dressing and prevention of disability implementation impacts on the limitation of social consequences of the disease should be documented.

Outlook for the Next Decade

While studies to elucidate the mode of transmission continue so that possible preventive strategies can be developed, the short- to medium-term priorities are to improve the diagnosis and treatment of patients. For diagnosis, there are two potential rapid tests that are likely to be in field use in the coming years. The first is the direct detection of mycolactone using a simplified thin layer chromatography. Preliminary results from human samples are promising, and larger field trial is planned for 2015–2016 in Benin, DRC, and Ghana. The second is the antigen capture test converted into lateral flow format (Dreyer et al. 2015). In terms of therapy, there is a clinical trial in progress in Benin and Ghana comparing the efficacy of the standard treatment – rifampicin (oral) and streptomycin (injection) with rifampicin (oral) and clarithromycin (oral) given for 8 weeks. The objective is to develop a completely oral regimen to simplify the disease management in the field. This study is expected to be completed by 2017. In the meantime, national programs should intensify health education, and early detection efforts minimize late reporting of cases.

References

Ackumey MM, Gyapong M, Pappoe M, Kwakye-Maclean C, Weiss MG (2012) Illness meanings and experiences for pre-ulcer and ulcer conditions of Buruli ulcer in the Ga-West and Ga-South Municipalities of Ghana. BMC Public Health 12:264

Adusumilli S, Mve-Obiang A, Sparer T, Meyers W, Hayman J, Small PL (2005) *Mycobacterium ulcerans* toxic macrolide, mycolactone modulates the host immune response and cellular location of *M. ulcerans* in vitro and in vivo. Cell Microbiol 7:1295–1304

Amofah G, Bonsu F, Tetteh C, Okrah J, Asamoa K, Asiedu K, Addy J (2002) Buruli ulcer in Ghana: results of a national case search. Emerg Infect Dis 8:167–170

Andersen FO (1965) Mycobacterial skin ulcers-clinical experience. Cent Afr J Med 11:131–135

Asiedu K, Etuaful S (1998) Socioeconomic implications of Buruli ulcer in Ghana: a three-year review. Am J Trop Med Hyg 59(6):1015–1022

Aujoulat I, Johnson C, Zinsou C, Guedenon A, Portaels F (2003) Psychosocial aspects of health seeking behaviors of patients with Buruli ulcer in southern Benin. Trop Med Int Health 8:750–759

Bär W, Rüsch-Gerdes S, Richter E, de Bär Marquéz G, Dittmer C, Papsdorf H, Stosiek P, de Rijk PB, Meyers WM, Portaels F (1998) Mycobacterium ulcerans infection in a child from Angola: diagnosis by direct detection and culture. Trop Med Int Health 3:189–96

Barker DJ (1972) The distribution of Buruli disease in Uganda. Trans R Soc Trop Med Hyg 66:867–874

Barker DJ (1973) Epidemiology of *Mycobacterium ulcerans* infection. Trans R Soc Trop Med Hyg 67:43–50

Barker DJP, Clancey JK, Morrow RH, Rao S (1970) Transmission of Buruli disease. Br Med J 4:558

Barogui Y, Johnson RC, van der Werf TS, Sopoh G, Dossou A, Dijkstra PU, Stienstra Y (2009) Functional limitations after surgical or antibiotic treatment for Buruli ulcer in Benin. Am J Trop Med Hyg 81:82–87

Bayley AC (1971) Buruli ulcer in Ghana. Br Med J 2:401–402

Beissner M, Herbinger KH, Bretzel G (2010) Laboratory diagnosis of Buruli ulcer disease. Future Microbiol 5:363–370

Cassisa V, Chauty A, Marion E, Ardant MF, Eyangoh S, Cottin J, Aubry J, Koussemou H, Lelièvre B, Férec S, Tekaia F, Johnson C, Marsollier L (2010) Use of fine-needle aspiration for diagnosis of *Mycobacterium ulcerans* infection. J Clin Microbiol 48:2263–2264

Chukwuekezie O, Ampadu E, Sopoh G, Dossou A, Tiendrebeogo A, Sadiq L, Portaels F, Asiedu K (2007) Buruli ulcer, Nigeria. Emerg Infect Dis 13:782–783

Converse PJ, Xing Y, Kim KH, Tyagi S, Li S-Y, et al (2014) Accelerated detection of mycolactone production and response to antibiotic treatment in a mouse model of mycobacterium ulcerans disease. PLoS Negl Trop Dis 8(1):e2618

De Gentile PL, Mahaza C, Rolland F, Carbonnelle B, Verret JL, Chabasse D (1992) Cutaneous ulcer from *Mycobacterium ulcerans*. Apropos of 1 case in French Guiana. Bull Soc Pathol Exot 85:212–214

Debacker M, Zinsou C, Aguiar J, Meyers W, Portaels F (2002) *Mycobacterium ulcerans* disease (Buruli ulcer) following human bite. Lancet 360:1830

Debacker M, Zinsou C, Aguiar J, Meyers WM, Portaels F (2003) First case of *Mycobacterium ulcerans* disease (Buruli ulcer) following a human bite. Clin Infect Dis 36:e67–e68

Debacker M, Portaels F, Aguiar J, Steunou C, Zinsou C, Meyers W, Dramaix M (2006) Risk factors for Buruli ulcer, Benin. Emerg Infect Dis 12:1325–1331

Dobos KM, Small PL, Deslauriers M, Quinn FD, King CH (2001) *Mycobacterium ulcerans* cytotoxicity in an adipose cell model. Infect Immun 69:7182–7186

Dreyer A, Röltgen K, Dangy JP, Ruf MT, Scherr N, Bolz M, Tobias N, Charles Moes C, Vettiger A, Stinear T, Pluschke G (2015) Identification of the mycobacterium ulcerans protein

MUL_3720 as a promising target for the development of a diagnostic test for Buruli ulcer. PLoS Negl Trop Dis 9(2):e0003477. doi:10.1371/journal.pntd.0003477

Duker AA, Portaels F, Hale M (2006) Pathways of *Mycobacterium ulcerans* infection: a review. Environ Int 32:567–573

Durnez L, Suykerbuyk P, Nicolas V, Barrière P, Verheyen E, Johnson CR, Leirs H, Portaels F (2010) Terrestrial small mammals as reservoirs of *Mycobacterium ulcerans* in Benin. Appl Environ Microbiol 76:4574–4577

Eddyani M, Portaels F (2007) Survival of *Mycobacterium ulcerans* at 37 degrees C. Clin Microbiol Infect 13:1033–1035

Eddyani M, Ofori-Adjei D, Teugels G, De Weirdt D, Boakye D, Meyers WM, Portaels F (2004) Potential role for fish in transmission of *Mycobacterium ulcerans* disease (Buruli ulcer): an environmental study. Appl Environ Microbiol 70:5679–5681

Eddyani M, Debacker M, Martin A, Aguiar J, Johnson CR, Uwizeye C, Fissette K, Portaels F (2008) Primary culture of *Mycobacterium ulcerans* from human tissue specimens after storage in semisolid transport medium. J Clin Microbiol 46:69–72

Eddyani M, Fraga AG, Schmitt F, Uwizeye C, Fissette K, Johnson C, Aguiar J, Sopoh G, Barogui Y, Meyers WM, Pedrosa J, Portaels F (2009) Fine-needle aspiration, an efficient sampling technique for bacteriological diagnosis of nonulcerative Buruli ulcer. J Clin Microbiol 47:1700–1704

Elsner L, Wayne J, O'Brien CR, McCowan C, Malik R, Hayman JA, Globan M, Lavender CJ, Fyfe JA (2008) Localised *Mycobacterium ulcerans* infection in a cat in Australia. J Feline Med Surg 10:407–412

Faber WR, Arias-Bouda LM, Zeegelaar JE, Kolk AH, Fonteyne PA, Toonstra J, Portaels F (2000) First reported case of *Mycobacterium ulcerans* infection in a patient from China. Trans R Soc Trop Med Hyg 94:277–279

Fenner F (1950) The significance of the incubation period in infectious diseases. Med J Aust 2:813–818

Fraga AG, Cruz A, Martins TG, Torrado E, Saraiva M, Pereira DR, Meyers WM, Portaels F, Silva MT, Castro AG, Pedrosa J (2011) *Mycobacterium ulcerans* triggers T cell immunity followed by local and regional but not systemic immunosuppression. Infect Immun 79(1):421–430

Fyfe JA, Lavender CJ, Handasyde KA, Legione AR, O'Brien CR, Stinear TP, Pidot SJ, Seemann T, Benbow ME, Wallace JR, McCowan C, Johnson PD (2010) A major role for mammals in the ecology of *Mycobacterium ulcerans*. PLoS Negl Trop Dis 4:e791

George KM, Chatterjee D, Gunawardana G, Welty D, Hayman J, Lee R, Small PL (1999) Mycolactone: a polyketide toxin from *Mycobacterium ulcerans* required for virulence. Science 283:854–857

George KM, Pascopella L, Welty DM, Small PL (2000) A *Mycobacterium ulcerans* toxin, mycolactone, causes apoptosis in guinea pig ulcers and tissue culture cells. Infect Immun 68:877–883

Goutzamanis JJ, Gilbert GL (1995) *Mycobacterium ulcerans* infection in Australian children: report of eight cases and review. Clin Infect Dis 21:1186–1192

Guarner J, Bartlett J, Whitney EA, Raghunathan PL, Stienstra Y, Asamoa K, Etuaful S, Klutse E, Quarshie E, van der Werf TS, van der Graaf WT, King CH, Ashford DA (2003) Histopathologic features of *Mycobacterium ulcerans* infection. Emerg Infect Dis 9:651–656

Guédénon A, Portaels F (2000) Ulcère de Buruli: guide diagnostic à l'usage des professionnels de la santé. DGIS/DGCI, Belgique

Guerra H, Palomino JC, Falconí E, Bravo F, Donaires N, Van Marck E, Portaels F (2008) *Mycobacterium ulcerans* disease, Peru. Emerg Infect Dis 14:373–377

Hans-Moévi A, Sossou R, Boco V, Goudjo KPW, Johnson RC, Odulami H (2003) Aspets radiologiques des atteintes osseuses de la maladie de Buruli. J Afr Image 3:25–30

Hayman J (1993) Out of Africa: observations on the histopathology of *Mycobacterium ulcerans* infection. J Clin Pathol 46:5–9

Hayman J, McQueen A (1985) The pathology of *Mycobacterium ulcerans* infection. Pathology 17:594–600

Herbinger KH, Adjei O, Awua-Boateng NY, Nienhuis WA, Kunaa L, Siegmund V, Nitschke J, Thompson W, Klutse E, Agbenorku P, Schipf A, Reu S, Racz P, Fleischer B, Beissner M, Fleischmann E, Helfrich K, van der Werf TS, Löscher T, Bretzel G (2009) Comparative study of the sensitivity of different diagnostic methods for the laboratory diagnosis of Buruli ulcer disease. Clin Infect Dis 48:1055–1064

Herbinger KH, Beissner M, Huber K, Awua-Boateng NY, Nitschke J, Thompson W, Klutse E, Agbenorku P, Assiobo A, Piten E, Wiedemann F, Fleischmann E, Helfrich K, Adjei O, Löscher T, Bretzel G (2010) Efficiency of fine-needle aspiration compared with other sampling techniques for laboratory diagnosis of Buruli ulcer disease. J Clin Microbiol 48:3732–3734

Huygen K, Adjei O, Affolabi D, Bretzel G, Demangel C, Fleischer B, Johnson RC, Pedrosa J, Phanzu DM, Phillips RO, Pluschke G, Siegmund V, Singh M, van der Werf TS, Wansbrough-Jones M, Portaels F (2009) Buruli ulcer disease: prospects for a vaccine. Med Microbiol Immunol 198:69–77

Janssens PG, Pattyn SR, Meyers WM, Portaels F (2005) Buruli ulcer: an historical overview with updating to 2005. Bull Séances Acad R Sci Outre-Mer 51:265–299

Johnson PD, Veitch MG, Leslie DE, Flood PE, Hayman JA (1996) The emergence of *Mycobacterium ulcerans* infection near Melbourne. Med J Aust 164:76–78

Johnson RC, Ifebe D, Hans-Moevi A, Kestens L, Houessou R, Guédénon A, Meyers WM, Portaels F (2002) Disseminated *Mycobacterium ulcerans* disease in an HIV-positive patient: a case study. AIDS 16:1704–1705

Johnson RC, Makoutodé M, Sopoh GE, Elsen P, Gbovi J, Pouteau LH, Meyers WM, Boko M, Portaels F (2005) Buruli ulcer distribution in Benin. Emerg Infect Dis 11:500–501

Johnson RC, Nackers F, Glynn JR, de Biurrun Bakedano E, Zinsou C, Aguiar J, Tonglet R, Portaels F (2008) Association of HIV infection and Mycobacterium ulcerans disease in Benin. AIDS 23;22(7):901–903. doi: 10.1097/QAD.0b013e3282f7690a

Johnson PD, Azuolas J, Lavender CJ, Wishart E, Stinear TP, Hayman JA, Brown L, Jenkin GA, Fyfe JA (2007) *Mycobacterium ulcerans* in mosquitoes captured during outbreak of Buruli ulcer, southeastern Australia. Emerg Infect Dis 13:1653–1660

Kanga JM, Kacou ED (2001) Epidemiological aspects of Buruli ulcer in Côte d'Ivoire: results of a national survey. Bull Soc Pathol Exot 94:46–51, French

Kibadi K, Panda M, Tamfum JJ, Fraga AG, Longatto Filho A, Anyo G, Pedrosa J, Nakazawa Y, Suykerbuyk P, Meyers WM, Portaels F (2008) New foci of Buruli ulcer, Angola and Democratic Republic of Congo. Emerg Infect Dis 14:1790–1792

Kondo M, Kurokawa I, Ito Y, Yamanaka K, Yamazaki T, Mizutani H (2009) Leg ulcer caused by *Mycobacterium ulcerans* ssp. shinshuense infection. Int J Dermatol 48:1330–1333

Lavender CJ, Senanayake SN, Fyfe JA, Buntine JA, Globan M, Stinear TP, Hayman JA, Johnson PD (2007) First case of *Mycobacterium ulcerans* disease (Bairnsdale or Buruli ulcer) acquired in New South Wales. Med J Aust 186:62–63

Leigheb G, Cammarota T, Zavattaro E, Sarno A, Carriero A, Gambaro AC, Dossou A, Poggio F, Clemente C, Johnson RC, Sopoh G, Leigheb F (2008) Ultrasonography for the monitoring of subcutaneous damage in *Mycobacterium ulcerans* infection (Buruli ulcer). Ultrasound Med Biol 34:1554–1563

Lunn HF, Connor DH, Wilks NE, Barnley GR, Kamunvi FA, Clancey JK, Bee JD (1965) Buruli (mycobacterial) ulceration in Uganda (a new focus of Buruli ulcer in Madi district, Uganda): report of a field study. East Afr Med J 42:275–288

MacCallum P, Tolhurst JC, Buckle G, Sissons H (1948) A new mycobacterial infection in man. J Pathol Bacteriol 60:93–122

Marsollier L, Robert R, Aubry J, Saint André JP, Kouakou H, Legras P, Manceau AL, Mahaza C, Carbonnelle B (2002) Aquatic insects as a vector for *Mycobacterium ulcerans*. Appl Environ Microbiol 68(9):4623–4628

Marsollier L, Sévérin T, Aubry J, Merritt RW, Saint André JP, Legras P, Manceau AL, Chauty A, Carbonnelle B, Cole ST (2004) Aquatic snails, passive hosts of *Mycobacterium ulcerans*. Appl Environ Microbiol 70:6296–6298

Marsollier L, Aubry J, Milon G, Brodin P (2007) Aquatic insects and transmission of *Mycobacterium ulcerans*. Med Sci (Paris) 23:572–575

Mensah-Quainoo E, Yeboah-Manu D, Asebi C, Patafuor F, Ofori-Adjei D, Junghanss T, Pluschke G (2008) Diagnosis of *Mycobacterium ulcerans* infection (Buruli ulcer) at a treatment centre in Ghana: a retrospective analysis of laboratory results of clinically diagnosed cases. Trop Med Int Health 13:191–198

Merritt RW, Benbow ME, Small PLC (2005) Unraveling an emerging disease associated with disturbed aquatic environments: the case of Buruli ulcer. Front Ecol Environ 3:323–331

Meyers WM, Shelly WM, Connor DH, Meyers EK (1974) Human *Mycobacterium ulcerans* infections developing at sites of trauma to skin. Am J Trop Med Hyg 23:919–923

Meyers WM, Tignokpa N, Priuli GB, Portaels F (1996) *Mycobacterium ulcerans* infection (Buruli ulcer): first reported patients in Togo. Br J Dermatol 134:1116–1121

Minime-Lingoupou F, Beyam N, Zandanga G, Manirakiza A, N'Domackrah A, Njuimo S, Eyangoh S, Cottin J, Marsollier L, Marion E, Portaels F, Le Faou A, Bercion R (2010) Buruli ulcer, Central African Republic. Emerg Infect Dis 16:746–748

N'Zi KP, N'Dri K, Aka BR, Diabate AS, Ouattara DN, Djedje AT (1998) Radiographic aspects of osteoarticular complications in Buruli ulcers. Bull Soc Pathol Exot 91:229–231, French

Nackers F, Johnson RC, Glynn JR, Zinsou C, Tonglet R, Portaels F (2007) Environmental and health-related risk factors for *Mycobacterium ulcerans* disease (Buruli ulcer) in Benin. Am J Trop Med Hyg 77:834–836

Oliveira MS, Fraga AG, Torrado E, Castro AG, Pereira JP, Filho AL, Milanezi F, Schmitt FC, Meyers WM, Portaels F, Silva MT, Pedrosa J (2005) Infection with *Mycobacterium ulcerans* induces persistent inflammatory responses in mice. Infect Immun 73:6299–6310

Oluwasanmi JO, Solanke TF, Olurin EO, Itayemi SO, Alabi GO, Lucas AO (1976) *Mycobacterium ulcerans* (Buruli) skin ulceration in Nigeria. Am J Trop Med Hyg 25:122–128

Ouoba K, Sano D, Traoré A, Ouédraogo R, Sakandé B, Sanou A (1998) Buruli ulcers in Burkina Faso: apropos of 6 cases. Tunis Med 76:46–50

Peduzzi E, Groeper C, Schütte D, Zajac P, Rondini S, Mensah-Quainoo E, Spagnoli GC, Pluschke G, Daubenberger CA (2007) Local activation of the innate immune system in Buruli ulcer lesions. J Invest Dermatol 127:638–645

Phillips R, Horsfield C, Kuijper S, Lartey A, Tetteh I, Etuaful S, Nyamekye B, Awuah P, Nyarko KM, Osei-Sarpong F, Lucas S, Kolk AH, Wansbrough-Jones M (2005) Sensitivity of PCR targeting the IS2404 insertion sequence of *Mycobacterium ulcerans* in an Assay using punch biopsy specimens for diagnosis of Buruli ulcer. J Clin Microbiol 43:3650–3656

Phillips RO, Sarfo FS, Osei-Sarpong F, Boateng A, Tetteh I, Lartey A, Adentwe E, Opare W, Asiedu KB, Wansbrough-Jones M (2009) Sensitivity of PCR targeting *Mycobacterium ulcerans* by use of fine-needle aspirates for diagnosis of Buruli ulcer. J Clin Microbiol 47:924–926

Portaels F (1989) Epidemiology of ulcers due to *Mycobacterium ulcerans*. Ann Soc Belg Med Trop 69:91–103, Review. French

Portaels F (2004) Mycobacteria and tropical regions: from the environment to man. Med Trop 64:219–220, French

Portaels F, Aguiar J, Fissette K, Fonteyne PA, De Beenhouwer H, de Rijk P, Guédénon A, Lemans R, Steunou C, Zinsou C, Dumonceau JM, Meyers WM (1997) Direct detection and identification of *Mycobacterium ulcerans* in clinical specimens by PCR and oligonucleotide-specific capture plate hybridization. J Clin Microbiol 35:1097–1100

Portaels F, Elsen P, Guimaraes-Peres A, Fonteyne PA, Meyers WM (1999) Insects in the transmission of *Mycobacterium ulcerans* infection. Lancet 353:986

Portaels F, Chemlal K, Elsen P, Johnson PD, Hayman JA, Hibble J, Kirkwood R, Meyers WM (2001) *Mycobacterium ulcerans* in wild animals. Rev Sci Tech 20:252–264, Review

Portaels F, Zinsou C, Aguiar J, Debacker M, de Biurrun E, Guédénon A, Josse R, Lagarrigue V, Silva MT, Steunou C, Meyers WM (2003) Les atteintes osseuses de l'ulcère de Buruli: à propos de 73 cas. Bull Seances Acad R Sci Outre Mer 49:161–190

Portaels F, Johnson C, Aguiar J, Meyers WM, Debacker M (2008a) Etude de 106 cas d'ulcères de Buruli avec atteintes osseuses traités à Zagnanado, Bénin. Bull de l'ALLF 23:48–50

Portaels F, Meyers WM, Ablordey A, Castro AG, Chemlal K, de Rijk P, Elsen P, Fissette K, Fraga AG, Lee R, Mahrous E, Small PL, Stragier P, Torrado E, Van Aerde A, Silva MT, Pedrosa J (2008b) First cultivation and characterization *of Mycobacterium ulcerans* from the environment. PLoS Negl Trop Dis 2:e178

Pouillot R, Matias G, Mbondji Wondje C, Portaels F, Valin N, Ngoss F, Njikap A, Marsollier L, Fontanet A, Eyangoh S (2007) Risk factors for Buruli ulcer disease in Cameroon. PLoS Negl Trop Dis 1:e101

Ravisse P (1977) Skin ulcer caused by *Mycobacterium ulcerans* in Cameroon: clinical, epidemiological and histological study. Bull Soc Pathol Exot Fil 70:109–124, French

Rondini S, Mensah-Quainoo E, Troll H, Bodmer T, Pluschke G (2003) Development and application of real-time PCR assay for quantification of *Mycobacterium ulcerans* DNA. J Clin Microbiol 41:4231–4237

Ross BC, Marino L, Oppedisano F, Edwards R, Robins-Browne RM, Johnson PD (1997) Development of a PCR assay for rapid diagnosis of *Mycobacterium ulcerans* infection. J Clin Microbiol 35:1696–1700

Silva MT, Portaels F, Pedrosa J (2007) Aquatic insects and *Mycobacterium ulcerans*: an association relevant to Buruli ulcer control? PLoS Med 4:e63

Silva MT, Portaels F, Pedrosa J (2009) Pathogenetic mechanisms of the intracellular parasite *Mycobacterium ulcerans* leading to Buruli ulcer. Lancet Infect Dis 9:699–710

Simmonds RE, Lali FV, Smallie T, Small PL, Foxwell BM (2009) Mycolactone inhibits monocyte cytokine production by a posttranscriptional mechanism. J Immunol 182:2194–2202

Sizaire V, Nackers F, Comte E, Portaels F (2006) *Mycobacterium ulcerans* infection: control, diagnosis, and treatment. Lancet Infect Dis 6:288–296

Smith JH (1970) Epidemiologic observations on cases of Buruli ulcer seen in a hospital in the Lower Congo. Am J Trop Med Hyg 19:657–663

Stienstra Y, van der Werf TS, Guarner J, Raghunathan PL, Spotts Whitney EA, van der Graaf WT, Asamoa K, Tappero JW, Ashford DA, King CH (2003) Analysis of an IS2404-based nested PCR for diagnosis of Buruli ulcer disease in regions of Ghana where the disease is endemic. J Clin Microbiol 41:794–797

Stinear T, Ross BC, Davies JK, Marino L, Robins-Browne RM, Oppedisano F, Sievers A, Johnson PD (1999) Identification and characterization of IS2404 and IS2606: two distinct repeated sequences for detection of *Mycobacterium ulcerans* by PCR. J Clin Microbiol 37:1018–1023

Toll A, Gallardo F, Ferran M, Gilaberte M, Iglesias M, Gimeno JL, Rondini S, Pujol RM (2005) Aggressive multifocal Buruli ulcer with associated osteomyelitis in an HIV-positive patient. Clin Exp Dermatol 30:649–651

Torrado E, Adusumilli S, Fraga AG, Small PL, Castro AG, Pedrosa J (2007a) Mycolactone-mediated inhibition of tumor necrosis factor production by macrophages infected with *Mycobacterium ulcerans* has implications for the control of infection. Infect Immun 75:3979–3988

Torrado E, Fraga AG, Castro AG, Stragier P, Meyers WM, Portaels F, Silva MT, Pedrosa J (2007b) Evidence for an intramacrophage growth phase of *Mycobacterium ulcerans*. Infect Immun 75:977–987

Torrado E, Fraga AG, Logarinho E, Martins TG, Carmona JA, Gama JB, Carvalho MA, Proença F, Castro AG, Pedrosa J (2010) IFN-gamma-dependent activation of macrophages during experimental infections by Mycobacterium ulcerans is impaired by the toxin mycolactone. J Immunol 15;184(2):947–955. doi: 10.4049/jimmunol.0902717

van der Werf TS, Stinear T, Stienstra Y, van der Graaf WT, Small PL (2003) Mycolactones and *Mycobacterium ulcerans* disease. Lancet 362:1062–1064

van Zyl A, Daniel J, Wayne J, McCowan C, Malik R, Jelfs P, Lavender CJ, Fyfe JA (2010) *Mycobacterium ulcerans* infections in two horses in south-eastern Australia. Aust Vet J 88:101–106, Review

Wallace JR, Gordon MC, Hartsell L, Mosi L, Benbow ME, Merritt RW, Small PL (2010) Interaction of *Mycobacterium ulcerans* with mosquito species: implications for transmission and trophic relationships. Appl Environ Microbiol 76:6215–6222

Walsh DS, Portaels F, Meyers WM (2008) Buruli ulcer (*Mycobacterium ulcerans* infection). Trans R Soc Trop Med Hyg 102:969–978

Walsh DS, Eyase F, Onyango D, Odindo A, Otieno W, Waitumbi JN, Bulimo WD, Schnabel DC, Meyers WM, Portaels F (2009) Short report: Clinical and molecular evidence for a case of Buruli ulcer (Mycobacterium ulcerans infection) in Kenya. Am J Trop Med Hyg 81:1110–1113

Walsh DS, Portaels F, Meyers WM (2010) Recent advances in leprosy and Buruli ulcer (*Mycobacterium ulcerans* infection). Curr Opin Infect Dis 23:445–455

Walsh DS, Portaels F, Meyers WM (2011) Buruli ulcer: advances in understanding *Mycobacterium ulcerans* infection. Dermatol Clin 29:1–8

Watanabe T, Ohkusu K, Nakanaga K, Ishii N, Nakashima K, Shindo M, Yoshida Y, Yamamoto O (2010) Buruli ulcer caused by "*Mycobacterium ulcerans* subsp. shinshuense". Eur J Dermatol 20:809–810

WHO (2014) In: Portaels F (ed) Laboratory diagnosis of Buruli ulcer: a manual for health care providers. World Health Organization, Geneva, WHO/HTM/NTD/IDM/2014.1

Wold Health Organization (2015) Management of Buruli ulcer-HIV coinfection: Technical update. WHO/HTM/NTD/IDM/2015.01.Geneva http://apps.who.int/iris/bitstream/10665/154241/1/WHO_HTM_NTD_IDM_2015.01_eng.pdf: 21p

World Health Organisation (2004) Provisional guidance on the role of specific antibiotics in the management of *Mycobacterium ulcerans* disease (Buruli ulcer). WHO/CDS/CPE/GBUI.10, Geneva, http://whqlibdoc.who.int/hq/2004/WHO_CDS_CPE_GBUI_2004.10.pdf : 42p

World Health Organization (1997) WHO joins battle against a new emerging disease, Buruli ulcer. (Press release WHO/88), Geneva

World Health Organization (2000) Buruli ulcer: *Mycobacterium ulcerans* infection. In: Asiedu K, Scherpbier RW, Raviglione M (eds) WHO/CDS/GBUI/2000.1, Geneva. 160p

World Health Organization (2001a) Diagnosis of *Mycobacterium ulcerans* disease (Buruli ulcer). WHO/CDS/CPE/GBUI/2001.4, Geneva, http://whqlibdoc.who.int/hq/2001/WHO_CDS_CPE_GBUI_2001.4.pdf: 100p

World Health Organization (2001b) Management of *Mycobacterium ulcerans* disease (Buruli ulcer). WHO/CDS/CPE/GBUI/2001.3, Geneva, http://whqlibdoc.who.int/hq/2001/WHO_CDS_CPE_GBUI_2001.3.pdf: 80p

World Health Organization (2003) Buruli ulcer disease. *Mycobacterium ulcerans* infection. Wkly Epidemiol Rec 78:163–168

World Health Organization (2006) Buruli ulcer: prevention of disability (POD). WHO/CDS/NTD/GBUI/2006, Geneva, http://whqlibdoc.who.int/publications/2006/9241546816_eng.pdf: 115p

World Health Organization (2008a) Buruli ulcer: progress report, 2004–2008. Wkly Epidemiol Rec 83:145–156

World Health Organization (2008b) Prevention of disability in Buruli ulcer: basic rehabilitation-practical guide. WHO/HTM/NTD/IDM/GBUI/2008.1, Geneva, http://whqlibdoc.who.int/hq/2008/WHO_HTM_NTD_IDM_GBUI_2008.1_eng.pdf :104p

World Health organization (2009) Cotonou declaration on Buruli ulcer. WHO, Geneva, http://www.who.int/neglected_diseases/Benin_declaration_2009_eng_ok.pdf (accessed the 18/11/2010)

World Health Organization (2010a) Guidance on sampling techniques for laboratory-confirmation of *Mycobacterium ulcerans* infection (Buruli ulcer disease). http://www.who.int/buruli/Guidance_sampling_techniques_MU_infection.pdf. 5p

World Health Organization (2010b) Working to overcome the global impact of neglected tropical diseases: first WHO report on neglected tropical diseases. WHO/HTM/NTD/2010.1, Geneva, http://whqlibdoc.who.int/publications/2010/9789241564090_eng.pdf. 184p

World Health Organization (2012) Treatment of Mycobacterium ulcerans disease (Buruli ulcer): guidance for health workers. WHO/HTM/NTD/IDM/2012.1, Geneva, http://apps.who.int/iris/bitstream/10665/77771/1/9789241503402_eng.pdf. [Accessed the 6/10/13]: 73p

World Health Organization (2013) WHO meeting on Buruli ulcer control and research 25–27 Mar 2013: recommendations for control of Buruli ulcer. WHO headquarters, Geneva. http://www.who.int/buruli/Recommendations_Buruli_ulcer_2013.pdf. 4p

Dracunculiasis (Guinea Worm Disease)

Dieudonne P. Sankara, Andrew S. Korkor, Junerlyn Agua-Agum, and Gautam Biswas

Contents

Abstract Dracunculiasis, also known as guinea worm disease, is caused by the nematode *Dracunculus medinensis* that infects humans typically through unsafe drinking water. The disease occurs in the most remote and poor areas of the world. There is neither a vaccine to prevent nor medication to treat the disease. Nevertheless, the disease has been set for eradication since the 1980s and is eliminated from many of the endemic countries through preventive measures that include behavioural change in patients and communities, self-reporting of suspected cases to health workers or volunteers, filtering drinking water, drinking water from improved sources and preventing infected individuals from entering or swimming in drinking water sources. These are complemented by vector control and provision of improved

D.P. Sankara (✉) • J. Agua-Agum • G. Biswas
Department of Control of Neglected Tropical Diseases, World Health Organization, Avenue Appia 20, Geneva 1211, Switzerland
e-mail: sankarad@who.int

A.S. Korkor
Inter-country Support Team – West Africa, WHO Regional Office for Africa, Avenue de l'Indépendance No. 158, Ouagadougou 03 BP 7019, Burkina Faso

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_3

water sources. In 2015 the World Health Organization (WHO) declared that the disease had reached its lowest levels ever recorded to date. This chapter reviews, among other things, the epidemiology of the disease and the progress made in eradicating dracunculiasis since the eradication campaign began, the biology, the eradication strategies, current challenges to the eradication, further research for control and the outlook for the next 10 years.

Keywords Dracunculiasis • Guinea worm • Eradication

Introduction

Dracunculiasis, a parasitic disease caused by the nematode *Dracunculus medinensis*, is also known as guinea worm disease. *D. medinensis* is in the Spirurida order, an order of parasites that includes the filariae Wuchereria bancrofti, Brugia malayi and Loa loa. *Dracunculus medinensis* is a 60–120-cm-long nematode worm, known to humankind since antiquity. It is on the verge of being eradicated from the world, with only 126 cases being reported in 2014 (WHO 2015a). The first known mention of the disease was in the Turin Papyrus in the fifteenth century B.C. by the Egyptians; the disease has since been described by ancient Greek, Roman, Arab, Persian and Indian physicians (Groove 1900). Guinea worm disease derived its common name from its prevalence on the Gulf of Guinea (Palmer and Reeder 2001). The disease has rarely been fatal, and fatality was not typically caused by the primary infection but usually in cases of secondary infection of the exit site of the parasite that leads to sepsis or tetanus (Greenaway 2004). However, morbidity is a major concern. The disease is known to cause temporary incapacitation and sometimes is associated with permanent disability (Hopkins et al. 2000; WHO 1988), resulting in loss of income and reduced school attendance among the already deprived communities and households associated with the disease. The socio-economic consequences could be devastating. The Dogon people of Mali refer to dracunculiasis as "the disease of the empty granary" (Yoro, the empty granary. Film (35 mm) and videotape 1998) (Figs. 1 and 2).

Biology and Life Cycle

Dracunculiasis is transmitted to humans typically by drinking water from stagnant ponds and wells contaminated with infected fresh water small crustacean, copepods (*Cyclops)* (Fig. 4), the intermediate host (WHO 2012) which contains the larval stage of the parasite (*D. medinensis*). Man is the principal definitive host, but natural infections have been reported in a variety of animals including monkeys, herbivores, domestic and wild Canidae and Felidae (Macpherson et al. 2012).

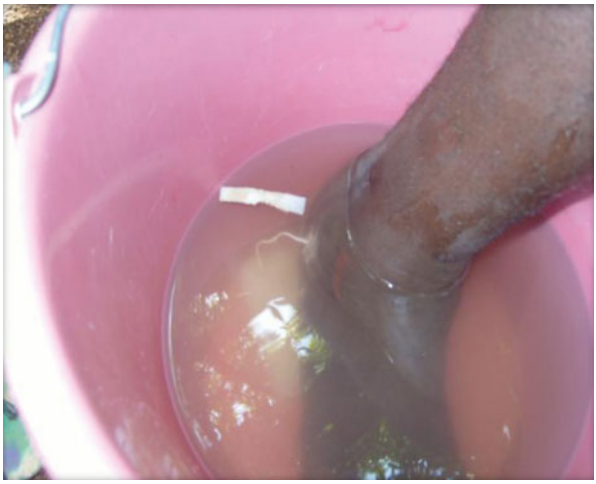


Fig. 1 A foot with an emerging worm immersed in a bucket of water (Controlled immersion) (Source: WHO)

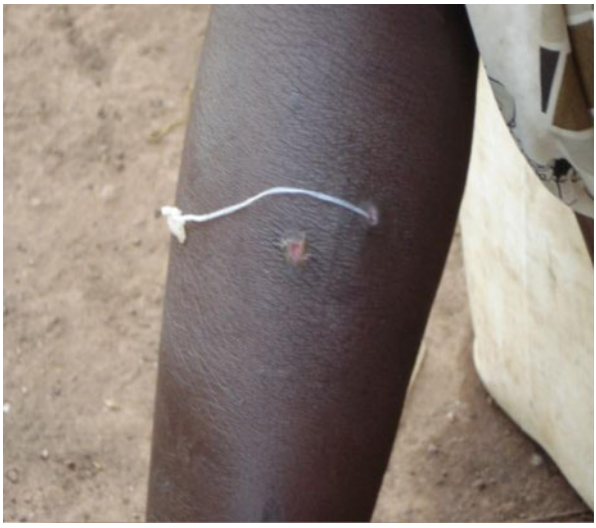


Fig. 2 An emerging worm wrapped around a stick (Source: WHO)

Following ingestion of water containing infected *Cyclops*, by humans, the cyclops are killed in the stomach upon which the infective larvae are liberated. The mature larvae penetrate the intestinal wall and migrate to the connective tissue of the host. The larvae develop inside the body. The male worm dies soon after impregnating the female which becomes fully mature female worms after 9–14 months at which time it can measure over a metre long. The adult fertilised female worm (Figs. 1 and 2) which harbours the larvae responsible for the disease is attracted to cool surfaces of the skin, emerging from the skin about a year after infection. The larvae are released from the uterus of the worm on contact with stagnant water by the adult worm. The first stage motile larvae are ingested by the cyclops in which they undergo development to the third larval infective stage in some 2 weeks, thus perpetuating the transmission cycle Fig. 5 (Muller 1985).

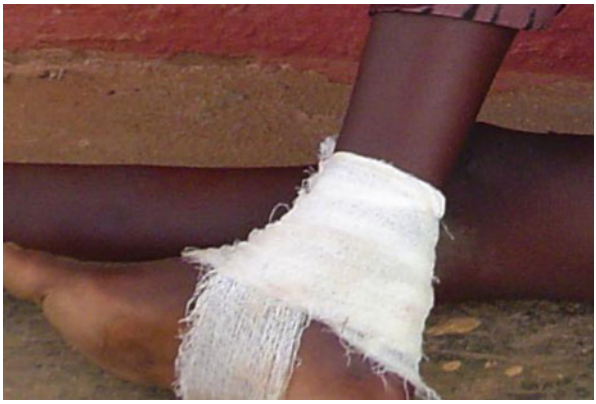


Fig. 3 Fully bandaged guinea worm disease lesion of the foot (Source: Ghana GWEP)

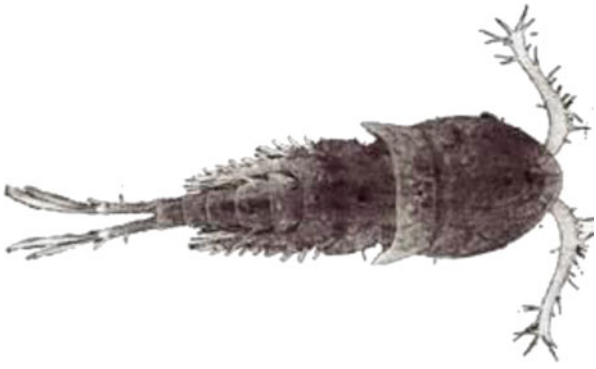


Fig. 4 Cyclops, the intermediate host for guinea worm

Clinical Presentation

Guinea worm presents as redness and tenderness of the skin from where the adult worm would emerge usually in the lower part of the leg.

However, the disease can present with worms emerging from any part of the body, including the breast, chest, back, abdomen, testes, periorbital tissue, lungs, pancreas or spinal cord.

There could also be general allergic symptoms which subside with the discharge of the larvae (Figs. 6 and 7).

The emergence of the worm – sometimes more than one – is accompanied by painful oedema, intense generalised pruritus, blistering and ulceration of the area from which the worm emerges. This painful process may incapacitate the affected person for a period lasting about 8 weeks or more. If the worm is broken before it is completely extruded from the skin, this could cause intense inflammatory reaction with pain, swelling, severe cellulitis and other pyogenic infections. Chronic complication such as encapsulation of the adult worm may occur when calcified remains of the worm persist in the extremity of the patient. This can result in recurrent pain

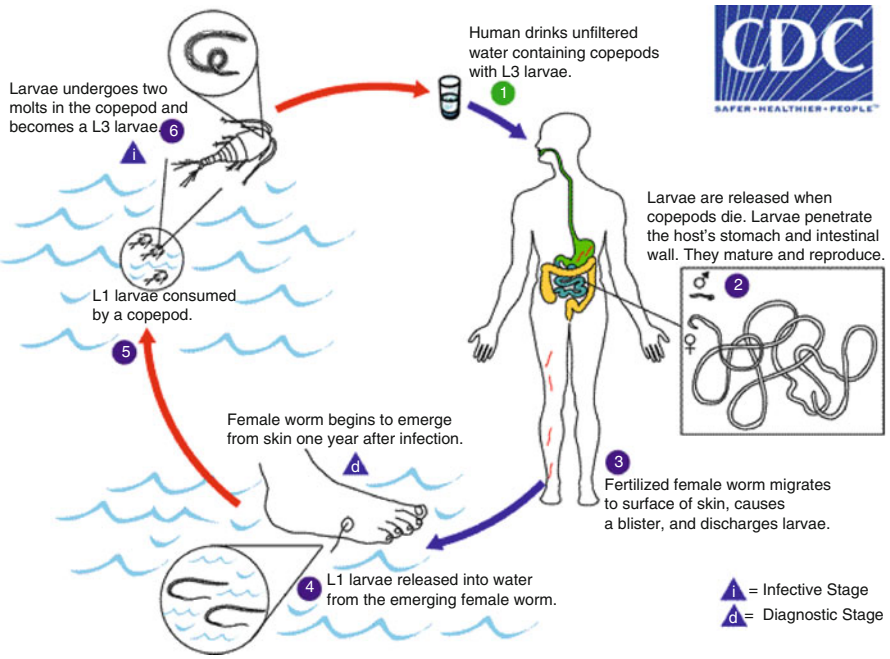


Fig. 5 Life cycle of guinea worm

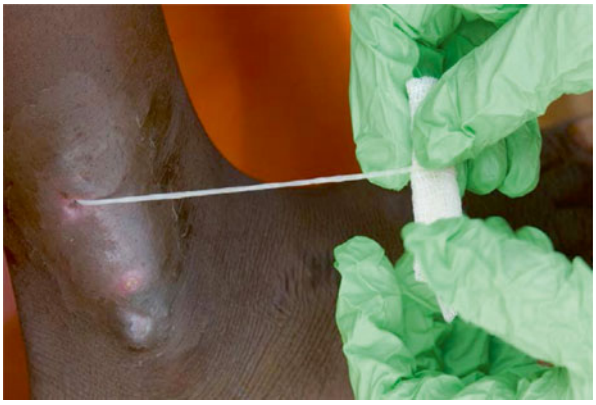


Fig. 6 Adult guinea worm from the leg (Source: Ghana GWEP)

and intermittent swelling of the extremity. In some cases, there is permanent scarring or deformity of the lower extremity, even after the worm has been extracted. Chronic pain may also persist for about 2 years or more. Infected individuals may have multiple worms exit at the same time. The success of the global campaign to eradicate the disease did not only reduce the number of cases recorded by year but also reduced the load of infection each individual may bear. In 2014, an average of

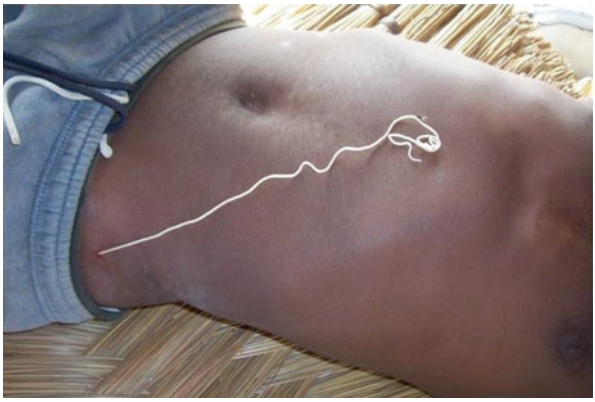


Fig. 7 Adult guinea worm from the body (Source: Ghana GWEP)

1.3 worms per case were recorded (maximum of 4 worms in one case) as compared with an average of 1.4 worms per case (maximum of 9 worms in one case) in 2013 and 1.7 worms per case (maximum of 21 worms in one case) in 2012 (WHO 2015a). There is no medicine to treat guinea worm, neither is there a vaccine to prevent the disease (Cairncross et al. 2002; Muller 1985; Issaka-Tinogah et al. 1994; Greenaway 2004). On the other hand, the transmission cycle can be interrupted (Belcher 1985) by preventing the contamination of sources of drinking water, filtering unsafe water with fine mesh strainers before consuming or drinking water from improved sources and by undertaking appropriate vector control interventions (Biswas et al. 2013).

The Disease Burden and Epidemiology

Distribution of the disease is determined largely by the availability of open stagnant water sources such as ponds and shallow or step wells and patients of dracunculiasis. Artificial ponds constitute often a main source of transmission. Transmission of the disease is seasonal and depends on climatic factors. In endemic areas of Africa, there are two broad patterns: in the Sahelian zone, transmission generally occurs during the rainy season (May to September); in the humid savannah and forest zones, transmission usually peaks during the dry season (September to January). However, there are local variations to these patterns (WHO 2015b).

Guinea worm affects rural populations whose livelihood depends on subsistence farming. Since the disease causes temporary disability, lasting from a few weeks to a few months, which may prevent patients from leaving their beds while the worm emerges, the cost in lost school attendance and revenue from decreased agricultural productivity for individuals and the community can be very high (Hopkins et al. 2000). The economic loss of dracunculiasis in India alone was estimated to be 11.7 million man-days annually among 4 % of the 12.2 million people living in endemic villages (Rao 1985). In 1985, researchers found that dracunculiasis had an impact

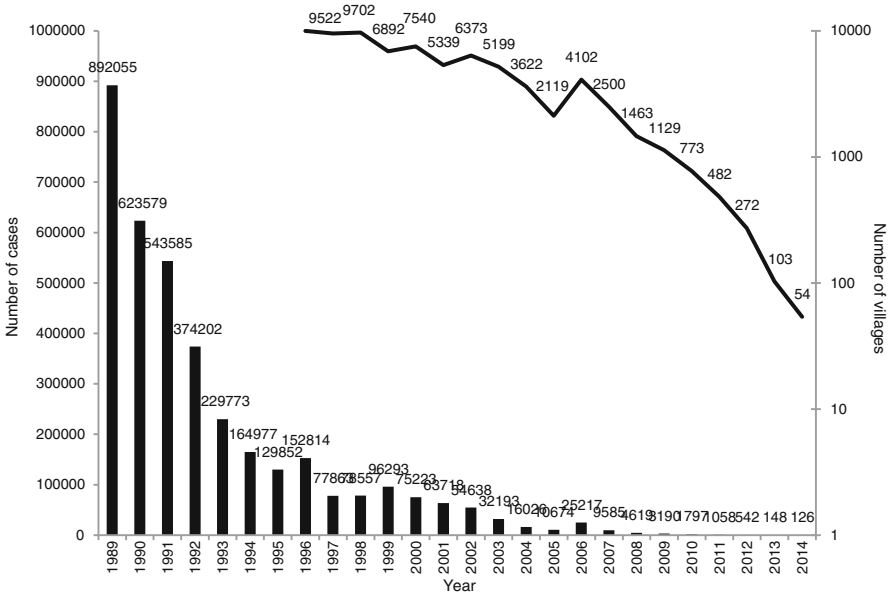


Fig. 8 Annual number of reported dracunculiasis cases and localities of case detection, worldwide, 1989–2014

on school attendance in Benin and Nigeria and on agriculture in Benin and Burkina Faso (WHO 1986, 1987). In 1987 a study in Nigeria estimated an annual loss of US$ 20 million per single crop (rice, yam and cassava) from farmers incapacitated by the disease for an average duration of 5 weeks (WHO 1988, 1990, 1998; Hopkins et al. 2000). The disease was therefore an important socio-economic toll on the affected communities and countries. The cost–benefit outcome of public health interventions was one of the factors that influenced the decision for eradication (Hopkins et al. 2000; Biswas et al. 2013).

In the late 1940s, more than 48 million people were estimated to be affected by the disease in Africa, India and the Middle East (Stoll 1947). By 1976, the WHO estimated that ten million dracunculiasis cases were reported globally, with less than 0.003 % cases being reported worldwide (WHO 1982). By the 1980s, the disease was known to be endemic in 20 countries including 17 countries in Africa, 2 countries in Asia and 1 country in the Middle East. During the mid-1980s, an estimated 3.5 million cases were reported yearly. As a result of efforts by national Guinea Worm Eradication Programmes since the 1980s, 17 countries have eliminated the disease, and transmission now remains endemic in only 4: Chad, Ethiopia, Mali and South Sudan (the separation of South Sudan from Sudan in 2011 accounts for the increase from 20 to 21 endemic countries). Since its inception, the Global Eradication Campaign has continued to progress steadily towards wiping dracunculiasis off the planet. In addition to the reduction of transmission zones to limited geographical foci, significant decreases in the incidence of dracunculiasis were noted; a total of

126 cases of dracunculiasis were reported in 2014 down from 892,055 cases reported in 1989 (more than 99 % reduction). The situation in 2014 also compared favourably with the situation in 2013 and 2012 when 148 cases (15 % reduction) and 542 cases (77 % reduction) were reported, respectively (Fig. 8).

On the recommendation of the International Commission for the Certification of Dracunculiasis Eradication (ICCDE) (1995–2015), the WHO has certified 198 countries, territories and areas, including 186 WHO Member States (Map 2) as free of guinea worm transmission. Eight countries remain to be certified: the four countries endemic for the disease (Chad, Ethiopia, Mali and South Sudan), the two remaining countries in the precertification stage (Kenya and Sudan) and Angola and the Democratic Republic of the Congo, which have had no recent history of the disease (WHO 2015a).

Control Tools and Eradication Strategies

The development of the dracunculiasis eradication strategies was based on evidence gathered from various studies on the disease, the effective interventions and lessons learnt from the effective smallpox eradication programme as well as from the non-conclusive malaria eradication programme (United States Centers for Disease Control and Prevention 1999; Grand Rounds: The Opportunity for and Challenges to Malaria Eradication 2011; Cairncross et al. 2002; Richards and Ruiz-Tiben 2011). The strategies adopted for eradication have largely withstood the scrutiny based on the evidence that 17 countries that were previously endemic in the 1980s interrupted the transmission of the disease and 15 of these countries are now certified as free of transmission by WHO (WHO 2015a; Biswas et al. 2013). The cost-effectiveness of the eradication strategies has been documented in various studies (Hopkins et al. 2000; Rao 1985; WHO 1986, 1987, 1988a, b, 1989a, 1990).

The strategies address the following areas:

(a) Surveillance for prompt detection of cases and reporting. Surveillance involved the community itself (supported by a supervisory structure) in detecting, containing and reporting dracunculiasis cases (Muller 2005). The objective of surveillance and reporting is to promptly detect all cases until the absence of transmission is confirmed worldwide. As the eradication process advances, a country endemic for the disease will go through the following stages: (i) endemicity, (ii) interruption of transmission and (iii) precertification. The precertification stage lasts at least 3 years, during which a country must sustain nationwide surveillance to demonstrate evidence of continued absence of transmission in order to be qualified for certification as dracunculiasis-free. (iv) Once WHO certifies a country free of dracunculiasis, it enters post-certification surveillance, which is continued until eradication of dracunculiasis is declared globally. To increase the sensitivity of the surveillance, the ICCDE recommends that national dracunculiasis eradication programmes announce a suitable cash reward for voluntary reporting of cases (WHO 1996). The current amount of the

reward in endemic countries and those in the pre- and post-certification stage ranges from US$ 40 to US$1160 (WHO 2015a). A global reward scheme similar to the one adopted by the Smallpox Eradication Campaign will be announced by WHO when the transmission of the disease is interrupted.

(b) Case management and containment by preventing infected persons from wading into drinking water sources. "A case of guinea worm disease is defined as a person exhibiting a skin lesion with emergence of a guinea worm" ideally, with laboratory confirmation." (WHO Collaborating Center for Research, Training and Eradication of Dracunculiasis, CDC 2014). A case is counted only once during the calendar year, that is, when the first worm emerges from that person. Other human lesions may mimic guinea worm disease (Eberhard et al. 2010, 2015), hence making laboratory confirmation necessary during the latter stage of the eradication effort. However, any suspect guinea worm disease case should be managed as a true case until proved otherwise through laboratory diagnosis or the worms fully expelled.

Every case detected should be treated and its further transmission prevented. The tried and tested treatment is as follows: when the worm begins slowly to extrude from the skin, the affected part is dipped in clean water or water is poured on the part to facilitate the emergence of the worm. The extruding worm is then gradually rolled out of the body using a gauze or a clean stick (matchstick) (Cairncross et al. 2002). The wound is properly bandaged to prevent secondary infection. The global eradication effort describes the management processes to be undertaken to prevent transmission of guinea worm disease from one patient to the other, and before a case of guinea worm disease is considered contained, the following have to be met:

- The case is detected before or within 24 h of the worm emergence.
- The patient:
  - Did not contaminate any water source since the worm emerged
  - Received proper care by cleaning and bandaging the wound until all the worms are fully expelled
  - Received health education on not entering any water source
- A supervisor verified the case as dracunculiasis within 7 days (WHO 2003).
- Temephos is used if there is any uncertainty about contamination of sources of drinking water or if a source of drinking water is known to have been contaminated.

Within the context of the eradication effort, the management of a case of guinea worm disease extends beyond the individual suffering from the disease. It involves the commitment, collaboration and collective effort of the community volunteer, the patient's family and the community in which he lives, to guarantee that all the criteria above are met, since some criteria, such as early case detection, case confinement, effective education and abate application, will, to a large extent, also depend on factors within the community (mostly socio-economic and cultural).

To further ensure that the case is appropriately contained, patients are being hospitalised and treated in existing health facilities or temporary camps, to prevent patient contact with unsafe drinking water sources. Health education is provided until all worms are expelled.

Painkillers, such as aspirin or ibuprofen, can help reduce pain and swelling. Antibiotic ointment can help prevent secondary bacterial infections, or antibiotic treatment may become necessary to treat secondary infection or cellulitis.

Optimal daily case management involves the following steps:

1. First, each day, the affected body part is immersed in a container of water to encourage more of the worm to come out.
2. Next, the wound is cleaned.
3. Then, gentle traction is applied to the worm to slowly pull it out. Pulling stops when resistance is met to avoid breaking the worm. Because the worm can be as long as 1 m in length, full extraction can take several days to weeks.
4. The worm is then wrapped around a rolled piece of gauze or a stick to maintain some tension on the worm and encourage more of the worm to emerge. This also prevents the worm from slipping back inside. Afterwards, topical antibiotics are applied to the wound to prevent secondary bacterial infections.
5. The affected body part is then bandaged with fresh gauze to protect the site. Medicines, such as aspirin or ibuprofen, are given to help ease the pain of this process and reduce inflammation (Fig 9).

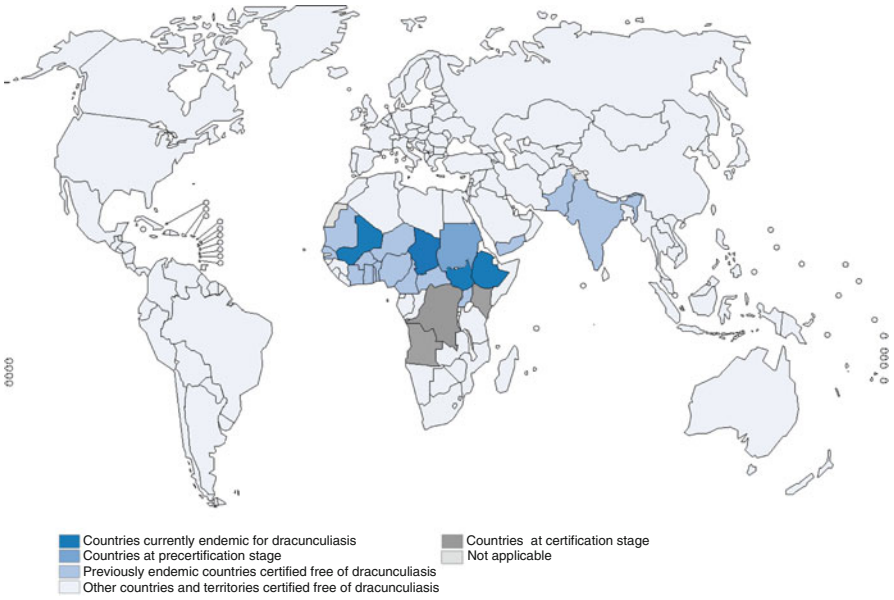


Fig. 9 Status of certification

6. These steps are repeated every day until the whole worm is successfully pulled out.

In order to prevent contamination, the infected person is not allowed to enter drinking water sources throughout the treatment. This can be achieved by properly educating the patient and at the same time sensitising his/her household to support him/her to comply.

(c) Access to improved drinking water supply

With a strong and culturally sensitive community health education, geographical access to improved drinking water sources can make a difference in guinea worm disease-affected communities. Ways and means to provide affected communities with improved drinking water supplies include the following: (i) constructing barriers to prevent humans from entering surface drinking water sources, (ii) protecting hand-dug wells with walls and sinking deep bore wells and (iii) filtering surface drinking water through filters (Brieger et al. 1997; WHO 1989a). Access to improved drinking water sources in communities endemic for the disease provides a sustainable solution for dracunculiasis eradication, as experienced in the Islamic Republic of Iran, Saudi Arabia and Uzbekistan (Biswas et al. 2013). Efforts to provide safe drinking water are ongoing in the remaining endemic areas. Communities affected by the disease are prioritised for providing access to improved water sources.

(d) Vector control by treating the contaminated stagnant drinking water sources with a larvicide, temephos.

Temephos application to unsafe stagnant drinking water sources is effective in killing the cyclops, the intermediate host. Temephos application must be initiated within 14 days of case detection and then be carried out regularly at monthly intervals until no case is reported and/or at least 1 month after the risk of transmission in the locality ends. It is labour-intensive (Cairncross et al. 2002) and not always easy to carry out in some difficult to reach places. However, when implemented systematically – covering all eligible unsafe water sources in a given endemic area – temephos application is effective in the reduction of guinea worm disease cases (Chippaux et al. 1991; Lyons 1973).

(e) Community-based health education and mobilisation for increased community adherence to control interventions including filtering all unsafe drinking water through cloth filters to prevent infection. The overarching goal of the health education and social mobilisation is to encourage affected communities to adopt healthy behaviour to prevent and ultimately interrupt the disease transmission. Community volunteers and their supervisors (health staff) deliver simple and easy to understand messages (Cairncross et al. 2002) to community members with the aim that communities adopt the above-mentioned strategies and protect themselves from the disease and to avoid its propagation.

Challenges Towards Eradication of Guinea Worm Disease

The current challenges to eradication of dracunculiasis are to interrupt transmission in the few last foci of the four remaining countries and ensure surveillance in all other countries and areas at risk of disease reintroduction. The eradication campaign is paying greater attention to the following challenges to programme implementation, which can be grouped in three tiers:

- Insecurity that prevents full programme roll out in some part of South Sudan, northern regions of Mali and recently in Chad with ensuing movements of population within and outside of national borders
- Need for continued nationwide surveillance and awareness of the reward scheme to report and investigate every suspected case
- An unusual epidemiology where a large number of infected dogs are observed in Chad with cases in humans appearing to be sporadic and to a lesser extent a lingering recurrence of low level of human cases in Ethiopia with few confirmed cases in animals.

Chad

The sporadic and dispersed pattern of human cases from apparent epidemiologically unconnected villages since 2010 and the documentation of a large number of infected dogs with an apparent temporal relationship to the intense artisanal fishing industry in the same at-risk area in 2012–2015 along the Chari River basin suggest an unusual and potentially novel transmission pattern in humans. The worms emerging from dogs are indistinguishable by polymerase chain reaction (PCR) analysis from those emerging from humans (Eberhard 2014) occasional and accidental dracunculiasis infection in dogs has also been noted in other countries; however, the situation in Chad is exceptional because infections in dogs outnumbered those in humans by about nine times in 2014 only.

Measures to reduce transmission of guinea worm infections to and from dogs and humans are being implemented. However, this outbreak of dog infections in Chad and the need to understand this rare epidemiology are the current challenges facing the dracunculiasis eradication efforts.

Ethiopia

For the last 5 years, there has been a persistent low-level transmission resulting in a yearly reporting of a few number of human cases. In addition, sporadic infections in animals were noted in 2013 (three dogs and one baboon), in 2014 (three dogs and one baboon) and in 2015 (January–June) (one dog, one baboon) from the same areas from which human cases are being reported.

The recent increase in insecurity in South Sudan has caused people to move across the border into camps in Ethiopia. By the end of June 2015, more than 200,000 individuals from South Sudan were living in refugee camps in Ethiopia.

Mali

The country remains the only country in West Africa where indigenous transmission of dracunculiasis is still occurring. Since March 2012, security concern in the north of the country is an impediment to programme implementation. There has been an improvement in security in 2013 and part of 2014, making it possible for surveillance to be strengthened in the Gao, Timbuktu and Mopti regions; in Kidal region, security has remained a major obstacle. Nonetheless, efforts are being made by the programme to carry out active surveillance covering all the localities that reported the case in 2012 and 2013; no dracunculiasis case was reported in Kidal region in 2014. There is a risk of spread of the disease in the neighbouring countries. Hence, in order to prevent such spread of the disease, intensification of surveillance activities is being maintained in the Malian refugee camps in Burkina Faso, Mauritania and Niger (WHO 2015a).

South Sudan

Due to the increased insecurity in the country since December 2013, the lack of access to certain areas makes surveillance and implementation of interventions difficult. Fortunately, most of the areas in Eastern Equatoria State where transmission occurs continue to be accessible, and an all-out effort is being carried out in the field to ensure interruption of transmission at the earliest. Despite the security concern, South Sudan has made tremendous progress in reducing the incidence of the disease. For the first time in history, South Sudan reported zero cases for seven consecutive months (November 2014–May 2015). With the sustained efforts by the government and its partners, the prospect of stopping transmission in South Sudan by 2016 is plausible.

Need for Further Research for Additional Control Measures

Guinea worm disease is on the verge of being eradicated with a few small pockets yet to be cleared. However, given the unusual transmission pattern in Chad – one of the few foci yet to be cleared of the infection – it is important to understand the factors that drive this phenomenon. The needed crucial research is under way to investigate this transmission dynamics in order to identify appropriate ways to accelerate

the interruption of transmission in Chad. The following areas of research are requiring attention.

Research to:

- Identify the implications of guinea worm infection in dogs on the transmission in humans
- Help to understand the dynamics of guinea infection in dogs given the discovery of infection in dogs in Chad
- Unravel the reasons for the continued low levels of transmission in Ethiopia and appropriate ways to overcome it
- Address the operational challenge of vector control in large water bodies

Conclusion and Outlook

A painful and debilitating disease, dracunculiasis, is on the verge of eradication despite issues of security and current epidemiological challenges, as a result of a highly focused international public health initiative that uses inexpensive, practical interventions in target areas (Hopkins et al. 2000). The global eradication effort is led by national governments and communities, with the support of a coalition of partners including The Carter Center, WHO, WHO Collaborating Center for Research, Training, and Eradication of Dracunculiasis at the US-CDC, UNICEF as well as many donors.

With only 126 cases reported in 2014, and the disease being limited to 54 foci in South Sudan, Chad, Mali and Ethiopia, the eradication of the disease is knocking at the door. From January to July 2015, only 10 cases in humans were reported in Chad (7), Ethiopia (2) and South Sudan (1) as compared with 52 cases reported for the same period in 2014 in Chad (9), Ethiopia (2) and South Sudan (41). It has taken countries varying periods of time to interrupt transmission and reach zero indigenous cases. The possible determinants of the progression to eradication have been the shear burden of the disease at the onset of the programmes and country-specific operational and contextual challenges (Rwakimari and Hopkins 2006; WHO 1988a, b).

The last stage of the programme is the most difficult; it requires more concentrated, concerted and focused efforts on surveillance, not only in endemic areas but also in areas free of transmission but at risk of importation from endemic areas (WHO 2015c).

Continued and increased national political support for eradication is needed to strengthen the intensification of interventions including facilitating access by health workers to areas with security concerns and epidemiological challenges. During this decade, this ancient scourge will likely be defeated. However, finishing the last mile of dracunculiasis eradication will require the full resolve of all the affected countries, supporting partners, donors and endemic communities to make an all-out effort with zero tolerance for any slippage in order to achieve this target. The main

challenges concern security, especially in certain areas of Mali and South Sudan where it has implications within and beyond their borders due to population movements, and the unusually high number of dogs with confirmed guinea worm infections in Chad, which poses epidemiological and biologic questions. However, these challenges could be overcome by making best use of all opportunities while maintaining quality surveillance in guinea worm-free areas to prevent any introduction or re-establishment of new foci of transmission resulting from imported cases due to population movements (WHO 2015a).

Once eradicated, dracunculiasis will be the first parasitic human disease to be extinct and the first disease eradication campaign to be carried out and successfully concluded without vaccine or medicine and solely by using public–private sector partnerships to fund and support community-level interventions and innovative incentives to empower exceptional community involvement (Barry 2006; Molyneux 2004). The programme will leave a legacy of public health goods in terms of access to improved drinking water, improved surveillance and no school absenteeism or lack of income due to incapacitation from the disease (Biswas et al. 2013).

Acknowledgements Dr. Dirk Engels for his guidance and encouragement in preparing this section, Mrs. Lakshmi Jonnalagedda for editing the text and to all the health officials and volunteers in the field for fighting against the disease interaction with whom over period of time has resulted in much of the material for this paper.

Disclaimer The authors are staff members of the World Health Organization. The authors alone are responsible for the views expressed in this publication, and they do not necessarily represent the decisions, policy or views of the World Health Organization. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

References

Barry M (2006) Slaying the little dragons: lessons from the dracunculiasis eradication program. Am J Trop Med Hyg 75:1–2

Belcher D (1985) Opportunities for control of dracunculiasis: transmission of epidemiology. In: LS, Ruskin FR (ed) Workshop on opportunities for control of dracunculiasis. National Academy Press, Washington, pp 1–7

Biswas G, Sankara D, Agua-Agum J, Maiga A (2013) Dracunculiasis (guinea worm disease): eradication without a drug or a vaccine. Philos Trans R Soc Lond B Biol Sci 368:20120146

Brieger W, Otusanya S, Adeniyi D, Tijani J, Banjoko M (1997) Eradicating guinea worm without wells: unrealized hopes of the water decade. Health Policy Plan 12(4):354–362

Cairncross S, Muller R, Zagaria N (2002) Dracunculiasis (guinea worm disease) and the eradication initiative. Clin Microbiol Rev 15(2):223–246

Centers for Disease Control and Prevention (1999) Global disease elimination and eradication as public health strategies. Morb Mortal Wkly Rep (MMWR Suppl) 48:16–22; 46–48
Chippaux J, Laniyan I, Akogbeto M (1991) Evaluation de l'efficacité du Témephos dans la lutte contre la dracunculose. Ann Soc Belg Med Trop 71:279–285
Eberhard ML (2014) The peculiar epidemiology of dracunculiasis in Chad. J Trop Med Hyg 90(1):61–70
Eberhard M, Ruiz-Tiben E, Korkor A, Roy S, Downs P (2010) Emergence of onchocerca volvulus from skin mimicking dracunculiasis medinensis. Am J Trop Med 83(6):1348–1351
Eberhard M, Thiele E, Yembo G, Yibi M, Cama V, Ruiz-Tiben E (2015) Thirty-seven human cases of sparganosis from ethiopia and South Sudan caused by Spirometra Spp. Am Soc Trop Med Hyg 15(0236):350–355
Grand rounds: the opportunity for and challenges to malaria eradication (2011) MMWR Morb Mortal Wkly Rep 60(15):476–480
Greenaway C (2004) Dracunculiasis (guinea worm disease). Can Med Assoc 170(4):495–500
Groove D (1900) A history of human helminthology. CAB International, Wallingford
Hopkins DR, Ruiz-Tiben E, Ruebush TK, Diallo N, Agle A, Withers CJ (2000) Dracunculiasis eradication: delayed, not denied. Am J Trop Med Hyg 62(2):163–168
Issaka-Tinogah A, Magnussen P, Bloch P, Yakubu A (1994) Lack of effect of ivermectin on prepatent guinea-worm: a single-blind, placebo-controlled trial. Trans R Soc Trop Med 88(3):346–348
Lyons G (1973) The control of guinea-worm with abate: a trial in a village of North-West Ghana. Bull WHO 49:215–216
Macpherson CN, Meslin FX, Wandeler A (2012) Dogs, zoonoses and public health. CAB International. London. 237–239
Molyneux DH (2004) "Neglected" diseases but unrecognised successes-challenges and opportunities for infectious disease control. Lancet 364(9431):380–383
Muller R (1985) Life cycle of dracunculus medinensis. In: Workshop on opportunities for control of dracunculiasis: contributed papers. National Academy Press, Washington:13–17
Muller R (2005) Guinea worm disease – the final chapter? Trends Parasitol 21(11):521
Palmer P, Reeder M (2001) Guinea worm infection (dracunculiasis). Retrieved 27 Sept 2012, from The Imaging of Tropical Diseases: http://tmcr.usuhs.mil/tmcr/chapter27/intro.htm
Rao C (1985) Epidemiology of dracunculiasis in India. In: Workshop on opportunities for control of dracunculiasis, contributed papers, Delhi. National Academy Press, Washington: 25–31
Richards FO, Ruiz-Tiben E (2011) Dracunculiasis eradication and the legacy of the smallpox campaign: what's new and innovative? What's old and principled? Vaccine 29:D86–D90
Rwakimari J, Hopkins R-T (2006) Uganda's successful guinea worm eradication. Am J Trop Med Hyg 75(1):3–8
Stoll N (1947) This wormy world. J Parasitol Feb. 33 (1):1–18
WHO Collaborating Center for Research, Training and Eradication of Dracunculiasis, CDC (2014) The carter center. Retrieved 21 July 2015, from http://www.cartercenter.org/resources/pdfs/news/health_publications/guinea_worm/wrap-up/228.pdf
World Health Organization (1982) Dracunculiasis surveillance. Wkly Epidemiol Rec 57(9):65–72
World Health Organization (1986) Global surveillance summary – 1985. Wkly Epidemiol Rec 61(5):29
World Health Organization (1987) Dracunculiasis, global surveillance summary -1986. Wkly Epidemiol Rec 62(45):337
World Health Organization (1998) Dracunculiasis, global surveillance summary -1997. Wkly Epidemiol Rec 73(18):129–135
World Health Organization (1988) Dracunculiasis: global surveillance summary-1987. Wkly Epidemiol Rec 49(2):375–378
World Health Organization (1989) Dracunculiasis: global surveillance summary- 1988. Wkly Epidemiol Rec 64(39):297–302

World Health Organization (1990a) Dracunculiasis: global surveillance summary, 1989. Wkly Epidemiol Rec 65(30):229–233
World Health Organization (1990b) Dracunculiasis, global surveillance summary, 1989. Wkly Epidemiol Rec 65(30):229–236
World Health Organization (1996) Criteria for the certification of dracunculiasis eradication. Retrieved 20 July 2015, from http://whqlibdoc.who.int/hq/1996/WHO_FIL_96.188.pdf?ua=1
World Health Organization (2003) Dracunculiasis eradication: case definition, surveillance and performance indicators. Wkly Epidemiol Rec 78(37):323–328
World Health Organization (2012) Dracunculiasis (guinea-worm disease). In: Working to overcome. World Health Organization, Geneva:103–106
World Health Organization (2015a) Dracunculiasis eradication: global surveillance summary, 2014. Wkly Epidemiol Rec 90(19):201–215
World Health Organization (2015b) Dracunculiasis. Retrieved 20 July 2015, from http://www.who.int/dracunculiasis/disease/disease_more/en/
World Health Organization (2015c) Dracunculiasis. Retrieved 20 July 2015, from http://www.who.int/dracunculiasis/en/
Yoro, the empty granary. Film (35 mm) and videotape (1998) [Motion picture]

Human African Trypanosomiasis (HAT)

Pascal Lutumba, Enock Matovu, and Marleen Boelaert

Contents

Abstract Human African trypanosomiasis (HAT) found only in sub-Saharan Africa is caused by the parasite *Trypanosoma brucei* which is transmitted by tsetse flies. Only two subspecies of *T.brucei* are pathogenic for humans: *T.b. gambiense* and *T.b. rhodesiense*. HAT is endemic in 36 sub-Saharan countries, and 98 % of all reported HAT cases are due to *T. b. gambiense.* Sixty-nine million persons in Africa are at risk of HAT. The number of HAT cases reported globally decreased fivefold

P. Lutumba (✉)
Department of Epidemiology, Institut National de Recherche Biomédicale (INRB), Kinshasa, Democratic Republic of Congo

Tropical Medicine Department, Faculty of Medicine, Kinshasa University (UNIKIN), Kinshasa, Democratic Republic of Congo
e-mail: pascal_lutumba@yahoo.fr

E. Matovu
College of Veterinary Medicine, Animal Resources and Biosecurity, Makerere University, Kampala, Uganda

M. Boelaert
Department of Public Health, Institute of Tropical Medicine–Antwerp, Antwerp, Belgium

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_4

in the last decade which has encouraged WHO to set a target to eliminate HAT as a public health problem by the year 2020, aiming for zero transmission by the year 2030. Tsetse flies do not lay eggs, but the female fly deposits a single mature larva in humid soil. The larva pupates and emerges as an adult fly 20–80 days later. A female fly produces only three to five larvae during her lifetime that typically lasts for 3 months, making the intrinsic growth rate of tsetse populations rather low. An infected tsetse fly injects the infective form of the parasites into the mammalian host when it feeds. These parasites undergo, and are able to switch, their antigenic variation of their variant surface glycoprotein (VSG) coat, allowing them to escape the host immune response. This phenomenon of antigenic variation makes the development of an effective vaccine unlikely. The disease affects mainly the lymphoid system, heart, lungs and brain manifesting as intermittent fever, general malaise, severe headache, joint pains and muscle aches, pruritus, urticaria or facial oedema. Lymphadenopathy is common with the classical Winterbottom's sign. Patients with the meningo-encephalitic stage suffer continuous headaches with poor response to painkillers and show more specific neurological signs of the rather typical sleep disturbances. Diagnosis of HAT is a three-step procedure: (i) screening test to identify HAT suspects, (ii) confirmatory parasitological tests and (iii) staging. Treatment is based on the stage of illness, current options being pentamidine, suramin, melarsoprol, eflornithine and the nifurtimox-eflornithine combination therapy (NECT). Two strategies are used for the reduction or interruption of HAT transmission: elimination of the parasite reservoir and vector control. This last decade has seen several breakthroughs in clinical R&D for HAT, bringing new diagnostics and drugs to patient care, but effective and efficient implementation of these new tools in HAT control and proper treatment of patients will require further research.

Keywords Human African trypanosomiasis • Epidemiology • Control • Integration

Epidemiology of the Disease

Human African trypanosomiasis (HAT) or sleeping sickness is a disease caused by the parasite *Trypanosoma brucei* and transmitted by tsetse flies belonging to the genus *Glossina*. As this vector is restricted to sub-Saharan Africa, so is the disease. Only two subspecies of *T.brucei* are pathogenic for human beings: *T.b. gambiense* and *T.b. rhodesiense. T.b. gambiense* causes a slowly progressive form of the disease in West and Central Africa, while *T.b. rhodesiense* is responsible for a more acute disease pattern in East and southern Africa (WHO 2013). HAT is endemic in 36 sub-Saharan countries, of which 24 are affected by *T. b. gambiense* – representing 98 % of all reported HAT cases – while 13 countries are affected by *T.b. rhodesiense* (Franco et al. 2014b; WHO 2013). WHO (2013) estimates that 69 million persons in Africa are at risk of HAT, of which 57 million are exposed to *T.b. gambiense*. Three countries have more than 70 % of their population living in endemic areas: the

Democratic Republic of Congo (DRC) (36.2 million), Uganda (10 million) and Angola (4.7 million) (see Fig. 1). Figure 2 shows the geographic distribution of cases over the decade (2000–2009). The Democratic Republic of Congo alone reported more than 80 % of the 2012 cases, followed by the Central African Republic (319 cases), South Sudan (317 cases) and Chad (197 cases). According to WHO, the number of HAT cases reported globally decreased fivefold in the last decade, from 37,991 in 1998 to 7216 cases in 2012 (Fig. 3). Encouraged by this decrease that was attributed to the intensified control efforts, WHO has set a target to eliminate HAT as a public health problem by the year 2020 and zero transmission by the year 2030 (WHO 2013). The successes of this ambitious approach will rely on commitment of

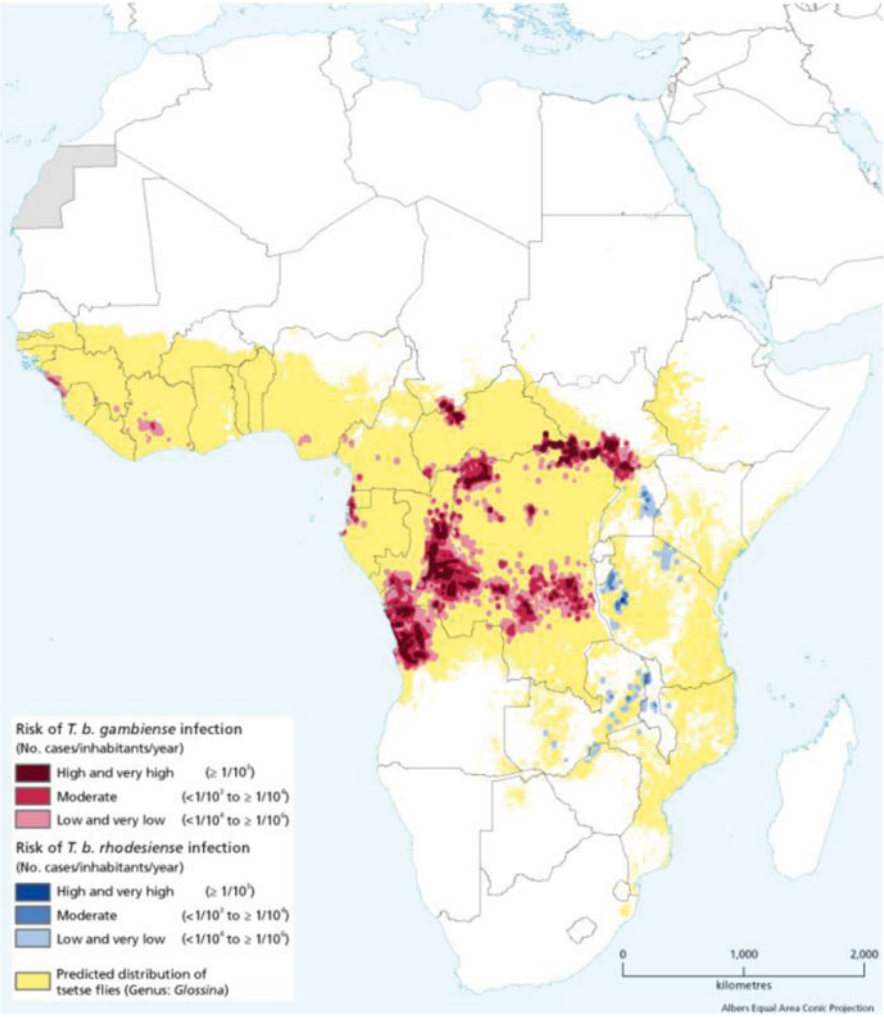


Fig. 1 Population at risk for HAT (Simarro et al. 2012a)

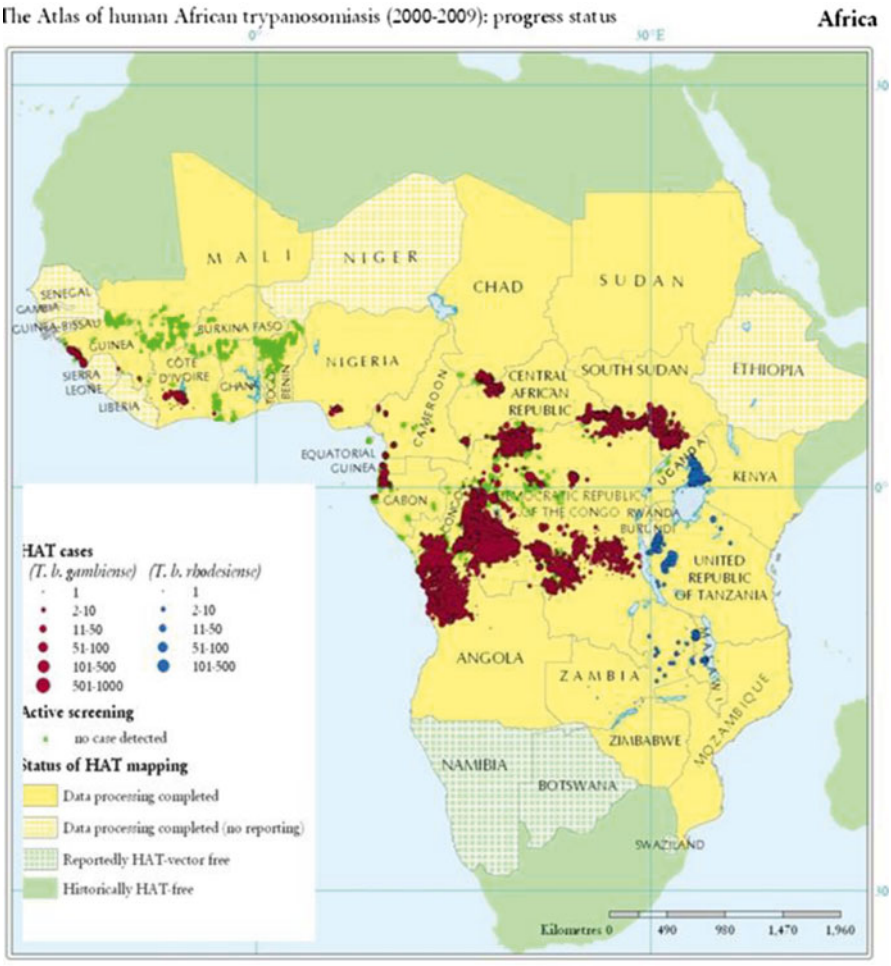


Fig. 2 Geographic distribution of HAT cases reported in the period 2000–2009 (Simarro et al. 2010)

both international players and the national control programmes of endemic countries.

Nonetheless, trends in HAT case numbers should be interpreted with caution, as the number of cases detected is directly related to the intensity of the active population screening efforts. The apparent dip in case numbers in 1991 visible on Fig. 3 is an artefact and explained by the interruption of the Belgian bilateral aid to that time Zaïre that halted all the mobile teams screening for HAT in the country for a prolonged period. Several authors warned about underreporting of the true number of HAT cases. Robays et al. (2004) estimated that in 1997–1998, between 40 and 50 % of *T.b. gambiense* HAT cases in the community were not detected by active case finding campaigns in DRC. A substantial number of people refused to participate in

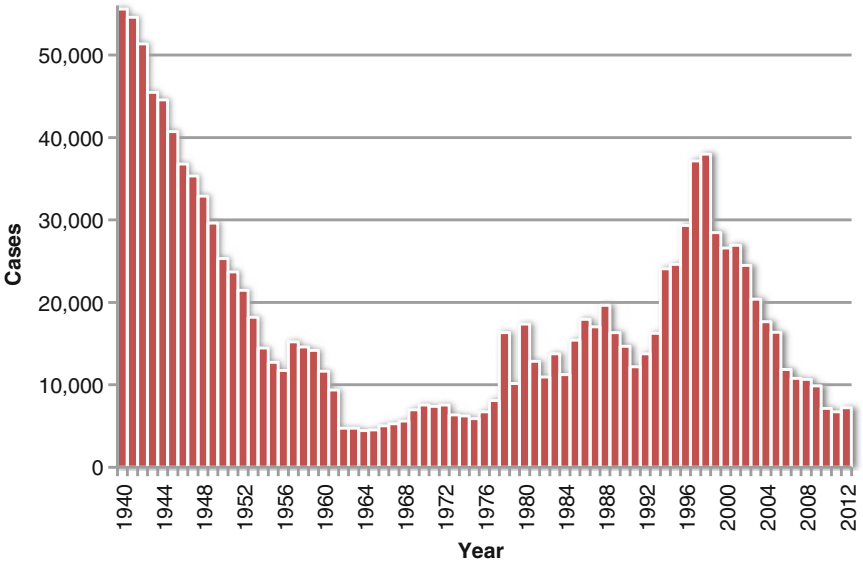


Fig. 3 Total number of new cases of HAT reported to WHO, 1940–2012 (Franco et al. 2014a)

the screening, and the sequence of confirmatory tests used at that time was of poor sensitivity. Fèvre et al. (2008) reported that in a localised epidemic in Uganda with 500 reported cases, approximately 300 additional cases died undiagnosed in the community. HAT also typically flares up in areas affected by civil war and insecurity. As HAT is fatal in the majority of the cases in the absence of treatment, missed HAT cases may never make it into the records (Jamonneau et al. 2012; Pepin and Meda 2001). The underreporting ratio may have improved in recent years due to intensified control efforts (WHO 2013).

Public Health Impact in Sub-Saharan Africa

The decreasing trend in HAT case numbers is reflected in the recent Global Burden of Disease estimates. In 2010 the HAT-related burden was estimated to cause a loss of 560,000 (95 % confidence interval 76,000–1,766,000) DALYs per year. This was a 72.5 % reduction from the 1990 DALY estimate, when HAT was thought to cause the loss of two million DALYs per year (Murray et al. 2012). Although the global HAT prevalence decreases, sleeping sickness remains a major public health problem in communities at risk, which are mainly the rural poor. In the Democratic Republic of Congo (DRC), the most affected country, the number of years of life lost (YLL) per death caused by HAT was estimated at 27 years (Lutumba et al. 2007). Politi et al. (1995) estimated that in Uganda, the number of DALYs incurred per premature death of *T. b. rhodesiense* HAT was 25. These high numbers are due

to the fact that HAT mainly affects adolescents and young economically active adults and secondly that it is inevitably fatal in untreated individuals. The use of DALYs for expressing the HAT burden has been criticised since the global burden of disease rankings at country or region level does not reflect the devastating socio-economic impact of the disease on the affected communities. HAT is a highly clustered disease, and country or regional averages may therefore be misleading. Within the HAT foci, the prevalence can be high, often around 1 % and higher in epidemic contexts. In the absence of control, the prevalence can rise relatively rapidly, sometimes to affect over half of the population of certain villages. Thus, the impact of this disease can be very heavy in specific foci (Fevre et al. 2008).

Sleeping sickness patients require a great deal of supportive care from their relatives. Seeking a diagnosis and obtaining treatment is often costly and time-consuming. There have been a few attempts to quantify the full costs borne by households with a HAT patient which includes care during hospitalisation and at home, seeking a diagnosis, lost income, medical fees, transport, etc. Lutumba et al. (2007) investigated the burden of HAT in a rural community of the Democratic Republic of Congo in a retrospective household survey. The burden of HAT on households and livelihoods was high, between 1.5 and 10 months of income, even though diagnostics and HAT drugs were provided free of charge by the national control programme (Lutumba et al. 2007). In the Republic of Congo-Brazzaville, the cost to households with HAT patients who were correctly diagnosed and treated came to an amount equivalent to 2.6–5 months of household income generated from agriculture (Gouteux et al. 1987). The cost of illness due to HAT borne by households is thus considerable and can compromise the timely uptake of HAT treatment. Households need to take their time to prepare themselves and mobilise resources, relying on the solidarity of the extended family before presenting themselves for treatment. This high cost for the household may partly explain the low participation rates at active population screening sessions organised by the national HAT control programmes because people fear of being identified as a HAT case and having to bear the high costs (Robays et al. 2007). Moreover, diagnosis and treatment require often long and invasive medical procedures that also act as a deterrent for persons to freely present themselves for the treatment or the required post-treatment follow-up to confirm cure.

Biology

Vector and Parasite Life Cycle

Thirty-one different species of tsetse fly (genus *Glossina*) (Fig. 4) can transmit HAT; these belong to one of three subgroups, fusca, palpalis or morsitans. In general terms, species of the morsitans group are involved in the transmission of *T. b. rhodesiense*, while species of the fuscipes and the palpalis group are mainly involved in the transmission of *T.b. gambiense*. The most important species involved are

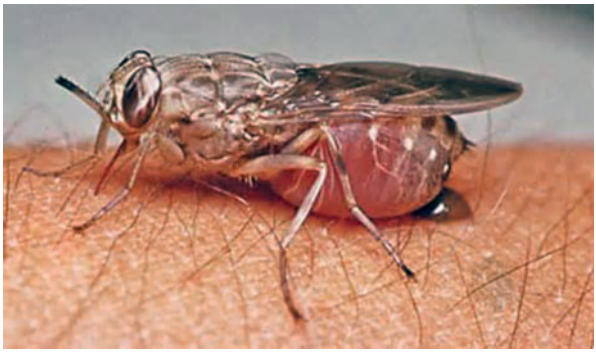


Fig. 4 Adult tsetse fly

G. palpalis palpalis, *G. palpalis gambiensis*, *G. tachinoides*, *G. fuscipes quanzensis, G. fuscipes martini* and *G. fuscipes fuscipes.* The latter is the major vector of both forms of HAT in Uganda. Tsetse flies have a peculiar reproductive cycle; they do not lay eggs, but the female fly deposits a single mature larva in humid soil. The larva burrows into the soil, pupates and emerges as an adult fly 20–80 days later (Fig. 4). A female fly will only produce three to five such larvae during her lifetime, that typically lasts for 3 months (2 months for males). As such, the intrinsic growth rate of tsetse populations is rather low.

When a male or female tsetse fly feeds on a *Trypanosoma*-infected mammalian host, the parasites enter the digestive tract of the fly. During the following 3–5 weeks, they undergo several differentiation steps, from dividing midgut forms to the migrating epimastigote forms, which develop in the salivary glands of the fly into the infective metacyclic forms. The latter will be injected during the next blood meal into the mammalian host (see Figs. 5 and 6).

Injected into human skin, the trypanosome parasites will first proliferate at the site of the tsetse fly bite. The local inflammation reaction can lead to a trypanosomal chancre (also called 'trypanome') and some local lymphadenopathy. Waves of trypanosomes then invade the bloodstream (Brun et al. 2010) and differentiate as dividing slender forms, intermediate forms and stumpy forms. The latter do not replicate but are adapted to differentiate again into procyclic forms if taken up by a tsetse fly.

The parasites have a unique system of antigenic variation of their variant surface glycoprotein (VSG) coat, which allows them to escape the host immune response (Sternberg 2004). This coat of about ten million copies of a single VSG is strongly immunogenic, and the infected person produces a high amount of specific anti-VSG IgM antibodies that are able to destroy the majority of the circulating parasite population. However, the parasite is able to switch to the expression of different variants of VSG, and those that have switched their VSG in the meantime will survive and replicate. The variable antigens released repeatedly in the blood are responsible for a profound dysregulation of the immune response and cytokine production resulting in immunosuppression. This phenomenon of antigenic variation makes the development of an effective vaccine unlikely (Magez et al. 2010).

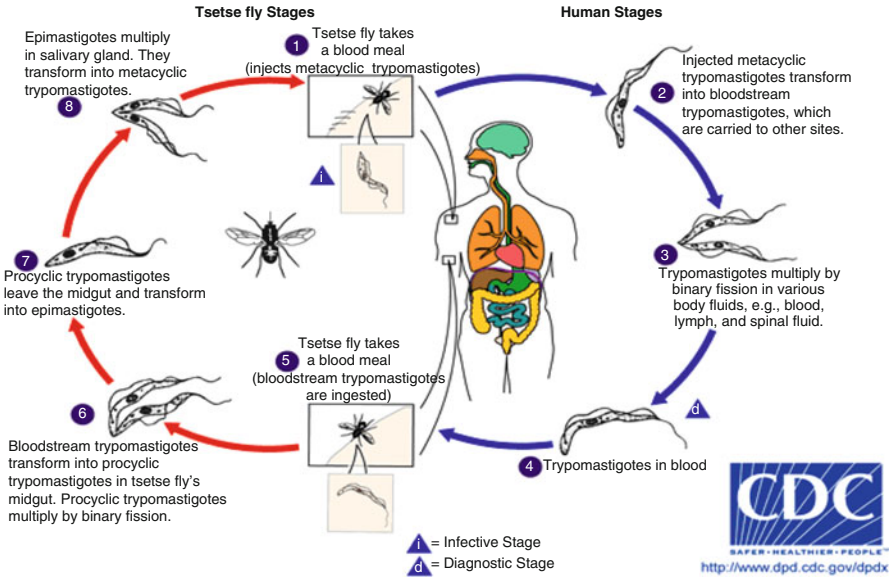
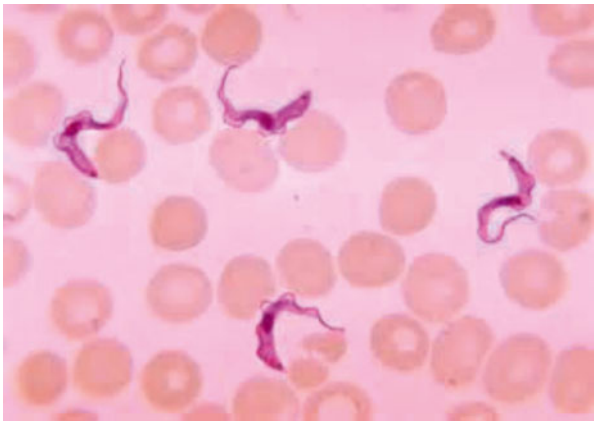


Fig. 5 Life cycle of Trypanosoma spp. (CDC 2015)

Fig. 6 Trypanosomes



Mode of Transmission

T. b. rhodesiense HAT is a zoonosis. Its transmission is predominantly maintained in an animal reservoir of cattle and game. In countries where the reservoir is mainly wild game, sporadic transmission to humans including tourists visiting National Parks is occasionally reported. Countries such as Tanzania, Zambia and Malawi have conservation areas within HAT endemic regions. Such a complex transmission cycle involving protected animal species makes it impossible to envisage elimination of *T. b. rhodesiense* HAT. However, in Uganda, all recognised HAT endemic regions are outside conservation areas, which makes effective control more feasible.

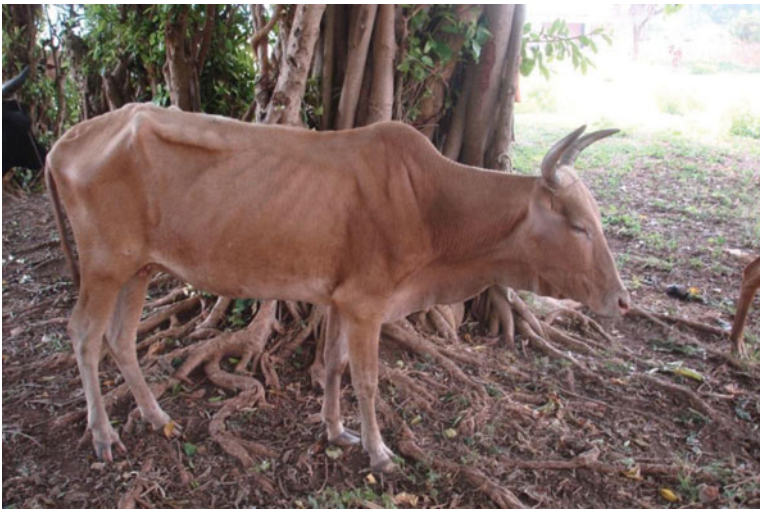


Fig. 7 Animals chronically infected with *T. brucei* exhibit symptoms similar to those of late stage HAT. The cattle in this picture from a *T. b. rhodesiense* endemic district of eastern Uganda was found to be co-infected with *T. congolense* (the cause of African Animal Trypanosomiasis) and *T. b. rhodesiense*, confirming the role of animal reservoirs in transmission of the acute form of HAT.

Due to population growth, most wild animals living outside conservation areas have been decimated by hunting and other activities that alter their natural habitats. Thus, domestic animals are currently the most important reservoirs of the disease in the country (Hide et al. 1996; Hide 1999). A previous study in Busoga demonstrated that *T. b. rhodesiense* HAT is up to five times more likely to be transmitted through a cattle-fly-human cycle than by a human-fly-human cycle (Hide et al. 1996) (Fig. 7).

Gambiense HAT on the contrary is maintained by the human-tsetse fly-human cycle. Very rarely the parasite is transmitted by blood transfusion, or across the placenta. The role of an animal reservoir in *T.b.gambiense* HAT is debated. The first indication that some *T. brucei* isolates from animals are infective to man came from Denecke (1941), who infected himself with a parasite strain from a dog in Equatorial Guinea. Van Hoof et al. (1947) proved the potential reservoir role of the pig for *T. b. gambiense* by experimentally infecting pigs with parasite strains from human origin and realised 10 passages and later up to 20, without losing its infectivity for man. The same researchers were also able to show that a *T. b. gambiense* strain isolated from a human could infect goats, sheep and dogs (Van Hoof 1947). More recent investigations using modern molecular tools have confirmed the presence of *T. b. gambiense* in pigs in Cameroon and Ivory Coast (Jamonneau et al. 2004; Nkinin et al. 2002). Infection was also detected in several primates, lizards and rodents (Molyneux 1973) using the same technology. Eight out of 24 different wild animal species were infected with *T. b. gambiense* in an HAT focus in Cameroon, such as monkeys, ungulates, carnivores and rodents such as *Cricetomys gambianus*, the Gambian pouched rat (Herder et al. 2002). Although it is commonly accepted that *T. b. gambiense* is maintained by the human reservoir, this does not exclude that in

some foci of Gambian sleeping sickness, both an animal and human reservoir may coexist (WHO 2013). Mathematical modelling pointed repeatedly to the role of animal reservoirs in maintaining transmission in interepidemic periods.

Pathogenesis

The disease affects mainly the lymphoid system, heart, lungs and brain. Gambiense HAT evolves in two stages. The first stage is haemato-lymphatic, when proliferating trypanosomes spread from the inoculation site. Parasitaemia is typically low (less than 100 parasites per ml of blood) and fluctuating. In the second or late stage (also called meningo-encephalic stage), parasites will cross the blood-brain barrier (Kennedy 2013; Lundkvist et al. 2004). The parasites invade perivascular areas with subsequent infiltration in the white matter first, then later in the grey matter of the brain. The clinical syndrome is explained by the invasion of the choroid plexus, thalamus, the area postrema and median eminence. In this second stage, signs of myocarditis (Blum et al. 2009), cerebral and meningeal oedema and punctuate haemorrhages are typically observed. Mott cells, plasma cells containing immunoglobins, are characteristic for the infection. The severity of pathological lesions correlates only partially with parasitaemia (WHO 2013).

Cases of asymptomatic chronic carriers of the infection have been described (Ilboudo et al. 2014; Jamonneau et al. 2012). Some asymptomatic individuals who refused treatment and were followed up for long periods (5–15 years) were shown to eliminate the parasites from circulation coupled with a decline in the serological response. However, it is unclear whether these cure spontaneously; these cases of asymptomatic infection are often too rare (Jamonneau et al. 2012) to enable conclusive investigation of this phenomenon.

Clinical Presentation

Signs and symptoms of HAT differ according to the stage of the disease. Symptoms in the early stage are not specific and include intermittent fever, general malaise, severe headache, joint pains and muscle aches (Kennedy 2013). Sometimes patients have pruritus, urticaria or facial oedema. The trypanosoma or chancre is the typical primary lesion in HAT caused by *T. b. gambiense,* but it is rarely observed in practice, as opposed to *T. b. rhodesiense* where the chancre is occasionally observed. Lymphadenopathy is more common: axillary and inguinal in East African HAT while cervical lymphadenopathy is more often present in the West African type. The classical Winterbottom's sign is an enlarged gland of the posterior cervical triangle, which is painless and feels firm, rubbery and mobile.

The duration of the first stage in gambiense HAT varies from a few months to several years, while for *T. b. rhodesiense,* it is a matter of weeks to a few months.

Fig. 8 Patient with HAT in the meningo-encephalitic phase

In the meningo-encephalitic stage, the patient suffers continuous headaches with poor response to painkillers and shows more specific neurological signs. These are the rather typical sleep disturbances, with daytime somnolence and nocturnal insomnia (Fig. 8) leading to a disappearance of the circadian rhythm of sleep and wakefulness, mental confusion and a wide range of psychiatric disorders including personality disorders, behavioural changes and mood alterations. Other neurological symptoms include abnormal reflexes such as Babinski's sign, exaggerated osteotendinous reflexes and clonus, tone disorders (either hypertonia or hypotonia), abnormal movements, sensory disorders (Kerandel's sign), paraesthesia, Hoffman's sign and loss of sense of position, coordination disorders including ataxia and abnormal gait, convulsions, incontinence and archaic reflexes (Kennedy 2008, 2013). Other features include amenorrhoea, infertility, abortion and wasting (Kennedy 2013).

The very diverse clinical picture mimics a range of other diseases such as AIDS, schizophrenia and TB, and clinicians may easily miss the diagnosis if they are not familiar with the disease. This is particularly a problem for clinicians dealing with imported cases in non-endemic areas, e.g. in urban areas. Moreover, control strategies against HAT in such urban areas are not well defined (Ebeja et al. 2003).

Diagnosis

HAT diagnosis is based on laboratory tests due to the absence of specific clinical signs. Because of the toxicity of the drugs currently in use and the different stages of the disease, diagnosis of HAT occurs in three steps: (i) screening test to identify

HAT suspects, (ii) confirmatory parasitological tests and (iii) staging (Mitashi et al. 2012). The latter is required for clinical management as drugs that do not pass the brain-blood barrier can only be prescribed to patients in the early stage of the disease.

Screening The most widely used screening test in gambiense HAT is the card agglutination test for trypanosomiasis (CATT) based on the antigen LiTat 1.3 (Magnus et al. 1978). Its sensitivity and specificity reportedly vary between 68.8–100 and 83.5–99.3 (Mitashi et al. 2012). Although its cost is affordable, limiting factors are the need for cold chain storage, the 50-dose format leading to loss of non-used doses and the need for a 12 volt power source. Since 1997, CATT has been used on a large scale in active population screening, with up to three million tests per year used by mobile teams. During the last 5 years, rapid diagnostic tests (RDT) were developed based on the antigens LiTat 1.3 and 1.5 (Buscher et al. 2013, 2014; Jamonneau et al. 2015; Sternberg et al. 2014). The first generation of these RDTs is based on native antigens and is available as individual cassette or strip test with results available after 15–20 min. Its sensitivity and specificity vary between 89.0–99.6 and 95.0–99.0 (Buscher et al. 2013, 2014; Jamonneau et al. 2015; Sternberg et al. 2014). Second-generation RDTs based on recombinant antigens are now in clinical development (Sternberg et al. 2014) and they include antigens other than the LiTats traditionally used in the CATT and the first-generation RDTs in order to improve specificity.

Confirmation All current HAT confirmatory tests are based on microscopic examination for the visualisation of parasites resulting in a specificity approaching 100 % if carried out by trained staff. However, there is no single confirmatory test that has a satisfactory sensitivity, and in practice combinations of several are used in sequence. These include lymph node aspirates in suspects with cervical adenopathy, blood or cerebrospinal fluid for direct examination of Giemsa stained smear, capillary tube centrifugation (CTC), quantitative buffy coat (QBC) or the mini anion exchange centrifugation technique (mAECT). The most sensitive tests are the mAECT and CTC, but they require expertise and equipment such as a centrifuge and light source which may not always be available in rural, HAT endemic areas. The sensitivity of CTC varies between 44.3 and 93.0, and its cost is estimated to be 0.76 €. The sensitivity of mAECT varies between 75.3 and 90.9 %, and its cost is estimated to be 3–5 €.

Staging In confirmed HAT patients, a lumbar puncture (Fig. 8) is done for staging of the disease. When parasites are visualised in the cerebrospinal fluid and/or the number of white blood cells is higher than 5/mm^3 (Malvy and Chappuis 2011), the patient is considered to be in the late stage of the disease. If CSF is sampled in a collection tube with a tapered tip followed by a light centrifugation and examination of the base (modified single centrifugation), this can increase the sensitivity of detection of parasitised CSF (Fig. 9).

Other tests Molecular diagnostic tests have been developed mainly for species identification and are not used so far in clinical diagnostic algorithms. Methods have

Fig. 9 Lumbar puncture for staging of HAT during an active screening session in DRC

been recently reviewed by Büscher and Deborggraeve (2015). Differentiation between *T.b. rhodesiense* and *T.b.gambiense* by PCR is based on two specific genes: *T.b.gambiense*-specific glycoprotein (TgsGP) and serum resistance-associated gene (SRA) (Simarro et al. 2012b; Urech et al. 2011). However, this specific PCR-targeted TgsGP and SRA gene are not very sensitive, as the two specific genes are present in a single copy in the trypanosome genome (Mitashi et al. 2013; Mugasa et al. 2014). PCR is limited by lack of standardisation and the use of sophisticated equipment, which confines its use to reference and research laboratories. Some recent advances have tried to circumvent this. The loop-isothermal amplification of DNA (LAMP) was developed as a promising tool for field diagnosis of HAT. Unlike PCR, LAMP does not require the thermocycler for DNA amplification. The sensitivity of LAMP varies in laboratory conditions between 76.9 and 93.0, and specificity ranges 92.8–100 (Mitashi et al. 2013; Mugasa et al. 2014). The cost of an LAMP reaction tube is around 5€. Its effectiveness in the field is currently being evaluated. Other simplified molecular methods include the nucleic acid sequence-based amplification (NASBA) and FISH (fluorescent in situ hybridisation) based on the use of the fluorescent oligonucleotide probes to detect and localise specific target nucleic acid sequences. These methods require more evaluation before they can be recommended for field use. Several countries are presently evaluating LAMP alongside

conventional screening and parasitological techniques in intensified efforts towards HAT elimination.

Treatment

Current treatment regimens for HAT depend on the stage of the disease but also on the infecting parasite subspecies. Currently, four drugs and one drug combination are available: pentamidine, suramin, melarsoprol, eflornithine and the nifurtimox-eflornithine combination therapy (NECT). Pentamidine is the first-line drug for *gambiense* HAT at the first stage. It is administered at the dosage of 4 mg/kg/day during 7 days by intramuscular injection (WHO 2013). Other treatment regimens are being evaluated such as 3 days instead of 7, but the results are not available yet. Pentamidine is a drug known since 1940 and is indicated for gambiense HAT; however, it has also shown its effectiveness in the treatment of *rhodesiense* HAT in travellers (Simarro et al. 2012b; Urech et al. 2011). The therapeutic efficacy of pentamidine is 93–98 %, and this cure rate has not changed for decades (WHO 1998). The major side effect is the immediate hypotension observed in 10 % of the cases.

The first-line treatment for stage I *rhodesiense* HAT is suramin, in use since 1920, and is usually administered intravenously at dosage of 20 mg/Kg (maximum 1 g). Patients receive a dose once a week during 5 weeks which is preceded by a testing dose at 4–5 mg/kg (WHO 2013). Side effects are rare but can be severe due to early or late hypersensitivity, urticaria or exfoliative dermatitis. The associated renal impairment is reversible once treatment ceases.

For the second-stage gambiense disease, NECT is the first-line treatment. Eflornithine is administered at 400 mg/kg/day intravenously in two intravenous perfusions (diluted in 250 physiological fluid) for 7 days in addition to oral nifurtimox at 15 mg/kg/day for 10 days. NECT effectiveness is reportedly 97.7 % (Priotto et al. 2009). Major side effects have been observed in a small proportion including neurological and psychiatric problems such as convulsions and agitations. Case fatality rates observed under NECT treatment vary from 0.5 to 1.6 % (Alirol et al. 2013; Schmid et al. 2012; WHO 2013).

Second-stage *rhodesiense* HAT is still treated with melarsoprol at 22 mg/kg/day intravenously for 10 days (WHO 2013). Its effectiveness is 99 %. However, its major side effect is reactive encephalopathy in 5–18 % of the cases with a lethal outcome in 10–70 % of the reacting cases (Pepin and Milord 1994; WHO 1998). In Uganda and Tanzania, death rates of up to 8.4 % and 9.4 % of treated patients respectively, were reported (WHO 2013).

In the case of treatment failure or contraindications for certain drugs, the first-line treatment needs to be replaced by one of the above-mentioned drugs as monotherapy (WHO 2013). The basis for the therapeutic choice of second-line drugs is quite empirical since the mechanisms of treatment failure are not well understood and the choice is left to the clinician. This is a gap that needs more particular attention.

The majority of drugs used for the treatment of sleeping sickness are more than 70 years old and the choice is limited. In the 1990s, eflornithine was developed and the NECT combination regimen was adopted in 2010 after a multicentre phase III study had shown its efficacy. Besides these drugs, there are multiple products being currently evaluated at different clinical phases. Fexinidazole and benzoxaboroles (SCYX-7158), oral tablets that could be active on both stages of the disease, are the most promising and could revolutionise control and treatment strategies (Jacobs et al. 2011; Tarral et al. 2014; Torreele et al. 2010). Once proved safe and effective against both disease stages, the need for staging that relies on the dreaded lumbar puncture could be overcome.

Control Tools and Strategies

There are two main strategies for reduction or interruption of HAT transmission: (i) elimination of the parasite reservoir and (ii) vector control. For the elimination of the parasite reservoir, two interventions are generally used by national control programmes: active and passive screening. For gambiense HAT, where the main reservoir is human, active screening is the most effective (but the most costly) strategy because it can identify patients in an early stage while passive screening mostly identifies patients in the second stage (Hasker et al. 2011; WHO 2013) (Fig. 10).

In active screening, control programmes usually deploy mobile teams generally composed of seven to eight persons. These mobile teams travel from village to village and examine the entire population using CATT as screening and a battery of confirmation tests. When HAT is confirmed, a lumbar puncture is required to determine the stage of the disease in the patient. All confirmed cases are referred to dedicated treatment centres. Early-stage patients receive treatment as outpatients, while late-stage patients require hospitalisation, although in some countries such as Uganda, both

Fig. 10 Mobile team for HAT screening at work in a village in DRC

stages are handled as inpatients. The impact of a population screening (or active case finding) strategy on *T.b.gambiense* transmission is not well documented, and the optimal frequency of screening rounds is a subject of debate (Abel et al. 2004; Bruneel et al. 1994; Simarro et al. 1991; Van Nieuwenhove et al. 2001). WHO (1998) recommends one screening round per year in a typical endemic situation although some national control programmes perform two rounds a year. Successful active case finding must be frequently undertaken, cover a high proportion of the population at risk, use very sensitive tests and provide sufficient capacity to treat the cases (WHO 1998). Under such circumstances, a decrease in the annual HAT detection rate to levels below 0.1 % would be expected (Van Nieuwenhove et al. 2001). The reservoir of HAT cases could then be reduced so as to interrupt transmission for some years. For *rhodesiense* HAT, active screening is not relevant due to the acute and epidemic aspect of the disease as well as the domestic and wild animal reservoirs keeping transmission still active. Its screening activities are therefore mostly performed during epidemics to identify as many cases as possible for adequate treatment (Franco et al. 2014b; WHO 2013). The 'one health' approach of identifying and treating humans and domestic animals could also reduce *T.b. rhodesiense* (WHO 2013).

A consensus for passive screening strategies to control the disease has not been reached yet; however, a well-thought-out strategy could play an important role in epidemiological surveillance and reorientate active screening. Effective passive screening requires HAT diagnostic expertise at numerous health facilities, which is often absent. It was reported that patients present themselves more than seven times to health centres before proper diagnosis is established. This is usually when the patient is already in the second stage of the disease (Brun et al. 2010), which is even more difficult to treat due to the associated drug toxicity complications.

Vector control against tsetse flies has long been considered as an important strategy to reduce the impact of HAT on people and livestock. Early attempts to control tsetse flies were based on clearing land to remove their habitat and killing wildlife to remove tsetse hosts (Lancien 1991). Vector control interferes with transmission of human and animal trypanosomiasis by reducing its reservoir in both humans and animals. Various strategies are used, such as traps, screens and targets and insecticides (Abd-Alla et al. 2013; Bouyer et al. 2007; Bouyer 2008; Kgori et al. 2006; Lindh et al. 2012; Vreysen 2001); the sterile insect technique is not yet widely applicable. Currently, the most frequently used methods are traps and small insecticide-treated targets (tiny targets) (Lindh et al. Torr 2012). Noteworthy however is that in many countries, vector control is not given the attention it would deserve to suppress populations and considerably hamper disease transmission.

All methods have the potential to diminish the density of tsetse flies considerably; however, their cost and the time that the area remains tsetse free vary. Despite the remarkable reduction of tsetse fly density, the efficacy of vector control in reducing transmission is not well established. A number of authors claim an effect of traps on the tsetse fly population, but most were small-scale projects that took place in low prevalence foci, and these studies primarily assessed the costs and the feasibility, while the effect on transmission remained unclear (Gouteux et al. 1982, 1986; Gouteux and Lancien 1986; Gouteux and Sinda 1990; Lancien 1991; Laveissiere

et al. 1994). However, mathematical modelling suggests that vector control may have a significant impact on the incidence of HAT (Artzrouni and Gouteux 1996, 2001). A study conducted by Simarro (Simarro et al. 1991) in Equatorial Guinea compared the addition of tsetse trapping to population screening in one HAT focus to exclusive population screening in two other foci. This trial showed a more rapid reduction of HAT prevalence in the focus with vector control. However, HAT was also eliminated after a single year in the two control foci with population screening only, and the paper concludes that vector control in addition to population screening was not cost-effective. The recently developed tiny targets were deployed at a cost of USD 85.4 per km^2 (Shaw et al. 2015). This tool is currently in evaluation for its effectiveness in reducing tsetse population and in reducing or even eliminating HAT.

Until now, most HAT control programmes in the *T.b. gambiense* foci are nearly entirely based on population screening with a very limited role for vector control; this is in sharp contrast with the *T.b. rhodesiense* area in East Africa (Welburn et al. 2001). Many argue that vector control is often not a priority in *T.b. gambiense* control programmes because treatment of infected people is imperative for ethical reasons and funding for it is more easily found than for vector control. The limited budgets and the current instability in countries like South Sudan and others in central Africa make it difficult for a HAT control programme to divert the scarce resources from case finding. Given these historical factors and the continued uncertainty on effectiveness and cost-effectiveness of vector control, HAT control programmes simply do not invest in vector control in the *T.b. gambiense* areas. Besides, the notion that humans are the major reservoir of gambiense HAT warrants that surveillance and treatment of identified cases take centre stage. Historically a number of foci have been brought under control solely by active case finding programmes with a very limited contribution of vector control (Abel et al. 2004; Bruneel et al. 1994; Frezil and Coulm 1977; Paquet et al. 1995; Simarro et al. 2001). However, annual active case finding activities for more than 15 years did not bring the HAT epidemic under control in two provinces of the Democratic Republic of Congo, Bandundu and Kasai, which account now for more than half of the annually reported worldwide cases (Hasker et al. 2012). Difficulties in securing sufficient participation of the population to screening sessions are definitely one of the reasons (Robays et al. 2004). Mpanya et al. (2012) have demonstrated that sociocultural factors constitute an important barrier for participation to active screening. However, another factor might be that disease transmission may be more intense in these provinces than elsewhere or, else, the presence of an animal reservoir that is to date not fully understood.

Challenges of Programme Implementation

With the intensified control efforts of recent years, the number of HAT cases has decreased considerably. However, with these decreasing numbers, the marginal cost per case detected increases, and the population loses its motivation to participate in the campaigns. This loss of efficiency of current control measures is of

great concern. Moreover, since HAT control depends on external aid for over 90 % (Lutumba et al. 2005), the commitment of funding agencies for HAT control is crucial and donor fatigue because of dwindling case numbers is an even bigger threat. It is well known that abandoning HAT control activities usually results in recrudescence of the disease (Hasker et al. 2012; Moore and Richer 2001). In addition to this, the populations living in an unstable sociopolitical context or war zones (North East Congo, South Sudan and Central African Republic) or those living in inaccessible zones for various reasons are in need of alternative control strategies. In the short term, alternative, innovative and cost-effective strategies should be established to facilitate further decrease of the HAT prevalence even in remote areas. Several alternatives have been proposed and are in the process of validation. This includes the possibility of mini-teams to perform rapid tests or CATT in a house-to-house visit mode with or without the possibility for confirmation testing. These mini-teams could travel by bike or motorcycle and be integrated in the local health care services. Several studies to measure the efficiency of such measures, their impact on the transmission of the disease and further epidemiological surveillance are currently ongoing. Indeed, HAT control needs more than ever an adequate, cost-effective and feasible system to detect as soon as possible recrudescence of the disease to undertake the required adequate actions. Other research projects investigate the process of integrating these HAT control activities within the local health centres to include screening, confirmation, treatment and vector control.

Further Research for Policy and Control

This last decade has seen several breakthroughs in clinical R&D for HAT, bringing new diagnostics and drugs to patient care. Two oral drugs (fexinidazole, benzoxaboroles) are currently under evaluation in clinical trials. If the safety profile of these drugs allows it, a drastic simplification of the diagnostic algorithms could become possible, to possibly eliminate the parasitological confirmation and/or staging steps. An RDT which is sufficiently sensitive and specific would allow treatment with the new safe molecules in a single step, if such were the case.

Future implementation research will have to focus on the effective and efficient implementation of these new tools in HAT control and proper treatment of patients. This operational research should aim at a better integration of control measures in the health system in general and a rational and effective surveillance of HAT. This research will have to be accompanied by qualitative components that will allow the documentation on the perception and acceptability towards new tools and strategies not only of the community but from health care workers as well. The evidence generated by this research will therefore allow the political decision makers to revise strategic documents in order to integrate the new tools and make HAT control more efficient (Franco et al. 2014b).

Outlook for the Next Decade

While the numbers of HAT cases reported globally have been decreasing over the past decade, it is too early to consider that the problem is globally brought under control. Endemic countries as well as the donor community must be warned against the dangers of laxity in control efforts that would accompany such declines in incidence, for such would be an opportune moment for the HAT resurgence. West African HAT affects communities in a prolonged way, as the disease tends to flare up again in the so-called historic foci several years after it was brought under control (WHO 2013). While there is consensus that HAT control should be a sustained and uninterrupted effort, it is unclear today what type of surveillance should be exerted once the incidence rates in a region have been brought to very low levels and the large-scale population screening campaigns become hugely inefficient. To eliminate HAT as a public health problem, it is thus compulsory to apply enormous efforts and secure continuous support from funding agencies and the affected countries themselves. Moreover, the surveillance needs to be maintained for many years after HAT case numbers de facto have decreased to virtual zero, in order to effectively interrupt the transmission cycle. It would be worthwhile to undertake some modelling to suggest at what level of prevalence post-control that recrudescence of the infection is unlikely to occur. The inefficiency of active case finding by the current mobile teams could be addressed by using alternative and innovative screening methods but also by integrating these effective methods in the local health care system. However, this health care system will have to be sufficiently functional and capable of organizing such control activities to detect recrudescence of the disease timely, and this remains a huge challenge in countries as DRC that are home to 80 % of the current HAT burden (Mitashi et al. 2015).

References

Abd-Alla AM, Bergoin M, Parker AG, Maniania NK, Vlak JM, Bourtzis K, Boucias DG, Aksoy S (2013) Improving Sterile Insect Technique (SIT) for tsetse flies through research on their symbionts and pathogens. J Invertebr Pathol 112(Suppl):S2–S10

Abel PM, Kiala G, Loa V, Behrend M, Musolf J, Fleischmann H, Theophile J, Krishna S, Stich A (2004) Retaking sleeping sickness control in Angola. Trop Med Int Health 9(1):141–148

Alirol E, Schrumpf D, Amici HJ, Riedel A, de Patoul C, Quere M, Chappuis F (2013) Nifurtimox-eflornithine combination therapy for second-stage gambiense human African trypanosomiasis: medecins sans frontieres experience in the Democratic Republic of the Congo. Clin Infect Dis 56(2):195–203

Artzrouni M, Gouteux JP (1996) Control strategies for sleeping sickness in Central Africa: a model-based approach. Trop Med Int Health 1(6):753–764

Artzrouni M, Gouteux JP (2001) A model of Gambian sleeping sickness with open vector populations. IMA J Math Appl Med Biol 18(2):99–117

Blum JA, Schmid C, Burri C, Hatz C, Olson C, Fungula B, Kazumba L, Mangoni P, Mbo F, Deo K, Mpanya A, Dala A, Franco JR, Pohlig G, Zellweger MJ (2009) Cardiac alterations in human

African trypanosomiasis (T.b. gambiense) with respect to the disease stage and antiparasitic treatment. PLoS Negl Trop Dis 3(2):e383
Bouyer J (2008) Does isometamidium chloride treatment protect tsetse flies from trypanosome infections during SIT campaigns? Med Vet Entomol 22(2):140–143
Bouyer J, Stachurski F, Kabore I, Bauer B, Lancelot R (2007) Tsetse control in cattle from pyrethroid footbaths. Prev Vet Med 78(3–4):223–238, available from: PM:17126431
Brun R, Blum J, Chappuis F, Burri C (2010) Human African trypanosomiasis. Lancet 375(9709):148–159
Bruneel H, van den Eeckhout A, Molisho D, Burke J, Degroof D, Pepin J (1994) Control of trypanosoma gambiense trypanosomiasis. Evaluation of a strategy based on the treatment of serologically suspected cases with a single dose of diminazene. Ann Soc Belg Med Trop 74(3):203–215
Buscher P, Deborggraeve S (2015) How can molecular diagnostics contribute to the elimination of human African trypanosomiasis? Expert Rev Mol Diagn 15(5):607–615
Buscher P, Gilleman Q, Lejon V (2013) Rapid diagnostic test for sleeping sickness. N Engl J Med 368(11):1069–1070
Buscher P, Mertens P, Leclipteux T, Gilleman Q, Jacquet D, Mumba-Ngoyi D, Pyana PP, Boelaert M, Lejon V (2014) Sensitivity and specificity of HAT Sero-K-SeT, a rapid diagnostic test for serodiagnosis of sleeping sickness caused by Trypanosoma brucei gambiense: a case-control study. Lancet Glob Health 2(6):e359–e363
CDC. Life cycle of Trypanosoma spp. Available from: http://www.cdc.gov/dpdx/trypanosomiasisAfrican/index.html. Accessed 28 Jul 2015
Denecke K (1941) Menschen pathogene Trypanosome des Hundes auf Fernando-Po. Ein beitrag zur Epidemiologie der Schlafkrankheit. Arch Hyg Bakteriol 166:331–348
Ebeja AK, Lutumba P, Molisho D, Kegels G, Miaka Mia BC, Boelaert M (2003) Sleeping sickness in the region of the town of Kinshasa: a retrospective analysis during the surveillance period 1996–2000. Trop Med Int Health 8(10):949–955
Fevre EM, Wissmann BV, Welburn SC, Lutumba P (2008) The burden of human African trypanosomiasis. PLoS Negl Trop Dis 2(12):e333
Franco JR, Simarro PP, Diarra A, Jannin JG (2014a) Epidemiology of human African trypanosomiasis. Clin Epidemiol 6:257–275
Franco JR, Simarro PP, Diarra A, Ruiz-Postigo JA, Jannin JG (2014b) The journey towards elimination of gambiense human African trypanosomiasis: not far, nor easy. Parasitology 141(6):748–760
Frezil JL, Coulm J (1977) Present concept of strategy against sleeping sickness in the Democratic Republic of Congo. Ann Soc Belg Med Trop 57(4–5):315–322
Gouteux JP, Lancien J (1986) The pyramidal trap for collecting and controlling tsetse flies (diptera: glossinidae). Comparative trials and description of new collecting technics. Trop Med Parasitol 37(1):61–66
Gouteux JP, Sinda D (1990) Community participation in the control of tsetse flies. Large scale trials using the pyramid trap in the Congo. Trop Med Parasitol 41(1):49–55
Gouteux JP, Challier A, Laveissiere C, Couret D (1982) The use of screens in the anti-tsetse campaign in the forest zone. Tropenmed Parasitol 33(3):163–168
Gouteux JP, Lancien J, Noireau F, Sinda D (1986) Control of vectors by trapping and its impact on sleeping sickness in a zone of high density of Glossina fuscipes quanzensis (Lefini River, People's Republic of the Congo). Trop Med Parasitol 37(2):101–104
Gouteux JP, Bansimba P, Noireau F, Frezil JL (1987) Cost of the individual treatment of trypanosoma brucei gambiense trypanosomiasis in a focus of infection in Niari (Congo). Med Trop (Mars) 47(1):61–63
Hasker E, Lumbala C, Mbo F, Mpanya A, Kande V, Lutumba P, Boelaert M (2011) Health care-seeking behaviour and diagnostic delays for human African trypanosomiasis in the Democratic Republic of the Congo. Trop Med Int Health 16(7):869–874

Hasker E, Lutumba P, Chappuis F, Kande V, Potet J, De Weggheleire A, Kambo C, Depoortere E, Pecoul B, Boelaert M (2012) Human african trypanosomiasis in the Democratic Republic of the Congo: a looming emergency? PLoS Negl Trop Dis 6(12):e1950

Herder S, Simo G, Nkinin S, Njiokou F (2002) Identification of trypanosomes in wild animals from southern Cameroon using the polymerase chain reaction (PCR). Parasite 9(4):345–349

Hide G (1999) History of sleeping sickness in East Africa. Clin Microbiol Rev 12(1):112–125

Hide G, Tait A, Maudlin I, Welburn SC (1996) The origins, dynamics and generation of Trypanosoma brucei rhodesiense epidemics in East Africa. Parasitol Today 12(2):50–55

Ilboudo H, Bras-Goncalves R, Camara M, Flori L, Camara O, Sakande H, Leno M, Petitdidier E, Jamonneau V, Bucheton B (2014) Unravelling human trypanotolerance: IL8 is associated with infection control whereas IL10 and TNF alpha are associated with subsequent disease development. PLoS Pathog 10(11):e1004469

Jacobs RT, Nare B, Wring SA, Orr MD, Chen D, Sligar JM, Jenks MX, Noe RA, Bowling TS, Mercer LT, Rewerts C, Gaukel E, Owens J, Parham R, Randolph R, Beaudet B, Bacchi CJ, Yarlett N, Plattner JJ, Freund Y, Ding C, Akama T, Zhang YK, Brun R, Kaiser M, Scandale I, Don R (2011) SCYX-7158, an orally-active benzoxaborole for the treatment of stage 2 human African trypanosomiasis. PLoS Negl Trop Dis 5(6):e1151

Jamonneau V, Ravel S, Koffi M, Kaba D, Zeze DG, Ndri L, Sane B, Coulibaly B, Cuny G, Solano P (2004) Mixed infections of trypanosomes in tsetse and pigs and their epidemiological significance in a sleeping sickness focus of Cote d'Ivoire. Parasitology 129(Pt 6):693–702

Jamonneau V, Ilboudo H, Kabore J, Kaba D, Koffi M, Solano P, Garcia A, Courtin D, Laveissiere C, Lingue K, Buscher P, Bucheton B (2012) Untreated human infections by trypanosoma brucei gambiense are not 100% fatal. PLoS Negl Trop Dis 6(6):e1691

Jamonneau V, Camara O, Ilboudo H, Peylhard M, Koffi M, Sakande H, N'Dri L, Sanou D, Dama E, Camara M, Lejon V (2015) Accuracy of individual rapid tests for serodiagnosis of gambiense sleeping sickness in West Africa. PLoS Negl Trop Dis 9(2):e0003480

Kennedy PG (2008) Diagnosing central nervous system trypanosomiasis: two stage or not to stage? Trans R Soc Trop Med Hyg 102(4):306–307

Kennedy PG (2013) Clinical features, diagnosis, and treatment of human African trypanosomiasis (sleeping sickness). Lancet Neurol 12(2):186–194

Kgori PM, Modo S, Torr SJ (2006) The use of aerial spraying to eliminate tsetse from the Okavango Delta of Botswana. Acta Trop 99(2–3):184–199

Lancien J (1991) Campaign against sleeping sickness in South-West Uganda by trapping tsetse flies. Ann Soc Belg Med Trop 71(Suppl 1):35–47

Laveissiere C, Sane B, Meda HA (1994) Measurement of risk in endemic areas of human African trypanosomiasis in Cote d'Ivoire. Trans R Soc Trop Med Hyg 88(6):645–648

Lindh JM, Goswami P, Blackburn RS, Arnold SE, Vale GA, Lehane MJ, Torr SJ (2012) Optimizing the colour and fabric of targets for the control of the tsetse fly glossina fuscipes fuscipes. PLoS Negl Trop Dis 6(5):e1661

Lundkvist GB, Kristensson K, Bentivoglio M (2004) Why trypanosomes cause sleeping sickness. Physiology (Bethesda) 19:198–206

Lutumba P, Robays J, Miaka Mia BC, Mesu VK, Molisho D, Declercq J, Van der Veken W, Meheus F, Jannin J, Boelaert M (2005) Trypanosomiasis control, Democratic Republic of Congo, 1993–2003. Emerg Infect Dis 11(9):1382–1388

Lutumba P, Makieya E, Shaw A, Meheus F, Boelaert M (2007) Human African trypanosomiasis in a rural community, Democratic Republic of Congo. Emerg Infect Dis 13(2):248–254

Magez S, Caljon G, Tran T, Stijlemans B, Radwanska M (2010) Current status of vaccination against African trypanosomiasis. Parasitology 137(14):2017–2027

Magnus E, Vervoort T, Van Meirvenne N (1978) A card-agglutination test with stained trypanosomes (C.A.T.T.) for the serological diagnosis of T. B. gambiense trypanosomiasis. Ann Soc Belg Med Trop 58(3):169–176

Malvy D, Chappuis F (2011) Sleeping sickness. Clin Microbiol Infect 17(7):986–995

Mitashi P, Hasker E, Lejon V, Kande V, Muyembe JJ, Lutumba P, Boelaert M (2012) Human african trypanosomiasis diagnosis in first-line health services of endemic countries, a systematic review. PLoS Negl Trop Dis 6(11):e1919

Mitashi P, Hasker E, Ngoyi DM, Pyana PP, Lejon V, Van der Veken W, Lutumba P, Buscher P, Boelaert M, Deborggraeve S (2013) Diagnostic accuracy of loopamp trypanosoma brucei detection kit for diagnosis of human African trypanosomiasis in clinical samples. PLoS Negl Trop Dis 7(10):e2504

Mitashi P, Hasker E, Mbo F, Van Geertruyden JP, Kaswa M, Lumbala C, Boelaert M, Lutumba P (2015) Integration of diagnosis and treatment of sleeping sickness in primary healthcare facilities in the Democratic Republic of the Congo. Trop Med Int Health 20(1):98–105

Molyneux DH (1973) Isolation of trypanosoma (trypanozoon) brucei gambiense in rabbits by the intratesticular inoculation technique. Ann Trop Med Parasitol 67(4):391–397

Moore A, Richer M (2001) Re-emergence of epidemic sleeping sickness in southern Sudan. Trop Med Int Health 6(5):342–347

Mpanya A, Hendrickx D, Vuna M, Kanyinda A, Lumbala C, Tshilombo V, Mitashi P, Luboya O, Kande V, Boelaert M, Lefevre P, Lutumba P (2012) Should I get screened for sleeping sickness? A qualitative study in Kasai province, Democratic Republic of Congo. PLoS Negl Trop Dis 6(1):e1467

Mugasa CM, Katiti D, Boobo A, Lubega GW, Schallig HD, Matovu E (2014) Comparison of nucleic acid sequence-based amplification and loop-mediated isothermal amplification for diagnosis of human African trypanosomiasis. Diagn Microbiol Infect Dis 78(2):144–148

Murray CJ et al (2012) Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the global burden of disease study 2010. Lancet 380(9859):2197–2223

Nkinin SW, Njiokou F, Penchenier L, Grebaut P, Simo G, Herder S (2002) Characterization of trypanosoma brucei s.l. subspecies by isoenzymes in domestic pigs from the Fontem sleeping sickness focus of Cameroon. Acta Trop 81(3):225–232

Paquet C, Castilla J, Mbulamberi D, Beaulieu MF, Gastellu Etchegorry MG, Moren A (1995) Trypanosomiasis from trypanosoma brucei gambiense in the center of north-west Uganda. Evaluation of 5 years of control (1987–1991). Bull Soc Pathol Exot 88(1):38–41

Pepin J, Meda HA (2001) The epidemiology and control of human African trypanosomiasis. Adv Parasitol 49:71–132

Pepin J, Milord F (1994) The treatment of human African trypanosomiasis. Adv Parasitol 33:1–47

Politi C, Carrin G, Evans D, Kuzoe FA, Cattand PD (1995) Cost-effectiveness analysis of alternative treatments of African gambiense trypanosomiasis in Uganda. Health Econ 4(4):273–287

Priotto G, Kasparian S, Mutombo W, Ngouama D, Ghorashian S, Arnold U, Ghabri S, Baudin E, Buard V, Kazadi-Kyanza S, Ilunga M, Mutangala W, Pohlig G, Schmid C, Karunakara U, Torreele E, Kande V (2009) Nifurtimox-eflornithine combination therapy for second-stage African trypanosoma brucei gambiense trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. Lancet 374(9683):56–64

Robays J, Bilengue MM, Van der Stuyft P, Boelaert M (2004) The effectiveness of active population screening and treatment for sleeping sickness control in the Democratic Republic of Congo. Trop Med Int Health 9(5):542–550

Robays J, Lefevre P, Lutumba P, Lubanza S, Kande Betu KMV, Van der Stuyft P, Boelaert M (2007) Drug toxicity and cost as barriers to community participation in HAT control in the Democratic Republic of Congo. Trop Med Int Health 12(2):290–298

Schmid C, Kuemmerle A, Blum J, Ghabri S, Kande V, Mutombo W, Ilunga M, Lumpungu I, Mutanda S, Nganzobo P, Tete D, Mubwa N, Kisala M, Blesson S, Mordt OV (2012) In-hospital safety in field conditions of nifurtimox eflornithine combination therapy (NECT) for T. b. gambiense sleeping sickness. PLoS Negl Trop Dis 6(11):e1920

Shaw AP, Tirados I, Mangwiro CT, Esterhuizen J, Lehane MJ, Torr SJ, Kovacic V (2015) Costs of using "tiny targets" to control glossina fuscipes fuscipes, a vector of gambiense sleeping sickness in Arua District of Uganda. PLoS Negl Trop Dis 9(3):e0003624

Simarro PP, Sima FO, Mir M, Mateo MJ, Roche J (1991) Control of human African trypanosomiasis in Luba in equatorial Guinea: evaluation of three methods. Bull World Health Organ 69(4):451–457

Simarro PP, Franco JR, Asumu PN (2001) Has the focus of human African trypanosomiasis in Luba, Equatorial Guinea been eradicated? Med Trop (Mars) 61(4–5):441–444

Simarro PP, Cecchi G, Paone M, Franco JR, Diarra A, Ruiz JA, Fevre EM, Courtin F, Mattioli RC, Jannin JG (2010) The atlas of human African trypanosomiasis: a contribution to global mapping of neglected tropical diseases. Int J Health Geogr 9:57

Simarro PP, Cecchi G, Franco JR, Paone M, Diarra A, Ruiz-Postigo JA, Fevre EM, Mattioli RC, Jannin JG (2012a) Estimating and mapping the population at risk of sleeping sickness. PLoS Negl Trop Dis 6(10):e1859

Simarro PP, Franco JR, Cecchi G, Paone M, Diarra A, Ruiz Postigo JA, Jannin JG (2012b) Human African trypanosomiasis in non-endemic countries (2000–2010). J Travel Med 19(1):44–53

Sternberg JM (2004) Human African trypanosomiasis: clinical presentation and immune response. Parasite Immunol 26(11–12):469–476

Sternberg JM, Gierlinski M, Bieler S, Ferguson MA, Ndung'u JM (2014) Evaluation of the diagnostic accuracy of prototype rapid tests for human African trypanosomiasis. PLoS Negl Trop Dis 8(12):e3373

Tarral A, Blesson S, Mordt OV, Torreele E, Sassella D, Bray MA, Hovsepian L, Evene E, Gualano V, Felices M, Strub-Wourgaft N (2014) Determination of an optimal dosing regimen for fexinidazole, a novel oral drug for the treatment of human African trypanosomiasis: first-in-human studies. Clin Pharmacokinet 53(6):565–580

Torreele E, Bourdin TB, Tweats D, Kaiser M, Brun R, Mazue G, Bray MA, Pecoul B (2010) Fexinidazole–a new oral nitroimidazole drug candidate entering clinical development for the treatment of sleeping sickness. PLoS Negl Trop Dis 4(12):e923, available from: PM:21200426

Urech K, Neumayr A, Blum J (2011) Sleeping sickness in travelers – do they really sleep? PLoS Negl Trop Dis 5(11):e1358

Van Hoof LM (1947) Observations on trypanosomiasis in the Belgian Congo. Trans R Soc Trop Med Hyg 40(6):728–761

Van Nieuwenhove S, Betu-Ku-Mesu VK, Diabakana PM, Declercq J, Bilenge CM (2001) Sleeping sickness resurgence in the DRC: the past decade. Trop Med Int Health 6(5):335–341

Vreysen MJ (2001) Principles of area-wide integrated tsetse fly control using the sterile insect technique. Med Trop (Mars) 61(4–5):397–411

Welburn SC, Fevre EM, Coleman PG, Odiit M, Maudlin I (2001) Sleeping sickness: a tale of two diseases. Trends Parasitol 17(1):19–24

WHO (1998) Control and surveillance of African trypanosomiasis. Report of a WHO expert committee. World Health Organ Tech Rep Ser 881:I–114

WHO (2013) Control and surveillance of human African trypanosomiasis. World Health Organ Tech Rep Ser 984:1–237

Leishmaniasis

Asrat Hailu, Daniel Argaw Dagne, and Marleen Boelaert

Contents

A. Hailu (✉)
Department of Microbiology, Immunology & Parasitology, School of Medicine, Addis Ababa University, Addis Ababa, Ethiopia
e-mail: hailu_a2004@yahoo.com

D.A. Dagne
Department of Control of Neglected Tropical Diseases (HTM/NTD), World Health Organization, 20, Avenue Appia, Geneva CH-1211, Switzerland
e-mail: daniel@who.int

M. Boelaert
Department of Public Health, Institute of Tropical Medicine, Nationalestraat 155, Antwerpen 2000, Belgium
e-mail: mboelaert@itg.be

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_5

Abstract Visceral leishmaniasis is widespread in East Africa with several foci in Ethiopia, Kenya, Somalia, South Sudan, Sudan, and Uganda. Outside this subregion, sporadic cases have been reported from Chad, Niger, Burkina Faso, and the Gambia. It causes frequent outbreaks in the savanna and forest areas where sand flies live around termite mounds and in soil cracks. Cutaneous leishmaniasis occurs throughout western and eastern Africa. A belt runs from Mauritania, Senegal, Burkina Faso, and Mali in the West, through Niger, Nigeria, and Cameroon, to Chad, Sudan, and Ethiopia in the East. Though their recognition as public health problem is growing, the leishmaniases remain one of the most neglected tropical diseases. Their control is still hampered by a lack of safe and efficacious drugs, easy diagnostics and effective vaccine, and vector control tools, especially so in sub-Saharan Africa.

Keywords Visceral leishmaniasis • Cutaneous leishmaniasis • HIV-leishmania coinfection • Sub-Saharan Africa • Epidemiology • Diagnosis • Treatment • Geographical distribution

Introduction

The leishmaniases are a diverse group of neglected tropical diseases affecting humans in 98 countries but all caused by at least 20 species of the protozoan parasite of the genus *Leishmania.* The disease manifestations range from self-healing cutaneous leishmaniasis (CL) to the mutilating mucocutaneous leishmaniasis (MCL) or diffuse cutaneous leishmaniasis and the life-threatening visceral leishmaniasis (VL). The World Health Organization (WHO) estimates there are approximately 0.2–0.4 million of new VL cases and 0.7–1.2 million of new CL cases per year (http://www.who.int/mediacentre/factsheets/fs375/en/). The disease does not rank high either on the political or on the research agenda of many countries as it typically affects the poorest of the poor (Boelaert et al. 2009).

At least 20 leishmania species are known to cause leishmaniases in man. The parasites are transmitted to humans through the bite of a blood-sucking female sand fly. Over 90 species of sand flies are proven or suspected to transmit the diseases in various parts of the world (WHO 2010). The parasites are morphologically dimorphic in their life cycle, transforming from the extracellular promastigote stage in the sand fly gut to the intracellular amastigote stage in the mammalian host. Several leishmania species are transmitted in a zoonotic cycle, with dogs or rodents as animal reservoir, but others are strictly anthroponotic.

VL is endemic in at least 79 countries with an estimated annual incidence of 200,000–400,000 new cases per year (Alvar et al. 2012), over 90 % being reported from the Indian subcontinent, East Africa, and Brazil. Two distinct leishmania species cause VL: *Leishmania donovani* and *L. infantum/L. chagasi*, which are transmitted by sand flies of the genera *Phlebotomus* and *Lutzomyia. L. infantum/chagasi*

is found mainly in the Mediterranean littoral (North Africa, South Europe, and western Middle East) and South America, whereas *L. donovani* is restricted to the Indian subcontinent and sub-Saharan Africa and occurs sporadically in isolated foci of the Arabian subcontinent. Previously, *L. archibaldi* and *L. infantum* were also considered to cause VL in sub-Saharan Africa. However, recent molecular and evolutionary genetic analyses have annulled the existence of *L. archibaldi* as a separate species, and a revision of the taxonomy has led to a consensus that only *L. donovani* is causing VL in sub-Saharan Africa (Jamjoom et al. 2004).

With the advent of the HIV/AIDS epidemic, coinfection of HIV and VL has become an emerging public health problem and a challenge to clinical management of patients (Alvar et al. 2008). At least 35 countries in the world have reported cases of *HIV-leishmania* coinfections.

CL is caused by several species (or species complexes), mainly *L. braziliensis*, *L. guyanensis*, *L. panamensis*, *L. peruviana*, *L. mexicana*, *L. amazonensis*, *L. venezuelensis*, *L. major*, *L. tropica*, and *L. aethiopica*. Each year approximately 0.7–1.2 million cases of CL occur in at least 87 countries, the highest burden being in just 10 countries (Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica, and Peru (Alvar et al. 2012). In the Old World, major foci of anthroponotic *L. tropica* transmission stretch from India through central and western Asia into northern Africa; zoonotic transmission of *L. major* occurs from central Asia through western Asia into northern Africa, and *L. aethiopica* is confined to East Africa. However, the spectrum of skin pathology, the varied responses to treatments, the multitude of sand fly species and animal reservoirs involved in the life cycle, and the epidemiological complexities make these diseases intricately complex.

We will discuss below in more detail the epidemiological and clinical features of VL and CL in sub-Saharan Africa.

Visceral Leishmaniasis in Sub-Saharan Africa

Geographical Distribution

The eastern region of Africa is the epicenter of the VL epidemic and the major subregion of sub-Saharan Africa that is endemic to VL. On a global level, the subregion is the second important VL endemic zone, next to the Indian subcontinent, and leads to over 50,000 new cases each year (Alvar et al. 2012). The disease is widespread in this region with several foci identified in Ethiopia, Kenya, Somalia, South Sudan, Sudan, and Uganda. Isolated cases of VL have also been reported from Eritrea and from the Republic of Djibouti. Sporadic cases are also reported from Chad. The epidemiology varies hugely with geographical locations and ecological settings and typically exhibits micro-focal variation in its clinical and epidemiological characteristics.

The most important VL foci in the eastern Africa region are described below and shown in Fig. 1.

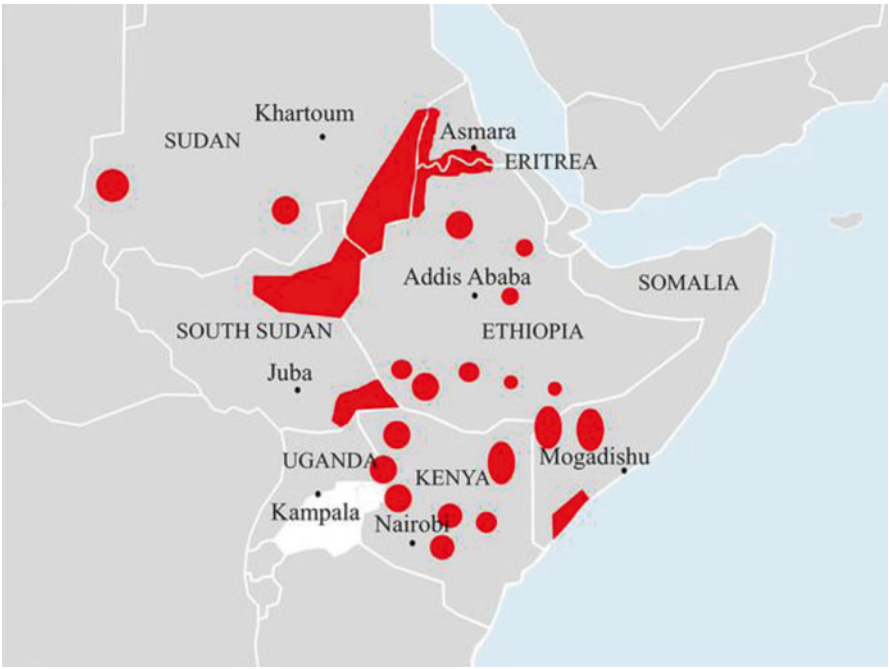


Fig. 1 The geographical distribution of visceral leishmaniasis in Eastern Africa sub-region

Eritrea The eastern lowlands that abound the Red Sea littoral, which includes localities of Algena and Nakfa (Northern Red Sea Region), the western lowlands of Anseba region (lowlands around Keren) bordering Kassala region in eastern Sudan, and Teseney (Gash-Barka region) in the west bordering northwest Ethiopia and Kassala in eastern Sudan are localities with potential VL transmission (Ayele and Ali 1984; Hailu et al., unpublished; Malaria Consortium 2010).

Ethiopia The disease is widespread throughout the lowlands, being reported from over 40 isolated localities. Metema-Humera lowlands, which accounts for 60 % VL cases in Ethiopia, and the lowlands in South and southwest Ethiopia, e.g., Segen, Woitu, and Omo river plains, are the major endemic regions (Hailu et al. 2006). Other foci are in Borena and Guji zones (Moyale, Yabelo, Genale, Dawa) and in Burji district – South Ethiopia. Emerging VL foci have been identified in southeast Ethiopia, e.g., in Liben district (Guji zone of Oromia), and further east in the Somali region (Afder, Gode; Wabe Shebelle area) – eastern Ethiopia.

The 2005 outbreak in Libo Kemkem and Fogera districts (South Gondar zone) in Lake Tana Basin was curtailed after the lives of hundreds were claimed (Alvar et al. 2007). This outbreak has been attributed to large-scale seasonal migration of highlanders to the lowlands of northwest Ethiopia – a hot spot of VL transmission. An increasing number of VL cases are also being reported from Tahtay Adiyabo,

Badme, and Welkait districts in north Ethiopia (Hailu et al., unpublished). There also appears to be some isolated foci of VL in northeast Ethiopia (Timuga and Waja zone, middle and lower Awash valleys) and in the dry river valleys and gorges of central Ethiopia (Hailu et al., unpublished).

Kenya: The main VL foci are found in the Rift Valley counties (West Pokot, Baringo, Samburu), some localities of the northern county (i.e. Marsabit), eastern counties (Machakos, Kitui, Mwingi, Makueni), and northeastern counties (Mandera, Wajir, and Garissa) (Schaefer et al. 1994; Marlet et al. 2003; Tonui 2006). In the northeast, refugee camps around Dadaab and Hagadera have been affected. Secondary foci of VL are suspected to exist in areas around Turkana and the coastal counties (Tonui 2006).

The Republic of Djibouti Isolated cases are reported (Pratlong et al. 2005), but the exact locations of the transmission areas are unknown.

Somalia The geographical distribution of VL in Somalia is not very well known due to the absence of a surveillance system. An endemic source of kala-azar was first described by Baruffa (1965), and cases were reported from hospitals in Mogadishu and Kismayo. Presently, it is known to be endemic in the regions of Bay, Bakool, Gedo, and western Hiiraan (Marlet et al. 2003; Raguenaud et al. 2006). Based on historically documented cases, the Middle Shabelle and Lower Juba regions can be considered endemic.

South Sudan The catchment area of the White Nile in South Sudan is the main VL transmission area and includes the northern foci (Unity, Upper Nile, and Jonglei states) and the southern foci (eastern Equatoria State). Highly affected areas include localities like Bentiu in Unity State; Lankien in Jonglei State; and Paloich, Malakal, Ulang, Kiech Kuon, and Nasir in Upper Nile state. The Kapoeta focus is situated in eastern Equatoria (Abubakar et al. 2014). In South Sudan, epidemic hot spots are known to shift from location to location.

Sudan Gedaref State in eastern Sudan is presently the main VL focus in Sudan. The endemic localities in Gedaref State are located in the large expanse of forested landmass, including Dinder National Park, that are found north and east of the Rahad River and southwest of Atbara River. This region borders the lowlands of northwestern Ethiopia. In the past, major VL outbreaks have occurred in Blue Nile State (reviewed in: Osman et al. 2000) just north of Upper Nile state (South Sudan) and in displaced people in Khartoum in the late 1980s. Other foci are found in Sennar, Darfur, and Kordofan states (Malaria Consortium 2010).

Uganda VL has a limited distribution in the northeastern region of the country, mainly in Pokot region that is contiguous with the Kenyan VL focus in Pokot region (Kolaczinski et al. 2008). The majority of the patients come from Nakapiripirit District, while other adjacent districts are also reporting sporadic cases.

Chad VL has occurred sporadically in the N'Djamena and Lake Chad areas, with foci extending eastward throughout southern Chad (Sirol et al. 1976).

Transmission Pattern, Incidence Rates, and Impact

The transmission patterns of VL in sub-Saharan Africa exhibit significant variation between the different ecological foci. In East Africa, VL is characterized by two distinct disease ecologies, and each exhibits a specific clinical phenotype. VL in Sudan is characterized by high frequency of lymphadenopathy and high rates of Post-kala-azar dermal leishmaniasis (which sharply contrasts with the lower rates in neighboring countries). Moreover, the response to treatment does seem lesser in Sudan with various antileishmanial drugs, e.g., paromomycin (Hailu et al. 2010) and liposomal amphotericin B (Khalil et al. 2014) than in other patient cohorts in neighboring countries. Entomological and parasitological data also show the existence of possibly two ecotypes of VL in the East African region.

Based on 2004–2009 data, the annual incidence of VL in eastern Africa was estimated between 29,400 and 56,700 (Alvar et al. 2012), with Sudan and South Sudan accounting for nearly 80 % of the burden. Based on this estimate, the annual incidence ranges per country were as follows: Sudan (15,700–30,300), South Sudan (7400–14,200), Ethiopia (3700–7200), Somalia (1400–2700), Kenya (610–1200), Uganda (350–520), and Eritrea (200–400).

Because VL has a focal distribution, the global figures do not reflect the real importance of VL in certain communities. Reported incidence rates of kala-azar in endemic areas vary between 2/1000 person-years in Kenya (Schaefer et al. 1995) and 6.9/1000 person-years in Ethiopia (Ali and Ashford 1994). In a community in eastern Sudan, a 38.5/1000 person-years incidence rate was documented (Zijlstra et al. 1994). These relatively low incidence rates reflect the endemic state, but VL can also strike populations that are weakened for other reasons with devastating epidemics.

In Sudan, since Neave reported the first case of VL in 1904, the disease had an endemic appearance until the 1940s. The first outbreak reaching epidemic proportions was reported by Stephenson near the town of Melut in Upper Nile province, where 300 cases occurred with a case fatality rate of 80 % (Stephenson 1940). The second major outbreak was reported in 1956 with reportedly "thousands of cases" surveyed in southern Fung. Sati investigated and confirmed the outbreak in a small community of 5000, the Jum Jum tribe, among which the disease had an attack rate of 10 % and a case fatality ratio (CFR) of 41 % (Sati 1958). Since then, VL has continued unabated in Sudan in its endemic or epidemic form, often exacerbated by the cumulative effects of famine and civil war (de Beer et al. 1991; Seaman et al. 1996). Seaman et al. (1996) described a devastating epidemic in South Sudan where over the period 1984–1994, an estimated 100,000 VL deaths occurred in a group of 280,000 people living in western Upper Nile province. Forced migration due to the civil war was a major factor in transmission, and the poor nutritional status of the population contributed to the high mortality rates. This region of South Sudan has paid a huge death toll due to VL, depicting the significance of the disease to humankind.

A recent outbreak has similarly affected the highlands of northern Ethiopia, even though the death toll was much lower than in South Sudan (Alvar et al. 2007). There

is consensus among experts that over many decades, the incidence of VL in Ethiopia has increased. This is largely attributed to migrations and new settlements driven by war or dire economic conditions in the region. The large-scale agricultural farms that attract several thousands of manual laborers, often recruited from poor farming communities of the highland fringes, are a major factor. A case in point is that of northwestern Ethiopia, where the incidence has in two decades increased tenfold from just a few hundred in the mid-1990s (numbers were 56 in 1995 and 165 in 1996). Population movements or invasion of previously unoccupied habitats by way of new settlement schemes or deforestation by large-scale farms have probably led to a closer association between humans and the animal reservoirs creating conducive environment for increased transmission. This phenomenon appears to be a consistent pattern throughout the eastern Africa region. Food insecurity forcing people to migrate or leading to widespread malnutrition and unusual rainfall patterns were considered to have played an important role in the emergence of VL as an important health problem in Bakool region of Somalia (Marlet et al. 2003).

HIV-VL coinfection can also be one of the drivers of transmission, as coinfected cases are very infectious to sand flies. In Ethiopia, coinfection affects specific risk groups, e.g., military personnel and migrant workers. Presently significant percentages (10–40 %) of VL patients in northern Ethiopia suffer from the coinfection, and there are some indications that it is also a growing problem in South Sudan and Sudan.

The Disease: Clinical Manifestations, Diagnosis, and Treatment

Clinical Features of VL, Complications, and Comorbidities

Visceral leishmaniasis manifests as a prolonged but irregular fever with weight loss, hepatosplenomegaly, lymphadenopathy, pancytopenia, and hypergammaglobulinemia (Fig. 2). Thrombocytopenia may cause uncontrollable epistaxis or bleeding from other sites. The course of the disease is insidious, yet carries a high risk of mortality in the advanced stages, which is characterized by emaciation, severe anemia, bleeding, jaundice, diarrhea, and severe neutropenia. Comorbid conditions – mainly superinfections (e.g., bacterial pneumonia) – and late presentations are risk factors for adverse prognosis and death. Differential diagnosis for VL must consider malaria, relapsing fever, typhoid fever, schistosomiasis, tuberculosis, AIDS, brucellosis, chronic hepatitis, cirrhosis, lymphomas, and leukemia (http:www.who.int/leishmaniasis/surveillance/.../en/WHO_LEISH_96.40.pdf). In American VL, HIV coinfection, dyspnea, bacterial infections, and age <5 or >40–45 were identified as significant predictors of bad prognosis (Belo et al. 2014). Similarly, among northern Ethiopian patients, age above 45, HIV coinfection, edema, severe malnutrition, pneumonia, tuberculosis, and vomiting were associated with high mortality (Herrero et al. 2009). Bacterial sepsis was a common finding among northern Ethiopian VL patients, 17.1 % (12 out of 70) in HIV-negative and 30.8 % (3 out of 13) in

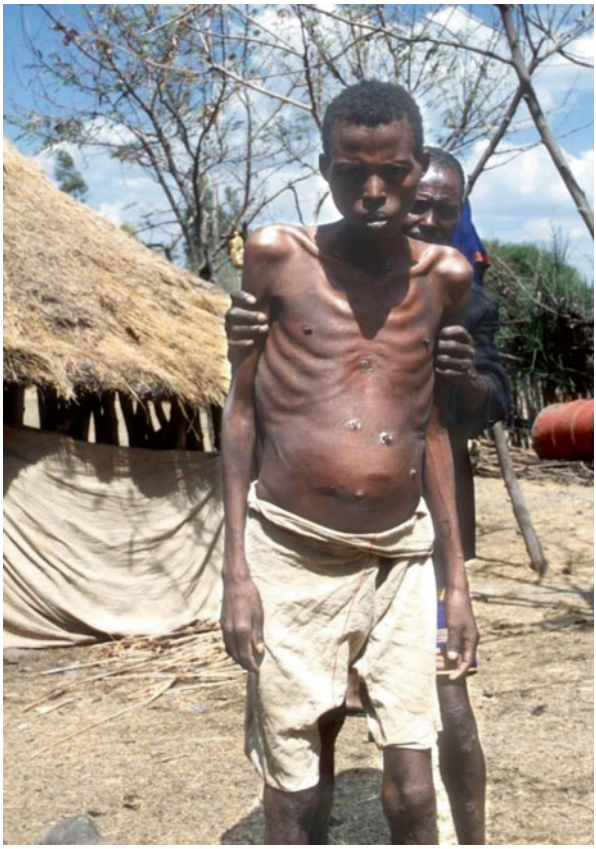


Fig. 2 Late stage visceral leishmaniasis

HIV-positive patients (Endris et al. 2014). Malnutrition and intestinal parasitosis were highly prevalent among VL patients in northern Ethiopia (Mengesha et al. 2014; Endris et al. 2014). Malaria coinfection exacerbates signs and symptoms of VL and complicates the presentation at onset. In a retrospective case-control study among Sudanese patients, emaciation, anemia, jaundice, and mortality were found to be positively associated with malaria coinfection (van den Bogaart et al. 2013). Pulmonary tuberculosis, pneumonia, and diarrhea are common comorbid conditions that could lead to death. Hyperglobulinemia is a typical feature of VL that accompanies profound cellular immune suppression. The suppression of cell-mediated immunity predisposes patients to intercurrent infections with pulmonary tuberculosis and pneumonia. In Mediterranean VL, 50 % of patients with HIV coinfection met the AIDS-defining criteria during the first episode of VL (Russo et al. 2003). There is now consensus that VL should be considered as an AIDS-defining illness (stage IV diagnosis) irrespective of the CD4 count. HIV coinfection in VL is associated with failure of treatment and frequent relapses. Coinfected patients tend to enter a chronic carrier state despite high parasitemic index in multiple organs.

Post-kala-azar dermal leishmaniasis (PKDL) is a dermal complication of visceral leishmaniasis mostly occurring in treated patients. It is characterized by macular, maculopapular, and nodular rashes in the skin especially in the exposed body parts (mainly in the face, neck, trunk, and limbs). Mucosal involvement is a common complication. Ocular involvement can manifest as blepharoconjunctivitis or pan-uveitis (el Hassan et al. 1998) with a risk of causing blindness (Khalil et al. 2011). Most PKDL lesions in sub-Saharan Africa are self-resolving; however, severe and chronic lesions tend to be persistent, requiring treatment. The incidence of PKDL in treated VL patients can be higher than 50 % in Sudanese patients, whereas it is around 5–10 % in the Indian subcontinent (Ganguly et al. 2010). Interestingly, the interval between treatment for VL and emergence of PKDL also varies between the two continents, being within 6 months in Sudan and 2–3 years in India (Zijlstra et al. 2003). PKDL is associated with *L. donovani* and hence found in sub-Saharan Africa (mainly in Sudan and in northern Ethiopia to a lesser extent) and Asia except in HIV-coinfected patients where PKDL could also be associated with *L. infantum* infection. PKDL is also considered to play a role in transmission of VL, especially in the inter-epidemic period (Zijlstra et al. 2003). Several theories and hypotheses (parasite factors, immune pathogenesis, environmental factors, etc.) have been suggested to explain the pathogenesis of PKDL.

PKDL-like lesions are also reported in HIV-coinfected patients and are often regarded as either atypical presentation of HIV/AIDS (Boumis et al. 2006) or as a feature of IRIS in patients on HAART (Antinori et al. 2007; Gelanew et al. 2010; Celesia et al. 2014). Khalil et al. (2013) discussed PKDL as a paradoxical IRIS in HIV-negative VL patients.

Diagnosis of VL

In hospital settings, VL is diagnosed by parasitological examination of smears from stained tissue aspirates obtained either from the spleen, bone marrow, or lymph nodes. The choice of organ for tissue aspirates varies from facility to facility, country to country, and level of expertise and experience. In Sudan, most aspirates are from lymph nodes (Babiker et al. 2007), partly due to the high frequency of lymphadenopathy. In Ethiopia, Kenya, and Uganda, tissue aspirates are often obtained either from the spleen or bone marrow. Tissue aspiration procedures are generally considered invasive and thus not used at lower health facility settings. Instead, in peripheral health facilities, parasitological diagnosis is replaced by clinical diagnosis and/or serological tests. In VL control programs, the diagnostic approach is well articulated in national diagnosis and treatment guidelines and is guided by an algorithm that provides sign- and symptom-based case definition and often requiring the conduct of a serological test, usually a rapid test. When these are well organized, the approach helps to reduce morbidity and mortality from VL. However, the clinical symptoms and signs of VL can still be confused with other co-endemic diseases and require reasonable clinical skills. Malaria is often co-endemic as is schistosomiasis

and brucellosis. An operational case definition, therefore, requires exclusion of malaria.

Splenic samples are the most sensitive to detect amastigote stages of the parasite in stained tissue. Technically, splenic aspiration requires specific skill and could carry a risk of internal bleeding. Bone marrow punctures are painful to the patients and also less sensitive than splenic aspirates. Lymph node aspiration is simple and safe, but the least sensitive, aside from being somewhat painful.

To date, the majority of serological tests target the detection of antibodies rather than antigens in blood samples. Direct agglutination test (DAT) is the most frequently used antibody test owing to its relative simplicity of sample collection and test performance and the visual detection of end results. DAT can be performed on blood samples collected on Whatman filter papers. However, the test still requires basic laboratory facilities and a trained technician to perform titrations. In addition, test results are not readily available, requiring some hours of incubation.

Field-adapted rapid diagnostic tests have been developed and made available commercially as point-of-care tests. The development of rapid diagnostic tests has revolutionized the diagnosis of VL in control programs. Among the few rapid diagnostic tests that have evolved, the rk39 immunochromatographic (ICT) test in a dipstick or cassette format is best known and has been most extensively validated so far (Boelaert et al. 2014). Its sensitivity was found slightly lower in East Africa compared to the Indian subcontinent, and a negative test does not rule out completely the probability of VL. In such cases, a second more sensitive test as the DAT is recommended. A new immunochromatographic test, the rk28 that combines rk39 with other recombinant antigens (rk9, rk16, and rk26) is currently under clinical evaluation.

A latex agglutination test, KATEX, has also been developed for antigen detection in urine. Initial field trials have necessitated further improvements – a Cochrane analysis showed an overall sensitivity of only 63.6 % (Boelaert et al. 2014). Loop-mediated isothermal amplification (LAMP) is a simple molecular test for field use currently under development and clinical evaluation.

Treatment of VL in Sub-Saharan Africa

Until recent years, the standard treatment regimen for primary VL in sub-Saharan Africa was based upon a 30-day course of pentavalent antimonial compounds: sodium stibogluconate (SSG) or meglumine antimoniate (MA). Second-line treatments depended on availability of other medications (e.g., amphotericin B deoxycholate, usually in its lipid formulation). In the past, access to and options of treatments were limited. Presently, the main drugs which are in use for VL treatment include one or a combination of the following: proprietary sodium stibogluconate (Pentostam®, GSK), the generic sodium stibogluconate (SSG) produced by Albert David (Delhi, India), Glucantime® (meglumine antimoniate) produced by Aventis Pharma, miltefosine (Impavido ®), amphotericin B deoxycholate (Fungizone, Squibb), AmBisome® produced by Gilead Scientific Inc. in the USA, and

paromomycin (aminosidine sulfate) produced by Gland Pharma in India. Among these, miltefosine is the only oral treatment. Not all these drugs are included in the national essential drug list of the affected countries in the region, and supplies mostly come through international donors.

The WHO has recommended a 17-day course of combined SSG (20 mg/kg) and paromomycin (15 mg/kg) as a first-line treatment for eastern Africa region (WHO 2010). However, the 30-day course of pentavalent antimonials remains effective in sub-Saharan Africa. Paromomycin and miltefosine, when used as monotherapy, are less effective in sub-Saharan Africa compared to India, and their use is likely to be confined in combined treatments. In sub-Saharan Africa VL, AmBisome should be given in higher doses, for a total dose of 30 mg/kg in HIV-negative VL and at least 40 mg/kg in HIV-positive VL patients.

In eastern Africa, PKDL heals spontaneously within a year in 85 % of the cases (http://apps.who.int/iris/bitstream/10665/78608/1/9789241505215__eng.pdf). Treatment is indicated in patients with persistent lesions or in those where PKDL lesions are severe and disfiguring (grade II and III, WHO classifications), including those patients with ocular or oral mucosal involvement.

The WHO recommendations for PKDL treatment in the region include the following options: (1) a 30–60-day course of SSG, (2) a combination of paromomycin (17 days, 11 mg/kg base per day) and SSG (17–60 days, 20 mg/kg per day), and (3) liposomal amphotericin B (20 days, 2.5 mg/kg per day). Anecdotal data show that miltefosine could be an option to treat PKDL in HIV-coinfected patients (Belay et al. 2006) and may also be used in extended doses (28–60 days) in HIV-negative PKDL patients (unpublished observations). These regimens are protracted and not ideal, and thus, new short-course treatment regimens are urgently needed.

Patients with concomitant anterior uveitis and blepharoconjunctivitis need special precautions due to the high risk of inflammation that could lead to blindness during treatment (Khalil et al. 2011). A coadministration of steroid and atropine eye drops is recommended (el Hassan et al. 1998).

HIV–Leishmania Coinfection in Sub-Saharan Africa

In the northwestern lowlands of Ethiopia, high HIV infection among VL patients, up to 40 %, have been reported (Alvar et al. 2008; Diro et al. 2014). Such a high rate of coinfection in this area is unique and is attributed to the seasonal migration of teenagers and young adults to the lowlands of northern Ethiopia seeking employment in commercial-scale farms. In the agricultural fields of northern Ethiopia, most men are exposed to sand fly bites, while at the same time being predisposed to encounters of commercial sex. In northwest Ethiopia, the incidence of VL has increased since 1995 and expanded geographically. Whether or not HIV has played a role in this expansion is debated upon. However, the increasing agricultural activity and influx of huge populations to the lowlands have clearly led to an increasing burden of VL and HIV coinfection. Previously, Hailu and Berhe (2002) reported

HIV coinfection rate higher than 50 % among patients admitted in Addis Ababa hospitals. These patients were among those diagnosed in the late 1990s and early 2000s, and 98 % were soldiers or policemen that have been exposed to leishmania parasites in rural areas.

HIV coinfection of individuals exposed to leishmania has several untoward clinical and epidemiological consequences in both the HIV and leishmania infections. Firstly, HIV increases the risk of VL development in endemic areas due to the high risk of reactivation in the immune-compromised individuals (Saporito et al. 2013; Monge-Maillo et al. 2014). Secondly, HIV coinfection may obscure the diagnoses of VL due to atypical clinical presentations. Splenomegaly is often less frequent among HIV-coinfected patients (Cota et al. 2014); dermal manifestations are commoner (Ritmeijer et al. 2001; Puig and Pradinaud 2003; Gelanew et al. 2011), and invasion of mucosal membranes takes place (Puig and Pradinaud 2003). Thirdly, VL patients with HIV coinfection are difficult to treat and at high risk of eventually relapsing (Alvar et al. 2008; Diro et al. 2014). These patients are likely to suffer from intercurrent infections/illnesses requiring multiple treatments alongside the treatments for HIV and leishmania, and the majority of the drugs have well-documented toxicity that needs to be monitored. Fourthly, immune recovery-associated inflammatory syndrome could ensue during antiretroviral therapy and make the management ever challenging. Fifthly, early stages of HIV and leishmania infections may progress rapidly to AIDS and overt VL, respectively (Alvar et al. 2008). Sixthly, coinfected individuals, especially once VL is manifested, are highly infective to sand flies as they harbor high numbers of amastigotes in their peripheral blood (Molina et al. 2003).

Sand Flies: Ecology and Vector Capacity

Sand fly (Fig. 3) species transmitting VL in eastern Africa include *P. orientalis* (Gebre-Michael et al. 2010; Elnaiem 2011) and *P. martini* (Perkins et al. 1988; Gebre-Michael and Lane 1996). These species are restricted to specific habitats and affect the distribution of the disease. The latter species is uniquely associated with eroded termite hills in the arid and semiarid lowlands of southern Ethiopia (Gebre-Michael and Lane 1996), the Kapoeta focus in South Sudan (Elnaiem 2011), Kenya (Mutinga 1991), Somalia (Elnaiem 2011), and Uganda (Kolaczinski et al. 2008; Elnaiem 2011).

The main visceral leishmaniasis endemic areas in Sudan, South Sudan, and north Ethiopia are found in the Acacia-Balanites forests where *P. orientalis* is abundantly found during the drier seasons, usually between January and May. This species has been found naturally infected with *L. donovani* in Sudan (Schorscher and Goris 1992; Elnaiem et al. 1998; Hassan et al. 2008) and southwest Ethiopia (Hailu et al. 1995). Another species involved in VL transmission is *P. celiae* (Gebre-Michael and Lane 1996). Suspected, but unproven sand fly vector species are *P. vansomerenae* (Perkins et al. 1988; Gebre-Michael et al. 2013; Marlet et al. 2003), *P. alexandri* (Balkew et al. 1999), and *P. rodhaini* (Elnaiem et al. 2011). The latter was implied to transmit *L. donovani* between wild animal reservoir hosts in eastern Sudan.

Fig. 3 Sand fly

Animal Reservoirs of VL in Sub-Saharan Africa

Efforts to incriminate the potential animal reservoir(s) of VL in sub-Saharan Africa started in the 1950s and 1960s, especially in Sudan and Kenya. The work of Hoogstraal and colleagues in South Sudan demonstrated a few natural infections of rodents and small carnivores. Among rodents, natural infections were found in *Rattus rattus*, the spiny mouse (*Acomys sp*.) and *Arvicanthis niloticus* (Hoogstraal et al. 1963). Other species found with natural infections of leishmania were *Felis serval* and *Genetta sp.* (Hoogstraal and Dietlein 1964), a jackal (Sixl et al. 1987) and the Egyptian mongoose (Elnaiem et al. 2001). In Kenya, among 1128 wild rodents examined, none were found infected with *L. donovani* (Githure et al. 1996).

Dogs were among the most suspected domestic animals. A high rate of natural infection was found among 69 dogs examined in Barbar El Fugara, Gedaref State in Sudan (Dereure et al. 2003). However, in 2002, low rates of serological and PCR positivity were found among 87 dogs examined near Dinder National Park in eastern Sudan (Hassan et al. 2009). In an epidemiological investigation of the Libo Kemkem VL epidemic (north Ethiopia), a few PCR-confirmed infections of domestic dogs were also found (Bashaye et al. 2009). Contrastingly, Kalayou et al. (2011) reported a high seroprevalence rate among dogs in surveys carried out in north Ethiopia. In Kenya, there was also a report of natural infection of dogs (Mutinga et al. 1980).

Overall, the animal reservoir studies carried out so far remain inconclusive. Based on the field studies to date, no animal species could be singled out as a culprit. As a consequence, most authors and experts in the field of leishmaniasis prefer to consider VL in sub-Saharan Africa predominantly anthroponotic. Without precluding the existence of a natural source of infection in wild animals, many experts

would agree on the fact that the major epidemics of VL in sub-Saharan Africa are outcomes of man-to-man transmission, as has occurred in the war-ravaged South Sudan and in the intensified agricultural activities of north Ethiopia. However, the stable VL endemic regions of south Ethiopia, Kenya, and Uganda do suggest a role for a zoonotic cycle.

Regarding domestic animals other than dogs, serological surveys have indicated a high rate of seropositivity in donkeys, cows, sheep, and goats (Mukhtar et al. 2000).

Cutaneous Leishmaniasis in Sub-Saharan Africa

Geographical Distribution

In sub-Saharan Africa, *cutaneous leishmaniasis* is caused by *L. major*, *L. tropica*, *L. aethiopica*, or *L. donovani*. CL has been reported from 26 countries in the sub-Saharan region. There is no detailed epidemiological information about the exact burden and geographic distribution of the disease by country for most of the sub-Saharan Africa countries (Alvar et al. 2012).

Cutaneous leishmaniasis caused by *L. major* (also known as zoonotic or rural zoonotic cutaneous leishmaniasis) is the most widely distributed form. It has been reported from Burkina Faso, Cameroon, Central African Republic, Chad, Ethiopia, Ghana, Guinea, Guinea-Bissau, Kenya, Mali, Mauritania, Niger, Nigeria, Senegal, and Sudan. The lesions are painless unless complications occur. The lesions are often multiple, severely inflamed and ulcerated and heal within 2–8 months. In non-immune individuals, multiple confluent lesions are observed that are prone to secondary infection. Such lesions are often slow to heal and may leave large, disfiguring, or disabling scars.

Cutaneous leishmaniasis caused by *L. aethiopica* is prevalent in Ethiopia and has also been reported from Kenya and Uganda. It usually causes localized cutaneous nodular lesions and sometimes affects the nostrils and lips (Fig. 4) resulting in oronasal leishmaniasis or diffuse cutaneous leishmaniasis. Most lesions evolve slowly and may spread locally. Ulceration is late or sometimes absent. Spontaneous healing typically takes place within 2–5 years.

Cutaneous leishmaniasis caused by *L. tropica* (also known as anthroponotic or urban cutaneous leishmaniasis) is rare in sub-Saharan Africa. Sporadic cases have been reported from Ethiopia, Kenya, and Namibia. It causes painless, dry ulcers of the skin, which usually heal spontaneously within about 1 year, or sometimes longer, often leading to disfiguring scars.

Mucocutaneous Leishmaniasis

Mucosal lesions of leishmaniasis (Fig. 4) are rarely seen in the eastern hemisphere. It can be caused by any of the leishmania species. Mucosal lesions of the buccal mucosa or larynx caused by *L. infantum*, *L. major*, and *L. tropica* may present in

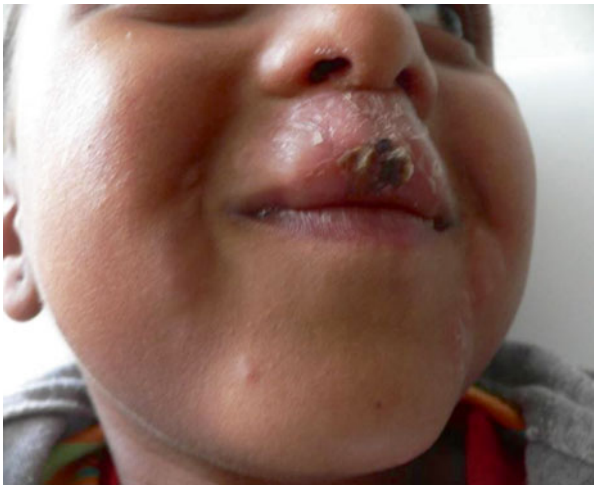


Fig. 4 Mucocutaneous leishmaniasis

elderly people or people with minor forms of immunosuppression. In sub-Saharan Africa very few cases of mucocutaneous leishmaniasis has been reported from Chad and Sudan and many cases from Ethiopia. Two cases of mucosal leishmaniasis have been reported from Senegal. Commonly, *L. aethiopica* infections tend to be infiltrative at the site of lesions, especially when lesions occur in the lip and nose, and produce starkly edematous chronic inflammation of the face involving the lips and nose.

Diffuse Cutaneous Leishmaniasis

Diffuse cutaneous leishmaniasis is caused by *L. aethiopica* and is characterized by widely disseminated cutaneous macules, papules, nodules, or plaques, or by diffuse infiltration of the skin, especially on extensor surfaces of the limbs and on the face, where thickening of the eyebrows and ear lobes may resemble lepromatous leprosy (Fig. 5). There is no ulceration. This disease does not heal spontaneously, and relapses are frequent after treatment. Most cases are reported from Ethiopia.

Transmission Pattern, Incidence Rates, and Impact

In sub-Saharan Africa, *L. major* and *L. aethiopica* cause zoonotic cutaneous leishmaniasis. The risk may be increased with expansion of agricultural projects and irrigation systems. These development activities and ecological changes are accompanied by the intrusion of large numbers of nonimmune immigrants into an existing sylvatic cycle of leishmaniasis. Transmission to humans is favored by the practice of sleeping outdoors without a bednet during the hot season. The risk for infection

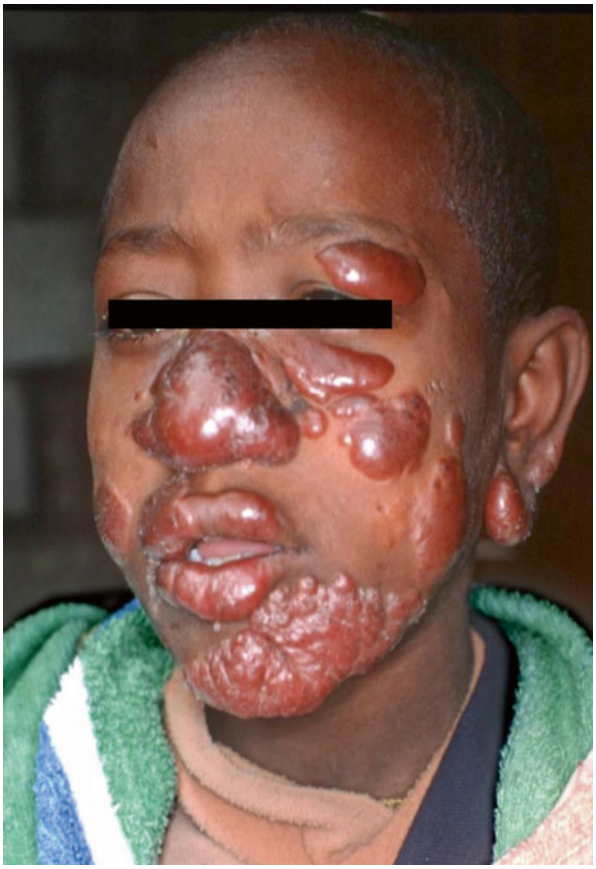


Fig. 5 Diffuse cutaneous leishmaniasis

is also increased by activities such as tourism and pilgrimages to endemic areas. In foci of cutaneous leishmaniasis caused by *L. aethiopica* in the highlands of Ethiopia and other places in East Africa, increased human–fly contact occurs in villages built on rock hills or river banks, which are the natural habitat of hyraxes (reservoir hosts) and the sand fly vectors (*P. longipes* and *P. pedifer)*.

Recently, increasing numbers of cases of cutaneous leishmaniasis have been reported from Ouagadougou, Burkina Faso, where a major outbreak occurred in the period 1999–2001 that continued with high incidence until 2005 (Bamba et al. 2013). In the Volta region in Ghana, in the period 2002–2003 around 8876 cases of possible CL have been reported after a survey that followed the outbreak in the area (Kweku et al. 2011). Outbreaks due to *L. aethiopica* have been described in the northwest, central, and southern parts of Ethiopia (Seid et al. 2014).

The Disease: Clinical Features, Diagnosis, and Treatment

Clinical Features

The clinical manifestations of cutaneous leishmaniasis vary according to species, but usually the lesion starts as a papule or nodule at the site of inoculation; it grows slowly, taking at least 1 week to reach its final size. A crust develops centrally, which may fall away, exposing an ulcer up to 5 cm in diameter with a raised edge and variable surrounding induration, which heals gradually over months or years. This often leaves a depressed scar with altered pigmentation. The differential diagnosis of cutaneous leishmaniasis is very broad as CL may resemble other skin conditions, such as staphylococcal or streptococcal infection, mycobacterial ulcer, leprosy, fungal infection, cancer, sarcoidosis, and tropical ulcer. As the clinical presentation of cutaneous leishmaniasis lacks specificity, and treatment is costly, long, or toxic, diagnostic confirmation is necessary.

Parasitological Diagnosis

Parasitological diagnosis remains the reference standard in diagnosis of cutaneous leishmaniasis because of its high specificity. The sensitivity varies over a wide range depending on the geographical location, species involved, and stage of the lesion. Multiple parasitological diagnostic tests should therefore be performed on each patient. Parasitological diagnosis can be performed by skin scraping, fine-needle aspiration, or biopsy of lesions. The material obtained by any of these methods can be used for microscopic examination, culture, and molecular diagnostic techniques.

Microscopic examination of Giemsa-stained material is often the only available method at primary, secondary, or tertiary health-care level in endemic areas. Culture of the parasite using simple blood agar media allows species identification and characterization. Detection of parasite nucleic acids by molecular diagnosis, essentially by PCR-based methods, improves the diagnostic sensitivity and allows identification of the leishmania species. Both culture and molecular-based diagnosis require substantial laboratory infrastructure and technical expertise, limiting their use to reference laboratories.

Treatment

Many different therapeutic interventions, including topical, systemic, and nonpharmacological treatments, have been proposed for CL. CL is not a life-threatening condition, and severe complications are infrequent. As superficial secondary infections may complicate ulcerated CL, it is important to clean lesions. CL due to

L. major is usually associated with a self-cure rate >50 % at 6 months. Normally, the recommended drug or treatment approach in CL should not induce life-threatening complications; however, in severe cases, the risk–benefit ratio is different. The treatment decision is based firstly on the risk–benefit ratio of the intervention for each patient. The use of a treatment option with a risk for severe adverse events is acceptable if the patient suffers from numerous (typically, more than four), disfiguring face or complicated lesions, the size or location of which makes local therapy impossible, or if local therapy has been tried and failed. Appropriate attention to contraindications and follow-up are important. In patients with mild disease or with comorbid conditions, a safer treatment should be preferred, even if the level of evidence for efficacy is weak.

According to the recommendations of the WHO Technical Expert Group (WHO technical report series on the control of leishmaniasis # 949, 2010), local wound care with careful follow-up is indicated for patients fulfilling the following criteria:

- Confirmed or strongly suspected infection with *L. major*
- Fewer than four lesions requiring immediate treatment
- Lesions <5 cm in diameter
- No potentially disfiguring or disabling lesion (face, joints, toes, fingers)
- No immunosuppression
- Possibility for follow-up

The patient's agreement to this option must be obtained after a full explanation of the clinical risks and the inconvenience of other options. If at least one criterion is absent, local therapy should be proposed. Local therapy is an attractive option with little toxicity, but intralesional treatment and, to a much lesser degree thermotherapy, causes significant discomfort.

The options for *local therapy for L. major* are:

- Fifteen percent paromomycin/12 % methylbenzethonium chloride ointment twice daily for 20 days
- Intralesional antimonials, 1–5 ml per session plus cryotherapy (liquid nitrogen: 195 °C), both every 3–7 days (one to five sessions)
- Thermotherapy, one to two sessions with localized heat (50 °C for 30 s)
- Intralesional antimonials or cryotherapy independently, as above

Local therapy for ***L. tropica, L. aethiopica,* and L. infantum****

- Fifteen percent paromomycin/12 % methylbenzethonium chloride ointment, twice daily for 20 days
- Intralesional antimonials plus cryotherapy, as above
- Thermotherapy, one to two sessions with localized heat (50 °C for 30 s)
- Intralesional antimonials, alone, as above
- Cryotherapy, alone, as above

Systemic therapy in L. major

- Fluconazole, 200 mg oral daily for 6 weeks
- Pentavalent antimonials, 20 mg Sb5+/kg per day intramuscularly or intravenously for 10–20 days
- Pentavalent antimonials, 20 mg Sb5+/kg per day intramuscularly or intravenously plus pentoxifylline, 400 mg three times a day for 10–20 days

*Systemic therapy in L. tropica and L. infantum**

- Pentavalent antimonials, 20 mg Sb5+/kg per day intramuscularly or intravenously for 10–20 days
- Pentavalent antimonials, 15–20 mg Sb5+/kg per day intramuscularly or intravenously for 15 days plus oral allopurinol 20 mg/kg for 30 days, to treat leishmaniasis recidivans caused by *L. tropica*

*Systemic therapy in **L. aethiopica***

- Pentavalent antimonials 20 mg Sb5+/kg per day intramuscularly or intravenously plus paromomycin, 15 mg (11 mg base)/kg per day intramuscularly for 60 days or longer to treat diffuse cutaneous leishmaniasis.
- Anectodal observations indicate miltefosine could be a treatment option for *L. aethiopica* infections. This needs to be verified by well-documented studies. An in vitro study using the amastigote–macrophage model has also confirmed the high susceptibility of *L. aethiopica* to miltefosine (Utaile et al. 2013).

HIV–Leishmania Coinfection in Patients with CL

Cutaneous leishmaniasis and HIV coinfection have been reported from Ethiopia, Burkina Faso (Guiguemdé et al. 2003), and Sudan (Mukhtar et al. 2010). The coinfection translates into atypical CL presentations including extensive ulceration or dissemination, increased mucosal involvement, erysipeloid, sporotrichoid forms, and multiple locations.

Sand Flies

In most of the 26 endemic countries in sub-Saharan Africa, the vectors are unknown. However, the following sand fly species were identified as proven and suspected vectors so far: *P. duboscqi*, *P. bergeroti*, *P. longipes*, *P. pedifer*, *P. sergenti*, *P. saevus*, *P. papatasi*, *and P. rossi* (Maroli et al. 2013; Gebre-Michael et al. 2004; Hailu et al. 2006).

Animal Reservoirs

Rock hyraxes (Procavia capensis and Heterohyrax brucei) and several rodent species (e.g., *Arvicanthis* spp., *Tatera* spp., *Xerus* spp., etc.) are known or suspected animal reservoir hosts of cutaneous leishmaniasis in sub-Saharan African countries (Gramiccia and Gradoni 2005; Hailu et al. 2006).

Perspectives on Leishmaniasis Control and Research for the Next Decade

Epidemiology

Unfortunately, leishmaniasis in the sub-Saharan region remains a largely ignored and a poorly described disease. The control of the leishmaniases from sub-Saharan Africa requires a better description of the epidemiology and understanding of factors that sustain transmission. The complexity and the host of biological factors that characterize the disease epidemiology and clinical presentations need to be unraveled. The basic biology, pathogenesis, and ecology of the diseases still have many unknowns that need to be addressed. Access to knowledge and tools that could be used to predict outbreaks is limited.

Today tremendous efforts are made to eliminate VL from the Indian subcontinent. The lessons learned will be vital to the planning of a similar elimination program in sub-Saharan Africa. However, it is clear that VL in sub-Saharan Africa is a much more complex disease, requiring the unraveling of knowledge gaps that abound pathogenesis, transmission, sand fly biology, and ecology. The role of asymptomatic infections of humans in transmission is currently a subject under investigation. Ongoing studies by xenodiagnosis are expected to give some clues.

Diagnosis and Treatment

Efforts to simplify diagnostic and treatment approaches should be intensified, as these are crucial for control. The development of an rK39-based antibody detection test has been a major breakthrough for VL control programs, but it is certainly not a panacea. The use of these tests is restricted to patients (1) who have a clear clinical syndrome of febrile splenomegaly and (2) who had no VL ever before and this due to the well-known limitations of antibody detection. Many people who live in endemic villages develop an asymptomatic infection and clear it without ever needing treatment, but they will show a positive rK39-RDT. Also,

after treatment, a genuine VL patient will keep its antibodies for a median 9 months, and a positive test in a patient relapsing with fever is by no means diagnostic for VL. The current antibody detection technology used in the VL RDTs neither does it allow the monitoring of treatment outcome nor confirmation of cure or diagnosis of relapse. Moreover, the rK39-based antibody detection tests are not optimally sensitive in East Africa, and a negative test does not rule out disease. Therefore, improved rapid tests are needed, preferably based on antigen detection systems.

Investment in drug development is badly needed to fill the pipeline with novel compounds, as the efficacy of all of the newly developed drugs has been suboptimal in East Africa. There is a need for practical tools to monitor emerging drug resistance. The challenges of clinical management of HIV/leishmanial coinfection are not well addressed.

Prevention

An effective vaccine would significantly improve VL control, as would new methods of vector control to prevent human infection. Insecticide-treated nets (ITNs) have been evaluated for the control of VL and CL; however, their effectiveness is very variable depending on the context. There are currently no arguments for the wide-scale use of ITNs alone for interrupting transmission of endemic VL in sub-Saharan Africa where transmission is largely in extradomestic environments.

Conclusion

In so far as VL and PKDL are anthroponotic, their treatment not only reduces morbidity and mortality but also curtails transmission. Given the current absence of a vaccine and effective vector control tools, it is likely that early diagnosis by passive and active surveillance using a combination of screening and confirmatory tests coupled with prompt treatment will be the cornerstone of the control strategy for the years to come. While control efforts need to be enhanced, research needs to be carried out in deciphering transmission dynamics that will be a stepping point for future elimination of VL in sub-Saharan Africa. The ministries of health, disease control programs, and other stakeholders together with academic institutions should draw a common agenda to promote research directed toward control of VL. Ease of access to tested and proven VL control tools, be it novel diagnostics and treatments, should be guaranteed by way of registration and quality-assured procurement and supply. Access to diagnostics and treatment is undoubtedly the single most important element of the control of the leishmaniasis in sub-Saharan Africa today.

References

Abubakar A, Ruiz-Postigo JA, Pita J, Lado M, Ben-Ismael R et al (2014) Visceral leishmaniasis outbreak in south Sudan 2009–2012: epidemiological assessment and impact of a multisectoral response. PLoS Negl Trop Dis 8(3):e2720. doi:10.1371/journal.ontd.0002720

Ali A and Ashford RW (1994) Visceral leishmaniasis in Ethiopia. IV. Prevalence, incidence and relation of infection to disease in an endemic area. Ann Trop Med Parasitol 88(3):289–293

Alvar J, Bashaye S, Argaw D, Cruz I, Aparicio P, Kassa A et al (2007) Kala-azar outbreak in Libo Kemkem, Ethiopia: epidemiologic and parasitologic assessment. Am J Trop Med Hyg 77(2):275–282

Alvar J, Aparicio P, Aseffa A, Den Boer M, Canavate C, Dedet JP et al (2008) The relationship between leishmaniasis and AIDS: the second 10 years. Clin Microbiol Rev 21(2):334–359

Alvar J, Velez ID, Bern C, Herrero M, Desjeux P, Cano J, Jannin J et al (2012) Leishmaniasis worldwide and global estimates of its incidence. PLoS One 7(5):e35671. doi:10.1371/journal.pone.0035671

Antinori S, Longhi E, Bestetti G, Piolini R, Acquaviva V, Foschi A et al (2007) Post-kala-azar dermal leishmaniasis as an immune reconstitution inflammatory syndrome in a patient with acquired immune deficiency syndrome. Br J Dermatol 157(5):1032–1036

Ayele T, Ali A (1984) The distribution of visceral leishmaniasis in Ethiopia. Am J Trop Med Hyg 33(4):548–552

Babiker ZO, Davidson R, Mazinda C, Kipngetich S, Ritmeijer K (2007) Utility of lymph node aspiration in the diagnosis of visceral leishmaniasis in Sudan. Am J Trop Med Hyg 76(4):689–693

Balkew M, Hailu A, Berhe N, Gemetchu T (1999) Leishmaniasis in the lower Omo plains, southwest Ethiopia: the sand fly fauna. Ethiop Med J 37:31–40

Bamba S, Gouba A, Drabo MK, Nezien D, Bougoum M, Guiguemdé TR (2013) Epidemiological profile of cutaneous leishmaniasis: retrospective analysis of 7444 cases reported from 1999 to 2005 at Ouagadougou, Burkina Faso. Pan Afr Med J 14:108. doi:10.11604/pamj.2013.14.108.1140

Baruffa G (1965) Kala-azar among the nomads of the middle Webi shebeli region; first report of a confirmed endemic source of kala-azar in Somalia. Trans R Soc Trop Med Hyg 59(6):705–708

Bashaye S, Nombela N, Argaw D, Mulugeta A, Herrero M, Nieto J et al (2009) Risk factors for visceral leishmaniasis in a new epidemic site in Amhara Region, Ethiopia. Am J Trop Med Hyg 81(1):34–39

Belay AD, Asafa Y, Mesure J, Davidson RN (2006) Successful miltefosine treatment of post-kala-azar dermal leishmaniasis occurring during antiretroviral therapy. Ann Trop Med Parasitol 100(3):223–227

Belo VS, Struchiner CJ, Barbosa DS, Nascimento BW, Horta MA, da Silva ES, Werneck GL (2014) Risk factors for adverse prognosis and death in American visceral leishmaniasis: a meta-analysis. PLoS Negl Trop Dis 8(7):e2982. doi:10.1371/journal.pntd.0002982

Boelaert M, Meheus F, Sanchez A, Singh SP, Vanlerberghe V, Picado A, Meessen B, Sundar S (2009) The poorest of the poor: a poverty appraisal of households affected by visceral leishmaniasis in Bihar, India. Trop Med Int Health 14(6):639–644

Boelaert M, Verdonck K, Menten J, Sunyoto T, van Griensven J, Chappuis F, Rijal S (2014) Rapid tests for the diagnosis of visceral leishmaniasis in patients with suspected disease. Cochrane Database Syst Rev 6:CD009135. doi:10.1002/14651858.CD009135.pub2

Boumis E, Chinello P, Della Rocca C, Paglia MG, Proietti MF, Petrosillo N (2006) Atypical disseminated leishmaniasis resembling post-kala-azar dermal leishmaniasis in an HIV-infected patient. Int J STD AIDS 17(5):351–353

Celesia BM, Cacopardo B, Massimino D, Gussio M, Tosto S, Nunnari G, Pinzone MR (2014) Atypical presentation of PKDL due to Leishmania infantum in an HIV-infected patient with relapsing visceral leishmaniasis. Case Rep Infect Dis 2014:370286. doi:10.1155/2014/370286

Cota GF, de Sousa MR, de Mendoca AL, Patrocinio A, Assuncao LS, de Faria SR, Rabello A (2014) Leishmania-HIV co-infection: clinical presentation and outcomes in an urban area in Brazil. PLoS Negl Trop Dis 8(4):e2816. doi:10.1371/journal.pntd.0002816

de Beer P, el Harith A, Deng LL, Semiao-Santos SJ, Chantel B and van Grootheest M. (1991) A killing disease epidemic among displaced Sudanese population identified as visceral leishmaniasis. Am J Trop Med Hyg 44(3):283–289

Dereure J, El-Safi SH, Bucheton B, Boni M, Kheir MM, Davoust B et al (2003) Visceral leishmaniasis in eastern Sudan: parasite identification in humans and dogs; host-parasite relationships. Microbes Infect 5(12):1103–1108

Diro E, Lynen L, Ritmeijer K, Boelaert M, Hailu A (2014) Visceral leishmaniasis and HIV coinfection in east Africa. PLoS Negl Trop Dis 8(6):e2869. doi:10.1371/journal.pntd.0002869

El Hassan AM, Khalil EA, el Sheikh EA, Zijlstra EE, Osman A, Ibrahim ME (1998) Post kala-azar ocular leishmaniasis. Trans R Soc Trop Med Hyg 92(2):177–179

Elnaiem DE (2011) Ecology and control of the sand fly vectors of Leishmania donovani in east Africa, with special emphasis of Phlebotomus orientalis. J Vector Ecol 36(Suppl 1):S23–S31. doi:10.1111/j.1948-7134.2011.00109.x

Elnaiem DA, Ward RD, Hassan HK, Miles MA, Frame IA (1998) Infection rates of Leishmania donovani in Phlebotomus orientalis from a focus of visceral leishmaniasis in eastern Sudan. Ann Trop Med Parasitol 92(2):229–232

Elnaiem DA, Hassan MM, Maingon R, Nureldin GH, Mekawi AM, Miles M, Ward RD (2001) The Egyptian mongoose, Herpestes ichneumon, is a possible reservoir host of visceral leishmaniasis in eastern Sudan. Parasitology 122(Pt 5):531–536

Elnaiem DE, Hassan HK, Osman OF, Maingon RD, Killick-Kendrick R, Ward RD (2011) A possible role for Phlebotomus (Anaphlebotomus) rodhaini (Parrot, 1930) in transmission of Leishmania donovani. Parasite Vectors 4:238. doi:10.1186/1756-3305-4-238

Endris M, Takele Y, Woldeyohannes D, Tiruneh M, Mohammed R, Moges F et al (2014) Bacterial sepsis in patients with visceral leishmaniasis in Northwest Ethiopia. Biomed Res Int 2014:361058. doi:10.1155/2014/361058

Ganguly S, Das NK, Barbhuiya JN, Chatterjee M (2010) Post-kala-azar dermal leishmaniasis – an overview. Int J Dermatol 49(8):921–931

Gebre-Michael T, Lane RP (1996) The roles of Phlebotomus martini and P. celiae (Diptera: Phlebotominae) as vectors of visceral leishmaniasis in the Aba Roba focus, southern Ethiopia. Med Vet Entomol 10(1):53–62

Gebre-Michael T, Balkew M, Ali A, Ludovisi A, Gramiccia M (2004) The isolation of *Leishmania tropica* and *L. aethiopica* from Phlebotomus (Paraphlebotomus) species (Diptera: Psychodidae) in the Awash Valley, northeastern Ethiopia. Trans R Soc Trop Med Hyg 98(1):64–70

Gebre-Michael T, Balkew M, Berhe N, Hailu A, Mekonnen Y (2010) Further studies on the phlebotomus sandflies of the kala-azar endemic lowlands of Humera-Metema (north-west Ethiopia) with observations on their natural blood meal sources. Parasite Vectors 3(1):6. doi:10.1186/1756-3305-3-6

Gebre-Michael T, Balkew M, Yimer M, Hailu A (2013) First record of Phlebotomus (Synphlebotomus) vansomerenae (Diptera: Psychodidae) in Ethiopia. J Med Entomol 50(3):659–663

Gelanew T, Amogne W, Abebe T, Kuhls K, Hailu A, Schonian G (2010) A clinical isolate of *Leishmania donovani* with ITS1 sequence polymorphism as a cause of para-kala-azar dermal leishmaniasis in an Ethiopian human immunodeficiency virus-positive patient on highly active antiretroviral therapy. Br J Dermatol 163(4):870–874

Gelanew T, Hurissa Z, Diro E, Kassahun A, Kuhls K et al (2011) Disseminated cutaneous leishmaniasis resembling post-kala-azar dermal leishmaniasis caused by Leishmania donovani in three patients co-infected with visceral leishmaniasis and human immuno-deficiency virus/acquired immune-deficiency syndrome in Ethiopia. Am J Trop Med Hyg 84:906–912

Githure JI, Ngumbi PM, Anjili CO, Luqalia R, Mwanyumba PM, Kinoti GK, Koech DK (1996) Animal reservoirs of leishmaniasis in Marigat, Baringo District, Kenya. East Afr Med J 73(1):44–47

Gramiccia M, Gradoni L (2005) The current status of zoonotic leishmaniases and approaches to disease control. Int J Parasitol 35(11–12):1169–1180

Guiguemdé RT, Sawadogo OS, Bories C, Traore KL, Nezien D, Nikiema L, Pratlong F, Marty P, Houin R, Deniau M (2003) Leishmania major and HIV co-infection in Burkina Faso. Trans R Soc Trop Med Hyg 97(2):168–169

Hailu A, Berhe N (2002) The performance of direct agglutination tests (DAT) in the diagnosis of visceral leishmaniasis among Ethiopian patients with HIV co-infection. Ann Trop Med Parasitol 96(1):25–30

Hailu A, Balkew M, Berhe N, Meredith SE, Gemetchu T (1995) Is Phlebotomus (Larroussius) orientalis a vector of visceral leishmaniasis in south-west Ethiopia? Acta Trop 60(1):15–20

Hailu A, Gebre-Michael T, Berhe N, Balkew M (2006) Leishmaniasis in Ethiopia. In: Kloos H, Berhane Y, Hailemariam D (eds) The ecology and epidemiology of health and disease in Ethiopia, 1st edn. pp 615–634

Hailu A, Musa A, Wasunna M, Balasegaram M, Yifru S, Mengistu G, Hurissa Z et al (2010) Geographical variation in the response of visceral leishmaniasis to paromomycin in East Africa: a multicentre, open-label, randomized trial. PLoS Negl Trop Dis 4(10):e709. doi:10.1371/journal.pntd.0000709

Hassan MM, Elamin EM, Mukhtar MM (2008) Isolation and identification of Leishmania donovani from Phlebotomus orientalis, in an area of eastern Sudan with endemic visceral leishmaniasis. Ann Trop Med Parasitol 102(6):553–555

Hassan MM, Osman OF, El-Raba'a FM, Schallig HD, Elnaiem DE (2009) Role of domestic dog as reservoir host of Leishmania donovani in eastern Sudan. Parasite Vectors 2(1):26. doi:10.1186/1756-3305-2-26

Herrero M, Orfanos G, Argaw D, Mulugeta A, Aparicio P, Parreno F et al (2009) Natural history of visceral leishmaniasis outbreak in highland Ethiopia. Am J Trop Med Hyg 81(3):373–377

Hoogstraal H, Dietlein DR (1964) Leishmaniasis in the Sudan Republic: recent results. Bull World Health Organ 31(1):137–143

Hoogstraal H, Heyneman D, Dietlein DR, Browne HG, Reid TP, van Peenen PFD, Saber AH, Rohrs LC (1963) Leishmaniasis in the Sudan Republic: epidemiological findings. Bull World Health Organ 28(2):263–265

Jamjoom MB, Ashford RW, Bates PA, Chance ML, Kemp SJ, Watts PC, Noyes HA (2004) Leishmania donovani is the only cause of visceral leishmaniasis in East Africa; previous descriptions of L. infantum and "L. archibaldi" from this region are a consequence of convergent evolution in the isoenzyme data. Parasitology 129(Pt4):399–409

Kalayou S, Tadelle H, Bsrat A, Abebe N, Haileselassie M, Schallig HD (2011) Serological evidence of Leishmania donovani infection in apparently healthy dogs using direct agglutination test (DAT) and rk39 dipstick tests in Kafta Humera, north-west Ethiopia. Transbound Emerg Dis 58(3):255–262

Khalil EA, Musa AM, Younis BM, Elfaki ME, Zijlstra EE, Elhassan AM (2011) Blindness following visceral leishmaniasis: a neglected post-kala-azar complication. Trop Doct 41(3):139–140

Khalil EA, Khidir SA, Musa AM, Musa BY, Elfaki ME, Elkadaru AM et al (2013) Post-kala-azar dermal leishmaniasis: a paradigm of paradoxical immune reconstitution syndrome in non-HIV/AIDS patients. J Trop Med 2013:275253. doi:10.1155/ 2013/275253

Khalil EA, Weldegebreal T, Younis BM, Omollo R, Musa AM, Hailu W et al (2014) Safety and efficacy of single dose versus multiple doses of AmBisome for the treatment of visceral leishmaniasis in eastern Africa: a randomized trial. PLoS Negl Trop Dis 8(1):10.1371/journal.pntd.0002613

Kolaczinski JH, Reithinger R, Worku DT, Ocheng A, Kasimiro J, Kabaterine N, Brooker S (2008) Risk factors of visceral leishmaniasis in east Africa: a case-control study in Pokot territory of Kenya and Uganda. Int J Epidemiol 37(2):344–352

Kweku MA, Odoom S, Puplampu N, Desewu K, Nuako GK, Gyan B, Raczniak G, Kronmann KC, Koram K, Botero S, Boakye D, Akuffo H (2011) An outbreak of suspected cutaneous leish-

maniasis in Ghana: lessons learnt and preparation for future outbreaks. Glob Health Action 4. doi:10.3402/gha.v4i0.5527

Malaria Consortium (2010) Leishmaniasis control in eastern Africa: past and present efforts and future needs. Situation and gap analysis. Available: http://www.malariaconsortium.org/userfiles/file/NTD%20Resources/VL%20EA%20Situation%20Analysis%20Fina_Janl.pdf. Accessed 20 Oct 2014

Marlet MV, Wuillaume F, Jacquet D, Quispe KW, Dujardin JC, Boelaert M (2003) A neglected disease of humans: a new focus of visceral leishmaniasis in Bakool, Somalia. Trans R Soc Trop Med Hyg 97(6):667–671

Maroli M, Feliciangeli MD, Bichaud L, Charrel RN, Gradoni L (2013) Phlebotomine sandflies and the spreading of leishmaniases and other diseases of public health concern. Med Vet Entomol 27(2):123–147

Mengesha B, Endris M, Takele Y, Mekonnen K, Tadesse T, Feleke A, Diro E (2014) Prevalence of malnutrition and associated risk factors among adult visceral leishmaniasis patients in northwest Ethiopia: a cross sectional study. BMC Res Notes 7:75. doi:10.1186/1756-0500-7-75

Molina R, Gradoni L, Alvar J (2003) HIV and the transmission of Leishmania. Ann Trop Med Parasitol 97(Suppl 1):29–45

Monge-Maillo B, Norman FF, Cruz I, Alvar J, Lopez-Velez R (2014) Visceral leishmaniasis and HIV coinfection in the Mediterranean Region. PLoS Negl Trop Dis 8(8):e3021. doi:10.1371/journal.pntd.0003021

Mukhtar MM, Sharief AH, el Saffi SH, Harith AE, Hiqazzi TB, Adam AM, Abdalla HS (2000) Detection of antibodies to Leishmania donovani in animals in a kala-azar endemic region in eastern Sudan: a preliminary report. Trans R Soc Trop Med Hyg 94(1):33–36

Mukhtar MM, Elamin EM, Bakhiet SM, Kheir MM, Ali AB (2010) First report on Leishmania major/HIV coinfection in a Sudanese patient. East Mediterr Health J 16(6):702–703

Mutinga MJ (1991) A review of investigations on leishmaniasis vectors in Kenya. Parassitologia 33(Suppl):453–461

Mutinga MJ, Ngoka JM, Schnur LF, Chance ML (1980) The isolation and identification of leishmanial parasites from domestic dogs in Machakos District of Kenya, and the possible role of dogs as reservoir hosts of kala-azar in east Africa. Ann Trop Med Parasitol 74(2): 139–144

Osman OF, Kager PA, Oskam L (2000) Leishmaniasis in the Sudan: a literature review with emphasis on clinical aspects. Trop Med Int Health 5(8):553–562

Perkins PV, Githure JI, Mebrahtu Y, Kiilu G, Anjili C, Ngumbi PS et al (1988) Isolation of Leishmania donovani from Phlebotomus martini in Baringo district, Kenya. Trans R Soc Trop Med Hyg 82(5):695–700

Post-kala-azar dermal leishmaniasis: a manual for case management and control: report of a WHO consultative meeting, Kolkata, India, 2–3 July 2012. http://apps.who.int/iris/bitstream/10665/78608/1/9789241505215__eng.pdf

Pratlong F, Debord T, Garnotel E, Garrabe E, Marty P, Raphenon G, Dedet JP (2005) First identification of the causative agent of visceral leishmaniasis in Djibouti: Leishmania donovani. Ann Trop Med Parasitol 99(1):21–25

Puig L, Pradinaud R (2003) Leishmania and HIV co-infection: dermatological manifestations. Ann Trop Med Parasitol 97(Suppl 1):S107–S114

Raguenaud ME, Jansson A, Vanlerberghe A, Deborggraeve S, Dujardin JC, Orfanos G et al (2006) Epidemiology and clinical features of patients with visceral leishmaniasis treated by an MSF clinic in Bakool region, Somalia, 2004–2006. PLoS Negl Trop Dis 1(1):e85

Ritmeijer K, Veeken H, Melaku Y, Leal G, Amsalu R et al (2001) Ethiopian visceral leishmaniasis: generic and proprietary sodium stibogluconate are equivalent; HIV co-infected patients have a poor outcome. Trans R Soc Trop Med Hyg 95:668–672

Russo R, Laguna F, Lopez-Velez R, Medrano FJ, Rosenthal E, Cacopardo B, Nigro L (2003) Visceral leishmaniasis in those infected with HIV: clinical aspects and other opportunistic infections. Ann Trop Med Parasitol 97(Suppl 1):99–105

Saporito L, Giammanco GM, De Grazia S, Colomba C (2013) Visceral leishmaniasis: host-parasite interactions and clinical presentation in the immunocompetent and in the immunocompromised host. Int J Infect Dis 17(8):e572–e576. doi:10.1016/j.ijid.2012.12.024

Sati MH (1958) Early phases of an outbreak of kala-azar in the Southern Fung. Sudan Med J 1:98–111

Schaefer KU, Kurtzhals JA, Sherwood JA, Githure JI, Kager PA, Muller AS (1994) Epidemiology and clinical manifestations of visceral and cutaneous leishmaniasis in Baringo District, Rift Valley, Kenya. A literature review. Trop Geogr Med 46(3):129–133

Schaefer KU, Kurtzhals JA, Gachihi GS, Muller AS and Kager PA (1995) A prospective sero-epidemiological study of visceral leishmaniasis in Baringo District, Rift Valley Province, Kenya. Trans R Soc Trop Med Hyg 89 (5):471–475

Schorscher JA, Goris M (1992) Incrimination of Phlebotomus (Larroussius) orientalis as a vector of visceral leishmaniasis in western upper Nile Province, southern Sudan. Trans R Soc Trop Med Hyg 86(6):622–623

Seaman J, Mercer AJ, Sondorp HE, Herwaldt BL (1996) The epidemic of visceral leishmaniasis in western upper Nile, southern Sudan: course and impact from 1984 to 1994. Int J Epidemiol 25(4):862–871

Seid A, Gadisa E, Tsegaw T, Abera A, Teshome A, Mulugeta A, Herrero M, Argaw D, Jorge A, Kebede A, Aseffa A (2014) Risk map for cutaneous leishmaniasis in Ethiopia based on environmental factors as revealed by geographical information systems and statistics. Geospat Health 8(2):377–387

Sirol J, Vedy J, Barabe P, Cesari C, Berger P (1976) Kala-Azar in the Republic of Chad. 6 year survey at the Central Hospital of N'Djamena (Fort-Lamy). Bull Soc Pathol Exot Fil 69(3):232–237

Sixl W, Sebek Z, Reinthaler F, Mascher F (1987) Investigations of wild animals as leishmania reservoir in south Sudan. J Hyg Epidemiol Microbiol Immunol 31(4 Suppl):483–485

Stephenson R (1940) An epidemic of kala-azar in the Upper Nile province of the Anglo-Egyptian Sudan. Ann Trop Med Parasitol 34:175–179

Tonui WK (2006) Situational analysis of leishmaniases research in Kenya. Afr J Health Sci 13(1–2):7–21

Utaile M, Kassahun A, Abebe T, Hailu A (2013) Susceptibility of clinical isolates of *Leishmania aethiopica* to miltefosine, paromomycin, amphotericin B and sodium stibogluconate using amastigote-macrophage in vitro model. Exp Parasitol 134(1):68–75. doi:10.1016/l.exppara.2013.01.022

Van den Bogaart E, Berkhout MM, Nour AB, Mens PF, Talha AB, Adams ER et al (2013) Concomitant malaria among visceral leishmaniasis in-patients from Gedarif and Sennar States, Sudan: a retrospective case-control study. BMC Public Health 13:332. doi:10.1186/1471-2458-13-332

World Health Organization (2010) Control of the Leishmaniases. In: WHO Technical Report Series 949: report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22–26 March 2010. World Health Organization, Geneva. http://whqlibdoc.who.int/trs/WHO_TRS_949_eng.pdf

World Health Organization (2013) Fact sheet no. fs375; updated January 2014. Available at: http://www.who.int/mediacentre/factsheets/fs375/en/

World Health Organization and Overseas Development Administration (1996) Manual on visceral leishmaniasis control. www.who.int/leishmaniasis/surveillance/.../en/WHO_LEISH_96.40.pdf

Zijlstra EE, el-Hassan AM, Ismael A and Ghalib HW (1994) Endemic kala-azar in eastern Sudan: a longitudinal study on the incidence of clinical and subclinical infection and post-kala-azar dermal leishmaniasis. Am J Trop Med Hyg 51(6):826–36

Zijlstra EE, Musa AM, Khalil EA, el-Hassan IM, el-Hassan AM (2003) Post-kala-azar dermal leishmaniasis. Lancet Infect Dis 3(2):87–98

Leprosy

Benedict Okoe Quao and Ekow Amankrah-Otabir

Contents

Abstract From its East Africa origin, leprosy has afflicted humans since ancient times. The tide turned against the disease from the 1980s when effective multidrug therapy was introduced worldwide. By 2005, all countries in sub-Saharan Africa had attained the WHO elimination target of prevalence less than 1 per 10,000 population. Africa accounts for 9 % of global leprosy prevalence and new case detection with a worrying number of new cases having significant disability at diagnosis. Public stigma has also contributed to the persistence of segregated settlements for leprosy sufferers, long after cure. No case in sub-Saharan Africa has been linked to the recently discovered *Mycobacterium lepromatosis*. Leprosy spread is believed to be by droplet and skin transmission with growing evidence for zoonotic spread from infected armadillos,

B.O. Quao (✉) • E. Amankrah-Otabir
Ghana Leprosy Service Headquarters, Ankaful Leprosy General Hospital, Ankaful, Cape-Coast, Ghana
e-mail: benedict.quao@gmail.com

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_6

a species not found outside the Americas. The presentation of leprosy in sub-Saharan Africa is as elsewhere, varying between two polar states of tuberculoid and lepromatous leprosy and modified by complications including acute reactions.

Clinical diagnosis and classification of leprosy at present are most amenable for treatment purposes, with the continuous supply of effective MDT being the backbone of leprosy control activities. There is a greater push towards reducing the disability burden with improvement of the generally weak African health care systems within which leprosy services are provided and increased involvement of sufferers and the community being key strategies. A fixed-duration course of rifampicin and dapsone, with addition of clofazimine in multibacillary disease, remains the mainstay of treatment.

Leprosy control activities are now suffering from reduced attention on both global and subregional scales, and the knowledge of front-line health care workers regarding leprosy is dwindling. With leprosy likely to remain with us for the foreseeable future, more research and political will are required to sustain the gains and possibly accelerate us to true elimination.

Introduction

Leprosy is a chronic mildly infectious disease which has inflicted man for several centuries and principally affects the skin and peripheral nerves and, in some cases, mucous membranes. It has historically been known for its complications of clawing and resorption of digits which contributes to the public stigma of the disease and negative treatment meted out to sufferers in our societies. Although exact figures over time are unavailable, it is estimated that about three million people could be currently living with some impairment or disability arising from leprosy (World Health Organization [WHO] Expert Committee on Leprosy 1998).

The disease is also named Hansen's disease after the Norwegian physician Gerhard Armauer Hansen who first demonstrated *Mycobacterium leprae* in infected tissue samples under the microscope in 1873. This was also the first time a bacterium was linked to a disease in man and thus an important milestone in the battle against infectious diseases.

Leprosy has existed for millennia, long before this feat. Descriptions fitting leprosy had been recorded in ancient manuscripts from India dating as far back as 600 BC and in early Chinese medical publications around 400 BC. The theory of leprosy originating in India and being spread westward by returning soldiers of Alexander the Great was however disputed in 2005 after molecular studies by Monot et al. (2005) suggested an East African origin, more specifically from Ethiopia. It is also now believed that it is rather colonialism and the slave trade that promoted the worldwide spread of the disease from its Eastern African origin (Monot et al. 2005).

Since ancient times, many different methods including the use of natural oils and mercury were used in trying to cure the disease with no notable success. The disease remained largely incurable causing great disfigurement and disability in sufferers

and was greatly feared throughout the world. As it was believed to be highly contagious, sufferers were quarantined in leprosy colonies or "leprosaria" where they remained till their death. It was not until the 1940s with the successful use of promin and its derivative dapsone that an effective treatment was finally found.

From the 1940s, dapsone monotherapy became the mainstay of leprosy treatment although fraught with many challenges. Therapy was long-term, associated with clinical overload and noncompliance and soon; widespread resistance to dapsone monotherapy began to emerge. Multidrug therapy (MDT) for leprosy was introduced in the 1980s and allowed treatment of individuals within their communities for shorter periods (World Health Organization 1982). Since 1995, the World Health Organization has supplied free effective MDT drugs worldwide which, together with early case detection and increased control efforts, have contributed to a significant decline in leprosy prevalence over the past two and a half decades.

Epidemiology of the Disease

Distribution and Burden

Leprosy is most prevalent in but not limited to the tropics. It is well known that leprosy was in times past, very common in Europe far from the tropics, with sufferers saddled with clanging bells about their waists to announce their presence. Many however attribute the decline of the prevalence of leprosy in Europe and the rest of the advanced world more to the advent of industrialization and consequent improvements in living conditions rather than some climatic feature or drug treatment alone.

WHO statistics on leprosy, in spite of the challenges with the timeliness and variations in the data submitted year on year, give the best picture of the current distribution of this ancient scourge. The number of new cases from Europe and North America does not reflect on global distribution maps but is virtually insignificant. According to WHO figures (Barua 2013), Southeast Asia alone contributes about two-thirds of worldwide leprosy prevalence and new case detection, with the Americas (mainly South America) and Africa following in that order. In 2012 Africa accounted for 9 % of global leprosy prevalence and new case detection (Barua 2013).

In spite of the regional distribution of leprosy outlined above, the disease appears to be concentrated in only a few countries. Collected data from 2002 to 2012 indicate that less than 20 countries report more than 1000 new leprosy cases yearly, and these countries together account for as much as 95 % of the yearly new leprosy case detection worldwide (WHO 2013; World Health Organization, Regional Office for South-East Asia [WHO-SEARO] 2009a). In 2012 16 countries reported more than 1000 new cases of leprosy with 80 % of the yearly new leprosy case detection attributable to only 3 of these 16 countries – India, Brazil and Indonesia (WHO 2013). Of these 16 countries, there were 7 African countries – Cote D'Ivoire, Democratic Republic of Congo, Ethiopia, Madagascar, Nigeria, South Sudan and Tanzania (WHO 2013).

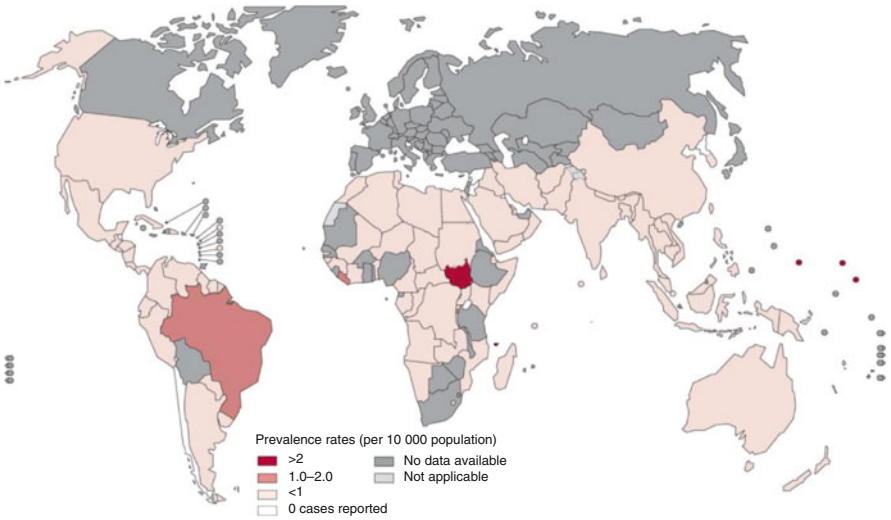


Fig. 1 Worldwide prevalence of leprosy as of January, 2012 (WHO Department of Control of Neglected Tropical Diseases 2012)

In 1991, the World Health Assembly set the goal of elimination of leprosy as a public health problem by the year 2000. This goal was successfully reached through concerted worldwide efforts and the widespread use of MDT in the year 2000, when prevalence of leprosy fell to below one case per 10,000 of population (WHO-SEARO 2009a). Individual countries continued in their efforts to achieve the elimination target, with all countries within the African region achieving the target by the end of 2005 (World Health Organization, Regional Office for Africa [WHO-AFRO] 2012). This apparent progress is yet to be fully translated to the subnational level, with several countries still having endemic pockets such as urban slums, remote mountainous areas and regions ravaged by conflict, whilst a few areas appear to be experiencing a re-emergence of the disease (WHO-AFRO 2012) (Fig. 1).

In spite of the widespread reduction in prevalence of leprosy cases registered for treatment, the decline in the new leprosy case detection rate has not been as dramatic (WHO-SEARO 2009a). This suggests that we may not actually have attained "true elimination" of leprosy with continued detection of new cases expected for many years to come. Although there has been a steady decline over the years, the number of new patients with significant disability, which is responsible for most of the negative social consequences such as stigma and impoverishment, has remained substantial, and the exact prevalence of permanent disability arising from leprosy is sadly not readily available (WHO-SEARO 2009a).

In 2011, there were 25,231 new cases of leprosy detected within the WHO African region alone with as many as 10 % of them having grade 2 disabilities (WHO-AFRO 2013). This lingering burden of the disease is now informing the strategies being employed to fight leprosy with a shift in recent times towards reducing the number of new cases with significant impairment at the time of diagnosis. The current strategy targets a 35 % reduction in the number of new leprosy cases with grade 2 disabilities per 100,000 population from the 2010 levels, and it is

Table 1 Score scale of leprosy burden indicators within the Africa region

Indicator	Burden Score according to Indicator level		
	High (score = 2)	Medium (score = 1)	Low (score = 0)
Detection number	>1000 new cases	500–1000 new cases	<500 new cases
Prevalence rate	>2/10,000	1–2/10,000	<1/10,000
Detection rate	>20/100,000	10–20/100,000	<10/100,000
Proportion of multibacillary cases[a]	<50 %	50–75 %	>75 %
Proportion of children[a]	>20 %	10–20 %	<10 %
Proportion of grade 2 disability[a]	>20 %	10–20 %	<10 %
Proportion of females[a]	<40 %	>60 %	30–60 %
Prevalence/detection ratio	>2	1–2	<1
Grade 2 disability per 100,000 population	>1	0.5–1	<0.5
Total	≥5	3–4	0–2

WHO-AFRO (2012, 2013)

[a]Amongst new cases detected within the year

hoped this will lead to improved efforts to detect cases earlier and to prevent and manage impairments and disabilities (WHO-SEARO 2009a).

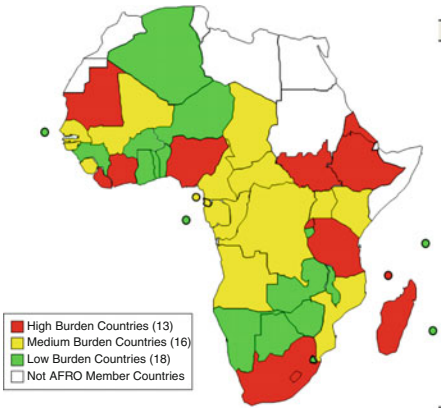
Leprosy disease burden is multifactorial and "can be measured in terms of the occurrence of reported new cases, the number of cases registered for treatment and the number of cases with disabilities" (WHO-SEARO 2009a p. 5). This new concept of leprosy burden can be stretched to also include the proportion of cases in remote and non-accessible areas, the resources available to support the leprosy programme and the impact of the stigma associated with the disease (WHO-AFRO 2012). In the Africa region, there are nine indicators used to determine the leprosy burden of each country (WHO-AFRO 2012, 2013). Table 1 shows the indicators used and the weighted score given to each.

Figure 2, shows the country distribution with regard to leprosy burden in the WHO-AFRO region (comprises most of the countries within sub-Saharan Africa).

Public Health Impact

A worrying observation about leprosy, as with most of the other neglected tropical diseases, is the predilection for the more underprivileged segments of societies, whose poor living conditions and weaker immune systems make them more vulnerable to the disease. Untreated the disease runs a protracted course causing damage mainly to peripheral nerves and resulting in deformities of the hands and feet as well as problems with vision.

These deformities of the hands, feet and eyes make manual tasks difficult and thus render many of those affected more impoverished since they are frequently unable to continue in their previous economic activity. In sub-Saharan Africa with



High Burden	Medium Burden	Low Burden
Comoros	Angola	Algeria
Cote d'Ivoire	Cameroon	Benin
Eritrea	Central African Republic	Botswana
Ethiopia	Chad	Burkina Faso
Lesotho	Congo	Burundi
Liberia	Democratic Republic of Congo	Cape Verde
Madagascar	Equatorial Guinea	Ghana
Mauritania	Gabon	Guinea
Nigeria	Gambia	Mauritius
Rwanda	Guinea Bissau	Malawi
South Africa	Kenya	Namibia
South Sudan	Mali	Niger
Tanzania	Mozambique	Sao Tome & Principe
	Senegal	Seychelles
	Sierra Leone	Swaziland
	Uganda	Togo
		Zambia
		Zimbabwe

Fig. 2 Leprosy burden within the WHO Africa Region (Onyeze 2013)

almost half of the population classified as poor (World Bank Group 2011) and many countries lacking well-established social welfare systems, the effect of leprosy "maiming" a family breadwinner is profound, depriving successive generations of any chance of breaking the cycle of poverty.

Stigma surrounding leprosy remains a significant problem for sufferers of the disease in this region where the disease process is poorly understood by much of the population. Many continue to be shunned by other members of their community in the belief that they are cursed with a highly contagious and untreatable disease. Permanent disability such as digit clawing provides a perpetual reminder long after cure, labelling and exposing sufferers to public discrimination and isolation.

The highly stigmatized environment in sub-Saharan Africa has contributed to the persistence of segregated settlements for leprosy sufferers, in spite of the worldwide abolishment of the concept of isolating leprosy patients. Many cured leprosy sufferers especially the ones with permanent deformities, in search of acceptance, escape from the harsh stigmatized and discriminatory setting within their former communities to set up dwellings near the former leprosaria from where they obtained treatment. In Ghana, for example, there are well-known settlements at Ho, Weija, Ankaful-fie and Nkanyina, amongst many others. Although the living conditions within these settlements may not be optimal, the "privileged ones" within them are more likely to benefit from hand-outs and support from aid agencies and philanthropists than those within the general community.

Basic Biology

Infective Agents and Life Cycle

Mycobacterium leprae had historically been the only known causative agent of leprosy until 2008 when a second agent *Mycobacterium lepromatosis* was linked to diffuse lepromatous leprosy (DLL), a unique form of leprosy endemic in Mexico

and the Caribbean (Han et al. 2008). Much of the work done in identifying this new species has been with archived and autopsied specimens, and *Mycobacterium lepromatosis* is still yet to be extensively demonstrated in other parts of the world outside Mexico (Han et al. 2012).

Since ancient times, leprosy has always been regarded as a disease of man. Nonetheless aside humans, *Mycobacterium leprae* has been shown to occur naturally in nine-banded armadillos, native to the Americas. These armadillos with their much cooler body temperatures which *M. leprae* species prefer are thought to have acquired the agent from original European human settlers to the Americas within the last half-millennium (Truman et al. 2011).

Leprosy bacilli are obligate intracellular bacteria, multiplying mainly in macrophages and nerve Schwann cells and, unlike other *Mycobacterium* species, fail to grow on artificial media once outside the human body (Han and Silva 2014). Although neither agent has been cultivated in any laboratory as yet, the successful inoculation of *M. leprae* in athymic (naked) mice and armadillos has permitted some limited research into the disease. Leprosy bacilli have a life span of about 6 months with the longest doubling time of any known bacterium. In the mouse footpad, *M. leprae* has a generation time of about 12–13 days during the exponential phase of growth (Yawalkar 2002).

Disease Transmission

Even though *Mycobacterium leprae* was the first microorganism to be linked with disease causation in man, the exact mode of transmission is not yet known and presents a major challenge to control efforts. The long incubation period of leprosy which ranges from 2 to 10 years but can be as long as 20 years complicates recalling of the initial exposure event, and many patients at the time of diagnosis usually have no history of apparent exposure to any known cases of leprosy. Nonetheless the observation over the years of increased occurrence of leprosy amongst household contacts has always suggested a direct human-to-human spread of the disease, driving the public fear that led to the ostracization of leprosy patients in former leper colonies and leprosaria.

Despite a deficiency of direct causal evidence, the skin and nasal routes are regarded as the most probable exit and entry routes of leprosy bacilli. Untreated multibacillary leprosy patients are deemed most infectious and are known to shed millions of leprosy bacilli in their nasal secretions daily. Skin transmission was originally thought to require broken skin owing to the confinement of leprosy granulomas to deeper layers of the dermis (Yawalkar 2002), but later demonstration of leprosy bacilli on the surface of skin of infected leprosy patients and their household contacts suggests intact skin may also play a role in transmission (Job et al. 2008). Naked mice, when exposed to leprosy bacilli by different routes, developed generalized disease only with topical nasal mucosa exposure and subcutaneous injection of bacilli (Chehl et al. 1985) giving further credence to the two routes being the likely portals of entry.

The exact mode of transfer of leprosy bacilli in man has also remained unclear although droplet transmission is generally regarded as the most plausible. Experimental evidence with naked mice suggests that infection occurs more readily with direct instillation of leprosy bacilli on traumatized nasal mucosa or tongue compared with other modes of transfer such as inhalation or feeding (McDermott-Lancaster and McDougall 1990). Direct skin-to-skin transmission, although thought to be theoretical possible, has also not been demonstrated as yet. Indirect transmission from environmental and other non-human sources such as arthropods and water has not been proven as yet, although there is evidence that leprosy bacilli shed into the environment may remain viable for periods up to 3–5 months, depending on the prevailing physical conditions (Truman and Fine 2010; Desikan and Sreevista 1995).

Recent evidence (Truman et al. 2011) points to the possibility of zoonotic spread of leprosy from infected nine-banded armadillos to humans, which may explain the occurrence of leprosy in individuals in the United States with no history of travel to leprosy-endemic areas. These armadillos, presumed to have been first infected by exploring European settlers to the Americas, are thought to have naturally occurring leprosy infections with as many as one in five armadillos being infected in some populations. The genetic study using *M. leprae* bacilli isolated from an armadillo and three individuals in the United States showed a similar genetic strain of *M. leprae* occurring in all cases, dissimilar to any of the strains reported from elsewhere in the world (Truman et al. 2011).

Disease Presentation

The development and expression of clinical leprosy in exposed individuals are highly modulated by immunological mechanisms. In the majority of individuals exposed to leprosy bacilli, subclinical infection does not progress to clinical disease, with only about 5 % of humans having genetic susceptibility to leprosy (De Messias-Reason et al. 2009). Furthermore in those in whom the infection becomes established, the form of leprosy they develop is dependent on their level of cell-mediated immunity, ranging between two polar states, tuberculoid leprosy (TT) and lepromatous leprosy (LL) (Ridley and Jopling 1966).

Tuberculoid leprosy is characterized by a strong cell-mediated immunity and low bacillary load with lesions limited to a few skin sites and/or nerves, whilst lepromatous leprosy is characterized by an absence of specific cell-mediated immunity and unchecked proliferation of leprosy bacilli resulting in diffuse lesions. The forms of leprosy in between these two extreme states are regarded as very unstable, tending to drift towards either pole depending on the individual's level of cell-mediated immunity. Both the internationally adopted 1953 Madrid congress classification, which was purely clinical, and the later Ridley-Jopling classification recognize these intermediate forms with the latter proposing three borderline states, namely, borderline tuberculoid (BT), mid borderline (BB) and borderline lepromatous leprosy (BL) to make up a five-group spectrum (Ridley and Jopling 1966).

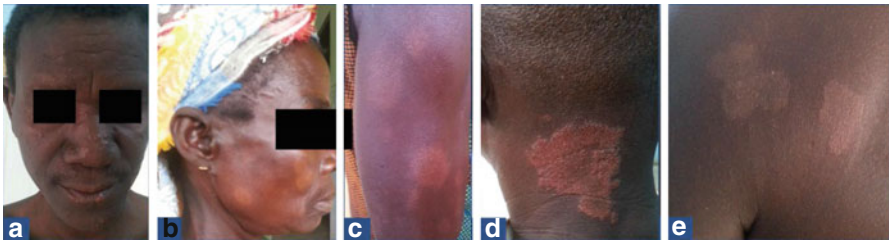


Fig. 3 (**a**) Facial papules and nodules in LL. (**b**) Hypopigmented macules and patches of BT with satellites. (**c**) BT lesions with satellites on arm. (**d**) Fairly well-defined early BT erythematous annular plaque with satellites. (**e**) Well-defined unilateral TT lesions (Pictures Source: Benedict Okoe Quao)

There is almost always skin involvement in leprosy, accompanied most of the time by nerve enlargement. Skin lesions may be hypopigmented or erythematous and range from macules and papules to nodules, plaques and infiltrations. Infrequently, a purely neural form of leprosy can also occur. The disease is thought to begin as indeterminate leprosy (IL), characterized by one or a few ill-defined skin lesions usually without loss of sensation and often missed, which progresses to one of the other forms of leprosy or resolves without treatment. The skin lesions of TT tend to be well-defined macules, asymmetrically or unilaterally distributed, sometimes having slightly raised margins and usually with a dry surface and early loss of sensation over lesion from the involvement of free nerve endings in skin. The appearance and distribution of skin lesions of BT are similar to those of TT but are more numerous with the presence of satellites (Ridley and Jopling 1966) (Fig. 3).

Skin lesions of LL are multiple and bilaterally and symmetrically distributed with initial erythematous macules and papules becoming plaques and nodules as the disease progresses (Ridley and Jopling 1966). LL is commonly associated with oedema of feet and lower legs, and in later stages patients may develop diffuse thickening and ridging of facial skin with thickening of nose and ears ("leonine facies") and loss of eye lashes (madarosis), keratitis, nasal ulceration and saddle-nose deformities as well as bone and teeth involvement (Ridley and Jopling 1966). BL closely resembles LL, but its lesions differ in that they are not as shiny and are more likely to have loss of sensation over them and their distribution is not as symmetrical, with sufferers sometimes presenting also with dimpled nodules and punched-out saucer-shaped plaques (Ridley and Jopling 1966). BB as the name suggests has balanced features of both TT and LL, tending towards symmetrical distribution with the presence of few satellites as in BT (Figs. 3 and 4).

Nerve involvement in leprosy is crucial in the development of deformities and disability which remain long after cure of leprosy sufferers. Neuropathy of a mixed type (Lastoria and Abreu 2014) occurs when leprosy bacilli invade and cause inflammation in peripheral nerve trunks, comprised of motor, sensory and sympathetic nerve fibres. This process is insidious in nature and may go on silent unless there is painful exacerbation as occurs during a reaction, when nerve fibre damage is also accelerated. Nerve involvement may manifest as neural thickening or

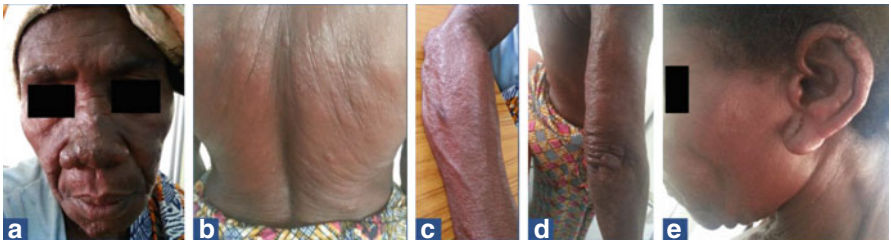


Fig. 4 Lepromatous leprosy. (**a**) "Leonine" facies with diffuse infiltration of facial skin. (**b**) Diffuse symmetrical skin nodules. (**c**) Dry skin. (**d**) Nodules at elbow. (**e**) Firm thickening of ear lobes (Pictures Source: Benedict Okoe Quao)

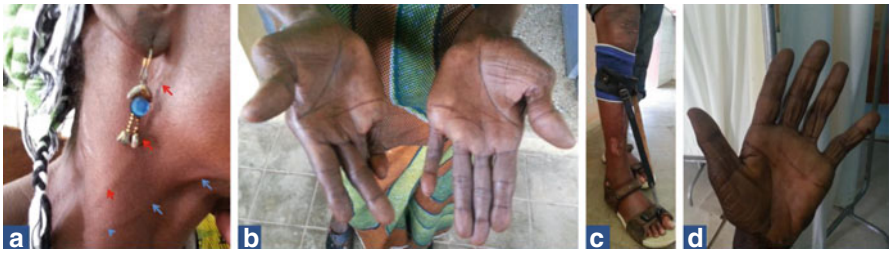


Fig. 5 Nerve involvement. (**a**) Enlarged great auricular (*red arrows*) and transverse cervical (*blue arrows*) nerves. (**b**) Ulnar nerve involvement with wasting and clawing of hands. (**c**) Correction of foot drop resulting from common peroneal nerve involvement. (**d**) Dry innervated hand (Pictures Source: Benedict Okoe Quao)

functional abnormalities such as loss of sensation, pain, increased sensation, muscle weakness or loss of autonomic function such as sweating (Fig. 5). Temperature discrimination is usually the first sensory modality to be lost, whilst joint position sense is rarely lost because the afferents are carried via tendons rather than within the nerve trunk (Malaviya 2003).

In TT, nerve involvement occurs early and is limited to gross and irregular enlargement of usually one peripheral nerve near the site of the skin lesion with nerve function impairment invariably present. The borderline forms of leprosy tend to have multiple peripheral nerves enlarged but not as irregularly and grossly thickened as occurs in TT. Nerve thickening does not occur early in pure LL, with peripheral nerves diffusely undergoing hyaline degeneration or fibrosis only in the late stages of the disease and resulting in symmetric anaesthesia of hands and feet, so-called glove-and-stocking anaesthesia (Ridley and Jopling 1966) (Fig. 5).

About a third of leprosy sufferers may experience a reactional state at some point in the course of the disease (Saunderson 2002). Triggers of the reactional state include vaccination, physical or emotional stress, pregnancy and surgery. Irrespective of the point during the course of disease they occur, reactions always require early recognition and prompt treatment since they are periods of accelerated nerve damage. Two main types of reactions are recognized; lepra type 1 (or reversal) reaction

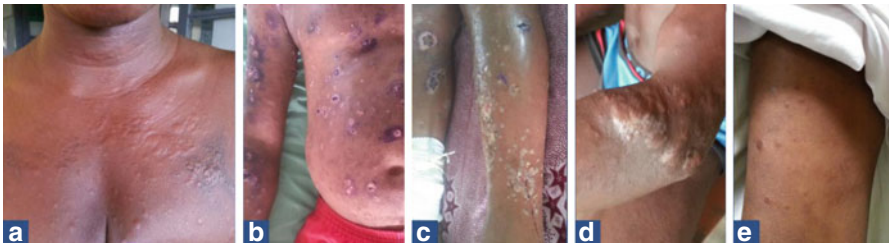


Fig. 6 Reactions in leprosy. (**a**) Tumid erythematous lesions in type 1 reaction (**b**) and (**c**) pustulating and ulcerating erythema nodusum leprosum (ENL) lesions. (**d**) Type 1 lesions complicated by bacterial skin infection with crusting. (**e**) Typical ENL lesions (Pictures Source: Benedict Okoe Quao)

and type 2 reaction (or erythema nodusum leprosum, ENL). Isolated inflammation of nerves (or neuritis) may also occur, in the absence of features of either type 1 or type 2 reactions. The so-called Lucio's phenomenon endemic in Mexico and characterized by necrotizing ulcerating lesions has so far not been described in African leprosy patients.

Type 1 reaction commonly occurs in BT patients but may also occur in any of the other borderline states and represents an upgrading of specific immunity against leprosy bacilli towards the TT pole. It is a type IV delayed-type hypersensitivity reaction. It may be the first presentation symptom although some patients may only experience a type 1 reaction after initiation of treatment, usually within the first 6 months, and rarely, up to 5 years after treatment when it is usually mistaken for a relapse (Saunderson 2002). In type 1 reaction, already existing lesions, which may have been unknown to the patient, become swollen, reddened and warm, and there may be associated facial and acral oedema. Key features of type 1 reaction are the involvement of nerves with tenderness and/or loss of function and absence of significant systemic symptoms (Fig. 6).

Type 2 reaction on the other hand occurs mainly in LL patients but may occasionally occur in BL patients. The body's humoral immunity reacts to antigenic proteins from killed and decomposing leprosy bacilli leading to the deposition of immune complexes in tissues. Most type 2 reactions will therefore occur within the first 3 years after initiation of treatment but in some cases may continue to recur even much longer after cessation of treatment (Saunderson 2002). In ENL, patients develop painful and reddened subcutaneous nodules mainly on the limbs unrelated to pre-existing leprosy skin lesions (Fig. 6). Unlike type 1, type 2 reactions are characterized by significant systemic symptoms such as fever, general malaise, muscle and joint aches and lymphadenopathy. Type 2 reactions may also involve other organs such as the eyes (iritis), testes (orchitis), liver and kidneys (deranged liver and kidney function tests) leading to permanent damage (Saunderson 2002).

Long-term sequelae of the disease which occur as permanent impairments/deformities or secondary damage to tissues resulting from these impairments/deformities tend to persist way beyond completion of leprosy treatment and may be the reason for seeking medical care. These problems include recurrent plantar ulcers, chronic

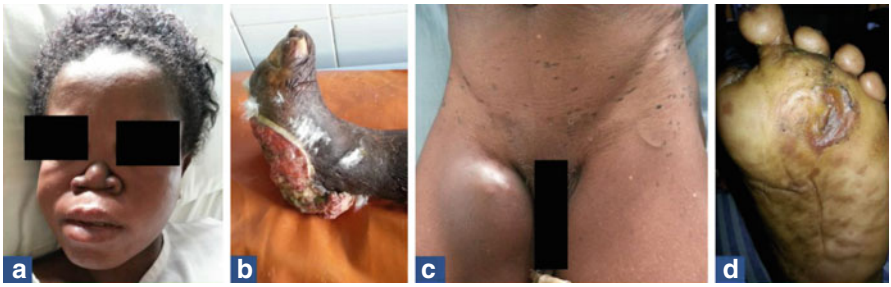


Fig. 7 (**a**) Saddle-nose deformity. (**b**) Squamous cell carcinoma complicating chronic foot ulcer. (**c**) Same patients with SCC in B. with inguinal lymph node involvement. (**d**) Plantar ulcer with absent big toe (Pictures Source: Benedict Okoe Quao)

HANDS AND FEET	
Grade 0	No anaesthesia, no visible deformity or damage
Grade 1	Anaesthesia present, but no visible deformity or damage
Grade 2	Visible deformity or damage present
EYES	
Grade 0	No eye problem due to leprosy; no evidence of visual loss
Grade 1	Eye problems* due to leprosy present, but vision not severely affected as a result (vision: 6/60 or better; can count fingers at 6 metres)
Grade 2	Severe visual impairment (vision worse than 6/60; inability to count fingers at 6 metres); also includes lagophthalmos, iridocyclitis and corneal opacities

Fig. 8 WHO Disability Grading System for grading impairments/deformities in leprosy (Brandasma and Van Brakel 2003)

osteomyelitis and recurrent burn injuries of extremities as well as poor vision resulting from any or a combination of ocular complications of the disease (Fig. 7). Assessment of the eyes, hands and feet, in accordance with the WHO disability grading system allows some standardized categorization of the severity of such impairment/deformities (Brandasma and Van Brakel 2003; WHO Expert Committee on Leprosy 1998) (Fig. 8).

Diagnosis

The diagnosis of leprosy requires not only detecting the presence of the disease but also being able to accurately classify leprosy for treatment, since different treatment regimens exist depending on the form of leprosy present. Improper classification

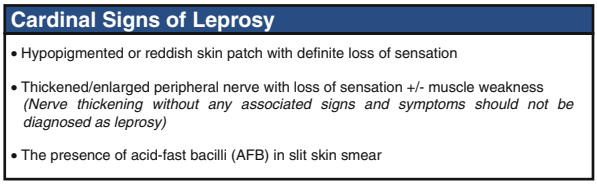


Fig. 9 Cardinal signs of leprosy (WHO Expert Committee on Leprosy 2012)

may lead to overtreatment or, more damaging to control efforts, undertreatment of the infection. Leprosy infection can be demonstrated and classified using different modalities, namely, clinical, bacteriological, immunological and histopathological methods. Diagnosis for treatment and control activities is nonetheless mainly clinical. In low-resource settings as pertains in much of sub-Saharan Africa, this has proven quite useful with low-level front-line healthcare staff able to be trained in the clinical diagnosis of leprosy.

The presence of at least one of three cardinal signs of leprosy is enough to make a diagnosis of leprosy (Fig. 9). Clearly, diagnosing leprosy in the late stages when the disease is easily recognizable is much easier than in the early stages, when the lesions are now forming. The importance of diagnosing leprosy early, however, cannot be overemphasized; late diagnosis has negative implications with regard to continued infectivity of untreated patients within the community and development of advanced disease with permanent deformities that will persist beyond cure by the time of initiation of treatment.

Regarding the individual criteria for diagnosing leprosy, the finding of anaesthetic skin patches appears to be the most sensitive, being present in about 70 % of all leprosy cases (ILA Technical Forum 2002). Although they generally appear much later in the course of the disease than do anaesthetic skin lesions, the finding of enlarged nerves is also very useful but requires the assessor to have knowledge of the proper examination technique. In low-resource settings, teaching front-line health care personnel to be able to check for just ulnar and peroneal nerve enlargement will suffice, since the vast majority of cases of leprosy-associated nerve enlargement will involve either or both of these nerves (Groenen and Saunderson 2001). The demonstration of acid-fast bacilli in a slit-skin smear, despite the challenges with its sensitivity, will appear to be the most specific with the presence of AFB almost invariably confirming leprosy (ILA Technical Forum 2002). Taken together, all three cardinal signs have a sensitivity of 97 % with a positive predictive value of 98 % (ILA Technical Forum 2002).

Considering the complexity of the existing classification of the different forms of leprosy, there was a need to have a simpler classification system which could be employed by front-line health care staff for treatment purposes (WHO 1982). In this regard, a number of "operational classifications" of leprosy have been postulated over the years with the current consensus allowing the use of clinical criteria alone, in the absence of reliable facilities for bacteriological examination of slit-skin smears (WHO Study Group on Chemotherapy of Leprosy 1994). Under the current operational classification system (WHO Expert Committee on Leprosy 2012), a patient with more than five skin lesions is deemed to have multibacillary (MB) leprosy, whilst a patient having one to five skin lesions will be classified as having

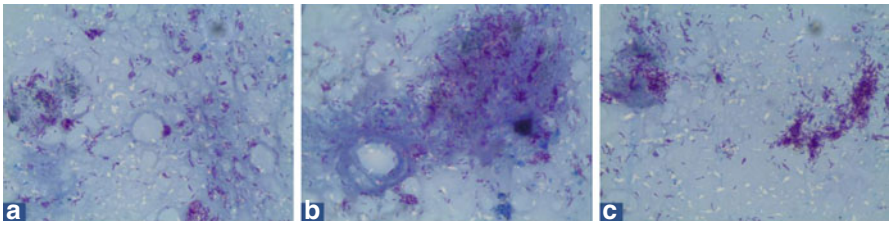


Fig. 10 Light micrographs of slit-skin smear from a patient with high bacillary load showing solid-staining rods; (**a**) and (**c**) AFB occur singly or in clumps. (**b**) AFB could be clumped together in large globi containing >100 bacilli (Credit: Smear by Mr. Arhin, Ankaful Leprosy General Hospital, Cape-Coast; Light micrograph by Dr. K. Akapko, Pathology Department, University of Cape-Coast School of Medical Sciences)

paucibacillary (PB) leprosy. When bacteriological examination is possible, all smear-positive cases are still to be classified as MB leprosy, irrespective of the number of skin lesions (WHO Expert Committee on Leprosy 1988).

The current WHO classification of leprosy using only clinical criteria has a reasonable balance of sensitivity and specificity, approaching 90 %, respectively, making it the best available option (Normal et al. 2004; Croft et al. 1998). This makes it a very convenient classification system for treatment of leprosy in low-resource settings with the obvious advantage of its simplicity of use. With respect to leprosy control challenges, using the number of skin lesions alone may however lead to a few MB patients being wrongly classified as PB leading to under treatment (Croft et al. 1998). This therefore calls for more research into newer diagnostic methods and the strengthening of health resources, particularly in sub-Saharan Africa, in order to overcome this challenge.

The gold standard for diagnosis remains the demonstration of granulomas and acid-fast bacilli (AFB) in skin and nerve biopsies using the bacterial index in granuloma (BIG), but this is highly invasive and requires a high level of resource not readily available in many care settings (Bhushan et al. 2008). Demonstration of acid-fast bacilli in slit-skin smears (SSS) stained with the Ziehl-Neelsen method is a good proxy to biopsy, although not as sensitive since skin smears do not reach the deep layers of the dermis where acid-fast bacilli in leprosy granulomas are confined, separated from the epidermis by a subepidermal clear zone (Bhushan et al. 2008; Ridley and Jopling 1966). Furthermore the sensitivity of bacteriological examination of slit-skin smears for acid-fast bacilli, found to range from as low as 10–50 % (ILA Technical Forum 2002), is greatly limited by the skill level of the laboratory personnel and is another major reason why slit-skin smears are no longer routinely required to diagnose and treat or declare cure of leprosy (Fig. 10).

The lepromin test is an immunologically based test modality that entails the intradermal injection of inactivated leprosy bacilli and the examination of injection site on day 3 and/or day 28 after injection. Although not routinely used in the diagnosis of leprosy, the test results do offer a clue as to the type of leprosy the individual has. The lepromin test positivity is dependent on the strength of the

cell-mediated immunity to leprosy and varies from strongly positive with TT leprosy, across the whole clinical spectrum, to virtually absent with LL leprosy. There are two reactions that indicate test positivity: the so-called early reaction occurring within 2 days of intradermal injection, marked by erythema with oedema and thickening of skin, and the classic "Mitsuda" reaction occurring 3–4 weeks after and characterized by the formation of a nodule, sometimes with ulceration (Dharmendra and Loew 2012).

Other promising test modalities include serology and tests based on the polymerase chain reaction (PCR), although the latter requires such a high level of technology that makes it only useful for research purposes. Since the 1980s when Brennan and Barrow described leprosy-specific phenolic glycolipid I (PGL-I) antibodies (1980), there has been a lot of research and development in this area to produce a rapid serological test that will be able to diagnose early/subclinical leprosy infection. Such a rapid diagnostic test for leprosy amenable for use in poor and remote areas as exist in many parts of sub-Saharan Africa will have obvious benefits with regard to breaking of the transmission chain early and prevention of deformities associated with late diagnosis of leprosy.

Towards the LL end of the disease spectrum, there is a good humeral response to leprosy with multibacillary leprosy patients tending to have higher anti-PGL-I antibody titres, which can be monitored and have been shown to fall progressively after initiation of treatment (Miller et al. 1987). There is evidence for the occurrence of higher anti-PGL-I antibody titres in household contacts of leprosy patients compared with apparently unexposed individuals and a higher risk of future disease conferred on the individual by the presence of anti PGL-I antibodies (Ulrich et al. 1991). Serological tests based on PGL-I are however not sensitive, particularly for paucibacillary cases with low or absent antibodies, and call for the inclusion of multiple recombinant antigens in the development of a reliable future serological screening test (Spencer et al. 2005; Ulrich et al. 1991). Anti-PGL-I antibodies may however still be useful for monitoring epidemiological changes within communities or amongst contacts although not specific enough to predict whom amongst exposed contacts will actually develop clinical disease (Ulrich et al. 1991).

Control Tools and Strategies

Since leprosy is still essentially a disease of man, early diagnosis and treatment of infected individuals are important to limit the spread and burden of the disease. The cornerstone of leprosy control activities thus remains the provision of effective multidrug therapy (MDT) to treat identified cases (WHO-SEARO 2009a). To ensure sustainability, leprosy services are being integrated into the general health care systems of endemic countries, so also to ensure that these services are easily accessible to leprosy sufferers devoid of stigma. Much effort will be needed to improve the generally weak health care systems within the sub-Saharan African subregion and to ensure continual availability of drugs at the points of care.

Although case identification remains largely passive, there is active surveillance of house-hold contacts of leprosy sufferers for several years after diagnosis and treatment, since there is a proven increased risk of leprosy in this subset of the population. There is however not enough evidence currently to support prophylactic treatment of household contacts (WHO-SEARO 2009a). In some hyperendemic hotspots and hard-to-reach areas such as those coming out of conflicts, intensive campaigns may be utilized to actively identify and treat leprosy cases although no real variation in approach to identification of new cases between low- and high-leprosy burden areas is prescribed.

There has been a slight shift in the current strategy of leprosy control to build on the successes so far, with the focus now placed on reducing the number of new cases detected with grade 2 disabilities. It is hoped that this will reduce the delays in diagnosis and in the initiation of MDT which in turn will likely lead to a reduction in new cases occurring within the population (WHO-SEARO 2009a). The current strategy utilizes the rate of new cases detected with grade 2 disabilities per 100,000 population as the driving indicator as it is less influenced by operational factors and readily allows for the estimation of underdetection as well as resources that will be required to deal with the disability burden (WHO-SEARO 2009a).

Regarding dealing with impairments/deformities, the current strategy continues to stress on community-based rehabilitation services alongside intensification of self-care programmes as well as strengthening of referral systems within the integrated health system to manage acute complications such as reactions. A key addition to the strategy is a greater inclusion of leprosy sufferers in helping to frame policy and to actively participate in efforts to reduce stigma and improve living standards of sufferers.

Chemotherapy-Based Strategies

Chemotherapy for leprosy comprises of multidrug therapy (MDT) and also medications used during reactions, which may occur anytime during the course of treatment or even after. MDT utilizes three effective first-line drugs, all possessing some bactericidal properties with different mechanisms of action, given over a fixed duration with the primary goal of achieving cure with little or no risk of relapse. This same concept underlines the successes chalked using combination therapy in the treatment of other conditions such as tuberculosis and human immunodeficiency virus (HIV).

The three standard first-line drugs are rifampicin, clofazimine and dapsone with rifampicin being the pillar of the various MDT regimens owing to its far greater bactericidal activity against leprosy bacilli. Six other drugs, namely, ofloxacin, clarithromycin, minocycline, moxifloxacin, rifapentine and TMC 207, have been shown to also have significant bactericidal effect against leprosy bacilli and are at different stages of clinical development, with some already being employed in second-line combinations when use of one of the standard drugs is not possible (WHO Expert Committee on Leprosy 2012; WHO-SEARO 2011). The MDT regimens differ depending on whether multibacillary or paucibacillary leprosy is being treated.

Table 2 Standard MDT for leprosy

Paucibacillary leprosy			
Duration: **6 months** (**completed in maximum 9 months**)			
Weight/age	**Drug**	**Monthly supervised dose**	**Daily unsupervised dose**
Adult (50–70 kg)	Rifampicin	600 mg	–
	Dapsone	100 mg	100 mg
Child (10–14 years)	Rifampicin	450	–
	Dapsone	50 mg	50 mg
Child <10 years	Rifampicin	10 mg/kg body weight	–
	Dapsone	2 mg/kg body weight	2 mg/kg body weight
Multibacillary leprosy			
Duration: **12 months** (**completed in maximum 18 months**)			
Weight/age	**Drug**	**Monthly supervised dose**	**Daily unsupervised dose**
Adult (50–70 kg)	Rifampicin	600 mg	–
	Clofazimine	300 mg	50 mg
	Dapsone	100 mg	100 mg
Child (10–14 years)	Rifampicin	450	–
	Clofazimine	150 mg	50 mg every other day
	Dapsone	50 mg	50 mg
Child <10 years	Rifampicin	10 mg/kg body weight	–
	Clofazimine	1 mg/kg alt days, depending on dosage	1 mg/kg alt days, depending on dosage
	Dapsone	2 mg/kg body weight	2 mg/kg body weight
Single lesion paucibacillary leprosy			
Duration: **single dose**			
Weight/age	**Treatment**		
Adult (50–70 kg)	Rifampicin (600 mg) + ofloxacin (400 mg) + minocycline (100 mg)		
Child (5–14 years)	Rifampicin (300 mg) + ofloxacin (200 mg) + minocycline (50 mg)		
Not recommended for pregnant women and children <5 years			

WHO Expert Committee on Leprosy (2012), WHO-Division of Drug Management and Policies (1998)

Six months of treatment with rifampicin and dapsone has been shown to be effective for paucibacillary leprosy with no need for extension when appropriately given (WHO Study Group on Chemotherapy of Leprosy (1994). In those with single-lesion PB leprosy however, treatment with a single-dose regimen comprising of rifampicin, ofloxacin and minocycline is possible (WHO-Division of Drug Management and Policies 1998). Therapy for MB leprosy involves the addition of clofazimine, and duration of treatment is much longer. WHO currently considers 12 months of treatment for MB leprosy as sufficient (WHO Expert Committee on Leprosy 1998), although some countries still treat MB leprosy for up to 24 months as per the original guidelines when MDT was first introduced. There is however an ongoing multicentric cohort study utilizing a shorter-course uniform MDT for treatment of both PB and MB leprosy cases which is showing promising results and may influence treatment of leprosy in the near future when finally completed (WHO-SEARO 2011) (Table 2).

Once started on MDT, a leprosy patient is generally regarded as uninfectious since a single dose of rifampicin drastically reduces the patient's viable bacilli load to such a level as to render him/her so (WHO-SEARO 2009b). Achieving cure however requires completion of the treatment course within the stipulated time. Whilst leprosy patients may have obvious economic and physical challenges commuting to health facilities at a distance for their monthly supervised doses, this enables care providers to trace patients who start defaulting early to ensure compliance to treatment. Generally underdeveloped sub-Saharan communities with lack of proper address systems and inadequate transport facilities present a major challenge in this regard. Nonetheless, patients' compliance can be maintained by adequately informing them about the course of the disease and the implication of incomplete treatment and ensuring that they can always receive MDT at health facilities within their localities.

Ensuring compliance to MDT is a crucial factor of the quality of case management since completing the whole fixed-course duration is required to cure the disease and hence reduce the potentially infective caseload in the community. It has been difficult to assess the quality of case management within the subregion over the years since the cure/treatment completion rate is not routinely reported by individual countries, resulting in the use of the prevalence/detection ratio (P/D ratio) as a proxy (WHO-AFRO 2012, 2013). This is not ideal because prevalence and detection rates, in particular, are influenced by other factors. Going forward, indicators like cure/treatment completion rates and defaulter rates as well as proportion of health facilities providing MDT will be monitored under the current strategy to ensure the quality of leprosy control services with regard to treatment remains high (WHO-SEARO 2012).

The WHO continues to play a leading role when it comes to managing the currently available drugs for treating leprosy. Since 1995, the WHO has supplied MDT to endemic countries for free thanks to the benevolence of institutions like the Nippon Foundation and Novartis, who have committed to continue supplying these drugs for the foreseeable future. With rifampicin critical to the current MDT regimens, it is necessary to continue surveillance for rifampicin resistance even though current levels are insignificant. In this regard, the WHO surveillance network actively collects slit-skin samples from MB patients from all over the world to test for drug resistance mutations using PCR technique (WHO-SEARO 2011).

The mainstay of treatment for reactions and isolated neuritis is steroids (prednisolone), although clofazimine may also be used in cases of severe erythema nodusum leprosum (ENL). Thalidomide is also useful in severe ENL, but may not be readily available owing to restrictions arising from its immense teratogenic potential. Other useful adjuncts in the management of reactions include rest and analgesics such as acetyl-salicylate and paracetamol, which may all but suffice in very mild cases of lepra reactions. It is important during reactions not to discontinue MDT if the patient is still undergoing treatment for leprosy.

Challenges in Programme Implementation

The great success achieved in attaining the target for leprosy elimination as a public health problem has come at a price. In the myriad of worldwide health problems, leprosy control activities now attract less financial support and attention coupled with a relative complacency on the part of national health bodies. It is hoped that with the current move towards incorporating the organization of leprosy control with other neglected tropical diseases, the much needed visibility for leprosy control activities will be attained.

Although the push to integration makes the sharing of some resources available to leprosy control services, it also means attention to some dedicated leprosy services is suffering. It is in this regard that improving political will and cross-sectorial collaboration have been made key pillars in the fight to further reduce the burden of leprosy. It also calls for strengthening of health systems particularly within leprosy-endemic countries so that leprosy sufferers all over sub-Saharan Africa can enjoy equitable, high-quality care wherever they may be.

It is also ironical that as we push towards integration of leprosy services within the general health care systems, the knowledge of front-line health care workers regarding leprosy appears to be on the decline since fewer cases of leprosy are now being seen. This has not been helped by the loss of expertise and knowledge to retirement, death and transfer of highly skilled leprosy health workers to other areas of need in the health sector. The leprosy stigma also continues to be a barrier, even amongst front-line health care workers who rather prefer to engage in more lucrative activities of other health programmes.

In Ghana, for instance, the use of innovative "information, education and communication" (IEC) techniques are being utilized to help overcome some of these challenges that will otherwise lead to late leprosy diagnosis and consequently increase the negative public health impact of the disease. Illustrative posters highlighting the early stages of leprosy have been designed for use by front-line health care workers, whilst public education is carried out with the aid of picture banners at market places and other public gatherings.

Further Research for Policy and Control

Much is still not known about the exact mode of transmission of leprosy, and there is a general paucity of knowledge regarding the recently discovered second causative agent *Mycobacterium lepromatosis*. This calls for more molecular studies to characterize both agents further and also to investigate possible non-human sources of leprosy infection that can negatively impact control efforts. To curtail transmission and development of advanced disease, we would require improved diagnostic modalities, particularly to help in the detection of subclinical infection. More studies

too will be required in the area of chemoprophylaxis in household contacts since there is currently no conclusive scientific evidence to be utilized in protecting this high-risk group.

The clinical management of leprosy has not changed much over the years. Drug trials involving some of the newer drugs and the formulation of other short-course combination therapies will help improve treatment quality and outcomes. More trials are also needed in the area of prevention and novel treatment of reactions to help drastically reduce the disability burden attributable to leprosy. More research is also required to improve the current operational and epidemiological tools utilized in leprosy control to help make further progress in reducing the burden of leprosy.

Conclusion and Outlook for the Next Decade

Although the leprosy prevalence rates have dramatically come down over the last two and a half decades and incidence rates of new leprosy cases continue to generally decrease over the years, it is becoming obvious that our current efforts appear to be stagnating, and eradication of leprosy will remain a dream, at least for now. More effort will have to be put into filling the knowledge gaps with research so that these can be employed in further accelerating the progress towards "real" elimination. It is likely, with the Bangkok declaration proposing the reduction of the burden of leprosy to one new case with grade 2 disability per million population by 2020, that leprosy control activities will maintain essentially the same focus going into the next decade.

References

Barua S (2013) Global leprosy situation and new challenges and priorities with reference to Bangkok Summit [Presentation to WHO-Afro Leprosy and HAT Managers and partners]. Annual Leprosy and Human African Trypanosomiasis Programme Review Meeting, Yaoundé, 11 Nov

Bhushan P, Sardana K, Koranne RV, Choudhary M, Manjul P (2008) Diagnosing multibacillary leprosy: a comparative evaluation of diagnostic accuracy of slit-skin smear, bacterial index of granuloma and WHO operational classification. Indian J Dermatol Venereol Leprol 74(4):322–326

Brandasma JW, Van Brakel WH (2003) WHO disability grading: operational definitions. Lepr Rev 74(4):366–373

Brennan PJ, Barrow WW (1980) Evidence for species-specific lipid antigens in Mycobacterium leprae. Int J Lepr Other Mycobact Dis 48(4):382–387

Chehl S, Job CK, Hastings RC (1985) Transmission of leprosy in nude mice. Am J Trop Med Hyg 34(6):1161–1166

Croft RP, Smith WC, Nicholls P, Richardus JH (1998) Sensitivity and specificity of methods of classification of leprosy without use of skin-smear examination. Int J Leprol 66(4):445–450

De Messias-Reason I, Kremsner PG, Kun JF (2009) Functional haplotypes that produce normal ficolin-2 levels protect against clinical leprosy. J Infect Dis 199(6):801–804

Desikan KV, Sreevista (1995) Extended studies on the viability of Mycobacterium Leprae outside the human body. Lepr Rev 66(4):287–295
Dharmendra, Loew J (2012) The immunological skin tests in leprosy. Part II. The isolated protein antigen in relation to the classical Matsuda reaction and the early reaction to lepromin. 1942. Indian J Med Res 136(3), 9p following 502
Groenen G, Saunderson P (2001) How to diagnose and treat leprosy (ILEP Learning Guide 1). The International Federation of Anti-Leprosy Associations, London
Han XY, Silva FJ (2014) On the age of leprosy. PLoS Negl Trop Dis 8(2), e2544. doi:10.1371/journal.pntd.0002544
Han XY, Seo Y-H, Sizer KC, Schoberle T, May GS, Spencer JS, Li W, Nair RG (2008) A new Mycobacterium species causing diffuse lepromatous leprosy. Am J Clin Pathol 130(6):856–864
Han XY, Sizer KC, Velarde-Felix JS, Frias-Castro LO, Vargas-Ocampo F (2012) The leprosy agents *Mycobacterium lepromatosis* and *Mycobacterium leprae* in Mexico. Int J Dermatol 51(8):952–959
ILA Technical Forum (2002) The diagnosis and classification of leprosy. Int J Leprol 70(1 [Suppl]):S23–S31
Job CK, Jayakumar J, Kearney M, Gillis TP (2008) Transmission of leprosy: a study of skin and nasal secretions of household contacts of leprosy patients using PCR. Am J Trop Med Hyg 78(3):518–521
Lastoria JC, Abreu MA (2014) Leprosy: review of the epidemiological, clinical, and etiopathogenic aspects – part 1. An Bras Dermatol 89(2):205–218
Malaviya GN (2003) Review: sensory perception in leprosy – neurophysiological correlates. Int J Lepr Other Mycobact Dis 71(2):119–124
McDermott-Lancaster RD, McDougall AC (1990) Mode of transmission and histology of M. Leprae infection in nude mice. Int J Exp Pathol 71(5):689–700
Miller RA, Gorder D, Harnisch JP (1987) Antibodies to phenolic glycolipid-I during long-term therapy: serial measurements in individual patients. Int J Lepr Other Mycobact Dis 55(4):633–636
Monot M, Honoré N, Garnier T, Araoz R, Coppee JY et al (2005) On the origin of leprosy. Science 308:1040–1042
Norman G, Joseph G, Richard J (2004) Validity of the WHO operational classification and value of other clinical signs in the classification of leprosy. Int J Lepr Other Mycobact Dis 72(3):278–283
Onyeze A (2013) Elimination of neglected tropical diseases in the African Region – an overview. [Presentation to WHO-Afro Leprosy and HAT Managers and partners]. Annual Leprosy and Human African Trypanosomiasis Programme Review Meeting, Yaoundé, 11 Nov
Ridley DS, Jopling WH (1966) Classification of leprosy according to immunity a five-group system. Int J Leprol 34(3):255–273
Saunderson P (2002) How to recognize and manage leprosy reactions (ILEP Learning Guide 2). The International Federation of Anti-Leprosy Associations, London
Spencer JS, Dockrell HM, Kim HJ, Marques MAM, Williams DL, Martins MVSB, Martins MLF, Lima MCBS, Sarno EN, Pereira GMB, Matos H, Fonseca LS, Sampaio EP, Ottenhoff THM, Geluk A, Cho S-N, Stoker NG, Cole ST, Brennan PJ, Pessolani MCV (2005) Identification of specific proteins and peptides in Mycobacterium leprae suitable for the selective diagnosis of leprosy. J Immunol 175(12):7930–7938
Truman R, Fine PEM (2010) "Environmental" sources of Mycobacterium Leprae: issues and evidence. Lepr Rev 81(2):89–95
Truman RW, Singh P, Sharma R, Busso P, Rougemont, Panis-Mondolfi A, Kapopoulou A, Brisse S, Scollard D, Gillis TP, Cole ST (2011) Probable zoonotic leprosy in the southern United States. N Engl J Med 364(17):1626–1633
Ulrich M, Smith PG, Sampson C, Zuniga M, Centeno M, Garcia V, Manrique X, Salgado A, Convit J (1991) IgM antibodies to native phenolic glycolipid-I in contacts of leprosy patients

in Venezuela: epidemiological observations and a prospective study of the risk of leprosy. Int J Lepr Other Mycobact Dis 59(3):405–415
WHO Expert Committee on Leprosy (1988) WHO Expert Committee on Leprosy: sixth report. (WHO Technical Report Series, No. 768). World Health Organization, Geneva
WHO Expert Committee on Leprosy (1998) WHO Expert Committee on Leprosy: seventh report (WHO Technical Report Series, No. 874). World Health Organization, Geneva
WHO Expert Committee on Leprosy (2012) WHO Expert Committee on Leprosy: eight report. (WHO Technical Report Series, No. 968). World Health Organization, Geneva
WHO Study Group on Chemotherapy of Leprosy (1994) Chemotherapy of Leprosy: report of a WHO Study Group (WHO Technical Report Series, No. 847). World Health Organization, Geneva
World Bank Group (2011) Poverty data – world development indicators. Available at: data.worldbank.org/topic/poverty. Accessed on 2nd Jul 2014
World Health Organization (1982) Chemotherapy of Leprosy for control programmes: report of a WHO Study Group (WHO Technical Report Series, No. 675). World Health Organization, Geneva
World Health Organization (2013) Global Leprosy: update on the 2012 situation. Wkly Epidemiol Rec 88(35):365–379
World Health Organization, Division of Drug Management and Policies (1998) WHO model prescribing information: drugs used in leprosy. World Health Organization, Geneva
World Health Organization, Department of Control of Neglected Tropical Diseases (2012) Leprosy prevalence rates, data reported to WHO as of January 2012. Available at: http://www.who.int/lep/situation/Leprosy_PR_2011.pdf. Accessed 25th June 2014
World Health Organization, Regional Office for Africa (2012) Progress towards the reduction of the burden of leprosy: leprosy is curable. World Health Organization, Regional Office for Africa, Brazzaville
World Health Organization, Regional Office for Africa (2013) Leprosy: facing the remaining challenges – The WHO African Region strategic plan for further reducing the burden of leprosy 2013–2013. World Health Organization, Regional Office for Africa, Brazzaville
World Health Organization, Regional Office for South-East Asia (2009a) Enhanced global strategy for further reducing the disease burden due to leprosy -plan period: 2011–2015. World Health Organization, Regional Office for South-East Asia, New Delhi
World Health Organization, Regional Office for South-East Asia (2009b) Report of the tenth meeting of the WHO Technical Advisory Group on Leprosy Control. World Health Organization, Regional Office for South-East Asia, New Delhi
World Health Organization, Regional Office for South-East Asia (2011) Report of the eleventh meeting of the WHO Technical Advisory Group on Leprosy Control. World Health Organization, Regional Office for South-East Asia, New Delhi
World Health Organization, Regional Office for South-East Asia (2012) Monitoring enhanced global strategy. World Health Organization, Regional Office for South-East Asia, New Delhi
Yawalkar SJ (2002) Leprosy for medical practitioners and paramedical workers, 7th edn. Novartis Foundation for Sustainable Development, Basle

Loiasis

Joseph Kamgno, Hugues Clotaire Nana-Djeunga, and Marc Kouam-Kenmogne

Contents

J. Kamgno (✉)
Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, 1364, Yaoundé, Cameroon

Centre for Research on Filariasis and Other Tropical Diseases (CRFilMT), 5797, Yaoundé, Cameroon
e-mail: kamgno@crfilmt.org

H.C. Nana-Djeunga
Centre for Research on Filariasis and Other Tropical Diseases (CRFilMT), 5797, Yaoundé, Cameroon

Parasitology and Ecology Laboratory, Department of Animal Biology and Physiology, Faculty of Science, University of Yaoundé 1, 812, Yaoundé, Cameroon

M. Kouam-Kenmogne
Department of Animal Production, University of Dschang, 222, Dschang, Cameroon

Centre for Research on Filariasis and Other Tropical Diseases (CRFilMT), 5797, Yaoundé, Cameroon

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_7

Abstract Loiasis, also known as African eye worm is a vector-borne parasitic disease caused by the filarial nematode *Loa loa* and transmitted by the bite of tabanid vectors (*Chrysops dimidiate*) from the genus *Chrysops*. The real burden of the disease is not known, but *L. loa* remains wrongly classified as a benign disease. Loiasis exists exclusively in Africa where it is mainly focalized in the big areas of Central Africa. The prevalence of the disease rarely exceeds 30 % in endemic communities; however, the disease has become important because of the serious adverse events which occur in some heavily infected patients after treatment with Mectizan for onchocerciasis or lymphatic filariasis. The life cycle of the parasite takes about 10 days in the vector (intermediate host) and about 3 months in humans (definite host). The passage of the adult worm in the bulbar conjunctiva is the classic manifestation of loiasis. Other manifestations are common migratory transient oedema (Calabar swellings). Both of these are used in the clinical diagnosis, complemented by microscopy for microfilaria. Rare but serious manifestations of *Loa loa* such as encephalitis, glomerular damage, retinal damage, endomyocardial fibrosis, albuminuria and hydrocele may also occur. Both surgical removal of adult worms and chemotherapy are used for managing *L. loa*. Currently Diethylcarbamazine (DEC), Mectizan®, mebendazole (MBZ) and albendazole (ALB)) are effective in varying degrees against mf and/or adult *L. loa*, while further research is needed to improve the efficacy of ALB in the management of *L. loa*.

Introduction

Loiasis is a parasitic disease due to the filarial nematode *Loa loa* (*L. loa*)(Guyot 1778) and transmitted by tabanid vectors from the genus *Chrysops* (Leiper 1912). *L. loa* is also known as the African eye worm because the most specific clinical manifestation of the disease is the migration of the adult worm under the conjunctiva of the eye of infected individuals. Although loiasis was reported as one of the most common reasons for medical consultation (Pinder 1988), its real

burden has never been evaluated; it remains wrongly qualified as a benign disease. It is a neglected condition among neglected tropical diseases (NTDs), which increasingly becomes important thanks to the serious adverse events arising in some patients heavily infected with *L. loa* and treated against onchocerciasis and/or lymphatic filariasis, another NTDs with dedicated control programmes.

Epidemiology of the Disease

Distribution and Burden

Loiasis was described as far back as the end of the sixteenth century in Congolese slaves taken to America. The disease disappeared from America at the end of the slavery and presently exists exclusively in Africa where it is mainly focalized in the big forest areas of Central Africa (Boussinesq and Gardon 1997; Hawking 1977; Rodhain and Rodhain-Rebourg 1973). Some restricted foci were described in Benin, Nigeria, Northern Cameroon, Chad and in South Sudan which constitutes the west and the northern boundary of the disease. Some cases of loiasis have also been described outside these areas, but they are probably imported cases (El Haouri et al. 2001).

Based on the recent vast surveys carried out by the African Program for Onchocerciasis Control (APOC) using the rapid mapping of *L. loa* (RAPLOA) strategy, the disease is found in two large foci with high prevalence: the west focus covering the south east of Nigeria, the south of Cameroon, Equatorial Guinea, Gabon, west of Congo, the Coastal plains of Angola, the Bas Congo in Democratic republic of Congo (DRC), the west of Central African Republic (CAR) and the south of Chad. The East focus covers the east of CAR, the south of Southern Sudan and the northeast of DRC (Zoure et al. 2011). A small focus is found at the boundary between Kenya and South Sudan.

The areas with low prevalence stretch from south west Benin to the West of Ethiopia and from the north of Angola to the central region of Chad (Fig. 1). These data are in accordance with the description made previously with the confirmation that *Chrysops dimidiata* has never been found in the west of Benin. Some *Chrysops silacea* specimen were reported in Ghana, but their vectorial capacity has never been studied (Boussinesq 2006). In the endemic areas, large foci are spread in the forest areas where there are appropriate biotopes for the development of the *Chrysops* vector*s*. Nevertheless, there are some areas in the savannah zones with "forest galleries" where the prevalence of loiasis is very high (above 50 %) (Kamgno and Boussinesq 2001). In these areas (forest galleries), the prevalence of the disease is higher than in the other forest areas probably because the installation of the infection is recent and that people are not immunologically protected from the infection as in the forest areas. Another explanation could be the concentration of vectors in "forest galleries", thus reducing the dilution phenomenon.

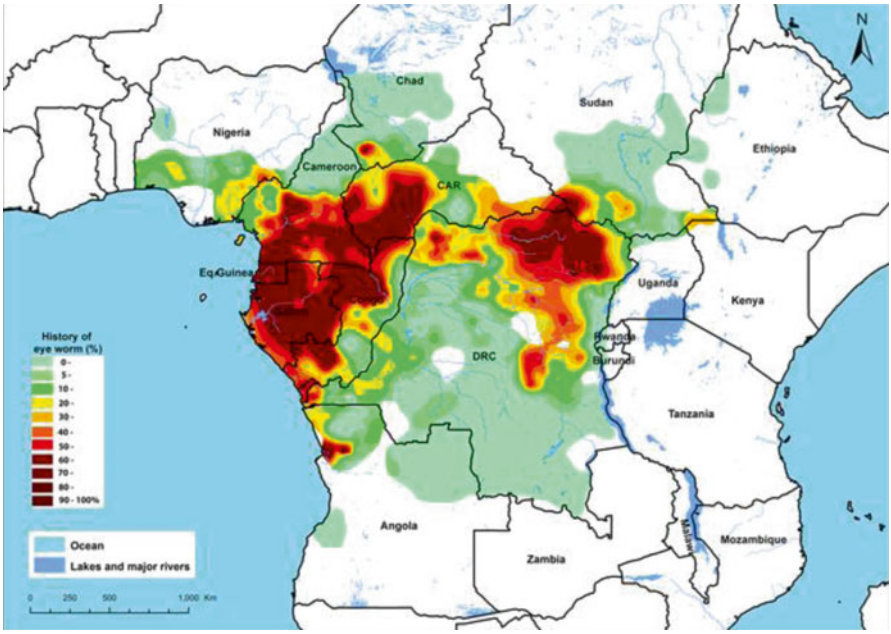


Fig. 1 Geographic distribution of *Loa loa* in Africa (©Zoure et al. 2011)

Public Health Impact in SSA

Loiasis is a complex infection since the prevalence of the disease rarely exceeds 30 % in endemic communities, even in areas where the vast majority of the populations presents with the infection. In Gabon, it was shown that from as early as 2 years of age, all the children have specific IgE antibodies to *L. loa* (Goussard et al. 1984). The impact of this disease is up to now not well studied. Loiasis was nonetheless described, in some endemic areas, as one of the main causes of medical consultation (Pinder 1988). Newly arrived people in endemic areas seem to develop, after infection, more clinical signs than the natives who, for some, however, have very high microfilaria (mf) loads (Churchill et al. 1996; Klion et al. 1991). The interest in loiasis was renewed as soon as serious adverse events (SAEs) were reported after administration of ivermectin (IVM) for the treatment of onchocerciasis in individuals harbouring high *L. loa* microfilaraemia. These SAEs consist of encephalopathy usually accompanied by retinal haemorrhages (Fobi et al. 2000); the outcome can be fatal, and individuals who survive an episode of SAE present with serious sequelae (Boussinesq 2006).

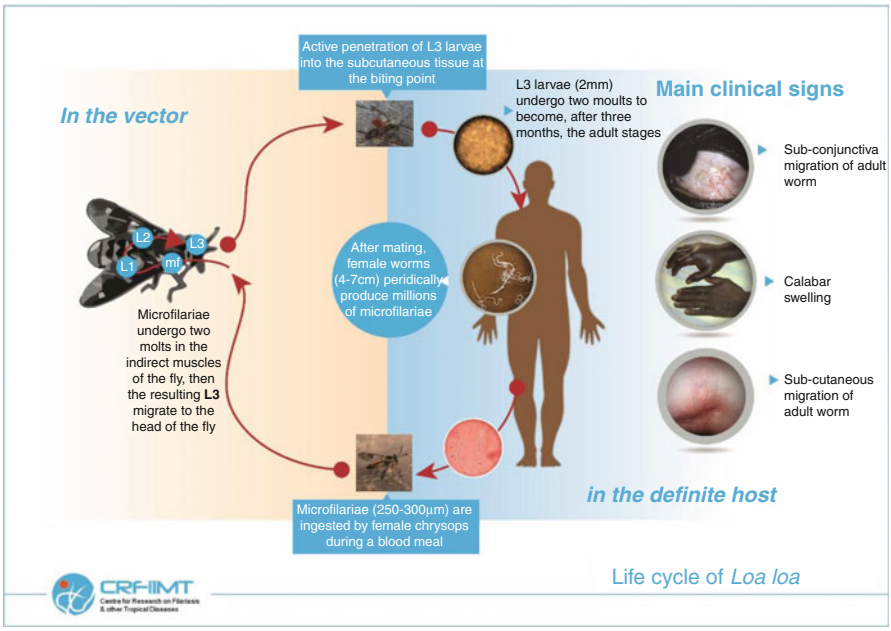


Fig. 2 Life cycle of the filarial nematode *Loa loa* (©CRFilMT)

Basic Biology

Life Cycle

The life cycle of *L. loa* takes place in two hosts, in humans (definitive hosts) and tabanids of the genus *Chrysops* (intermediate hosts or vectors) (Fig. 2).

In the Vector

L. loa mf (Fig. 3) are ingested by female Chrysops during a blood meal taken from an infected human host. These mf cross the peritrophic membrane and the wall of the digestive tract to reach the haemocoel of the fly, particularly in the adipose tissue of the abdomen. A phagocytosis of mf by fat cells then takes place and leads to the formation of a "filarial syncytium" within which metamorphosis takes place and leads to the infective larval stage (Lebied 1957). After 10 days, the infective larvae leave the fat cells and migrate to the chest and then to the head of the fly. During a new blood meal, the *Chrysops* release mf at the biting point.

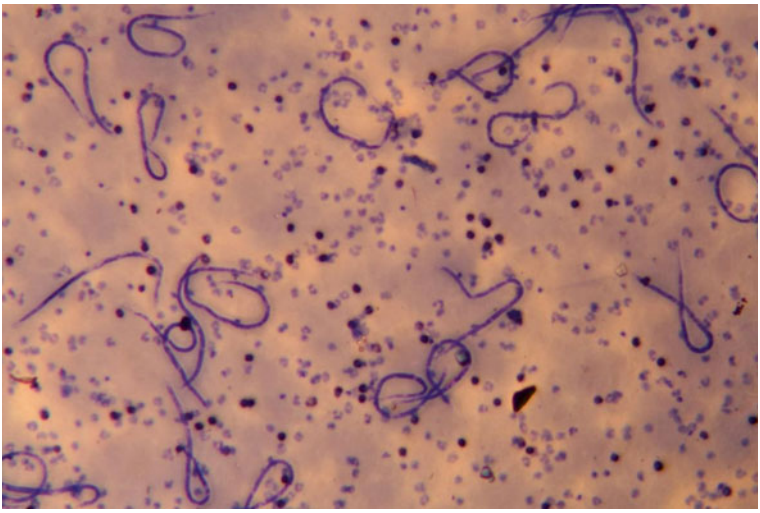


Fig. 3 Giemsa-stained thick blood film showing *L. loa* mf under optical microscope (©CRFilMT)

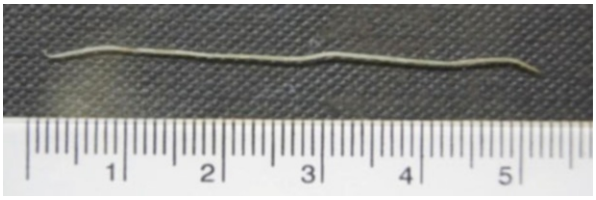


Fig. 4 Adult female *L. loa* (©CRFilMT)

In the Definitive Host (Human)

During the blood meal, the *Chrysops* make a laceration in the epidermis and dermis, which allows the active passage of larvae into the subcutaneous tissue. These larvae undergo two moults to become, after 3 months, the adult stages. The latter move and pass through the skin into the deeper connective tissue or under the conjunctiva of the eye. Mated females (Fig. 4) produce, periodically, mf which actively accumulate in the pulmonary capillaries during the night and are distributed passively in the peripheral blood during the day (Fain and Maertens 1973; Hawking 1955).

Mode of Transmission

Loiasis is a vector-borne parasitic disease. *Chrysops dimidiata*, commonly called the mango fly or the mangrove fly, and *C. silacea* are the most common vectors of *L. loa* in Central Africa (Fig. 5) (Kouam et al. 2013; Padgett and Jacobsen 2008).

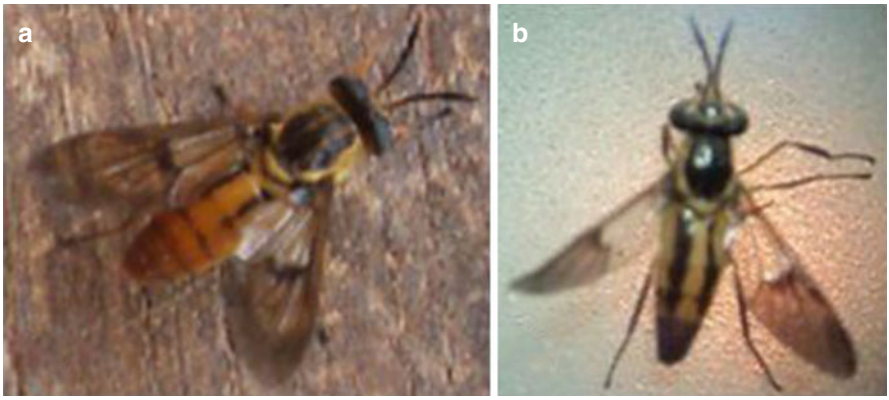


Fig. 5 *Chrysops silacea* (**a**) and *dimidiata* (**b**) (©CRFilMT)

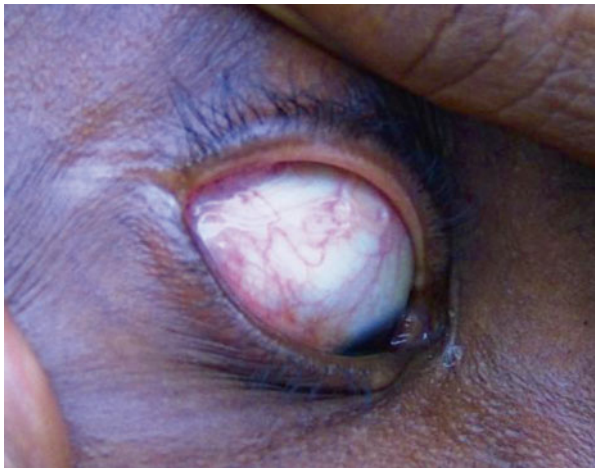


Fig. 6 Subconjunctival passage of the adult *Loa loa* in a patient suffering from loiasis (©CRFilMT)

These blood-sucking vectors have a day-biting activity which facilitates the transmission of the parasites from hosts to hosts due to the diurnal periodicity of their mf. Even though secondary, other *Chrysops* species are also able to transmit *L. loa* to humans (Duke 1955). *Chrysops langui* and *Chrysops centurionis* are the main vectors of simian strains of *Loa* which have a crepuscular activity.

Disease Presentation

The most classic manifestation of loiasis is the spectacular passage of the adult worm in the bulbar conjunctiva. This passage, which lasts from a few hours to over 24 h, can cause significant discomfort. It is often accompanied by severe swelling of the eyelids and the eyeball (Fig. 6).

Other manifestations of loiasis are the quite common migratory transient oedema, commonly called Calabar swellings (Fig. 7) (Gruntzig and Gewalt 1979). Their occurrence is caused by episodic microfilarial laying by female adult worms.

Lysis of mf leads to an allergic reaction responsible for oedema (Fain 1978). The latter may also be linked to the release of antigenic products by the adult worm (Negesse et al. 1985). This hypothesis is supported by observations made during the migration of adult worms in the bulbar conjunctiva. Indeed, this passage is often accompanied by severe swelling of the conjunctiva and periorbital tissues. Oedema due to loiasis is often associated with pruritus, arthralgia and headache (Carme et al. 1989). In an endemic area of Congo, 51 % of the population had had a history of Calabar swellings, and 69 % experienced the sub-conjunctiva migration of the adult worm in the last 12 months.

Apart from therapeutic accidents after treatment with DEC or IVM of patients harbouring high microfilarial loads, it seems that *L. loa* can cause spontaneously rare but serious manifestations such as encephalitis, glomerular damage, retinal damage, endomyocardial fibrosis, albuminuria and hydrocele (Languillat et al. 1977; Noireau et al. 1990). A case of pulmonary effusion due to loiasis has also been reported (Klion et al. 1992). Cases of intraocular migration of *Loa* adults or mf, as well as hemorrhagic and exudative retinopathy and filarial uveitis have been reported in Gabon. Retinal haemorrhages can cause large and sudden decrease in visual acuity and are in most cases irreversible (Védy et al. 1975).

Despite these clinical manifestations, loiasis is still considered as a benign disease probably because the rare lesions described in loiasis patients are hospital-based cases. A study performed in a loiasis hyperendemic area in Cameroon aiming at describing the clinical impact of loiasis, at the community level, showed that

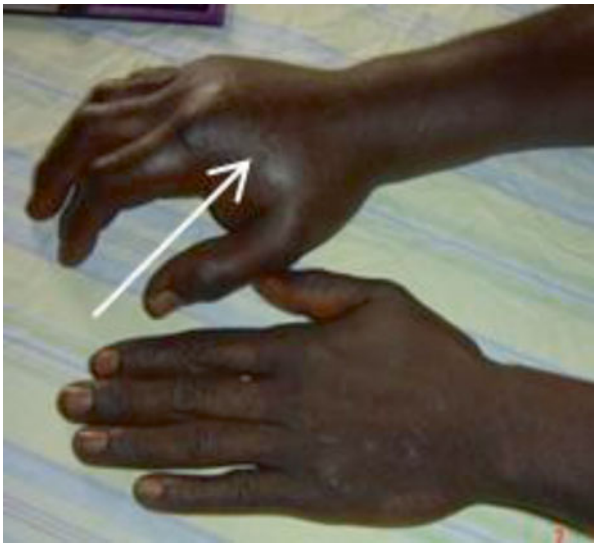


Fig. 7 Calabar swelling (*arrow*) in a patient suffering from loiasis (©CRFilMT)

some cardiac and ocular lesions (Fig. 8) may be attributed to loiasis (Kamgno et al. in preparation).

Diagnosis

The diagnosis of *L. loa* infections can be challenging, mostly because some parasite carriers are amicrofilaraemic, asymptomatic or present clinically several months or years after infection. Different diagnostic tools are available, and the choice of a particular diagnostic method depends on the resource available, the laboratory facilities and the objectives of the test (routine diagnosis, case report, epidemiological studies, etc.).

Clinical

These include Calabar swelling, visualization of adults worms migration across the eye into the subconjunctival tissues and surgical removal and identification of an adult worm under the skin. Eye worm passage on the surface of the eye, though limited to

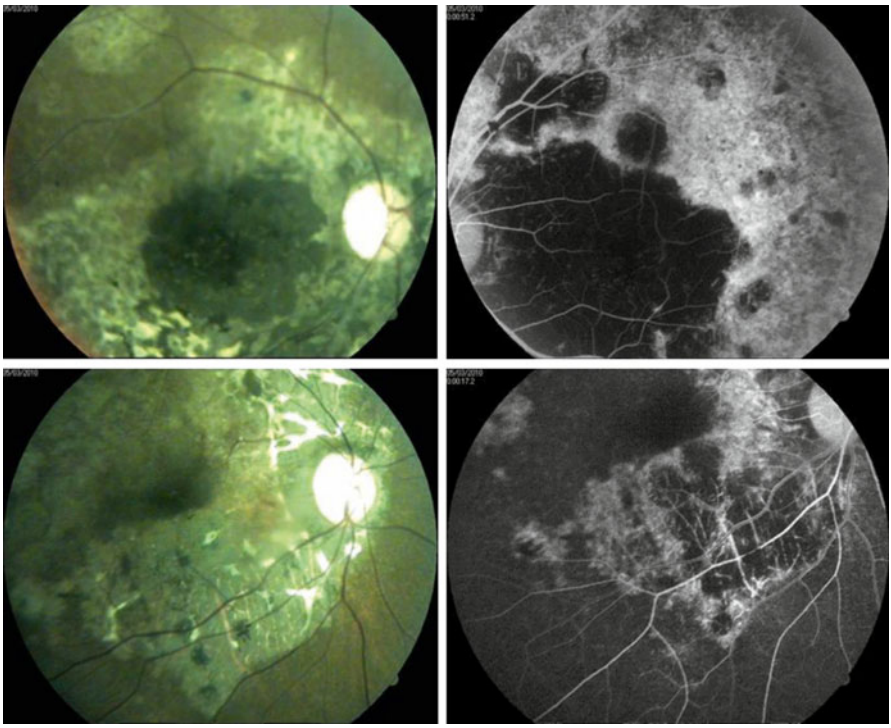


Fig. 8 Retinal lesions in individuals infected with *Loa loa* (©CRFilMT)

a very short timeframe (few hours to less than a week), proved to be a very useful tool in the mapping of loiasis using a rapid assessment procedure for loiasis (RAPLOA), which is based on a simple questionnaire on the history of eye worm (Zoure et al. 2011). Surgical removal and identification of adult worm for diagnosis purposes is not common but is often carried out in atypical cases of loiasis in patients living in non-endemic area but with a history of travel in endemic areas (Richardson et al. 2012).

Microscopical/Parasitological

So far microscopy is universally used for both epidemiological data collection and medical diagnosis of human loiasis. This is based on the demonstration of mf in Giemsa-stained thin or thick blood smears (Fig. 3). Due to the diurnal periodicity of *Loa* mf, peripheral blood collection for parasitological examination should be performed between 10 AM and 4 PM. In case of low number of circulating mf, concentration techniques such as nucleospore membrane filtration, Knott's concentration, leucoconcentration and saponin lysis may increase the sensitivity of the parasitological test. A calibrated tick blood smear to quantify the number of mf per µL or ml of blood may be performed for treatment purposes or epidemiological studies.

Serological

These are of limited number, including: immunoblotting assay (Egwang et al. 1989), enzyme-linked immunosorbent assays (ELISAs) (Akue et al. 1997, 1998; Toure et al. 1999b), *L. loa* SXP-1 (LlSXP-1) ELISA (Klion et al. 2003), luciferase immunoprecipitation systems (LIPS) and rapid LIPS format (QLIPS) assays (Burbelo et al. 2008). While immunoblotting and ELISA assays show poor specificity due to cross-reactivity with other filarial infections, the serologic assays based on the *L. loa* SXP-1 antigen and others reliably distinguish loiasis from other filarial and helminthic infections.

Molecular

There are various polymerase chain reaction (PCR)-based assays available which show higher sensitivity and specificity than the previously mentioned detection tests. Conventional PCR assays (Toure et al. 1997) as well as nested PCR assays targeting the repeat three region of the gene coding for *L. loa* 15 kDa polyprotein have been developed (Toure et al. 1998, 1999a). The nested PCR was shown to have 95 % sensitivity and 100 % specificity (Toure et al. 1998). Three other specific

nested PCRs targeting the internal transcribed spacer (ITS1) region of the DNA were developed for the differential detection of *L. loa*, *Mansonella perstans* and *Wuchereria bancrofti*, the three blood circulating mf (Jimenez et al. 2011). This same target (ITS1 region) was used by the same authors to develop species-specific polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) protocol for the differentiation of *L. loa* and *M. perstans* from *W. bancrofti*. Real-time PCR assays were also developed to demonstrate their utility for the diagnosis of filarial infections in mobile populations (Fink et al. 2011a) and to estimate the mf burden of blood samples in comparison with calibrated microscopy (Fink et al. 2011b).

Adequacy of the Diagnostic Methods

Microscopy examination is the tool mostly used in clinic and research settings, but some infected people are amicrofilaraemic (occult loiasis) (Dupont et al. 1988). Thus for cases of occult loiasis, microscopy is not adequate. Moreover, microscopy becomes a drudgery when large amounts of samples are to be processed for a screening study.

Serological tools may be used to handle very large amount of samples more conveniently than other available tools. However, they have some major shortcomings: they cannot distinguish between active and past infections, quantify microfilaraemia or be used in treatment trials to test for the efficacy of a drug.

Molecular tools are highly sensitive and specific, readily differentiating *L. loa* from other blood circulating mf, and most importantly they successfully quantify the amount of mf in blood samples from both microfilaraemic and amicrofilaraemic individuals (Fink et al. 2011b). The ability to quantify the number of mf even in blood samples from subjects with occult loiasis is a very important asset of the molecular tools, given the relevance of *Loa* microfilarial load in area co-endemic with *Onchocerca volvulus* and *W. bancrofti* where IVM is distributed. However, steps to make these tools practical in field settings are needed.

Clinical, parasitological, serological and molecular tools have shown sufficient sensitivity and specificity. Clinically, *Loa loa* is the only worm with subconjunctival migration of the adult. Concerning the parasitological examination, *Loa loa* microfilariae (Fig. 3) have day periodicity, and in endemic area *W. bancrofti* that has the same shape has night periodicity. Serological and molecular tool development and adoption usually require two major steps. The first step focuses on the development of the tool in laboratory conditions using laboratory strains of the target organism or the target organism maintained in laboratory conditions. The following step is the applicability of the assay using field samples for which the tool is being developed. This latter step is necessary to support the ability of the tool to discriminate the target organism. It also provides evidence of the reliability of the tool. Most of the *L. Loa* diagnostic tools such as calibrated microscopy and real-time PCR (Fink et al. 2011b).

Cost-Effectiveness

One of the main advantages of microscopy is probably its cost-effectiveness in comparison with other tools. Microscopy for *L. loa* detection is well suited for resource-poor laboratories, the only expensive appliance being the microscope. Consumables (slides, cover slides, capillary tubes, staining jars, etc.) and reagents (Giemsa stain, distilled water and absolute methanol) are affordable.

Serological and molecular tools require expensive equipment, consumables and reagents for their application. Even when the equipment is available, processing of large amount of samples is possible only for resource-rich laboratories due to the high cost of reagents and consumables. In addition, a serological tool dedicated to loiasis is not yet commercially available.

The Ideal Diagnostic Method

Tools are available for the diagnosis of loiasis as a parasitic disease. Nowadays the importance of loiasis is not related to its debilitating effect as a parasitic disease but to its potential to provoke severe adverse reactions in people with high *Loa* microfilarial load (>10,000 mf/ml of blood) who take IVM for the treatment of onchocerciasis or lymphatic filariasis. Loiasis therefore stands as a hindrance to the successful implementation of onchocerciasis and lymphatic filariasis control or elimination programmes. Since mass distribution of ivermectin is community based and those in charge of administering the drug are simple lay men and women, there is a need when distributing the drug, to distinguish between those qualified for the treatment from those that are not, by using a simple, rapid, reliable user-friendly tool. Consequently, an ideal diagnostic should be: able to diagnose high *Loa* microfilarial loads within a few minute, user-friendly and field applicable.

A recently developed rapid serological assay known as QLIPS (Burbelo et al. 2008) showed some promise towards development of point-of- care diagnostics.

Control Tools and Strategies

Key Tools and Strategies

Two main tools are currently used for the control of loiasis: adult worm removal and chemotherapy.

The removal of adult worms usually takes place during the subconjunctival migration of the latter. This action has a very limited impact on the person being dewormed since these worms represent only a small proportion of the total worms harboured by the host.

Four chemotherapeutic agents (diethylcarbamazine (DEC), IVM or Mectizan®, mebendazole (MBZ) and albendazole (ALB)) are effective against mf and/or adult *L. loa* (see details below). Only DEC is adulticidal and can be considered as a definitive therapy for loiasis. Despite the effectiveness of these drugs on *L. loa*, no large-scale control efforts have ever been implemented in affected areas for two main reasons. As with another filarial infection (mansonellosis), it has been difficult to associate loiasis with a clear and specific clinical picture, especially at the community level. This filariasis is then still considered as a benign or less pathogenic disease which might not need as much attention as the known debilitating diseases, namely, LF, which is responsible for the enlargement of lymphatic vessels, lymphoedema, and elephantiasis and onchocerciasis for which the striking symptoms are blindness and severe dermatitis (Wanji et al. 2003). Also, it was demonstrated that people harbouring high (>8000 mf/ml) or very high (>30,000 mf/ml) microfilarial loads can experience SAEs, with sometimes neurological consequences, when treated with DEC or IVM (Gardon et al. 1997a). Therefore individual case management has been suggested, especially for people living in endemic areas.

Pretreatments of infected individuals aiming at lowering the *Loa* microfilarial load before usage of a more powerful or definitive therapy have been recommended. Apheresis has been suggested, but the cost and the difficulty to implement this technique seriously limit its application. Unlike IVM and DEC, ALB does not lead to a marked decrease in *Loa* microfilarial load and can therefore be used as alternative to cytapheresis pretreatment to lower microfilarial loads before usage of DEC or IVM (Klion and Nutman 2010). Unfortunately, different regimens (Klion et al. 1993; Kamgno et al. in preparation) used, up to date, are not yet completely satisfactory. It is therefore important to prevent the infection or limit reinfestation.

To date, no vaccine is available to prevent becoming infected with *L. loa*, but weekly chemoprophylaxis with 300 mg DEC was found efficient for the prevention of loiasis. Vector control can also be useful in preventing the disease acquisition. Personal protection measures including insect repellents, treated or protective clothing or avoiding *Chrysops* breeding sites may prevent or reduce the risk of infection.

Effectiveness of the Tools and Strategies

There is a contrast between the efficacy and the safety of tools available for the treatment of loiasis, which renders the management of this infection very complex. In fact, the most effective drugs or tools useful in the control of *L. loa* infection are not really safe, at least when individuals are heavily infected, and the safer ones are not completely efficient. DEC and IVM are the most efficient chemotherapeutic agents against *L. loa*, but these two drugs also lead to SAEs with sometimes fatal outcome in patients harbouring high or very high microfilarial loads. In contrast, some benzimidazole (especially ALB) are safer for the treatment of *L. loa*-infected

patients (adverse effects have, up to now, never been observed even in people harbouring more than 50,000 mf/ml), but their effect on microfilarial loads is either low (around 20 % reduction of the initial microfilarial density) or often transitory and varies widely between patients (Boussinesq 2006).

Evidence for Choice of Tools and Strategies

Numerous literatures are available for the evaluation of the efficacy of chemotherapeutic agents on *L. loa* infection (Carme et al. 1991b; Chippaux et al. 1992; Duong et al. 1997; Gardon et al. 1997b; Garin and Garin 1951; Klion et al. 1999; Shookhoff and Dwork 1949; Tsague-Dongmo et al. 2002; Van Hoegaerden and Flocard 1985). For microfilaricidal assessment, that is, the evaluation of the efficacy of drugs on mf, the follow-up of post-treatment dynamics of the parasite density has been used (Chippaux et al. 1992; Duong et al. 1997; Gardon et al. 1997b). For macrofilaricidal effect – effect of drugs on adult worms – evidence of the efficacy of DEC was evaluated by observing degenerating adult worms under the skin (Bonnin and Moretti 1950). Direct approaches to evaluate drug efficacy are difficult since sourcing and studying adult worms (including the developmental stages they are harbouring) are very tedious and appear only possible after animals' sacrifice. Then, there is a need to develop robust and easier model systems – current models are time consuming and require large quantities of drugs – as well as diagnostic test to detect the presence of viable adult worms (Grand Challenge Exploration website).

Although performed on a limited number of subjects, the efficacy of apheresis in lowering *Loa* microfilarial loads was clearly demonstrated (Abel et al. 1986; Chandenier et al. 1987; Muylle et al. 1983). A progressive decrease in microfilarial densities was observed after a three-course session of *Loa* infected subject blood purification.

Apart from the DEC-based chemoprophylaxis of *L. loa* infection which has been clearly demonstrated, the other prevention methods including drugs (IVM), personal protection (*Chrysops* repellents, treated or protective clothing, etc.), vector control or vaccines were not really evaluated.

Sustainability and Cost-Effectiveness of the Tools/Strategies

The usage of tools to control loiasis is only applicable at individual level because the evaluation of the microfilarial load of the patient is a prerequisite for the treatment of loiasis. Individuals harbouring low microfilarial loads (>8000 mf/ml) can be cured by a 21 day regimen of DEC at a dose of 8–10 mg/kg/day (Klion and Nutman 2010). This treatment, although definitive, seems appropriate only for long-term visitors leaving in endemic areas, and would not be sustainable in autochthones living in the endemic area because of reinfestations. This is particularly true for

those subjects with high microfilarial levels for whom it is recommended to first lower their microfilarial densities by ALB whose efficacy is still questionable or by three apheresis sessions which are very expensive and difficult to implement.

Chemotherapy-Based Strategies

Evidence for Choice of Strategies

The optimal treatment strategy for loiasis relies on what is known about the efficacy and safety of the three drugs currently used to treat it: DEC, ALB and IVM. Regarding efficacy, the only one of the three drugs for which a macrofilaricidal effect has been demonstrated is DEC, as evidenced by the finding of dead and necrotic worms in biopsy specimens from post-treatment swellings (Bonnin and Moretti 1950) and an autopsy in nonhuman primates after treatment with DEC (Duke 1990). In 10–25 % of the cases, more than one course of DEC has to be given to achieve a complete cure; patients who are refractory to more than four courses are very rare (Gentilini and Carme 1981; Klion et al. 1999). DEC has an activity against the mf of *L. loa*, which are cleared from the peripheral blood within hours of DEC administration. Short courses of ALB have little effect on *L. loa* (Tabi et al. 2004; Tsague-Dongmo et al. 2002), but when given at a dose of 200 mg twice a day for 21 days, the drug has probably an embryotoxic effect (i.e. it interrupts embryogenesis in the uteri of the adult female worms) and perhaps also a macrofilaricidal effect (Klion et al. 1993). After a single dose of IVM (150 μg/kg), *Loa* microfilaraemia decreases by 70–80 % within the first 3 days (Kamgno et al. 2000; Paris et al. 1991; Richard-Lenoble et al. 1988). The densities then plateau or decrease more slowly and remain at very low values up to 1 year after treatment (Gardon et al. 1997b). Whether this is due to a partial macrofilaricidal or to an embryostatic effect (preventing the release of developed mf from the uteri of the adult female worms) is not known. Monthly treatment with IVM has a cumulative effect, leading after six doses to extremely low microfilarial densities, which remain so for at least several months (Kombila et al. 1998). Besides its effects on the parasite, IVM also has a beneficial effect on the clinical manifestations of loiasis and seems to prevent the reappearance of Calabar swellings for several months (Hovette et al. 1994). Lastly, as *L. loa* does not harbour *Wolbachia* endosymbionts (McGarry et al. 2003), antibiotics (doxycycline) are useless in the treatment of loiasis. Other agents have been used in the treatment of loiasis, including suramin (Klion et al. 1994) and the benzimidazole MBZ (Van Hoegaerden et al. 1987). Suramin and the benzimidazoles have activity against the adult worms, but the widespread use of Suramin is limited by its side effects which include pancytopenia and nephrotoxicity (Klion et al. 1999), while MBZ, which has a poor and variable absorption following oral administration, has been used with only limited success for the treatment of loiasis (Van Hoegaerden et al. 1987).

Now that the reasons for using the drugs mentioned above as first-line drugs are provided, it is necessary to point out that the treatment strategy depends firstly on the risk of adverse events, which is related to the patient's *Loa* microfilarial load. The latter must mandatorily be quantified before any therapy decision, by examining a calibrated Giemsa-stained thick blood smear (50 µL) prepared between 10:00 am and 2:00 pm, i.e. when *Loa* microfilaraemia in the peripheral blood is the highest. In countries located outside the loiasis distribution area, this assessment and the resulting treatment should be conducted in specialized units or by specialized physicians. DEC and IVM can induce potentially fatal encephalopathies in persons harbouring >30,000–50,000 mf/ml of blood (Fain 1978; Gardon et al. 1997a). Functional impairment without alteration of consciousness but requiring assistance for several days can occur after DEC administration in individuals with >2000 mf/ml (Carme et al. 1991a) and after IVM in patients with densities exceeding 8000 mf/ml (Gardon et al. 1997a). The use of ALB in loiasis patients is usually very safe (Klion et al. 1999). Given the risk of serious adverse events after DEC or IVM treatment, the following strategy has been proposed (Boussinesq 2012):

- If the patient's microfilarial density is below 2000 mf/ml, DEC can be administered straightaway. The first course should last 3–4 weeks and start with low doses (3 or 6 mg/day if mf are present in the blood, or 50 mg/day if the patient is amicrofilaraemic) divided into two or three doses. The dose is doubled every day until 400 mg/day (or 8–10 mg/kg/day) still divided in two to three doses. Treatment should be started in hospital, and oral antihistamines or corticosteroids may be useful in the first days to reduce the severity of side effects (pruritus, angiooedema, arthralgias, headache, fever, etc.) which occur in 50 % of the cases. As stated above, several courses of DEC may be needed. If the patient is refractory to DEC, a course of ALB (200 mg twice a day for 21 days) can be undertaken.
- In subjects with *Loa* microfilarial densities between 2000 and 8000 mf/ml, it is advisable to begin treatment by using IVM (a single dose of 150 µg/kg). Mild side effects similar to those mentioned above after DEC can occur. Treatment with IVM can be repeated at intervals of 1–3 months to reduce the microfilarial loads further. When the microfilaraemia is less than 2000 mf/ml, a course of DEC can be started, using the protocol proposed above.
- When the microfilarial loads are between 8000 and 30,000 mf/ml, IVM can also be given, but a close surveillance is needed, with hospitalization during the first 3–4 days. An alternative is to start with a course of ALB (200 mg twice daily for 21 days) which reduces the *Loa* microfilaraemia by 60 % at 6 months and to continue with IVM treatment with or without hospitalization depending on the microfilarial loads at that time.
- If the microfilaraemia exceeds 30,000 mf/ml, ALB is probably the best option, even if the effect of long courses of ALB has never been evaluated in patients with such high loads. Apheresis, which allows to rapidly reduce the loads by 75 % after three sessions, has also been proposed. However, this technique is expensive and probably indicated only exceptionally, given the usually mild manifestations of loiasis.

Gaps in Knowledge

Usually the age of subjects enrolled in therapeutic trials for loiasis is at least 5 years old probably either because the drug under trial is contraindicated for children less than 5 years, or, since mf have a cumulative effect on their host and microfilaraemia is very low in children, subject less than 5 years old do not develop symptoms. As seen above, treatment may be given according to the situation, either as a single dose (irrespective of the body weight) or per kg of body weight, but those receiving this therapy are always adults, not children. Consequently, the effect of treatment in children below 5 years old is unknown. Because young children are not treated, they may constitute a parasite reservoir likely to prolong or hamper any control program. A contemporaneous example is the African Program for Onchocerciasis Control (APOC) for which IVM is given only to people of at least 5 years old.

Another observation is the immunologically mediated difference to infection between natives from endemic areas who are frequently microfilaraemic, but often asymptomatic, and travellers or expatriates who visited endemic areas, who are in the majority amicrofilaraemic but suffer more from annoying manifestations, such as angiooedemas (Calabar swellings) (Klion et al. 1991). The mechanisms underlying this difference in immunological response are not well understood, and there is no indication that expatriates and natives from endemic areas with similar microfilaraemias respond differently to treatment in terms of efficacy (Churchill et al. 1996).

There is no report of a variation in efficacy of any currently used filaricid related to age or sex (Gardon et al. 1997a, b; Klion et al. 1999). However, some filaricidal agents such as IVM are contraindicated for children below 5 years old. As previously mentioned, these groups of untreated individuals are excluded from treatment during control programme and might thus contribute to the maintenance of infection.

DEC is known as the treatment of choice for amicrofilaraemic patients, but some studies have demonstrated a small number of people who did not respond to DEC treatment despite multiple courses of therapy (Klion et al. 1994, 1999). This finding suggests a development of drug resistance in the parasite or may be an insufficient host immune response since DEC killing does not occur in vitro. A combination of DEC and ALB has already been successfully used after failure of DEC alone (Klion et al. 1999). Various combinations are possible, depending on the initial mf load of the infected individual. There is a common agreement on the potential of combination therapy to slow down drug resistance because of the difference in the mechanism of action among the available drugs. Some impediments to the effective implementation of drug combination are the unavailability of DEC in some *Loa-endemic* countries and the ban of IVM in the USA where patients from *Loa*-endemic areas are frequently reported.

High *Loa* microfilarial load is known to be the main cause of post-IVM SAEs, but there is some controversy about the microfilarial density required to provoke SAEs. Indeed, the word “high” has been variously described as greater than 10,000

mf per millilitre of peripheral blood (mf/ml) before treatment at a consultation organized by the Mectizan® Donation Program (MDP) in Paris in October 1995 or greater than 30,000 mf/ml in a hospital study in Southern Cameroon (Ducorps et al. 1995) or greater than 50,000 mf/ml in a community trial in Southern Cameroon (Gardon et al. 1997a). Most of the data on SAEs used for various policy recommendations derived from SAE reports and medical records received by the MDP from onchocerciasis mass treatment programmes through a passive surveillance system. Also, it is unknown what the true numbers of SAE cases are, given the variability of reporting from the 34 onchocerciasis endemic countries that have had, or have, IVM mass treatment programmes.

Challenges of Programme Implementation

Presently, there is not a specific programme dedicated to *L. loa* infection. However, as loiasis is now a hindrance to the implementation of onchocerciasis control programme in areas of loiasis-onchocerciasis co-endemicity, it is expected that a particular attention will be paid to this infection. An important challenge of programme implementation is the unavailability of a safe drug which is practical for mass distribution. ALB is the only drug which does not induce SAEs in people with high *Loa* microfilarial loads (Klion et al. 1999), but a complete course of ALB treatment lasts 21 days. The long treatment course makes the use of ALB unrealistic in loiasis control programme. The remaining two drugs, DEC and IVM, both provoke SAEs, but unlike DEC which is not suitable for mass distribution in a loiasis control programme – treatment requires several doses for several consecutive days – IVM can be useful because it has been shown to markedly decrease *L. loa* microfilaraemia 6 and 12 months after a single dose (Gardon et al. 1997b). Nevertheless, care should be taken for the proper management of SAEs that are likely to occur before using IVM as a tool for loiasis control. In this respect, development of a diagnostic tool, practical in field conditions that may help to sort eligible individuals (people with low *Loa* microfilarial load) from ineligible ones (people with high *Loa* microfilarial load) prior to treatment, would be useful. The few ineligible persons will then become eligible after an ALB cure to lower the level of microfilarial density (Boussinesq 2012). While waiting for such a diagnostic tool to be developed, proper management will consist of prompt general nursing and nutritional care, as currently done within the onchocerciasis control programme framework.

Vector control is an alternative to mass human chemotherapy. The findings that the population density of adults *Chrysops* is fairly low (~1000/km^2) and their flight range usually not great (theoretical range : <6000 m and maximum distance: 4500 m) in secondary forest were very promising for use to limit loiasis in an effective vector control programme (Chippaux et al. 2000). Some promising methods have been attempted including the use of insecticides (Dieldrin, DDT) (Williams and Crewe 1967), creation of anthropic savannah hostile for *Chrysops* development around habitations (Gordon et al. 1950) and trapping (Fain 1978).

Further Research for Policy and Control

Very promising results have been obtained with ALB, but the efficacy of this drug is still limited, for an up to now unknown reason, to a small fraction of the population (Klion et al. 1993; Kamgno et al. 2015, submitted). Research is therefore needed to identify a drug which can efficiently lower *Loa* loads before the usage of IVM or DEC for a definitive therapy.

Before increasing efforts on an eventual curative treatment against loiasis, it is important to first clarify its medical or epidemiological impact on man. It is clear that if loiasis remains a so-called benign disease which poses problems only when onchocerciasis or lymphatic filariasis is targeted, it would be more valuable to increase efforts on the identification of the heavily infected individuals who can develop SAEs when treated for onchocerciasis or lymphatic filariasis. Indeed a very recent community-based trial with the aim to assess the epidemiological impact of loiasis has shown that this disease should not be taken into consideration only because of its implication in IVM or DEC-provoking SAEs (Kamgno et al. in preparation). Therefore, there is a need to find a way to treat loiasis not as a prerequisite in the treatment of onchocerciasis or lymphatic filariasis but because of its medical effects. So far, three drugs have been found to be efficient on mf and/or adult worms, but only DEC is adulticidal and can constitute a definitive treatment for loiasis.

Outlook for the Next Decade

Inspired by the World Health Organization's Roadmap on NTDs, the 2011 London Declaration perspective was to concentrate efforts to the end of game elimination of neglected tropical diseases (NTDs) or reductions in their impact to levels at which they are no longer considered as public-health problems by 2020. Up to now, loiasis is still consider as a benign disease and was not taken into account by the World Health Assembly (WHA) when selecting neglected tropical diseases targeted for elimination and/or eradication by 2020. It appears clear that the epidemiological impact of *L. loa* infection needs to be clarified in order to attract interest in this filariasis and to encourage the development of new effective, safe, inexpensive and tolerable medicines to treat populations at risk, especially those co-infected by lymphatic filariasis and/or onchocerciasis. Therefore, the proper understanding of the physiopathology of SAEs is urgently needed to safely treat loiasis and to achieve the goal of elimination for those diseases co-endemic with loiasis (lymphatic filariasis and onchocerciasis). Elimination of onchocerciasis and/or lymphatic filariasis can also be achieved in areas where loiasis is endemic after the detection (and exclusion from treatments) of individuals who harbour high levels of *L. loa*. Such a strategy would allow for the selection of individuals at risk of SAEs who can be treated by doxycycline against onchocerciasis and lymphatic filariasis, an antibiotic targeting endosymbiotic bacteria that is absent in *L. loa* (Holmes 2013). Research should

however focus on a doxycycline regimen applicable at the community level, since the 4–6-week course regimen currently being used is very difficult to implement as community intervention (Wanji et al. 2009). Nowadays, the integrated control of NTDs is very much encouraged since drugs currently donated by pharmaceutical partners are effective against several of these infections and in addition people can be infected with more than one neglected pathogen simultaneously (Grand Challenge Exploration website). Therefore, strategies which aim at treating multiple diseases at the same time are absolutely needed, and the integrated evaluation of these diseases is awaited.

References

Abel L, Ioly V, Jeni P, Carbon C, Bussel A (1986) Apheresis in the management of loiasis with high microfilariaemia and renal disease. Br Med J 292:24

Akue JP, Hommel M, Devaney E (1997) High levels of parasite-specific IgG1 correlate with the amicrofilaremic state in Loa loa infection. J Infect Dis 175:158–163

Akue JP, Hommel M, Devaney E (1998) IgG subclass recognition of Loa loa antigens and their correlation with clinical status in individuals from Gabon. Parasite Immunol 20:387–393

Bonnin H, Moretti G (1950) Preuves cliniques et biopsiques de l'action léthale d'un dérivé de la pipérazine sur la filaire Loa loa adulte. Bull Soc Pathol Exot 33:4

Boussinesq M (2006) Loiasis. Ann Trop Med Parasitol 100:715–731

Boussinesq M (2012) Loiasis: new epidemiologic insights and proposed treatment strategy. J Travel Med 19:140–143

Boussinesq M, Gardon J (1997) Prevalences of Loa loa microfilaraemia throughout the area endemic for the infection. Ann Trop Med Parasitol 91:573–589

Burbelo PD, Ramanathan R, Klion AD, Iadarola MJ, Nutman TB (2008) Rapid, novel, specific, high-throughput assay for diagnosis of Loa loa infection. J Clin Microbiol 46:2298–2304

Carme B, Mamboueni JP, Copin N, Noireau F (1989) Clinical and biological study of Loa loa filariasis in Congolese. AmJTrop Med Hyg 41:331–337

Carme B, Boulesteix J, Boutes H, Puruehnce MF (1991a) Five cases of encephalitis during treatment of loiasis with diethylcarbamazine. AmJTrop Med Hyg 44:684–690

Carme B, Ebikili B, Mbitsi A, Copin N (1991b) Therapeutic trial with ivermectin in loiasis with medium and high microfilaremia. Ann Soc Belg Med Trop 71:47–50

Chandenier J, Pillier-Loriette C, Datry A, Rosenheim M, Danis M, Felix H, Nozais JP, Gentilini M (1987) Value of cytapheresis in the treatment of loaiasis with high blood microfilaria levels. Results in 7 cases. Bull Soc Pathol Exot 80:624–633

Chippaux JP, Ernould JC, Gardon J, Gardon-Wendel N, Chandre F, Barberi N (1992) Ivermectin treatment of loiasis. Trans R Soc Trop Med Hyg 86:289

Chippaux JP, Bouchite B, Demanou M, Morlais I, Le Goff G (2000) Density and dispersal of the loaiasis vector Chrysops dimidiata in southern Cameroon. Med Vet Entomol 14:339–344

Churchill DR, Morris C, Fakoya A, Wright SG, Davidson RN (1996) Clinical and laboratory features of patients with loiasis (Loa loa filariasis) in the U.K. J Infect 33:103–109

Ducorps M, Gardon-Wendel N, Ranque S, Ndong W, Boussinesq M, Gardon J, Schneider D, Chippaux JP (1995) Secondary effects of the treatment of hypermicrofilaremic loiasis using ivermectin. Bull Soc Pathol Exot 88:105–112

Duke BO (1955) The development of Loa in flies of the genus Chrysops and the probable significance of the different species in the transmission of loiasis. Trans R Soc Trop Med Hyg 49:115–121

Duke BO (1990) Effect of diethylcarbamazine on adult Loa in monkeys. Ann Trop Med Parasitol 84:387–392
Duong TH, Kombila M, Ferrer A, Bureau P, Gaxotte P, Richard-Lenoble D (1997) Reduced Loa loa microfilaria count ten to twelve months after a single dose of ivermectin. Trans R Soc Trop Med Hyg 91:592–593
Dupont A, Zue-N'dong J, Pinder M (1988) Common occurrence of amicrofilaraemic Loa loa filariasis within the endemic region. Trans R Soc Trop Med Hyg 82:730
Egwang TG, Dupont A, Leclerc A, Akue JP, Pinder M (1989) Differential recognition of Loa loa antigens by sera of human subjects from a loiasis endemic zone. AmJTrop Med Hyg 41:664–673
El Haouri M, Erragragui Y, Sbai M, Alioua Z, Louzi, El Mellouki W, Sedrati O (2001) Cutaneous filariasis Loa Loa: 26 moroccan cases of importation. Ann Dermatol Venereol 128:899–902
Fain A (1978) Current problems of loaiasis. Bull World Health Organ 56:155–167
Fain A, Maertens K (1973) Notes sur la ponte des microfilaires chez loa loa et sur le degré de maturité des vers en migration. Bull Soc Pathol Exot 66:6
Fink DL, Fahle GA, Fischer S, Fedorko DF, Nutman TB (2011a) Toward molecular parasitologic diagnosis: enhanced diagnostic sensitivity for filarial infections in mobile populations. J Clin Microbiol 49:42–47
Fink DL, Kamgno J, Nutman TB (2011b) Rapid molecular assays for specific detection and quantitation of Loa loa microfilaremia. PLoS Negl Trop Dis 5:e1299
Fobi G, Gardon J, Santiago M, Ngangue D, Gardon-Wendel N, Boussinesq M (2000) Ocular findings after ivermectin treatment of patients with high Loa loa microfilaremia. Ophthalmic Epidemiol 7:27–39
Gardon J, GardonWendel N, DemangaNgangue D, Kamgno J, Chippaux J, Boussinesq M (1997a) Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. Lancet 350:18–22
Gardon J, Kamgno J, Folefack G, Gardon-Wendel N, Bouchite B, Boussinesq M (1997b) Marked decrease in Loa loa microfilaraemia six and twelve months after a single dose of ivermectin. Trans R Soc Trop Med Hyg 91:593–594
Garin C, Garin JP (1951) Treatment of filariasis from filaria loa by notezine. J Med Bordeaux Sud-Ouest 128:250–252
Gentilini M, Carme B (1981) Treatment of filariases in a hospital setting. Complications – results. Ann Soc Belg Med Trop 61:319–326
Gordon RM, Kershaw WE, Crewe W, Oldroyd H (1950) The problem of loiasis in West Africa with special reference to recent investigations at Kumba in the British Cameroons and at Sapele in Southern Nigeria. Trans R Soc Trop Med Hyg 44:11–47
Goussard B, Ivanoff B, Beville G, Garin Y (1984) Current aspects of the ELISA technic applied to the serological diagnosis of helminthiasis. Pathol Biol 32:1043–1049
Gruntzig J, Gewalt W (1979) Cameroon swelling; infection by the filaria Loa loa. Fortschr Med 97:1932–1937
Hawking F (1955) Periodicity of microfilariae of Loa loa. Trans R Soc Trop Med Hyg 49:132–142
Hawking F (1977) The distribution of human filariasis throughout the world, part III, Africa. Trop Dis Bull 74:8
Holmes D (2013) Loa loa: neglected neurology and nematodes. Lancet Neurol 12:631–632
Hovette P, Debonne JM, Touze JE, Gaxotte P, Imbert P, Fourcade L, Laroche R (1994) Efficacy of ivermectin treatment of Loa loa filariasis patients without microfilaraemias. Ann Trop Med Parasitol 88:93–94
Jimenez M, Gonzalez LM, Carranza C, Bailo B, Perez-Ayala A, Muro A, Perez-Arellano JL, Garate T (2011) Detection and discrimination of Loa loa, Mansonella perstans and Wuchereria bancrofti by PCR-RFLP and nested-PCR of ribosomal DNA ITS1 region. Exp Parasitol 127:282–286
Kamgno J, Boussinesq M (2001) Hyperendemic loaiasis in the Tikar plain, shrub savanna region of Cameroon. Bull Soc Pathol Exot 94:342–346

Kamgno J, Gardon J, Boussinesq M (2000) Analysis of the prevention of post-ivermectin Loa loa encephalopathy by administration of initial low dose. Med Trop 60:275–277
Klion AD, Nutman TB (2010) Loiasis and Mansonella infections, in Tropical Infectious Diseases: Principles, Pathogens and Practice. Third edition (Guerrant, RL, Walker, DH, Weller, PF, eds). Churchill Livingstone (New York)
Klion A, Massougbodji A, Sadeler B, Ottesen E, Nutman T (1991) Loiasis in endemic and nonendemic populations: immunologically mediated differences in clinical presentation. J Infect Dis 163:1318–1325
Klion AD, Eisenstein EM, Smirniotopoulos TT, Neumann MP, Nutman TB (1992) Pulmonary involvement in loiasis. Am Rev Respir Dis 145:961–963
Klion AD, Massougbodji A, Horton J, Ekoue S, Lanmasso T, Ahouissou NL, Nutman TB (1993) Albendazole in human loiasis: results of a double-blind, placebo-controlled trial. J Infect Dis 168:202–206
Klion AD, Ottesen EA, Nutman TB (1994) Effectiveness of diethylcarbamazine in treating loiasis acquired by expatriate visitors to endemic regions: long-term follow-up. J Infect Dis 169:604–610
Klion AD, Horton J, Nutman TB (1999) Albendazole therapy for loiasis refractory to diethylcarbamazine treatment. Clin Infect Dis: Off Publ Infect Dis Soc Am 29:680–682
Klion AD, Vijaykumar A, Oei T, Martin B, Nutman TB (2003) Serum immunoglobulin G4 antibodies to the recombinant antigen, Ll-SXP-1, are highly specific for Loa loa infection. J Infect Dis 187:128–133
Kombila M, Duong TH, Ferrer A, Perret JL, Marion MC, Nguiri C, Gaxotte P, Manfoumbi M, Richard-Lenoble D (1998) Short- and long-term action of multiple doses of ivermectin on loiasis microfilaremia. AmJTrop Med Hyg 58:458–460
Kouam KM, Tchatchueng-Mbougua JB, Demanou M, Boussinesq M, Pion SDS, Kamgno J (2013) Impact of repeated ivermectin treatments against onchocerciasis on the transmission of loiasis: an entomologic evaluation in central Cameroon. Parasite Vector 6:283
Languillat G, Garin Y, Tursz A, Beauvais B, Lariviere M (1977) Etiological study of low fertility in eastern Gaboon. III. Filarial endemicity (Loa loa, D. perstans). Prevalence of microfilariae in hydroceles (author's transl). Rev Epidemiol Sante Publique 26:273–282
Lebied B (1957) Iconography of the intrasynctial evolution of the Loa loa in Chrysops; preliminary note on the internal and external factors determining the evolutive cycle of Filariata (Scrjabin) in their intermediary hosts. Ann Soc Belg Med Trop 37:641–645
McGarry HF, Pfarr K, Egerton G, Hoerauf A, Akue JP, Enyong P, Wanji S, Klager SL, Bianco AE, Beeching NJ, Taylor MJ (2003) Evidence against Wolbachia symbiosis in Loa loa. Filaria J 2:9
Muylle L, Taelman H, Moldenhauer R, Van Brabant R, Peetermans ME (1983) Usefulness of apheresis to extract microfilarias in management of loiasis. Br Med J 287:519–520
Negesse Y, Lanoie LO, Neafie RC, Connor DH (1985) Loiasis: "Calabar" swellings and involvement of deep organs. AmJTrop Med Hyg 34:537–546
Noireau F, Apembet JD, Nzoulani A, Carme B (1990) Clinical manifestations of loiasis in an endemic area in the Congo. Trop Med Parasitol 41:37–39
Padgett JJ, Jacobsen KH (2008) Loiasis: African eye worm. Trans R Soc Trop Med Hyg 102:983–989
Paris L, Datry A, Durepaire R, Felix H, Gaxotte P, Danis M, Gentilini M (1991) Usefulness of ivermectin as initial treatment of loiasis. Presse Med 20:1393–1393
Pinder M (1988) Loa loa – a neglected filaria. Parasitol Today 4:279–284
Richard-Lenoble D, Kombila M, Rupp EA, Pappayliou ES, Gaxotte P, Nguiri C, Aziz MA (1988) Ivermectin in loiasis and concomitant O. volvulus and M. perstans infections. AmJTrop Med Hyg 39:480–483
Richardson ET, Luo R, Fink DL, Nutman TB, Geisse JK, Barry M (2012) Transient facial swellings in a patient with a remote African travel history. J Travel Med 19:183–185
Rodhain F, Rodhain-Rebourg F (1973) A propos de la distribution géographique de la loase. Med Mal Infect 11:8

Shookhoff HB, Dwork KG (1949) Treatment of Loa loa infections with hetrazan. AmJTrop Med Hyg 29:589–593

Tabi TE, Befidi-Mengue R, Nutman TB, Horton J, Folefack A, Pensia E, Fualem R, Fogako J, Gwanmesia P, Quakyi I, Leke R (2004) Human loiasis in a Cameroonian village: a double-blind, placebo-controlled, crossover clinical trial of a three-day albendazole regimen. AmJTrop Med Hyg 71:211–215

Toure FS, Egwang TG, Wahl G, Millet P, Bain O, Georges AJ (1997) Species-specific sequence in the repeat 3 region of the gene encoding a putative Loa loa allergen: a diagnostic tool for occult loiasis. AmJTrop Med Hyg 56:57–60

Toure FS, Kassambara L, Williams T, Millet P, Bain O, Georges AJ, Egwang TG (1998) Human occult loiasis: improvement in diagnostic sensitivity by the use of a nested polymerase chain reaction. AmJTrop Med Hyg 59:144–149

Toure FS, Leroy EM, Mavoungou E, Egwang TG (1999a) Sequence conservation of repeat 3 region of the gene coding for the 15 kDa polyprotein within human and simian Loa loa. J Med Primatol 28:57–61

Toure FS, Mavoungou E, Deloron P, Egwang TG (1999b) Comparative analysis of two diagnostic methods of human loiasis: IgG4 serology and nested PCR. Bull Soc Pathol Exot 92:167–170

Tsague-Dongmo L, Kamgno J, Pion SD, Moyou-Somo R, Boussinesq M (2002) Effects of a 3-day regimen of albendazole (800 mg daily) on Loa loa microfilaraemia. Ann Trop Med Parasitol 96:707–715

Van Hoegaerden M, Flocard F (1985) Mebendazole treatment of loaiasis. Lancet 1:1278

Van Hoegaerden M, Ivanoff B, Flocard F, Salle A, Chabaud B (1987) The use of mebendazole in the treatment of filariases due to Loa loa and Mansonella perstans. Ann Trop Med Parasitol 81:275–282

Védy J, Cahuzac G, Labegorre J (1975) Manifestations oculaires atypiques des filarioses à Loa loa. Méd Armées 3:8

Wanji S, Tendongfor N, Esum M, Ndindeng S, Enyong P (2003) Epidemiology of concomitant infections due to Loa loa, mansonella perstans and onchocerca volvulus in rain forest villages of Cameroon. Med Microbiol Immunol 192:15–21

Wanji S, Tendongfor N, Nji T, Esum M, Che JN, Nkwescheu A, Alassa F, Kamnang G, Enyong PA, Taylor MJ, Hoerauf A, Taylor DW (2009) Community-directed delivery of doxycycline for the treatment of onchocerciasis in areas of co-endemicity with loiasis in Cameroon. Parasite Vector 2:39

Williams P, Crewe W (1967) Studies on the control of the vectors of loiasis in West Africa. 8. An attempt to control loiasis at Kumba, West Cameroon. Ann Trop Med Parasitol 61:148–158

Zoure HG, Wanji S, Noma M, Amazigo UV, Diggle PJ, Tekle AH, Remme JH (2011) The geographic distribution of Loa loa in Africa: results of large-scale implementation of the Rapid Assessment Procedure for Loiasis (RAPLOA). PLoS Negl Trop Dis 5:e1210

Lymphatic Filariasis (Elephantiasis)

Yao Sodahlon, Mwele Malecela, and John O. Gyapong

Contents

Y. Sodahlon (✉)
Lymphatic Filariasis Elimination, Mectizan Donation Program, 325 Swanton Way, Decatur, Georgia, USA
e-mail: ysodahlon@taskforce.org

M. Malecela
National Lymphatic Filariasis Elimination Programme, National Institute for Medical Research, 2448 Ocean road, 9653, Dar-es-Salaam, Tanzania
e-mail: mmalecela@hotmail.com

J.O. Gyapong
School of Public Health, University of Ghana, LG571, Legon, Accra, Ghana
e-mail: jgyapong@ug.edu.gh

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_8

Abstract Sub-Saharan Africa (SSA) carries nearly one-third of the global burden of lymphatic filariasis (LF), a vector-borne and debilitating disease that afflicts the poorest population. *Wuchereria bancrofti* is the only species responsible for the disease and is mainly transmitted to humans by mosquito species belonging to *Anopheles* and *Culex*. The disease is estimated to be transmitted in 37 out of the 49 South Saharan countries with an estimated at-risk population of 432 million people. Recognizing the burden of the disease and the availability of new tools, the World Health Assembly took in 1997 the resolution WHA 50.29 calling for the elimination of the LF as a public health problem. The subsequent Global Programme to Eliminate Lymphatic Filariasis was set up with the aim to eliminate the disease by 2020. After more than a decade of program implementation in SSA, and despite available opportunities including the donation of the medicines, only 37 % of the populations in 24 countries that required mass drug administration were reached in 2013. The morbidity alleviation, the second pillar of the global program, is almost inexistent. This very slow program expansion is due to many factors including insufficient political commitment for adequate resources allocation for country programs, sociopolitical instability, and the prevalence of *Loa loa* infection in Central Africa that hampers the safe implementation of ivermectin-based mass treatment. Alternatives tools and strategies will be required to accelerate LF elimination in SSA by 2020.

Keywords Lymphatic filariasis • *Wuchereria bancrofti* • *Anopheles gambiae s.1* • *An. funestus* • *Culex quinquefasciatus* • Ivermectin • Albendazole

Introduction

Lymphatic filariasis (LF) is a debilitating mosquito-transmitted disease caused by the helminthes *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori* (WHO 1992). According to the recent reports, the disease is endemic in 72 countries with an estimated at-risk population of 1.39 billion people. Among the estimated 120 million people infected, 40 million suffer from the stigmatizing and disabling clinical manifestations of the disease, including 15 million who have lymphedema (elephantiasis), and 25 million men who have urogenital swelling, principally scrotal hydrocele (Zeldenryk et al. 2011; WHO 2010, 2011c).

In recognition of the global burden of LF, the World Health Assembly passed the resolution WHA 50.29 in 1997, calling for collaborative efforts by member states to eliminate the disease as a public health problem (WHA 1997). In 2000, the Global Program to Eliminate Lymphatic Filariasis (GPELF) was formed in response to the goal to eliminate the disease by 2020. The program adopted a two-pronged strategy: (1) to interrupt transmission of the causal parasite and (2) to alleviate morbidities associated with the disease (Ottesen 2000).

In sub-Saharan Africa (SSA), the focus of this chapter, *W. bancrofti* is the only species prevalent (WHO 1992) and is mainly transmitted to human by mosquito

species belonging to *Anopheles* and *Culex* (Brengues 1975; Simonsen et al. 2008). The disease is estimated to be endemic in 36 out of the 49 South Saharan countries with a total at-risk population of 432 million people accounting for nearly one-third of the global burden (WHO 2012a; Addiss and Global Alliance to Eliminate Lymphatic 2010). LF is co-endemic with other neglected tropical diseases (NTDs) in settings of extreme poverty, making efforts to control/eliminate a key strategic component for achieving Africa's Millennium Development Goals (MDGs) (Hotez and Kamath 2009).

The 2010 halfway WHO progress report (WHO 2010) showed that tremendous achievements had so far been made in SSA countries toward the 2020 elimination goals; however, a number of implementation challenges needed to be addressed, including the program expansion in the big countries (Hotez and Kamath 2009) as well as in post-conflict countries (Kelly-Hope et al. 2011), and in central African countries where the disease is co-endemic with *Loa loa* (Zoure et al. 2011).

Biology, Life Cycle, Disease Presentation

Parasite

In SSA, *Wuchereria bancrofti* is the species that causes lymphatic filariasis in humans (WHO 1992). The adult worms with a length of around 4–8 cm live in the lymphatic system, especially the lymphatic vessels and the nodes. The worm lives in mutual symbiosis with *Wolbachia endobacteria* which is essential for larval development and sex determination and responsible for a major part of the inflammation leading to symptoms (Arumugam et al. 2008). The adult worm is able to survive 5–8 years. During this period it releases into the lymphatic system and the blood millions of 100–150 μm long-sheathed microfilariae (L1 stage), at approximately 10,000 daily. The microfilariae (mf) are found in the peripheral blood all the time with a peak density between 9 pm and 4 am, concurrent with the period of most active feeding by the local vectors (Brengues 1975; WHO 1992). The nocturnal periodicity and the morphology of the mf are used to differentiate *W. bancrofti* infection from other species such as such us *L. loa* and some *Mansonella* species also endemic in SSA (Paily et al. 2009).

Vectors

Despite the absence of specific entomological data from many countries, the available bibliography suggests that *Anopheles gambiae s.1*., and *An. funestus* are the major vectors of *W. bancrofti* throughout SSA and the Indian Ocean Islands (Brengues 1975; Boakye et al. 2004; Simonsen et al. 2008). The same vectors are involved in the transmission of malaria which offers a good opportunity for integrated vector control (Bockarie et al. 2009; Ashton et al. 2011). In Eastern Africa,

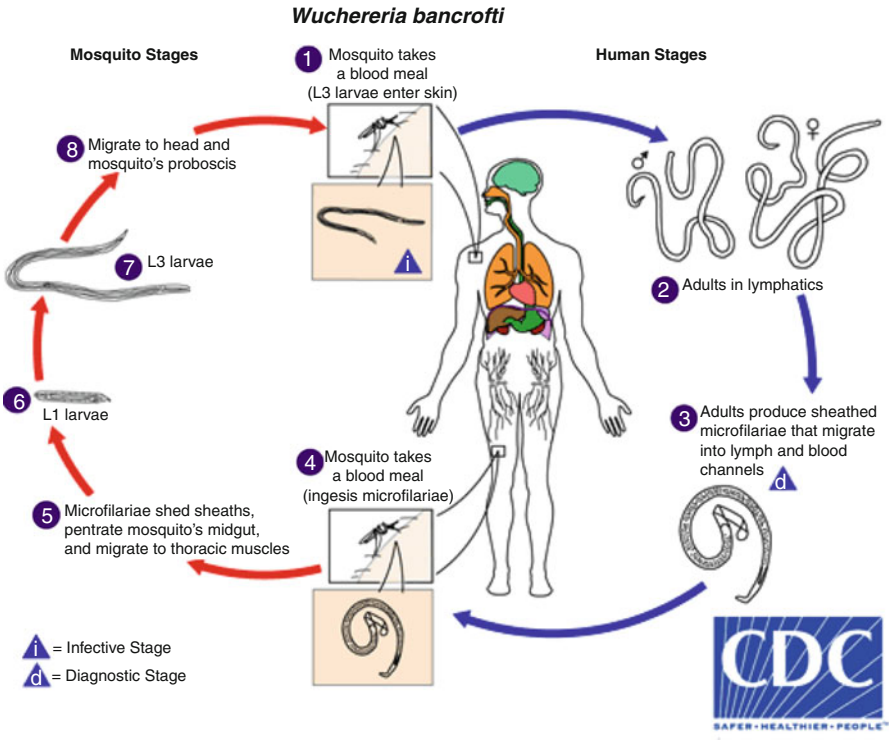


Fig. 1 Life cycle of *Wuchereria bancrofti*

especially in urban and semi-urban areas of the coastal areas, *Culex quinquefasciatus* is involved in the transmission of the disease (Hawking 1957; Simonsen et al. 2008). A recent study conducted in Ghana by Ughasi et al. (2012) reported that *Mansonia africana* and *Mansonia uniformis* are associated with the transmission of *W bancrofti* in Ghana and possibly in other parts of West Africa.

Transmission and Life Cycle

The extrinsic life cycle of the parasite is initiated when the mf are ingested by a mosquito vector during feeding on the host blood (Fig. 1). On maturity, most of the infective L3-stage larvae migrate to the head and proboscis of the mosquito, ready to be transmitted to the host during subsequent feeding. They develop to the adult L5 stage and the period of development and the longevity of the parasites vary according to the species of the nematode and the mammalian host (Paily et al. 2009). It was demonstrated in West Africa that in the absence of re-infestation, the microfilaremia can spontaneously disappear in about 5 years (Brengues 1975) corresponding to the life span of the adult worm.

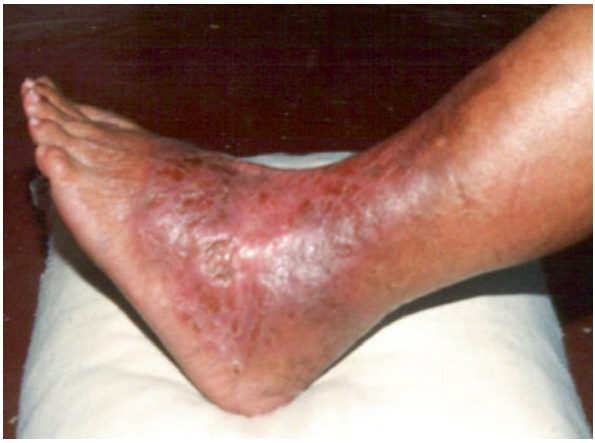


Fig. 2 Acute adenolymphangitis (ADL)

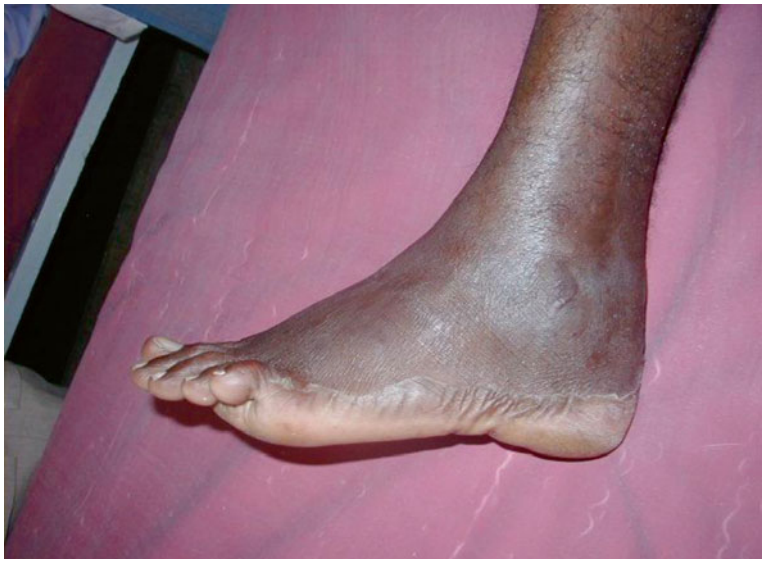


Fig. 3 Same patient recovering from ADL with peeling of skin and some residual swelling

Clinical Manifestations

With the discovery of more sensitive diagnostic tools, it is now well documented that the infection is acquired in childhood, a period during which damage to the lymphatic system takes place (Witt and Ottesen 2001; Shenoy and Bockarie 2011). Bancroftian filariasis is characterized by a wide range of clinical manifestations. The common clinical manifestations are acute adenolymphangitis (ADLA) (Figs. 2 and 3), lymphedema (Figs. 4 and 5), elephantiasis (Fig. 6), and hydrocele (Figs. 7 and 8) (WHO 1992).

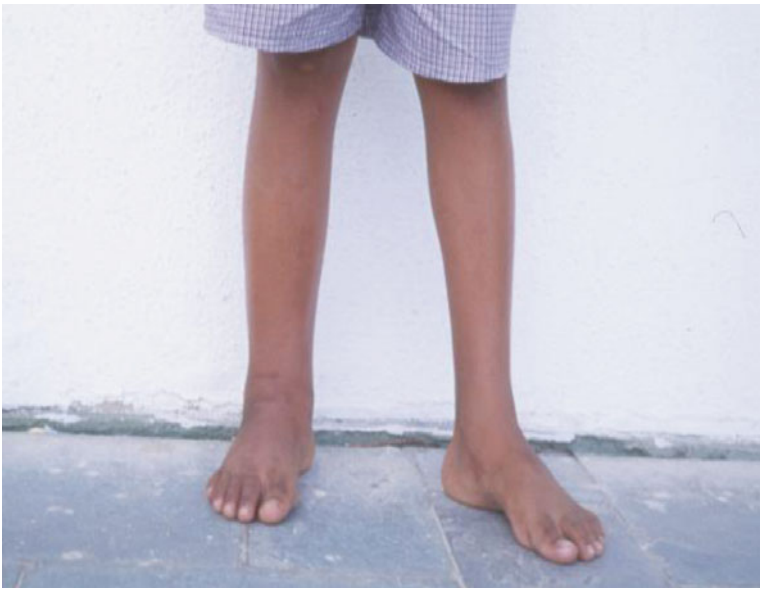


Fig. 4 Early lymphedema of the right foot

These symptoms and signs often cause considerable physical, psychological, and social disabilities to the patients (Krishna Kumari et al. 2005; Zeldenryk et al. 2011) and source of income loss (Babu et al. 2002). Other reported manifestations with no

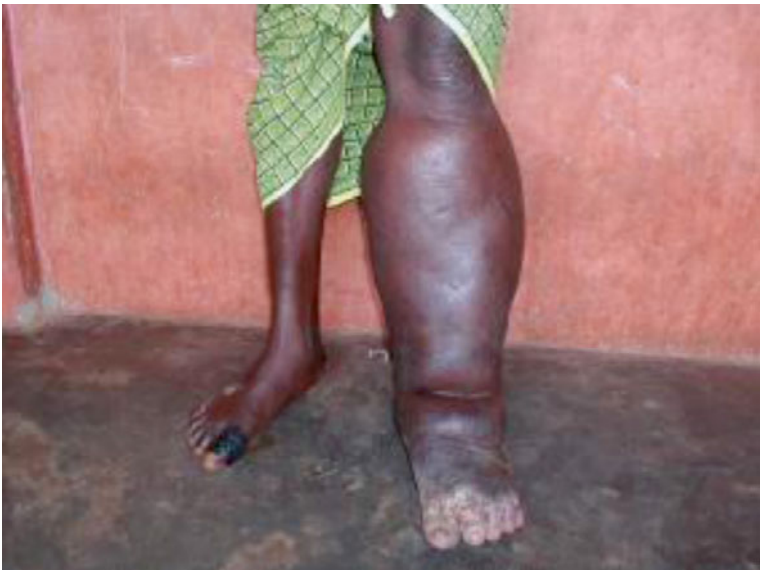


Fig. 5 Advanced lymphedema

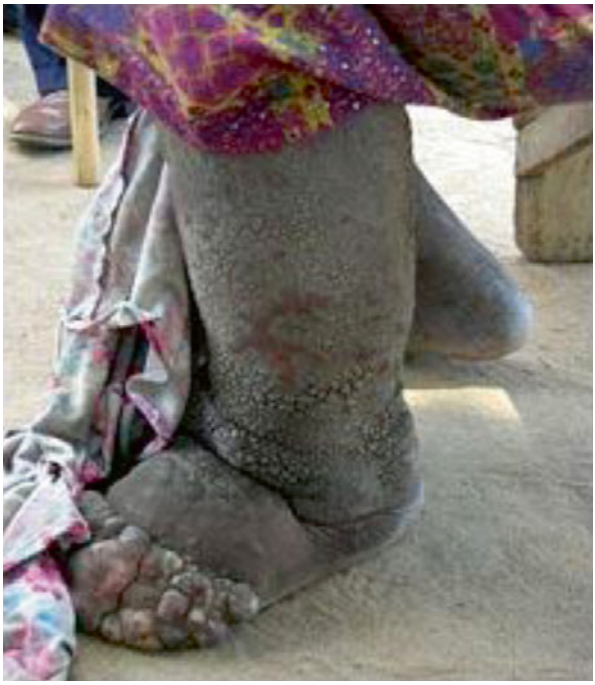


Fig. 6 Elephantiasis

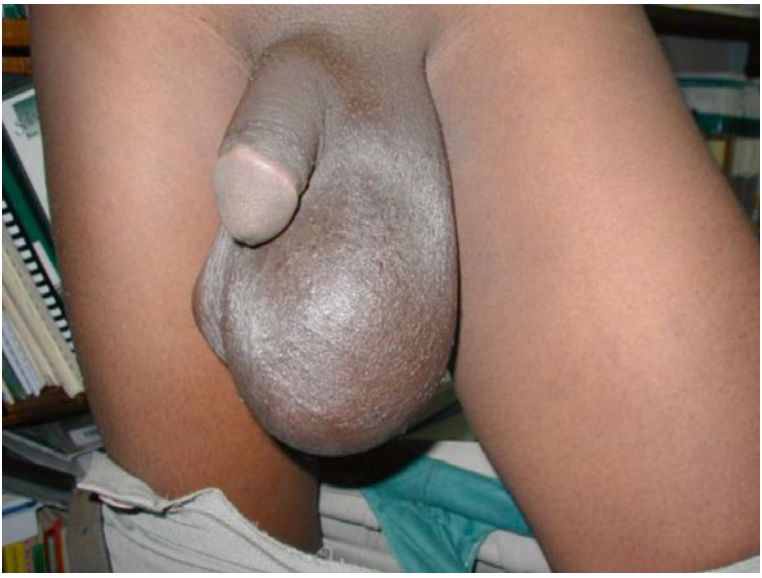


Fig. 7 Hydrocele

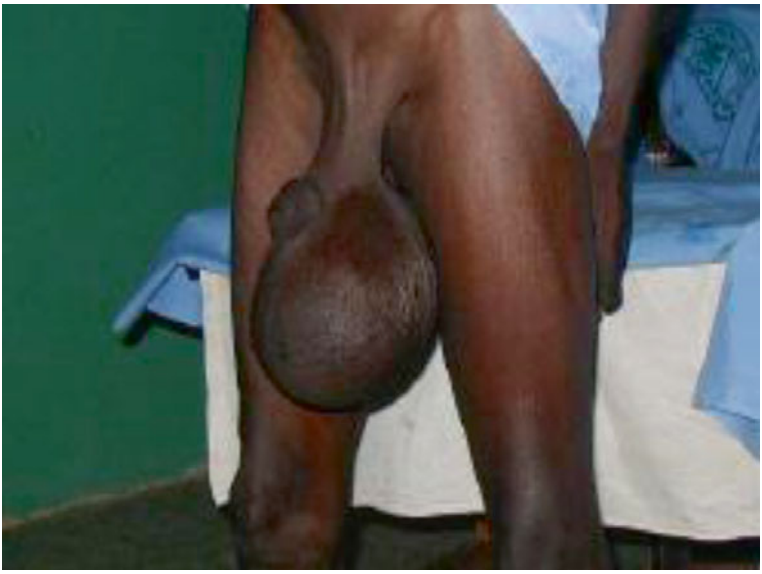


Fig. 8 Advanced hydrocele

public health importance are chyluria, lymphocele, scrotal lymphedema, tropical pulmonary eosinophilia, adenopathy, and hematuria (WHO 1992, 2011c).

Burden of Disease and Distribution in SSA

Distribution of the Infection

The discovery of the filarial antigen-based diagnostic test that can be used any time of the day (Weil et al. 1997) and the subsequent development of the Rapid Assessment of Geographical Distribution of Filariasis (RAGFIL) methodology by the Special Programme for Research and Training in Tropical Diseases (TDR) (Gyapong and Remme 2001) have accelerated the mapping of LF in SSA. As of 2012, though the mapping remains to be completed in 12 countries, the data generated so far (Fig. 9) suggested that the disease has focal distribution and the intensity of the infection varies by region. In the East-Southern African block, the endemicity levels are highest along the coastal areas and decline inwardly (Njenga et al. 2008; Simonsen et al. 2010). In the West-African block of countries, the pattern is variable in relation to coastal endemicity levels along the whole coast, but generally high prevalence rates are in inland countries (Gyapong et al. 2002, 1996). Though the mapping is not completed in Central Africa, there is an emerging pattern of relatively low endemicity (Carme 2010; Kelly-Hope et al. 2011).

Four countries (Burundi, Cape Verde Island, Mauritius, Rwanda, and Seychelles) have been removed from the list of endemic countries requiring intervention for

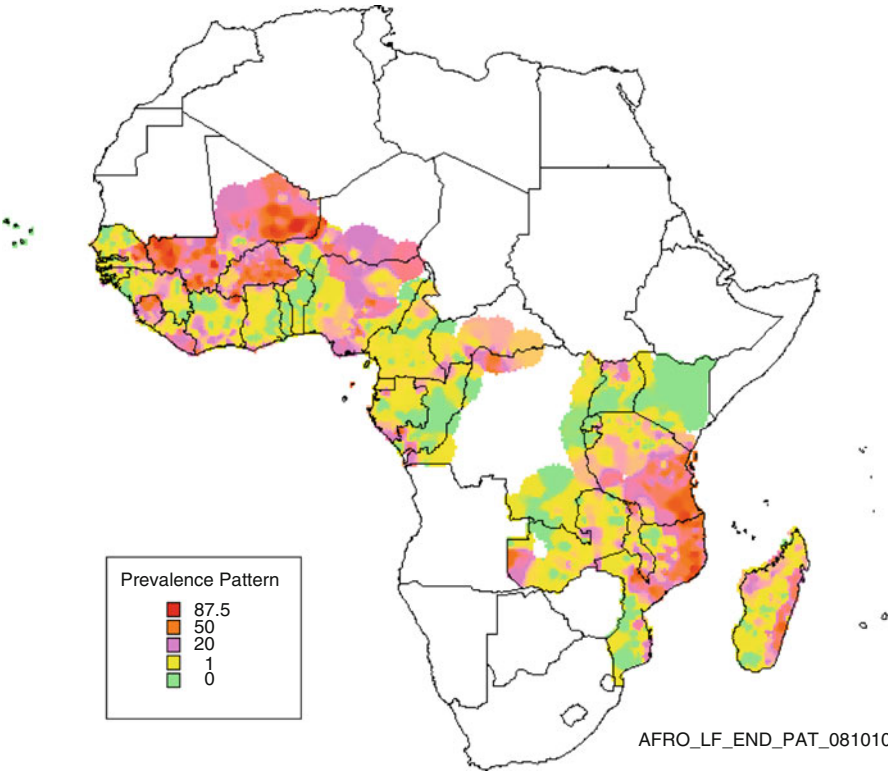


Fig. 9 Endemicity map in SSA as of Dec. 2012 (Courtesy WHO-Afro)

elimination following the review of the endemicity data by WHO in 2011 (WHO 2011a). Currently, the total population at risk for LF requiring intervention is estimated at more than 440 million people (WHO 2012a; Slater and Michael 2012). At the completion of the mapping, these estimates will certainly be dramatically revised down as a result of the focal distribution of LF in the region. Offering opportunity for co-implementation, LF is co-endemic with other filariasis such as onchocerciasis in 27 countries (Noma et al. 2002), *Loa loa* in 11 Central African countries and Nigeria (Zoure et al. 2011), and *Mansonella* species (*M. perstans* throughout the continent and *M. streptocerca* in West and Central Africa) (Simonsen et al. 2011; Carme 2010). LF is also co-endemic with other parasitic diseases such as soil-transmitted helminthiasis and schistosomiasis (Brooker 2010) and malaria (Manguin et al. 2010).

Morbidity

Estimating the morbidity prevalence in a country is the first step toward the elaboration of a management program and the mobilization of adequate resources for its implementation. In contrast to the mapping of transmission, though some attempts

at rapid assessment have been tried out in Nigeria and Togo (Mathieu et al. 2008; Akogun et al. 2011), a validated standard rapid method to assess the prevalence of morbidity remains to be developed. Only a few prevalence studies on morbidity have been conducted in the region. As a result, it is difficult to estimate the real burden of clinical manifestations in SSA. Surveys conducted in selected communities in Eastern and West Africa (Table 1) showed that hydrocele was the commonest clinical manifestation among adult males (7–34 %), whereas the reported prevalences for lymphedema were lower at 0–9 %. Some of the surveys showed that the prevalence of both conditions increases with age.

African settings, the disease is found to be associated with ridicule and isolation from community members, difficulty to find a spouse, and various degrees of sexual dysfunction (Gyapong et al. 2000; Richard et al. 2007; Person et al. 2009). The disease is mainly attributed to supernatural and spiritual factors which explain the treatment practices sought through traditional healers (Gyapong et al. 1996; Richard et al. 2007). Acute adenolymphangitis (ADL) is the major acute complication of both conditions. The incidence is estimated up to 95.9 per 1000 per annum among adults more than 10 years of age (Gyapong et al. 1996; Gyapong 2000). Individuals with lymphedema experienced more frequent acute episodes compared to those with hydrocele. ADL episodes ranged from one to five per annum. Each ADL episode can last in average 8.6 days and in 72.5 % of the episodes, the affected individuals were incapacitated and unable to do their normal activities for an average duration of 3.7 days (Gasarasi et al. 2000).

Available Control Tools and Strategies

The control of lymphatic filariasis in SSA is currently based on the strategies adopted globally aiming to eliminate the disease as a public health problem by 2020. The two adopted strategies are (1) to interrupt transmission of the causal parasite and (2) to alleviate morbidities associated with the disease (Ottesen 2000). Tools are developed and resources made available to facilitate the implementation of these strategies in the endemic countries.

Table 1 Prevalence of hydrocele and lymphedema in selected SSA communities

Country	Hydrocele (in men) %	Lymphedema %	Authors
Ethiopia	20.3	0	Jemaneh and Kebede (1995)
Kenya	10–34	2.4–8.5	Estambale et al. (1994), Mukoko et al. (2004), Njenga et al. (2007)
Malawi	13–17.9	1.3–3.7	Nielsen et al. (2002)
Tanzania	14.5–21.3	0.6–3.3	Simonsen et al. (1995)
Uganda	7–28	4–9	Onapa et al. (2001)
Ghana	32	3.6	Gyapong et al. (1994)
Nigeria	7–9.7	2.3–6	Okon et al. (2010), Uttah (2011)

Interrupt the Transmission of the Causal Agent

The major recommended tool to interrupt transmission is once yearly treatment with a single dose of two medicines administered together to the entire at risk population: albendazole (400 mg) plus either ivermectin (150–200 mcg/kg) or DEC (6 mg/kg) for 4–6 years. Three key steps to be followed by the national program for LF elimination are summarized on the Fig. 10.

Mapping

To identify the implementation units (IUs) that are eligible for mass drug administration (MDA), the mapping is conducted using the ICT cards based on WHO recommended rapid method (RAGFIL) (Gyapong and Remme 2001). An IU, generally a district, is eligible for MDA if the ICT ratio is ≥1 %. As shown in the Table 2, the mapping remains to be completed in 12 countries.

Mass Drug Administration

The following 28 South Saharan African countries where onchocerciasis is co-endemic are eligible for the use of combination of ivermectin (donated by Merck & Co, Inc., White House Station, USA) and albendazole (donated by GSK, Brentfort, UK) for LF elimination: Angola, Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo-Brazzaville, Côte d'Ivoire, Democratic Republic of Congo, Equatorial Guinea, Ethiopia, Gabon, Ghana, Guinea, Guinea-Bissau, Malawi, Mali, Mozambique, Niger, Nigeria, Senegal, Liberia, Sierra Leone, Sudan, South Sudan, Tanzania and Zanzibar, Togo, and Uganda. The remaining nine countries (marked * in Table 2) will be using DEC-based therapy (now supplied for free by Eisai Co., Ltd., Tokyo, Japan).

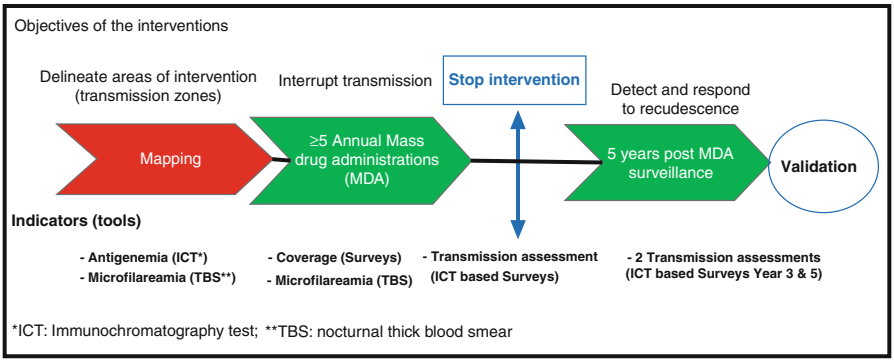


Fig. 10 Key programmatic steps toward the elimination of LF transmission

Table 2 Progress of LF elimination programmes in the SSA (as of Dec. 2013 (WHO 2014))

Status		Countries
Mapping	Not started ($n=1$)	Djibouti
	In progress ($n=9$)	Angola, Central African Republic, Democratic Republic of the Congo, Eritrea, Nigeria, Sudan, South-Sudan, Zambia, Zimbabwe
Mass drug administration	Not eligible for ($n=3$)	Burundi, Rwanda, Cape Verde
	Not started ($n=13$)	Angola, Chad, Democratic Republic of the Congo, Djibouti*, Equatorial Guinea, Eritrea*, Gabon, Gambia*, Guinea, Sao Tome and Principe*, South-Sudan, Zambia*, Zimbabwe*
	Scaling up ($n=11$)	Central African Republic, Congo, La Côte d'Ivoire, Ethiopia, Guinea Bissau, Madagascar*, Mozambique, Nigeria, Senegal, Sudan, United Republic of Tanzania
	Full scale (12)	Benin, Cameroon, Burkina Faso, Comoros*, Ghana, Kenya*, Liberia, Malawi, Mali, Niger, Sierra Leone, Uganda
Post-MDA surveillance	Part of the IUs ($n=6$)	Benin, Burkina Faso, Ghana, Mali, Nigeria, United Republic of Tanzania
	All IUs ($n=1$)	Togo

*Countries eligible to use DEC+albendazole for mass drug administration

The Distribution Strategies

In the endemic areas, the treatment is provided door to door to individuals of 5 years old and above using a network of community volunteers. The target is to reach at least 65 % of the total population. The under-5-year-old children, pregnant women, and heavily sick individuals are excluded from the treatment. In settings where LF is co-endemic with onchocerciasis, the MDAs are integrated targeting both infections. The integrated distribution strategies targeting other tropical diseases are more and more promoted in the continent (Kabatereine et al. 2010). The implementation of the recommended bi-therapy is contraindicated in areas co-endemic with *Loa loa* as it can be association with the occurrence of severe adverse events (Twum-Danso 2003). This constrains the expansion of Lymphatic Filariasis Elimination (LFE) in West and Central Africa, particularly in DRC where *Loa loa* is highly endemic (Zoure et al. 2011). As we can see in Table 2, 7 years from the elimination target, 15 countries are yet to start MDA and 11 are yet to cover all endemic districts.

Monitoring and Evaluation

The key indicators to monitor during the MDAs are the reported and surveyed geographic and therapeutic coverages and the impact of the intervention on nocturnal

microfilaremia in sentinel and spot-check sites. A manual has been developed and regularly updated by WHO to guide the program managers (WHO 2011b).

Stopping MDA

A transmission assessment survey (TAS) protocol has been developed by WHO to determine when to stop MDA in a given IU (WHO 2012c). It is estimated that following at least five rounds of MDA with effective coverage (≥65 % of the total population) and a microfilaremia ≤1 % in sentinel and spot-check sites, an implementation unit can be eligible to undergo the TAS. Table 2 shows that The TAS has been successful and the treatment stopped in Togo (Sodahlon et al. 2013) and in some implementation units of Benin, Burkina Faso, Ghana, Mali, Nigeria, and the United Republic of Tanzania. Those areas are currently under post-MDA surveillance.

Post-MDA Surveillance and Verification

The protocol currently recommended by WHO is to repeat the TAS 3 and 5 years following the end of MDAs. At least two additional rounds of MDAs must be implemented in an evaluation unit that did not satisfy the criteria set for a successful TAS. A country will be ready for validation if all the endemic IU successfully passed the 5 years post-MDA surveillance (WHO 2011b). Supplemental lab-based ongoing surveillance targeting both endemic and non-endemic districts is currently implemented in Togo (Mathieu et al. 2011). The xenomonitoring technics are yet to be developed.

Other Interventions

Albendazole in Monotherapy

WHO recently recommended following a meeting held in Accra in March 2012 (WHO 2012b) the use of albendazole only in mass drug administration once or twice yearly as alternative strategy for LF elimination in *L. loa* co-endemic areas. The strategy was endorsed during the 2013 Scientific Technical Advisory Group and is yet to be implemented in the eligible countries.

Integrated Vector Management

Because the parasite of LF is transmitted mainly in SSA by *Anopheles* mosquitoes, there is a growing advocacy for the use of integrated vector management to accelerate and sustain the elimination (Manga 2002; Bockarie et al. 2009; WHO 2011d).

The recent effort to reach universal coverage with insecticide-treated long-lasting nets (ITNs/LLINs) and the implementation of indoor residual spraying (IRS) for malaria control in Africa may significantly impact LF transmission in the region (Ashton et al. 2011; Kelly-Hope et al. 2013).

Drug Development

Anti-*Wolbachia* Therapy

The anti-*Wolbachia* therapy is currently under development based on the use of antibiotics to target the *Wolbachia* endosymbionts in *W. bancrofti* (Slatko et al. 2010). However, at present the recommended antibiotic doxycycline seems unlikely to be suitable for large-scale mass chemotherapy due to the long course (6 weeks) of daily treatment required to obtain desirable effects and the fact that this drug is contraindicated in young children and pregnant or potentially pregnant women. Research is currently underway to identify alternative antibiotics that exert an anti-Wolbachia effect with a shorter course of treatment (Taylor et al. 2013).

Alleviate Morbidities Associated with the Disease

Despite the availability of effective measures to treat and prevent clinical manifestations associated with lymphatic filariasis, this second pillar (alleviate morbidities associated with the disease) is neglected by most national elimination programs, the maximum attention being concentrated on MDA activities.

Lymphedema Management

The minimum treatment package recommended by WHO includes (i) hygiene, (ii) treatment and prevention of skin lesions trough, (iii) exercises, (iv) elevation of the afflicted limb, and (v) the wearing of comfortable shoes. The patients are trained to implement each component of the package on a daily basis. Training materials have been developed by WHO to promote this home-based self-care in the endemic countries. The evaluation in African settings showed that the home-based management of lymphedema is well accepted by the patients and has resulted in a drastic reduction of acute attacks and improvement of the quality of life of the patients enrolled in the program (Jullien et al. 2011; Mathieu et al. 2013). Despite the effectiveness and the acceptability of the self-care, only a few countries are implementing the lymphedema management at scale. NGDOs such as Handicap International and IMA World Health are supporting some projects in Benin, Burkina Faso, Ghana, Madagascar, and Togo. An example of an innovative fund

from Tanzania is the President Kikwete LF Fund, which was established in April 2008 to support patients suffering from the debilitating effects of lymphatic filariasis (Malecela et al. 2009). One of the first objectives of the project was to address the backlog of men needing hydrocele surgery. The total backlog at the time was 25,000 men.

Hydrocele Management

Three techniques for the management of hydrocele are available: (i) aspiration and sclerotherapy (Khaniya et al. 2009), (ii) eversion of the tunica vaginalis (Thomas et al. 2009), and (iii) excision of the tunica vaginalis (Noroes and Dreyer 2010). None of them is found to be the gold standard technique or recommended by WHO. Nevertheless, the procedure with total tunical resection and closure of the wound without drainage is the one being currently promoted in SSA especially in West Africa through a project supported by a Norwegian NGDO, Health and Development International (Mante and Gueye 2011). In 6 years, the initiative enabled training of 214 surgeons in 10 countries and the operation of 3000 cases. Projects of this kind will help clear the backlog of hydrocele surgery.

Control Strategies in SSA

Lymphatic filariasis control in Africa began in the 1940s with two main strategies: the use of diethylcarbamazine (DEC) commonly called banocide or hetrazan and mosquito control (which included source reduction). The strategies, however, were limited to small areas and pilot projects to determine whether the strategies would work. The chemotherapeutic approach was either treatment with DEC tablets or the use of DEC fortified salt. In East Africa attempts to control LF were carried out in the Ukara Islands of Lake Victoria in Tanzania mainland (then Tanganyika) and in the Pate Islands of Kenya (Hawking 1962). In his paper the eradication of filariasis on Ukara Island Jordan P. explains the approach of treating all microfilaraemics to reduce transmission and eventually eliminate the disease (Jordan 1959). Similar work was also carried out in prisoners (Davis and Bailey 1969). In West Africa similar work was done in Kerebe in the Gambia whereby DEC at doses of 5 and 2.5 mg/kg, respectively, were given to microfilaraemia-positive persons residing in the area (McGregor and Gilles 1956; McGregor et al. 1952). Other work in West Africa includes work done in Liberia (Zielke and Chlebowsky 1980; Chlebowsky and Zielke 1980) and in Senegal (Diallo et al. 1983). In the 1970s the importance of vector control as a strategy to control LF became more evident (White 1971), and hence there was a focus on spraying source reduction (Bushrod 1979), and in some later studies even building design that would reduce man-vector contact (Kolstrup et al. 1981). The efforts were carried out at a research level and were not coordinated.

Makunduchi in Zanzibar (Maxwell et al.1990) carried out a more coordinated and comprehensive approach, which involved killing larvae breeding in pit latrines using polystyrene beads together with the distribution of DEC. The intervention resulted in a major reduction in mosquito infectivity and a reduction of the infection in humans in a specific part of Unguja Island. Larviciding with *Bacillus sphaericus* was also carried out in open drains in the Zanzibar town (Maxwell et al. 1990). All in all most efforts in Africa focused on small areas with an aim to gain information on what strategies would be feasible for large-scale control. It was clear however that although some tools were available they could not be used widely. For example DEC, which was very effective in some areas, could not be used in onchocerciasis endemic areas for fear of ocular toxicity and the Mazzotti reaction. The Mazzotti reaction which may include anaphylactic shock is a result of the death of the microfilaria in the skin.

With more research came new tools; this included information that combinations of ivermectin and albendazole were effective in killing microfilariae. Then there was the development of rapid immunochromatographic tests, which would allow testing to be done during the day. This was a major revolution over the night blood testing which was inconvenient to the community. It was a major effort to get people to come and get tested between 22.00 and 0200 h. The new test made the possibility of testing during the day a reality. The major turning point for the LF program came with the adoption of the World Health Assembly Resolution in 1997 WHA 50.29. This was followed by donation of two drugs, albendazole and ivermectin, which were to be used for the interruption of transmission of LF in areas in Africa where LF and onchocerciasis were co-endemic. The resolution urged the member states among other things: "to strengthen local programmes and their integration with the control of other diseases, particularly at community level, in order to implement simple, affordable acceptable and sustainable activities, based on community wide treatment strategies, but supplemented where feasible by vector control and improved sanitation." The resolution urged the Director General among other things "to mobilize support for global and national elimination."

This resolution was the basis for defining a Global Strategy for Control of Lymphatic Filariasis. The strategy focused on mass chemotherapy using ivermectin and albendazole in countries in Africa where LF and onchocerciasis were co-endemic and DEC and albendazole in countries non-endemic for onchocerciasis. The other part of the strategy involved morbidity management for people who already had the debilitating manifestations of the disease. The focus was on alleviating symptoms of acute filarial attack and preventing bacterial superinfection in people with lymphedema and promoting surgery for those with hydroceles. It is against this backdrop that National Lymphatic Filariasis Elimination Programs (NLFEP) began in Africa under the auspices of the WHO Global Programme to eliminate LF. The programs always started off with mapping to find out the real extent of the infection and were based on measuring circulating filarial antigens in 100 people in an implementation unit. The methodology was based on studies on Rapid Geographical Assessment of Lymphatic Filariasis (RAGFIL) (Gyapong and Remme 2001; Gyapong et al. 2002) which

compared the use of the ICT test as a rapid method of determining the prevalence of LF in a particular area.

Following the development of initial country plan, NLFEP programs were launched in Africa in 2000 with three countries starting off, namely, Ghana, Tanzania, and Togo. The programs initially focused on MDA scaling up implementation units year after year. The programs then added a morbidity component at different stages of the program implementation. Out of the 37 countries in South Saharan Africa where MDA may be required for LFE with at-risk population estimated at 472 million, as of December 2013 only 24 have functional programs with about 140 million individuals who have been reached by at least one round of treatment (approximately 37 % of the population requiring treatment) (WHO 2010, 2011a, 2014). The program has been implemented at the village level with strong community support. Different approaches have been tried and tested in different places but the emphasis has been to focus on what works in the various communities. In some countries it has been the use of community drug distributors (CDDs) that were and are being used by the Onchocerciasis Programme in the community-directed treatment approach. Other methods have been the use of community/village health workers who are selected by the villagers (Gyapong et al. 2001; Amazigo et al. 2002). In Zanzibar, an approach of interpersonal communication COMBI (WHO 2002) was what was used where the distributors also gave intense health education on their visits. All in all there was no one size fits all and countries had to adapt to the delivery methods that allowed them maximum efficiency with limited disruption to health system activities (Fig. 11).

All countries had specific training programs where the distributors were trained either directly by staff at the national level or via a cascade method where the national level trained the trainers of trainers who then went on to train others. In Tanzania, for example, the national trainers trained the regional trainers. The regional trainers then trained the district leaders who then went out and trained the village health workers (Malecela et al. 2009). Messages were kept very simple throughout to ensure that key information was imparted to the distributors. These messages included what to do before the program began, including the importance of census for getting accurate numbers, what to do during MDA, and finally what to do after the MDA including ensuring that data summaries were sent to the districts. Another important component of the program is "advocacy and social mobilization," which also differs from country to country. This is the key to the success of the programs and needed to be carried out at all levels. In some cases, even within countries, social mobilization needed to be tailor-made to fit particular communities, e.g., migrants, fishermen, etc.

Challenges of Program Implementation

Like all public health programs, the LF program has many challenges as set out below.

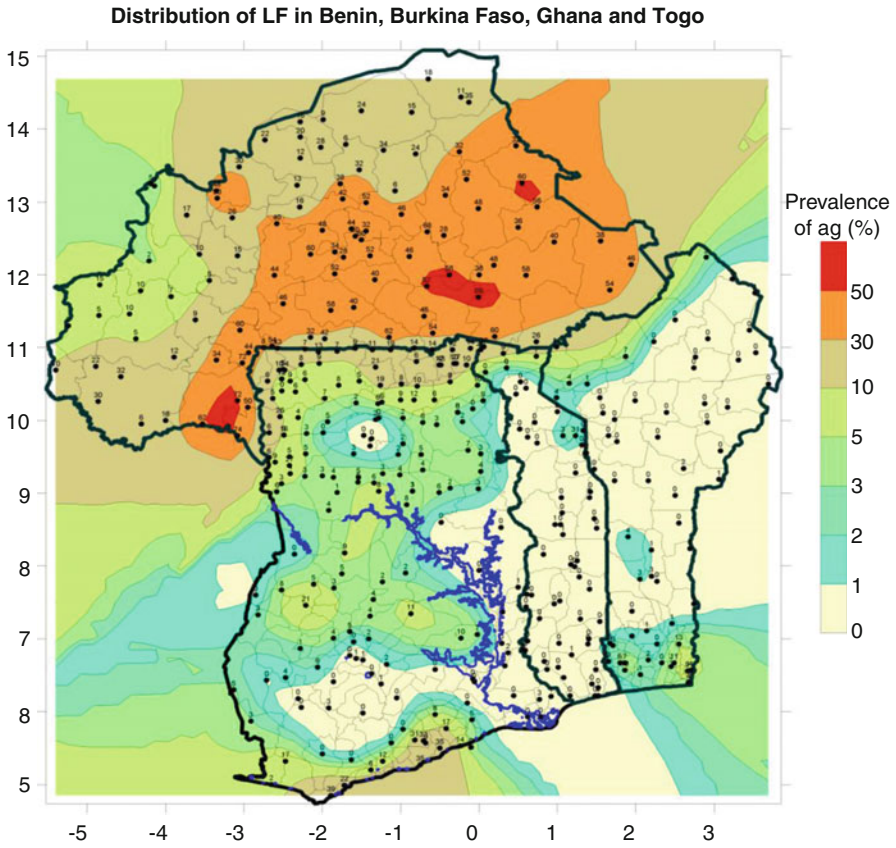


Fig. 11 LF endemicity map for West Africa (Gyapong et al. 2002)

Coverage

Coverage (geographical and treatment) is a major problem and this is for several reasons. One of the main reasons was the lack of clear understanding as to why one should take drugs when one was not sick or showing any symptoms of the disease. There were also myths and rumors about the drugs in that the drug was being used for birth control and that it could cause erectile dysfunction. In some areas it was because the social mobilization had not been inclusive. For example, engaging religious leaders and traditional healers was helpful in some areas of Tanzania. The issue of coverage becomes an even greater concern in areas of low endemicity where the symptoms of the disease, i.e., hydrocele and elephantiasis, are less obvious, hence making it difficult to convince people of the fact that they could be carrying the disease.

Funding

One of the other key problems of getting programs to expand has been funding. Initially programs were supported by partners to develop a proof of concept. They then insisted that countries take on the expansion which has been very slow in some of the countries. Districts were asked to budget for LF in a number of countries where a decentralized health system existed, but this was almost impossible given the competing priorities at district level. A clear approach to funding had not been established, and while there was a clear expansion plan for the elimination, there was no corresponding financial plan to go with it. The advent of the integrated NTD program has allowed the use of resources for preventive chemotherapy programs to be used for all seven PCT diseases (Kabatereine et al. 2010; Hanson et al. 2012; Hooper et al. 2013). This in some way has helped mobilize the core funding needed to support delivery while at the same time expand the programs at an unprecedented pace. The challenge now is that although the different disease programs are integrated for better functioning, they need to be integrated into the health system.

Capacity

Lack of capacity to carry out the programs is a challenge. This has been addressed by training through support from the Bill Melinda Gates Grant to the Global Alliance, which focused predominantly on training researchers at Masters and PhD level. The program was designed such that the students would work within their country programs on an issue relevant to the program research needs. This method has developed a cohort of leaders who are now leading NTD control programs in several countries in Africa. Capacity strengthening, however, includes it at the national level right down to the district level and finally to the village level where all the major work is done. Countries have adapted several capacity building models, and different programs have focused on different key areas: financial management, supply chain management, and interpersonal marketing skills. There is still a gap in the capacity needed to run these programs. It is envisaged that integrated NTD programs may be the answer to this crisis as all the single disease focal persons are now working together in one integrated program. Skills like entomology and pathology, which are still essential for LF, however, are yet to be addressed.

The Big Five

Another major challenge is that while there is great progress being made in Africa, there are five countries which account for 40 % of the burden on the continent.

These "big five" are the key to the elimination of LF in the African region specifically because of the numbers. The countries are Democratic Republic of Congo, Ethiopia, Nigeria and Sudan, and United Republic of Tanzania (mainland). Expanding the programs and reaching full geographic scale in these countries is a major undertaking but it is also what will increase the pace of elimination on the continent.

Hotspots

There is a need to understand "hotspots," that is, areas where MDA has gone on for several years, but the reduction in transmission has been slow. While the immediate response in such circumstances is the issue of low coverage, there might be other epidemiological, climatic, vectorial factors affecting transmission. These issues have not been adequately studied. Models however have suggested that in areas of higher endemicity, it could be more difficult to reach the target of elimination as even within those areas, there are focal points with continued transmission in spite of good coverage. This opens the door for further research in this field. There might need to be a different approach to address the issues in areas of higher endemicity.

Loa loa

Co-endemicity of LF and loiasis. An important challenge in addressing LF in Africa is the presence and level of endemicity of *Loa loa* in the Central part of Africa. Administration of ivermectin to individuals with *Loa loa* may result in *Loa loa* encephalopathy, which can eventually result in death (Twum-Danso 2003). Rapid assessment of *Loa loa* (RAPLOA) has been useful in determining which areas to treat (Zoure et al. 2011); however, more work needs to be done to find a more conclusive diagnostic test to avoid these extreme adverse events. WHO has recently recommended the use of albendazole only in these areas where LF is co-endemic with *Loa loa* in association with integrated vector management (WHO 2012b). In some situations the use of long-lasting insecticide nets has been useful in reducing LF in *Loa loa*-endemic areas (Richards et al. 2013). As the program expands more slowly than anticipated, it is clear that there has not been enough effort in taking advantage of synergies that exist between the various programs, as, for example, the effective use of community distributors to distribute commodities (nets and vitamin A) other than drugs for MDA (Anonymous 2010). Another area of convergence is home-based care for HIV where individuals who are trained to give care for HIV/AIDs patients can also support lymphedema management.

Indirect Impact

The Lymphatic Filariasis Programme in SSA has had far-reaching impact than just the health benefits to the victims of the infection. One important outcome from the LF programs is the ability to get commodities through it to areas "beyond the end of the road' (Haddad et al. 2008). It has increased the health systems outreach through a network, which goes even beyond the level of the village by reaching very remote settlements. The network can be used to distribute other commodities. It has created a good platform for other interventions that need to be delivered at the community level and improved intersectoral collaboration. With the current push on the use of community health workers (there are several millions already in action), the LF program is a good example of what works and that of best practices. The approaches however will be country specific, but it is clear that community health workers can be supported to carry out several interventions. In Ethiopia they have made great progress in maternal and child health (Medhanyie et al. 2012). The LF program has been a platform for health promotion activities and continues to be a wider platform as part of an integrated program. The program supports a sub-district health infrastructure, which is very much in line with primary health care and universal coverage. If well utilized, it can improve access to health prevention tools, resulting in gains in health promotion and behavioral change. Other health-related impact includes reduction in scabies, reduced anemia attributable to hookworm infection, and increase in school attendance (Molyneux and Nantulya 2005; Mohammed et al. 2012).

Further Research for Control and Elimination

The areas for research are very closely linked to the challenges faced by the program and are set out as follows:

(i) The big gap in the implementation of the LF program seen in the central part of Africa is a stumbling block for the success of the elimination in Africa, and it is evident that without addressing the *Loa loa* issue, the 2020 goals will not be reached.
(ii) The issue of severe adverse reaction during treatment of LF in *Loa loa-endemic* areas; therefore, it requires attention by expanding research in endemic countries and improving diagnostics or looking for alternative regimens for treatment of LF where it is co-endemic with *Loa loa*.
(iii) There is a need for operational research that deals with the expansion of MDA in post-conflict areas. These are also areas where sporadic MDA programs or nonexistent ones can result in untreated areas, which then adversely affects the whole concept of interrupting transmission.
(iv) The ecological determinants of transmission in "hotspots" where even after several rounds of MDA and in spite of good coverage there is still transmission

need to be studied. A better understanding of these hotspots including issues around climate and microecology of the area are critical in understanding how to design programs to address this phenomenon.

(v) Strategies for urban areas also need research especially since, as programs expand, large urban areas which in some cases have unplanned settlements with intense migration will need to be treated. The fundamental questions will be what approaches serve best in these areas. Research on how to attain good converge in these areas and sustain the program for the number of years it takes to interrupt transmission will be needed.

(vi) Research and development for a macrofilaricidal drug is another important area for the program in Africa. In this respect the ongoing research on the possible use of antibiotics as macrofilaricidal drugs is a priority.

(vii) As LFE moves toward the end game, xenomonitoring will become key and more and more pertinent as infections in humans decrease to levels below 1 %. Xenomonitoring is regarded by many as a possible surveillance tool. Operations research to make this tool user-friendly by countries who mount surveillance will be required

Outlook for the Next Decade

The next decade symbolizes the countdown to the targets set forth for the elimination of LF and reminds us all of the daunting task ahead of us. The focus needs to be on increasing geographical coverage especially of big countries and making funds available to ensure that drug delivery is optimally carried out. This is an issue both for the endemic countries as well as their partners. As countries come close toward elimination focus on transmission, assessment surveys need to be enhanced. The integrated NTD program has built on some of the successes of the LF program in a number of countries; this should continue as it maximizes use of minimum resources. Focus on technical expertise for LF needs to remain a priority especially toward the end game. As Africa primes itself for the elimination of LF, the issue of surveillance needs to be taken into consideration and linked to health system surveillance activity.

There is currently a lot of enthusiasm and good will by all in the NTD fraternity, in the march toward the elimination of LF. It is therefore envisaged that coverage, funding, improved treatment regimes, and social determinants will receive the needed attention. The next decade should therefore see a rapid decline in the prevalence of and ultimately the elimination of LF from, if not all, most of the endemic countries in SSA. Research to unravel the best way to manage urban filariasis will be intensified to help mop up infection in urban areas that have so far lagged behind in drug delivery. Given the positive strides already made with the research in the use of antibiotics against the *Wolbachia* in the filarial worm, it is expected that the optimum treatment regime (short course) with the use antibiotics or novel antibiotics will be found to be added to the current drugs used in the treatment of LF. That

being the case, this is likely to open up new avenues to the treatment of LF where it is co-endemic with *Loa* without the risk of severe adverse events.

During the next 10 years, many of the previously LF-endemic countries will be in the surveillance phase; the questions on whether or not recrudescence will actually occur and, when and if it occurs, how to manage it may be aided by the information obtained from continued modeling which can be tested with real field-generated data during the decade.

Conclusion

Lymphatic filariasis (LF) is a debilitating disease. Since WHO passed resolution WHA 50.29 in 1997, calling for collaborative efforts by member states to eliminate the disease as a public health problem, and the creation of the Global Program to Eliminate Lymphatic Filariasis (GPELF), considerable progress has been made toward elimination in several countries. The disease however continues to be a public health problem in many countries, especially in the very large countries, in countries where LF is co-endemic with *Loa loa*, and in certain urban areas. Provided mapping in some remaining countries is completed without delay, geographic and treatment coverage brought to the optimum, and urban filariasis attacked with the same fervor as has been done for rural filariasis; the prospects for total elimination is good. The donation of ivermectin and albendazole free of charge for treatment in SSA was a magnanimous gesture from the drug companies that has reduced the burden of managing this disease. Some of the good lessons learnt from the management of LF with the involvement of communities, communities at the helm of affairs in drug treatment and morbidity management, and the good practices put into play will be of practical use for other public health interventions. There is great optimism that lymphatic filariasis will be either entirely eliminated or close to be eliminated in SSA by 2020.

References

Addiss D, Filariasis Global Alliance to Eliminate Lymphatic (2010) The 6th Meeting of the Global Alliance to Eliminate Lymphatic Filariasis: a half-time review of lymphatic filariasis elimination and its integration with the control of other neglected tropical diseases. Parasit Vectors 3:100. doi:10.1186/1756-3305-3-100

Akogun OB, Akogun MK, Apake E, Kale OO (2011) Rapid community identification, pain and distress associated with lymphoedema and adenolymphangitis due to lymphatic filariasis in resource-limited communities of North-eastern Nigeria. Acta Trop 120(Suppl 1):S62–S68. doi:10.1016/j.actatropica.2011.03.008

Amazigo UV, Obono M, Dadzie KY, Remme J, Jiya J, Ndyomugyenyi R, Roungou JB, Noma M, Seketeli A (2002) Monitoring community-directed treatment programmes for sustainability: lessons from the African Programme for Onchocerciasis Control (APOC). Ann Trop Med Parasitol 96(Suppl 1):S75–S92

Anonymous (2010) Community-directed interventions for priority health problems in Africa: results of a multicountry study. Bull World Health Organ 88(7):509–518. doi:10.2471/blt.09.069203

Arumugam S, Pfarr KM, Hoerauf A (2008) Infection of the intermediate mite host with Wolbachia-depleted Litomosoides sigmodontis microfilariae: impaired L1 to L3 development and subsequent sex-ratio distortion in adult worms. Int J Parasitol 38(8–9):981–987. doi:10.1016/j.ijpara.2007.12.006

Ashton RA, Kyabayinze DJ, Opio T, Auma A, Edwards T, Matwale G, Onapa A, Brooker S, Kolaczinski JH (2011) The impact of mass drug administration and long-lasting insecticidal net distribution on Wuchereria bancrofti infection in humans and mosquitoes: an observational study in northern Uganda. Parasit Vectors 4:134. doi:10.1186/1756-3305-4-134

Babu BV, Nayak AN, Dhal K, Acharya AS, Jangid PK, Mallick G (2002) The economic loss due to treatment costs and work loss to individuals with chronic lymphatic filariasis in rural communities of Orissa, India. Acta Trop 82(1):31–38

Boakye DA, Wilson MD, Appawu MA, Gyapong J (2004) Vector competence, for Wuchereria bancrofti, of the Anopheles populations in the Bongo district of Ghana. Ann Trop Med Parasitol 98(5):501–508. doi:10.1179/000349804225003514

Bockarie MJ, Pedersen EM, White GB, Michael E (2009) Role of vector control in the global program to eliminate lymphatic filariasis. Annu Rev Entomol 54:469–487. doi:10.1146/annurev.ento.54.110807.090626

Brengues J (1975) In: ORSTOM (ed) La Filariose de Bancroft en Afrique de L'ouest, vol 79. Mémoires ORSTOM, Paris

Brooker S (2010) Estimating the global distribution and disease burden of intestinal nematode infections: adding up the numbers – a review. Int J Parasitol 40(10):1137–1144. doi:10.1016/j.ijpara.2010.04.004

Bushrod FM (1979) Studies on filariasis transmission in Kwale, a Tanzanian coastal village, and the results of mosquito control measures. Ann Trop Med Parasitol 73(3):277–285

Carme B (2010) Mapping of lymphatic filariasis: to be (in English) or not to be. Med Trop (Mars) 70(5–6):425–427

Chlebowsky HO, Zielke E (1980) Studies on Bancroftian filariasis in Liberia. West Africa. III. Efficacy of repeated treatment with diethylcarbamazine and vector control on the microfilarial reservoir in a rural population. Tropenmed Parasitol 31(2):181–193

Davis A, Bailey DR (1969) The effect of salt medicated with diethylcarbamazine in bancroftian filariasis. Bull World Health Organ 41(2):195–208

Diallo S, Bah IB, Victorius A, N'Dir O, Diouf F (1983) Effects of diethylcarbamazine on the transmission of Wucheria bancrofti in a Senegalese reservoir of lymphatic filariasis. Dakar Med 28(1):179–186

Estambale BB, Simonsen PE, Knight R, Bwayo JJ (1994) Bancroftian filariasis in Kwale District of Kenya. I. Clinical and parasitological survey in an endemic community. Ann Trop Med Parasitol 88(2):145–151

Gasarasi DB, Premji ZG, Mujinja PG, Mpembeni R (2000) Acute adenolymphangitis due to bancroftian filariasis in Rufiji district, south east Tanzania. Acta Trop 75(1):19–28

Gyapong JO (2000) Lymphatic filariasis in Ghana: from research to control. Trans R Soc Trop Med Hyg 94(6):599–601

Gyapong JO, Remme JH (2001) The use of grid sampling methodology for rapid assessment of the distribution of bancroftian filariasis. Trans R Soc Trop Med Hyg 95(6):681–686

Gyapong JO, Magnussen P, Binka FN (1994) Parasitological and clinical aspects of bancroftian filariasis in Kassena-Nankana District, upper east region, Ghana. Trans R Soc Trop Med Hyg 88(5):555–557

Gyapong JO, Adjei S, Sackey SO (1996a) Descriptive epidemiology of lymphatic filariasis in Ghana. Trans R Soc Trop Med Hyg 90(1):26–30

Gyapong JO, Gyapong M, Adjei S (1996b) The epidemiology of acute adenolymphangitis due to lymphatic filariasis in northern Ghana. Am J Trop Med Hyg 54(6):591–595

Gyapong M, Gyapong J, Weiss M, Tanner M (2000) The burden of hydrocele on men in Northern Ghana. Acta Trop 77(3):287–294

Gyapong M, Gyapong JO, Owusu-Banahene G (2001) Community-directed treatment: the way forward to eliminating lymphatic filariasis as a public-health problem in Ghana. Ann Trop Med Parasitol 95(1):77–86

Gyapong JO, Kyelem D, Kleinschmidt I, Agbo K, Ahouandogbo F, Gaba J, Owusu-Banahene G, Sanou S, Sodahlon YK, Biswas G, Kale OO, Molyneux DH, Roungou JB, Thomson MC, Remme J (2002) The use of spatial analysis in mapping the distribution of bancroftian filariasis in four West African countries. Ann Trop Med Parasitol 96(7):695–705. doi:10.1179/000349802125001735

Haddad D, Cross C, Thylefors B, Richards FO Jr, Bush S, Hopkins AD, Baker SK (2008) Health care at the end of the road: opportunities from 20 years of partnership in onchocerciasis control. Glob Publ Health 3(2):187–196. doi:10.1080/17441690801900134

Hanson C, Weaver A, Zoerhoff KL, Kabore A, Linehan M, Doherty A, Engels D, Savioli L, Ottesen EA (2012) Integrated implementation of programs targeting neglected tropical diseases through preventive chemotherapy: identifying best practices to roll out programs at national scale. Am J Trop Med Hyg 86(3):508–513. doi:10.4269/ajtmh.2012.11-1589

Hawking F (1957) The distribution of Bancroftian filariasis in Africa. Bull World Health Organ 16(3):581–592

Hawking F (1962) A review of progress in the chemotherapy and control of filariasis since 1955. Bull World Health Organ 27:555–568

Hooper PJ, Zoerhoff KL, Kyelem D, Chu B, Mann Flueckiger R, Bamani S, Bougma WR, Fleming F, Onapa A, Pare AB, Torres S, Traore MO, Tuinsma M, Linehan M, Baker M (2013) The effects of integration on financing and coverage of neglected tropical disease programs. Am J Trop Med Hyg. doi:10.4269/ajtmh.13-0018

Hotez PJ, Kamath A (2009) Neglected tropical diseases in sub-saharan Africa: review of their prevalence, distribution, and disease burden. PLoS Negl Trop Dis 3(8):e412. doi:10.1371/journal.pntd.0000412

Jemaneh L, Kebede D (1995) Clinico-epidemiological study of lymphatic filariasis southwestern Ethiopia. Ethiop Med J 33(3):143–153

Jordan P (1959) A pilot scheme to eradicate bancroftian filariasis with diethylcarbamazine; results of the first year's treatment. Trans R Soc Trop Med Hyg 53(1):54–60

Jullien P, Some J, Brantus P, Bougma RW, Bamba I, Kyelem D (2011) Efficacy of home-based lymphoedema management in reducing acute attacks in subjects with lymphatic filariasis in Burkina Faso. Acta Trop 120(Suppl 1):S55–S61. doi:10.1016/j.actatropica.2011.03.007

Kabatereine NB, Malecela M, Lado M, Zaramba S, Amiel O, Kolaczinski JH (2010) How to (or not to) integrate vertical programmes for the control of major neglected tropical diseases in sub-Saharan Africa. PLoS Negl Trop Dis 4(6):e755. doi:10.1371/journal.pntd.0000755

Kelly-Hope LA, Thomas BC, Bockarie MJ, Molyneux DH (2011) Lymphatic filariasis in the Democratic Republic of Congo; micro-stratification overlap mapping (MOM) as a prerequisite for control and surveillance. Parasit Vectors 4:178. doi:10.1186/1756-3305-4-178

Kelly-Hope LA, Molyneux DH, Bockarie MJ (2013) Can malaria vector control accelerate the interruption of lymphatic filariasis transmission in Africa; capturing a window of opportunity? Parasit Vectors 6:39. doi:10.1186/1756-3305-6-39

Khaniya S, Agrawal CS, Koirala R, Regmi R, Adhikary S (2009) Comparison of aspiration-sclerotherapy with hydrocelectomy in the management of hydrocele: a prospective randomized study. Int J Surg 7(4):392–395. doi:10.1016/j.ijsu.2009.07.002

Kolstrup N, McMahon JE, Magayuka SA, Mosha FW, Bushrod FM, Bryan JH (1981) Control measures against Bancroftian filariasis in coastal villages in Tanzania. Ann Trop Med Parasitol 75(4):433–451

Krishna Kumari A, Harichandrakumar KT, Das LK, Krishnamoorthy K (2005) Physical and psychosocial burden due to lymphatic filariasis as perceived by patients and medical experts. Trop Med Int Health 10(6):567–573. doi:10.1111/j.1365-3156.2005.01426.x

Malecela MN, Mwingira U, Mwakitalu ME, Kabali C, Michael E, Mackenzie CD (2009) The sharp end – experiences from the Tanzanian programme for the elimination of lymphatic filariasis: notes from the end of the road. Ann Trop Med Parasitol 103(Suppl 1):S53–S57. doi:10.1179/000349809x12502035776676

Manga L (2002) Vector-control synergies, between 'roll back malaria' and the Global Programme to Eliminate Lymphatic Filariasis, in the African region. Ann Trop Med Parasitol 96(Suppl 2):S129–S132

Manguin S, Bangs MJ, Pothikasikorn J, Chareonviriyaphap T (2010) Review on global co-transmission of human Plasmodium species and Wuchereria bancrofti by Anopheles mosquitoes. Infect Genet Evol 10(2):159–177. doi:10.1016/j.meegid.2009.11.014

Mante SD, Gueye SM (2011) Capacity building for the modified filarial hydrocelectomy technique in West Africa. Acta Trop 120(Suppl 1):S76–S80. doi:10.1016/j.actatropica.2010.09.008

Mathieu E, Amann J, Eigege A, Richards F, Sodahlon Y (2008) Collecting baseline information for national morbidity alleviation programs: different methods to estimate lymphatic filariasis morbidity prevalence. Am J Trop Med Hyg 78(1):153–158

Mathieu E, Dorkenoo A, Otogbe FK, Budge PJ, Sodahlon YK (2011) A laboratory-based surveillance system for Wuchereria bancrofti in Togo: a practical model for resource-poor settings. Am J Trop Med Hyg 84(6):988–993. doi:10.4269/ajtmh.2011.10-0610

Mathieu E, Dorkenoo AM, Morgah K, Datagni M, Cantey PT, Morgah K, Harvey K, Ziperstein J, Drexler N, Chapleau G, Sodahlon Y (2013) It is possible: availability of lymphedema case management in each health facility in Togo: program description, evaluation, and lessons learned. Am J Trop Med Hyg. doi:10.4269/ajtmh.12-0453

Maxwell CA, Curtis CF, Haji H, Kisumku S, Thalib AI, Yahya SA (1990) Control of Bancroftian filariasis by integrating therapy with vector control using polystyrene beads in wet pit latrines. Trans R Soc Trop Med Hyg 84(5):709–714

McGregor IA, Gilles HM (1956) Diethylcarbamazine control of bancroftian filariasis; follow-up of a field trial in West Africa. Br Med J 1(4962):331–332

McGregor IA, Hawking F, Smith DA (1952) The control of filariasis with hetrazan; a field trial in a rural village (Keneba) in the Gambia. Br Med J 2(4790):908–911

Medhanyie A, Spigt M, Kifle Y, Schaay N, Sanders D, Blanco R, GeertJan D, Berhane Y (2012) The role of health extension workers in improving utilization of maternal health services in rural areas in Ethiopia: a cross sectional study. BMC Health Serv Res 12:352. doi:10.1186/1472-6963-12-352

Mohammed KA, Deb RM, Stanton MC, Molyneux DH (2012) Soil transmitted helminths and scabies in Zanzibar, Tanzania following mass drug administration for lymphatic filariasis – a rapid assessment methodology to assess impact. Parasit Vectors 5:299. doi:10.1186/1756-3305-5-299

Molyneux DH, Nantulya V (2005) Public-private partnerships in blindness prevention: reaching beyond the eye. Eye (Lond) 19(10):1050–1056. doi:10.1038/sj.eye.6701961

Mukoko DA, Pedersen EM, Masese NN, Estambale BB, Ouma JH (2004) Bancroftian filariasis in 12 villages in Kwale district, Coast province, Kenya – variation in clinical and parasitological patterns. Ann Trop Med Parasitol 98(8):801–815. doi:10.1179/000349804x3225

Nielsen NO, Makaula P, Nyakuipa D, Bloch P, Nyasulu Y, Simonsen PE (2002) Lymphatic filariasis in Lower Shire, southern Malawi. Trans R Soc Trop Med Hyg 96(2):133–138

Njenga SM, Wamae CN, Njomo DW, Mwandawiro CS, Molyneux DH (2007) Chronic clinical manifestations related to Wuchereria bancrofti infection in a highly endemic area in Kenya. Trans R Soc Trop Med Hyg 101(5):439–444. doi:10.1016/j.trstmh.2006.09.006

Njenga SM, Wamae CN, Njomo DW, Mwandawiro CS, Molyneux DH (2008) Impact of two rounds of mass treatment with diethylcarbamazine plus albendazole on Wuchereria bancrofti infection and the sensitivity of immunochromatographic test in Malindi, Kenya. Trans R Soc Trop Med Hyg 102(10):1017–1024. doi:10.1016/j.trstmh.2008.04.039

Noma M, Nwoke BE, Nutall I, Tambala PA, Enyong P, Namsenmo A, Remme J, Amazigo UV, Kale OO, Seketeli A (2002) Rapid epidemiological mapping of onchocerciasis (REMO): its application by the African Programme for Onchocerciasis Control (APOC). Ann Trop Med Parasitol 96(Suppl 1):S29–S39

Noroes J, Dreyer G (2010) A mechanism for chronic filarial hydrocele with implications for its surgical repair. PLoS Negl Trop Dis 4(6):e695. doi:10.1371/journal.pntd.0000695

Okon OE, Iboh CI, Opara KN (2010) Bancroftian filariasis among the Mbembe people of Cross River state, Nigeria. J Vector Borne Dis 47(2):91–96

Onapa AW, Simonsen PE, Pedersen EM, Okello DO (2001) Lymphatic filariasis in Uganda: baseline investigations in Lira, Soroti and Katakwi districts. Trans R Soc Trop Med Hyg 95(2):161–167

Ottesen EA (2000) The global programme to eliminate lymphatic filariasis. Trop Med Int Health 5(9):591–594

Paily KP, Hoti SL, Das PK (2009) A review of the complexity of biology of lymphatic filarial parasites. J Parasit Dis 33(1–2):3–12. doi:10.1007/s12639-009-0005-4

Person B, Bartholomew LK, Gyapong M, Addiss DG, van den Borne B (2009) Health-related stigma among women with lymphatic filariasis from the Dominican Republic and Ghana. Soc Sci Med 68(1):30–38. doi:10.1016/j.socscimed.2008.09.040

Richard SA, Mathieu E, Addiss DG, Sodahlon YK (2007) A survey of treatment practices and burden of lymphoedema in Togo. Trans R Soc Trop Med Hyg 101(4):391–397. doi:10.1016/j.trstmh.2006.08.011

Richards FO, Emukah E, Graves PM, Nkwocha O, Nwankwo L, Rakers L, Mosher A, Patterson A, Ozaki M, Nwoke BE, Ukaga CN, Njoku C, Nwodu K, Obasi A, Miri ES (2013) Community-wide distribution of long-lasting insecticidal nets can halt transmission of lymphatic filariasis in Southeastern Nigeria. Am J Trop Med Hyg. doi:10.4269/ajtmh.12-0775

Shenoy RK, Bockarie MJ (2011) Lymphatic filariasis in children: clinical features, infection burdens and future prospects for elimination. Parasitology 138(12):1559–1568. doi:10.1017/s003118201100117x

Simonsen PE, Meyrowitsch DW, Makunde WH, Magnussen P (1995) Bancroftian filariasis: the pattern of microfilaraemia and clinical manifestations in three endemic communities of Northeastern Tanzania. Acta Trop 60(3):179–187

Simonsen PE, Malecela NM, Mackenzie CD (2008) Lymphatic filariasis. Research and control in Eastern and Southern Africa. DBL-Centre for Health Research and Development, Denmark

Simonsen PE, Pedersen EM, Rwegoshora RT, Malecela MN, Derua YA, Magesa SM (2010) Lymphatic filariasis control in Tanzania: effect of repeated mass drug administration with ivermectin and albendazole on infection and transmission. PLoS Negl Trop Dis 4(6):e696. doi:10.1371/journal.pntd.0000696

Simonsen PE, Onapa AW, Asio SM (2011) Mansonella perstans filariasis in Africa. Acta Trop 120(Suppl 1):S109–S120. doi:10.1016/j.actatropica.2010.01.014

Slater H, Michael E (2012) Predicting the current and future potential distributions of lymphatic filariasis in Africa using maximum entropy ecological niche modelling. PLoS One 7(2):e32202. doi:10.1371/journal.pone.0032202

Slatko BE, Taylor MJ, Foster JM (2010) The Wolbachia endosymbiont as an anti-filarial nematode target. Symbiosis 51(1):55–65. doi:10.1007/s13199-010-0067-1

Sodahlon YK, Dorkenoo AM, Morgah K, Nabiliou K, Agbo K, Miller R, Datagni M, Seim A, Mathieu E (2013) A success story: Togo is moving toward becoming the first Sub-Saharan African nation to eliminate lymphatic filariasis through mass drug administration and country-wide morbidity alleviation. PLoS Negl Trop Dis 7(4):e2080. doi:10.1371/journal.pntd.0002080

Taylor MJ, Hoerauf A, Townson S, Slatko BE, Ward SA (2013) Anti-wolbachia drug discovery and development: safe macrofilaricides for onchocerciasis and lymphatic filariasis. Parasitology 18: 1–9. doi:10.1017/s0031182013001108

Thomas G, Richards FO Jr, Eigege A, Dakum NK, Azzuwut MP, Sarki J, Gontor I, Abimiku J, Ogah G, Jindau MY, Jiya JY, Miri ES (2009) A pilot program of mass surgery weeks for treatment of hydrocele due to lymphatic filariasis in central Nigeria. Am J Trop Med Hyg 80(3):447–451

Twum-Danso NA (2003) Loa loa encephalopathy temporally related to ivermectin administration reported from onchocerciasis mass treatment programs from 1989 to 2001: implications for the future. Filaria J 2(Suppl 1):S7. doi:10.1186/1475-2883-2-s1-s7

Ughasi J, Bekard HE, Coulibaly M, Adabie-Gomez D, Gyapong J, Appawu M, Wilson MD, Boakye DA (2012) Mansonia Africana and Mansonia uniformis are vectors in the transmission of Wuchereria bancrofti lymphatic filariasis in Ghana. Parasit Vectors 5:89. doi:10.1186/1756-3305-5-89

Uttah EC (2011) Prevalence of endemic Bancroftian filariasis in the high altitude region of south-eastern Nigeria. J Vector Borne Dis 48(2):78–84

Weil GJ, Lammie PJ, Weiss N (1997) The ICT filariasis test: a rapid-format antigen test for diagnosis of bancroftian filariasis. Parasitol Today 13(10):401–404

WHA (1997) Resolution WHA50.29: elimination of lymphatic filariasis as a public health problem. In: Fiftieth World Health Assembly, Geneva

White GB (1971) The present importance of domestic mosquitoes (Culex pipiens fatigans Wiedemann) in East Africa and recent steps towards their control. East Afr Med J 48(6):266–274

WHO (1992) Lymphatic filariasis: the disease and its control. In: Fifth report of the WHO Expert Committee on Filariasis. World Health Organization, Geneva

WHO (2002) The global elimination of lymphatic filariasis: the story of Zanzibar. WHO, Geneva, WHO/CDS/CPS/SMT/2002.15

WHO (2010) Progress report 2000–2009 and strategic plan 2010–2020 of the global programme to eliminate lymphatic filariasis: halfway towards eliminating lymphatic filariasis. no. WHO/HTM/NTD/PCT/2010.6

WHO (2011a) Global Programme to eliminate lymphatic filariasis: progress report on mass drug administration, 2010. Wkly Epidemiol Rec 86(35):377–388

WHO (2011b) Lymphatic filariasis. Monitoring and epidemiological assessment of mass drug administration. A manual for National Elimination Programmes. no. WHO/HTM/NTD/PCT/2011.4

WHO (2011c) Managing morbidity and preventing disability in the Global Programme to Eliminate Lymphatic Filariasis: WHO position statement. Wkly Epidemiol Rec 86(51–52):581–585

WHO (2011d) WHO position statement on integrated vector management to control malaria and lymphatic filariasis. Wkly Epidemiol Rec 86(13):121–127

WHO (2012a) Global programme to eliminate lymphatic filariasis: progress report, 2011. Wkly Epidemiol Rec 87(37):346–356

WHO (2012b) Provisional strategy for interrupting Lymphatic filariasis transmission in loiasis-endemic countries. In: WHO (ed) 2012 [Report of the meeting on lymphatic filariasis, malaria and integrated vector management. Accra, Ghana, 5–9 March 2012]. WHO/HTM/NTD/PCT/2012.6. WHO, Geneva

WHO (2012c) Transmission assessment surveys in the Global Programme to Eliminate Lymphatic Filariasis: WHO position statement. Wkly Epidemiol Rec 87(48):478–482

WHO (2014) Global programme to eliminate lymphatic filariasis: progress report, 2013. Wkly Epidemiol Rec 89(38):409–418

Witt C, Ottesen EA (2001) Lymphatic filariasis: an infection of childhood. Trop Med Int Health 6(8):582–606

Zeldenryk LM, Gray M, Speare R, Gordon S, Melrose W (2011) The emerging story of disability associated with lymphatic filariasis: a critical review. PLoS Negl Trop Dis 5(12):e1366. doi:10.1371/journal.pntd.0001366

Zielke E, Chlebowsky HO (1980) Studies on bancroftian filariasis in Liberia. West Africa. V. The influence of treatment with diethylcarbamazine and vector control on the transmission of Wuchereria bancrofti. Tropenmed Parasitol 31(4):444–458

Zoure HG, Wanji S, Noma M, Amazigo UV, Diggle PJ, Tekle AH, Remme JH (2011) The geographic distribution of Loa loa in Africa: results of large-scale implementation of the Rapid Assessment Procedure for Loiasis (RAPLOA). PLoS Negl Trop Dis 5(6):e1210. doi:10.1371/journal.pntd.0001210

Onchocerciasis

Boakye A. Boatin and Uche Amazigo

Contents

B.A. Boatin (✉)
Insititute of Parasitology, McGill University and Lymphatic Filariasis Support Centre for Africa, PO Box CT 1380, Accra, Ghana
e-mail: baboatin@gmail.com

U. Amazigo
Independent Condsultant, Main Post Office, Okpara Avenue, PO Box 3397, Enugu, Enugu State, Nigeria
e-mail: Amazigo4@yahoo.com

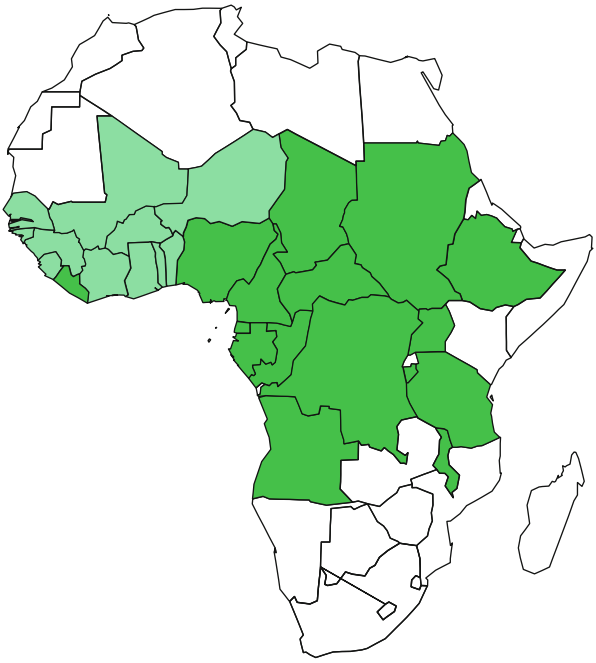
J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_9

Abstract Onchocerciasis, a dermic filariasis, is caused by the nematode *Onchocerca volvulus*. The disease is found in 30 African countries between latitudes 15° N and 14° S. About 37 million people are infected, 500,000 of whom are severely visually impaired. Worldwide, onchocerciasis is a very important infectious cause of blindness, being second only to trachoma in numbers of persons affected. Transmitted by a vector, *Simulium damnosum*, the adult parasite lives up to 14 years in humans producing millions of microfilaria which are responsible for the pathology of the disease. The disease presents as pruritus; onchodermatitis, including acute and chronic papular dermatitis; eye lesions of sclerosing keratitis and iridocyclitis; optic nerve disease; optic atrophy and choroidoretinitis; and in the worst case as blindness. There is evidence of protective immunity in onchocerciasis which could be at play in these lesions. Onchocerciasis is responsible for 1.49 million (disability-adjusted life years) DALYs annually, while troublesome itching accounts for 60 % of DALYs attributable to onchocerciasis. Individual diagnosis depends on symptomatology and parasitological tests, while community diagnosis is made through rapid epidemiological mapping which involves nodule palpation. Larviciding was used successfully for control in the West African Onchocerciasis Programme, while the African Programme for Onchocerciasis Control and Partners drive the control through community-directed treatment with ivermectin in the rest endemic African countries. Recent results which showed that the disease might have been eliminated in certain foci in Africa have informed the current paradigm change from control to the elimination of the disease. The prospects of elimination would imply extending opera-

tions beyond the currently covered areas, with the attendant management, financial, and logistic challenges. Some challenges of onchocerciasis control include (a) finding the optimum diagnostic tool, (b) how to minimize noncompliance with the drug treatment, (c) the best approach to obtain sustainability of the drug distribution program, (d) discovering an acceptable macrofilaricide which can either kill or sterilize the adult, (e) how to optimize treatment regime of possible antibiotic used to eliminate *Wolbachia*, and (f) how to discover early, any resistance to the current drug. All these require research which has always been central to the two control programs.

Introduction

Onchocerciasis also known as river blindness is a dermic filariasis which has been an important cause of blindness and debilitating skin lesions for several decades in Africa, Latin America, and a small portion in the Arabian Peninsula. The disease occurs in 37 countries. Thirty of these countries are found in Africa (Map 1), six in the Americas, and one (Yemen) in the Arabian Peninsula. Africa bears the biggest brunt of the disease and is by far the most affected continent both in terms of the extent of the distribution and the severity of the clinical manifestations of the disease. Onchocerciasis is a neglected tropical disease (NTD), affects the poor, causes poverty, and is an impediment to socioeconomic development. It remains a major parasitic endemic disease especially in Central and East Africa although a lot of progress in its control has been made in West



Map 1 Africa showing the countries that are endemic for onchocerciasis

Africa. Estimates from the WHO Expert Committee on Onchocerciasis in 1995 put the number of infected persons at about 17.7 million, about 270,000 of whom are blind and another 500,000 severely visually impaired (WHO 1995a). Over 99 % of the estimated 17.7 (currently estimated as to be about 40 million) persons infected with this filarial parasite live in Africa, while about 140,000 people in the Americas are infected with the worm. These estimates call for a revision, given the remarkable progress that has been made by the Onchocerciasis Control Programme in West Africa (OCP), the African Programme for Onchocerciasis Control (APOC), and the Onchocerciasis Elimination Programme in the Americas (OEPA). In Latin America and the Caribbean, onchocerciasis was found in Mexico, Guatemala, Colombia, Ecuador Venezuela, and Brazil, with 13 focal areas and 510,000 individuals at risk of infection (Basanez et al. 2006). There are eight focal areas with evidence of interruption of transmission (Ault 2007). In 2011, Colombia became the first country in the Americas to successfully eliminate onchocerciasis (PAHO). Reports from the Carter Center (July 2013) indicated that four out of the six of the endemic countries in the Americas have broken transmission of the disease nationwide. The disease is responsible for one million disability-adjusted life years (DALYs) annually. Worldwide, onchocerciasis is one of the most important infectious causes of blindness, being second only to trachoma in numbers of persons affected (Thylefors et al. 1995; Lewalen and Courtright 2001). Eye disease from onchocerciasis, therefore, represents the main public health challenge accounting for 40 % of DALYs although severe skin disease is also recognized as of public health significance (Hagan 1998). In the last two to three decades, a concerted effort has been made by the OCP and APOC to control the disease which has produced remarkable success, and results from Latin America (OEPA) and some parts of Africa (Diawara et al. 2009; JAF 2011) suggest that the disease has been or can be eliminated even with the currently available tool in most areas using the right strategy and if given the financial input and support. There are still challenges which open up the need for research to (a) find the optimum diagnostic tool, especially the one that is sensitive enough and specific for *Onchocerca* that can be used to assess whether or not onchocercal infection has been eliminated in a locality, (b) discover an acceptable macrofilaricide which can either kill or sterilize the adult worm and therefore help shorten the period of treatment, (c) find the best approach to obtain sustainability of the drug distribution program which is essential to maintain the pressure on the parasite, and (d) do research to discover early, any resistance to the current drug in use and the best way to overcome it.

Basic Biology, Life Cycle, and Disease Presentation

Basic Biology

The Parasite

The parasite which causes onchocerciasis is called *Onchocerca volvulus*. It is a nematode with man as the only definitive known reservoir. The adult worms (Fig. 1), both male (3–5 cm long) and female (30–80 cm), live in fibrous nodules found subcutaneously or deep in the connective and muscular tissues, with a tendency to overlie bony

Fig. 1 Coiled adult onchocercal male and female worms (Source: *TDR image* library)

prominences. The adult worm has a reproductive life span of about 9–11 years (Plaisier et al. 1991), although it may live up to about 15 years. A female worm when fertilized produces millions of embryos called microfilariae (mfs) which themselves live for about 2 years. The mfs (up to 300 um in length) when released by the adult worm migrate from the nodules, invading the skin, eyes, and some organs from where they are taken up through the bite of the vector, a blackfly. The mfs are occasionally also found in peripheral blood, urine, and sputum but are typically found in the skin and in the lymphatics of connective tissues. Different disease patterns – blinding onchocerciasis or dermal onchocerciasis – are associated with the different variants or strains of the parasite, each associated with the different subspecies of the vector. *O. volvulus*, like other filarial nematodes, shares an endosymbiotic relationship with the bacterium *Wolbachia*. In the absence of *Wolbachia*, there is inhibition of worm development, embryogenesis and fertility are blocked, and worm viability is reduced (Hoerauf et al. 2008).

Vector and Transmission

Onchocerciasis is transmitted by the female of small blackflies (Fig. 2) of the genus *Simulium*. The main vectors are the *Simulium damnosum s.l.* of which *S. sanctipauli* is mostly responsible for transmission in savannah areas, whereas *S. squamosum* subspecies are found in more forest areas in Africa. Other complexes are *S. neavei* also found in Africa and *S. ochraceum*, *S. metallicum*, *S. exiguum*, and *S. oyapockense* in the Americas (Crosskey 1990). The larvae and pupae require rapidly flowing well-oxygenated streams and rivers to develop (Blacklock 1926). *Simulium* therefore in general tends to stay and feed close to the breeding sites (fast-flowing river bodies) where they lay their eggs. *S. damnosum*, however, can fly long distances over 400–500 km when assisted by winds. *Simulium damnosum s.l.* has a wide distribution in Africa and Yemen and is the most important vector of the disease. *S. neavei*, the aquatic stages of which are found on freshwater crabs, on the other hand, transmit *O. volvulus* in East Africa. The association of *S. neavei* and the

Fig. 2 Blackfly (*Simulium damnosum*) taking a blood meal (*TDR image library)*

freshwater crabs has been exploited successfully in the eradication of onchocerciasis transmitted by *S. neavei* from some foci in Kenya and Uganda in East Africa.

The vectorial capacity of the blackfly has been an important factor in the propagation of transmission in the different ecosystems. In this respect, blackfly vectors in the Americas are less efficient in transmitting the parasite than those in Africa. In Africa, the forest vectors are less efficient transmitters than the savannah blackflies. As a general rule, blackfly species are best adapted to transmit corresponding *O. volvulus* parasites from their original region (Duke et al. 1991).

Life Cycle

The life cycle of *O. volvulus* begins when an infected blackfly deposits *O. volvulus* larvae into the human host when it takes a blood meal. These larvae develop into "viviparous" mature adult worms in about a year, and the fertilized worms release mfs (unsheathed) into the skin some 10–15 months after infection. The mfs then migrate throughout the body in the dermal layer, from where they can be taken up by the blood-feeding blackflies. The mfs migrate from the blackfly's midgut through the hemocoel to the thoracic muscles. There the mfs develop into first-stage larvae (L1) and subsequently into third-stage infective larvae (L3). The third-stage infective larvae migrate to the blackfly's proboscis and can infect another human when the fly takes a blood meal, thus completing the life cycle of the parasite. Development of the mfs from the L1 larvae through L3 infective larvae spans a period of 10–12 days (Fig. 3).

Disease Presentation

Clinical Presentation

The clinical manifestations of onchocerciasis occur 1–3 years after infection, when the adult worms begin producing mfs. Three major clinical presentations are recognized. These are predominantly dermal, lymphatic, and ocular in character and are as

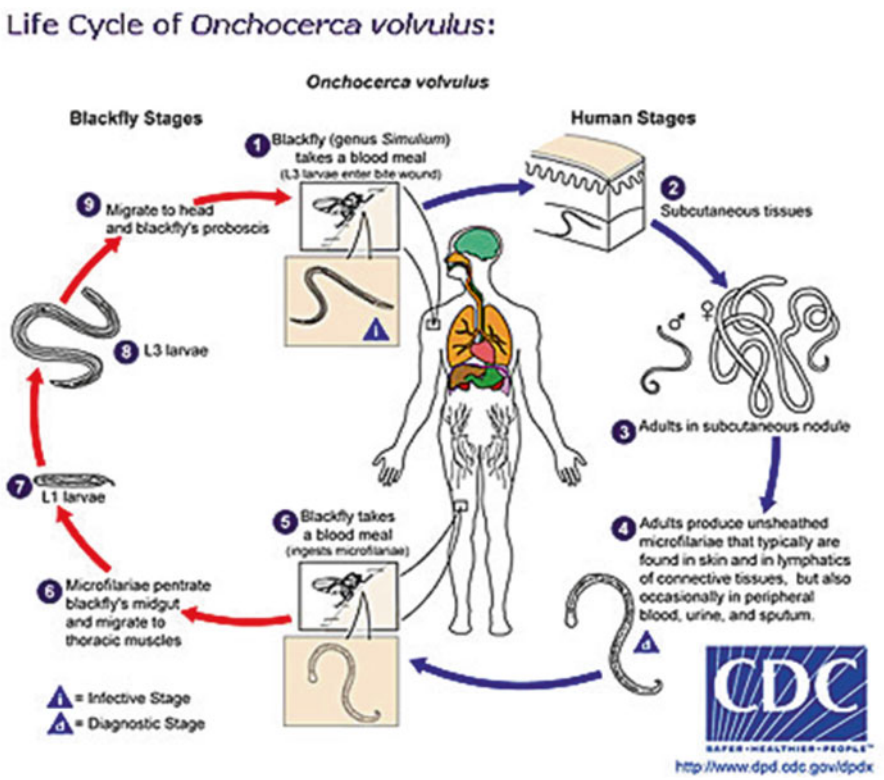


Fig. 3 Life cycle of onchocercal volvulus. CDC http.www.dcd.cdc.gov/dpdx

a result of host inflammatory reactions in the tissue to the dead microfilaria. Symptoms include severe itching, skin conditions including palpable nodules, and lymphatic involvement including lymphadenopathy, hanging groin, and lymphedema.

Dermal Lesions

The first signs that a person who has been infected with the *O. volvulus* parasite shows may include fever, neuralgic pain in joints, and transient rashes on the trunk (Fig. 4) and face. Some infected individuals may present with very intense itching. In others, there are disfiguring skin lesions which are a reaction to the intense skin irritation caused by the mfs. Severe "troublesome itching" is one of the most important symptoms of onchocerciasis (Brieger et al. 1998; WHO 1995b). This may affect more than 50 % of the populations in hyperendemic communities. In lightly infected persons, onchocerciasis skin lesions may present as acute onchodermatitis which is the most common symptom of the disease. Chronic onchodermatitis develops as a result of prolonged heavy microfilarial infection, and other skin manifestations – atrophy and depigmentation – do occur (Murdoch et al. 2002) (Fig. 5).

The clinical classification and grading system for onchocerciasis skin disease (OSD) was not clear until recently when Murdoch et al. (1993) instituted a system

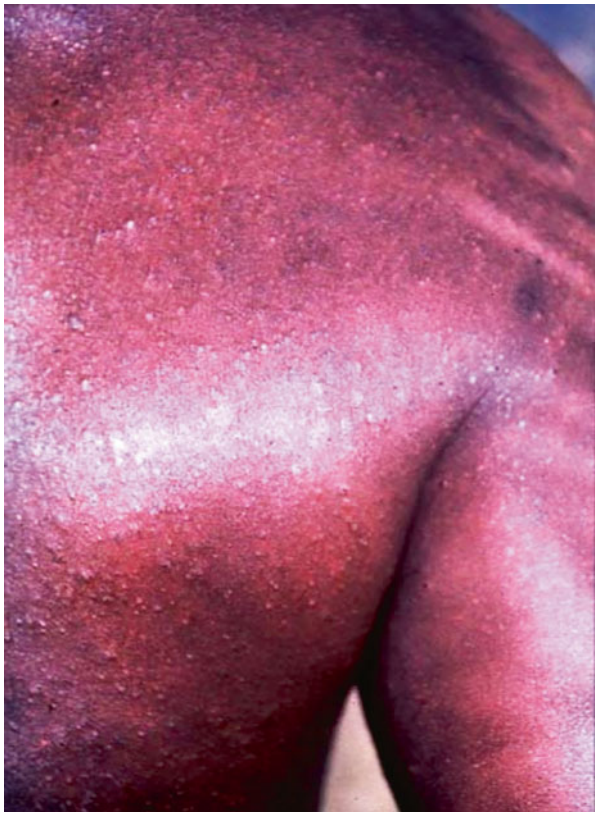


Fig. 4 Skin rash (acute papular onchodermatitis) (Source: www.stanford.edu)

which defines and provides appropriate descriptions of the skin changes and lesions associated with *O. volvulus* infection: acute papular onchodermatitis (APOD), chronic papular onchodermatitis (CPOD), lichenified onchodermatitis (LOD), skin atrophy (ATR), depigmentation (DPM, also known as leopard skin), troublesome itching (pruritus), and lymphatic involvement (LYM) plus hanging groin (HG). Murdoch's scheme has provided a platform for and the basis for comparisons in prevalence surveys, psychosocial and economic studies, and selection of clinical groups of patients for detailed immunological and genetic studies (Murdoch et al. 2010).

Ocular Lesions

Mfs migrate from the skin to enter the eyes where both dead and live mfs cause the ocular morbidity (Hall and Pearlman 1999; Pearlman and Hall 2000) and visual impairment, including permanent blindness. Visual loss from acute and chronic ocular disease of both the anterior segment (sclerosing keratitis and iridocyclitis) and posterior segments (optic nerve disease, optic atrophy, and choroidoretinitis) lesions occurs. Blindness appearing later in the disease is the most serious consequence of onchocerciasis (Dadzie et al. 1986). This may occur in one or both eyes (Fig. 6). Blindness due to onchocerciasis was

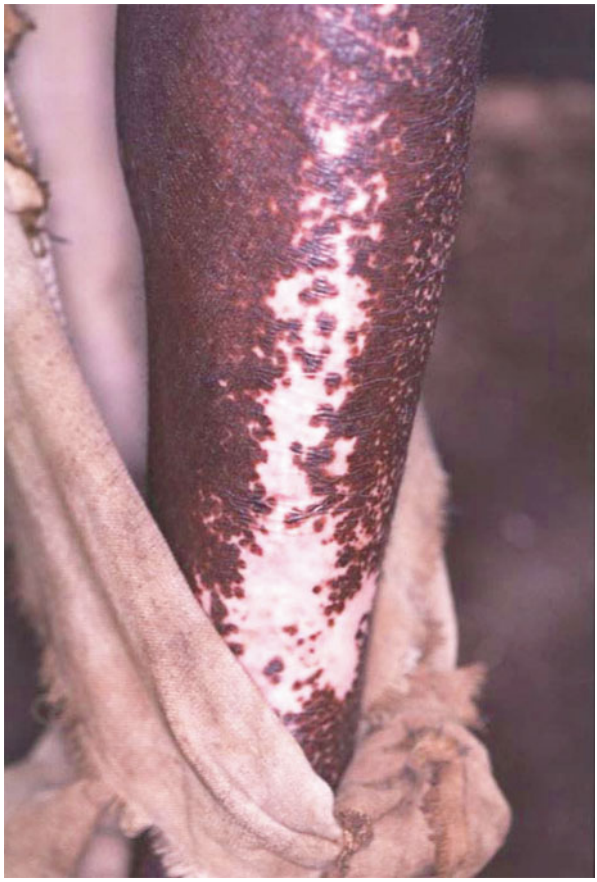


Fig. 5 Hypopigmentation (leopard skin) (TDR *image library*)

associated with the "proverbial" child leading his blind parent on a long stick, and acute onchocercal skin disease is progressively becoming scenes of the past, as control measures with ivermectin make a telling dent in the prevalence and incidence of the disease.

The severity of onchocercal ocular disease varies considerably between geographical zones. Blindness from onchocerciasis is extensive in hyperendemic populations in the West African savannah, while virtually no or little blindness is found in forest villages with a comparable intensity of infection. On the other hand, skin manifestations tend to be the main forms of disease in the forest areas. In Yemen and central Sudan, the major disease manifestation is Sowda, a pruritic skin condition affecting usually one limb. These differences may be attributed to the different vector–parasite complexes with strains of *O. volvulus* which differ in their pathogenicity (Zimmerman et al. 1992).

Other Manifestations

Systemic manifestations such as low body weight and diffuse musculoskeletal pain have been described. Some evidence suggests that onchocerciasis may present with neurohormonal involvement. Evidence also suggests that onchocerciasis is a risk

Fig. 6 Blindness from onchocerciasis (*TDR image library*)

factor for epilepsy (Druet-Cabanac et al. 1999; Pion et al. 2009) and may be responsible for a type of dwarfism (Kipp et al. 1996), hypo-sexual dwarfism (Nakalanga syndrome) in certain areas. A recent study investigated the association between onchocerciasis and increased risk of epilepsy and found that epilepsy prevalence increased, on average, by 0.4 % for each 10 % increase in onchocerciasis prevalence.

Immunity in Onchocerciasis

Onchocerciasis like other helminth infections tends to be long-lasting and shows high population prevalence. Part of the reason for this could be the fact that the onchocercal parasite has a long life span. It could also be due to the nature of the parasites in producing chronic and long-term infection through suppression of host immunity. Repeated infection in individuals living in the endemic areas results in cumulative infection which appears to drive the eventual symptoms and clinical manifestation. Studies on immunity in onchocerciasis have spanned several decades and have looked at both pre- and posttreatment immune conditions in onchoendemic communities. There is evidence of protective immunity in onchocerciasis, an assertion which is derived principally from the existence of noninfected individuals (endemic normals who are putatively immune (PI) living in endemic or

hyperendemic areas. Antibody and minimal cellular proliferative responses to parasite antigen reflect the systemic immune response of patients with onchocerciasis. Local and systemic immune mechanisms to contain inflammation (e.g., blocking antibodies, downregulating cytokines) are prominent in infected patients (Ottesen 1995). Soboslay et al. (1997) also showed that distinct states of *O. volvulus* infection correlate with a particular cellular and humoral immune response, while Elson et al. (1995) suggest that immunity to *Onchocerca volvulus* may in part be mediated by an antigen-specific Th I-type response. Additionally, concomitant protective immunity of infected humans prevents most of the newly acquired L3 infections from developing. Recent evidence suggests *Wolbachia* endobacteria (symbionts of arthropods and filarial nematodes) contain lipopolysaccharides that are released with the death of mfs and contribute to the inflammatory pathology associated with the disease (Taylor and Hoerauf 1999; Saint André et al. 2002; Taylor 2003; Taylor et al. 2005). A lot of progress has been made in understanding the nature of the immunity in onchocerciasis. More clarity is still needed with the host–parasite immune relationships, i.e., the type of protective immunity against onchocerciasis, given that the existence or induction of immunity in the treated, those that have been merely exposed, or infected individuals, could have an impact on long-term (drug treatment) control measures.

Geographical Distribution and Epidemiological Patterns

Onchocerciasis in Africa is found between latitudes 15° N and 14° S. It is present in Senegal in the west and in all the countries in between Ethiopia in the east and from Mali in the north to Malawi in the south (Map 1).

Geographical Distribution

The geographical distribution and the disease pattern of onchocerciasis vary between different zones. The vector–parasite complexes and clinical characteristics of the disease differ in a number of ways between the Latin American and the African infections as well as between geoclimatic zones within Africa and the Latin American foci (Duke 1981). These differences are attributable to parasite strains and their pathogenicity and the species of *Simulium* vectors, their biting behavior, flight range, and vectorial capacities.

Epidemiological Patterns of Disease

Two broad clinical–epidemiological patterns of the disease are present in Africa: blinding (savannah) and the non-blinding (forest). The savannah and rain forest forms of onchocerciasis both occur in West Africa and have been identified through

antigenic differences (Bryceson et al. 1976) and other immunological techniques (Lobos and Weiss 1985; Cianchi et al. 1985).

In general, the primary manifestations of onchocerciasis in the forest belts are of severe skin disease. In West Africa, blindness rates are significantly higher in savannah communities with mf prevalence of greater than 60 % (hyperendemic) compared to communities with similar prevalence in the rain forest (Anderson et al. 1976; Dadzie et al. 1989, 1990). In the most hyperendemic villages in the savannah areas, over 10 % of the population may be blind due to onchocerciasis. Without intervention more than 50 % of the total village population may become ultimately blind. In Central Africa, the pattern is less clear, with severe blinding as well as less blinding onchocerciasis occurring in both savannah and forest belts. Onchocercal skin disease is most prevalent in East Africa, while blindness due to onchocerciasis is rare (Brieger et al. 1998; WHO 1995b). Although onchocercal ocular disease and blindness are more prominent in savannah regions, onchodermatitis or onchocercal skin disease (OSD) has a higher prevalence in forest areas, possibly because of differences in *O. volvulus* strains. The importance of OSD as a contributor to the disease burden of onchocerciasis has been recognized relatively recently (Murdoch 2010) with troublesome itching accounting for 60 % of DALYs attributable to onchocerciasis.

Endemicity Levels and Severity of Disease

Onchocerciasis is a disease that largely manifests itself after many years of repeated infections (cumulative infections). How severe the disease is, therefore, depends on the intensity of infection, i.e., the level of mfs in the skin and elsewhere in the body, and the duration of infection. The location of the villages in which onchocerciasis is found is also very important. The closer the location to the rivers with blackfly breeding sites, the more important the disease is, in that virtually everybody above the age of 20 years will be infected and harbor dozens of adult worms that produce microfilariae. As one moves further away from the river, where the vector density is less, the prevalence and intensity of infection decline in relation to the distance to the vector breeding sites. Although the level of intensity of infection in an individual drives the manifestation of the diseases in the person, it is the community microfilaria load (CMFL) concept of a community level of infection, or level of endemicity, which is more important in the epidemiology of onchocerciasis and which becomes a very important monitoring factor in any control measure. In a control area where the drug, ivermectin (Mectizan®, Merck & Co.), is used, the CMFL in the community will fall faster than the prevalence of infection. There is also a linear relationship between the prevalence of onchocercal skin disease, eye disease, and blindness and the level of endemicity of the community. In the West African savannah, onchocerciasis becomes a major public health problem in hyperendemic communities which have a prevalence of infection greater than 60 % and the community microfilarial load (CMFL) exceeding ten microfilaria per skin snip (Remme et al. 2008). In such communities, blindness may affect more than 5 % of the population.

Such a situation is a threat to the survival of the village itself. It has been recognized that the fear of the disease has led to the depopulation of many fertile river valleys in the West African savannah. In this part of the world, onchocerciasis was therefore both an important public health problem and a major obstacle to socioeconomic development. Following many years of control effort in the West African savannah area, the high levels of blindness due to onchocerciasis are no longer encountered, due to the fact that children that were born after the control operations started were spared of the disease and its consequent blindness. Additionally the older people that were blind from onchocerciasis more often would have died out. This state of affairs has encouraged repopulation of hitherto desolate areas.

Disease Burden

Morbidity and Mortality

A combination of methods predominantly epidemiological (parasitological) surveys and more recently rapid epidemiological mapping (REMO) (nodule surveys) (Ngoumou et al. 1994) has been used to obtain the current estimates of onchocerciasis-infected people (Zoure et al. 2014; Noma et al. 2002). The estimates of mortality attributed to onchocerciasis were obtained from using demographic and retrospective data obtained from the Onchocerciasis Control Programme in West Africa (OCP) and Cameroon.

Putting all this together, it is estimated that worldwide, over 150 million people are at risk of acquiring *O. volvulus* infection of which over 99 % live in tropical Africa in some 30 countries. By the most current figures (2002), over 37 million people are estimated to be infected. The WHO Expert Committee on Onchocerciasis of 1995 put the infected at about 17.5 million. The current estimate of the infected is more than 10 years old. During this period, remarkable progress and impact have been made on the prevalence and incidence of the infection. Revision of the estimates of persons infected is therefore due.

The current estimate of disability-adjusted life years (DALYs) lost due to onchocerciasis is 1.49 million. Remme et al. (2006) recently revised this to three million. "Troublesome itching" now accounts for 60 % of DALYs attributable to onchocerciasis. Retrospective studies from the OCP suggested that the life expectancy of the blind was greatly reduced and that the mortality rate in blind adults on the average was three to four times greater than in the population who were fully sighted. More recent studies in the Cameroon also confirm that blindness gave rise to a significant increase in mortality among the blind. Detailed analysis of data from OCP showed that the excess mortality due to onchocerciasis was 0.05 deaths per years per thousands (Little et al. 2004). Additional analysis of the relationships between microfilarial load and blindness incidence and microfilarial load and excess human mortality has been investigated in the area covered during 1975 and 2002 by the OCP in West Africa with the conclusion that the excess relative risk of mortality is density dependent and more elevated in children.

Other Disease Burden

Patients with heavy microfilaria load may have infected lymph nodes which may lead to mild or generalized lymphadenopathy, hanging groin, and scrotal elephantiasis with hanging groin which could be a challenge for work in the peasants engaged almost exclusively in subsistence farming.

Onchocercal skin disease has been shown to be associated with a variety of psychosocial and economic effects. The disease also leads to stigmatization of affected persons and their families. Unsightly lesions from acute and chronic popular dermatitis limited the chances of adolescent girls finding marriage partners. Likewise negative sociocultural aspects of skin disease – people worried that skin disease would affect their ability to interact socially, fear of being ostracized, a feeling of low self-esteem, and children more likely to be distracted in school due to constant itching – have now been recognized.

In the post-control period in the original OCP areas, rapid repopulation of the areas that were previously abandoned for fear of the disease took place, with the consequent impact of population pressure on the environment. Controlled resettlement – with its economic dimensions at regulating the population resettlement in these oncho-free areas – had to be put in place as, for example, in countries like Burkina Faso and Ghana to ease this pressure.

Economic Impact

The constant and intense itching from onchocerciasis, the nuisance from the bites of the blackfly, and the impairment of vision due to the disease conspire to impact negatively on productivity, lead to diminished earnings, adversely affect supply of labor, and significantly reduce agricultural output. All these may result in the migration of communities away from fertile arable land for fear of acquiring the disease as well as the physical and psychosocial effects of the disease. On average persons that suffer from onchodermatitis have been found to spend an additional $8.10 over a 6-month period in comparison with their non-onchodermatitis counterparts from the same community and to spend an additional $6.75 seeking health care over the same period.

Diagnosis

Diagnosis of onchocerciasis is needed (a) for the diagnosis of the disease in individual patients, (b) to determine prevalence and endemicity of the disease over broad geographic areas for the planning of large-scale control programs such as in the OCP and APOC, (c) to assess impact of control measures, (d) to determine when to terminate mass drug administration (MDA), (e) for continued surveillance (Denery et al. 2010), and (f) for the purpose of validating the elimination of the disease.

Box 1
- Parasitological detection of microfilariae by skin biopsy
- Detection of microfilariae by ocular examination
- Detection of adult worm in subcutaneous nodules
- Skin test immediate hypersensitivity
- Delayed hypersensitivity
- Rapid diagnosis: nodule palpation
- Assessment of leopard skin
- Antibody detection complement fixation
- Passive hemagglutination
- Precipitation tests (gel diffusion)
- Indirect immunofluorescence
- Radioimmunoassay (RIA)
- Radioimmunoprecipitation
- Enzyme-linked immunosorbent assay [ELISA]
- Antigen/parasite gel diffusion product detection
- DNA probe PCR

Diagnosis of onchocerciasis is also required for specific epidemiological research including that for onchocercal infection in the blackfly vector and distinguishing between forest- and savannah-type infections. Parasitic diagnosis can, however, be difficult especially in light infections because of the limitations of the current diagnostic tools. Improved or new diagnostic tools which are very sensitive and highly specific are therefore required. Box 1 shows the various diagnostic tests for onchocerciasis, many of which are not used routinely.

Parasitological Diagnosis (Skin Snip Examination)

The demonstration of microfilariae in skin biopsies (WHO 1995) is the gold standard and definitive diagnosis of onchocerciasis (Vincent et al. 2000). It is the most appropriate for measuring the intensity of infection (Kale 1978). Parasitological examination of skin snip for *O. volvulus* is the most widely used diagnostic method. The test is carried out by taking skin snips from the right and left iliac crest using sterilized corneoscleral biopsy punches. The biopsies are placed in physiological saline at 37 °C and examined for the presence of microfilariae (mf) after 24-h incubation to confirm diagnosis. Emerging microfilariae are counted under a microscope. This technique has been fully described by Taylor and Green (1989). The motile mf may be counted under low-power microscopy, and the arithmetic mean of the mf skin density, expressed as numbers of microfilariae per mg, can then be determined (WHO 1987; Borsboom et al. 2003; Remme 2004; Ozoh et al. 2007;

Mas et al. 2006; Lipner et al. 2006). The mf count is also used to determine community microfilarial load (CMFL) by control programs (Remme et al. 1986).

Skin snips should be bloodless to avoid contaminating the snips with other blood-borne microfilariae, and disposable instruments are preferred where there is a risk of transmission of blood-borne pathogens. Repeated snipping because of the inconvenience is not popular in affected communities due to the pain it inflicts and because of the inconvenience (Boatin et al. 2002).

Microscopic demonstration of microfilariae is 100 % specific for onchocerciasis, but it has the following drawbacks: (a) too low a sensitivity to be useful in areas of low transmission or for monitoring drug efficacy (Udall 2007; Ayong et al. 2005; Vincent et al. 2000), or for detection of early disease with a small microfilarial load (Enk 2006); (b) invasiveness which limits its use in epidemiological surveys, because of high nonparticipation rate of people in endemic areas, which in the end could bias survey results (Tekle et al. 2012; Diawara et al. 2009) giving an underestimation of the disease risk or overestimation of the impact of a control program; (c) time-consuming in view of the nature of the disease which is found in remote areas "at the end of the road"; and (d) does not allow for the detection of prepatent infection, an important factor in the detection of reinfection post-vector control.

Skin Tests

There are two categories of skin tests based on examination of skin sensitivity to parasite which is the response to topically applied diethylcarbamazine citrate (DEC) – the "Mazzotti" patch test – and the examination of skin hypersensitivity in response to intradermal injection of parasite extracts. A positive Mazzotti (1948a) test is the presence of local pruritus and a papular rash under the patch. This test gave a 92 % positive reaction in microfilariae-positive individuals in the Sudan (Stingl et al. 1984). It has been used in the OCP area in West Africa to follow up on the transmission of *O. volvulus* in areas where the disease had been eliminated by vector control (Toe et al. 2000; Ozoh et al. 2007). The DEC patch test is very effective for detection of infection in children aged less than 15 years and can therefore be very useful for detecting recrudescence of infection in areas in which infection is believed to have been eliminated within the APOC area. It is therefore also a welcome advantage as it provides a noninvasive alternative to the skin snip although the latter remains the most suitable for accurate diagnosis (Boatin et al. 2002).

A new DEC patch (a transdermal application) was developed by TDR in collaboration with Lohmann Therapy System (LTS), Germany – the LTS-2 – with the purpose of improving on the reliability and standardization of the DEC patch test and for ease of use (TDR 2008). The LTS-2 test has proved from field trials in Mali and Senegal in 2008 to be a simple and noninvasive surveillance tool and highly specific in the onchocerciasis foci in West Africa, for early detection of recrudescence of transmission and infection in an area of low prevalence of infection. The two main operational challenges of DEC patch test are a failure of some people to return to have their patch examined post-application and some patches partially or completely being detached before they could be examined (Diawara et al. 2009). Other major

problems associated with the test are that of nonspecificity and cross-reactions which occur in individuals with other filariases due to the extensive antigenic similarity between these species of filarial worms. Where prevalence is low, PCR and DEC patch are more sensitive than skin snip, and the DEC patch provides a good alternative to skin snip alone in low prevalence areas (Boatin et al. 2002). It may however be hampered by varying degrees of sensitivity in different geographic areas.

Nodule Palpation: Detection of the Adult Worm

Adult worms are readily detectable by the presence of palpable nodules in infected patients. The discovery of a coil of hairlike white worms in an excised subcutaneous or intramuscular nodule in the appropriate epidemiologic setting is diagnostic of onchocerciasis on visual inspection. Most nodules have only three to five adults in them and less in hypoendemic areas. However, nodules containing as many as 50 adult worms have been found and liberated from the tissue by collagenase digestion.

The prevalence of onchocercal nodules in adult males, identified through simple nodule palpation at specified parts of the body, has also been shown to be reliable for community diagnosis of onchocerciasis (Whitword et al. 1999) although nodule palpation alone is too labor intensive to be enough to manage mass drug distribution programs (Remme 2004). Mass distribution programs need simpler and noninvasive methods to determine the population at high risk and those that require mass treatment with ivermectin (Edungbola et al. 1987). The rapid epidemiological mapping of onchocerciasis (REMO) tool developed by TDR and OCP as a simple and rapid test to determine communities at risk of onchocerciasis and requiring mass treatment (Ngoumou et al. 1994); Noma et al. 2002) has been an answer to this requirement, and it has been used extensively to map the distribution of onchocerciasis in APOC countries and target treatment to areas where the disease burden is high (Noma et al. 2002; Gemade et al. 1998; Mace et al. 1977).

Frequently there are additional nodules that are deeper and more difficult to detect. These conditions may lead to a substantial underestimation of nodules in women who have more subcutaneous fat and may have inhibitions about having a full examination. Nodules appear to have "preferred sites" that can vary according to geographical location.

A limitation of REMO is that (a) it uses nodule palpation which has poor sensitivity and specificity in low prevalence communities (Table 1); (b) nodule palpation provides little information about the state of the adult worm, which is of particular interest regarding effects of drugs on the adult worm in drug trials; and (c) subcutaneous nodules may not always be palpable and other types of nodular tissue such as lipomas, lymph nodes, and cysts can frequently be mistaken to be of onchocercal origin. The limitations notwithstanding REMO surveys have generated important database on the geographical distribution of onchocerciasis for more than 14,000 villages in sub-Saharan Africa, between 1997 and 2010 (WHO/APOC) with a good geographic coverage of all endemic areas in the 19 APOC countries, a useful data also for delineation of transmission zones (WHO 2010).

Table 1 Comparison of available diagnostic technique

Test	Specificity	Sensitivity	*Ochengi* interferes	Throughput	Cost	Application
Skin snip	–>100 %	Low	No	Low	Low	Field
Nodule palpation	Moderate	Low	No	High	Low	Field
Skin PCR	–>100 %	–>100 %	No	Low	High	Laboratory
Scratch PCR	–>100 %	–>100 %	No	Low	High	Laboratory
DEC patch	Variable	variable	No	Low	Low	Field
Ov16 ELISA	–>100 %	+60 (%)	???	High	Medium	Laboratory
Fly dissection	Low	Low	Yes	Low	Medium	Field
Pool screen PCR	–>100 %	–>100 %	No	High	Varies	Laboratory

Adapted from WHO/APOC meeting on feasibility of onchocerciasis elimination consultation, 2009

Other Diagnostic Tests

Slit Lamp Technique

Microfilariae can be observed directly using the slit lamp as they migrate into the anterior chamber of the eye (Enk 2006), and the examination allows the microfilarial load in the eye to be determined. The slit lamp technique has high specificity, but it is less commonly used for epidemiological purposes or by control programs as it requires expensive equipment and skilled personnel to perform it.

Ultrasound Examination

Adult worms in suspected nodules may be detected through ultrasound (Homeida et al. 1986; Poltera et al. 1987), but this has not yet been fully tested.

Immunological Tests

Antibody response to onchocercal infection could be detected in infected humans at 3 months and at more than 12 months, before parasitological detectable infection (Lobos et al. 1991a). This observation would make a viable immunological test a useful tool for control and elimination programs.

Immunological diagnostic tests are based on the detection of antibodies specific to filarial helminths in infected patients or, more recently, to detection of the antigen. Some of these tests, such as complement fixation tests, have been available for many years but have now been replaced by more sensitive enzyme-linked immunosorbent assay (ELISA) tests. The most common antigen used to stimulate an immune response has been from an extract of *Dirofilaria immitis*.

The limitations of immunological tests for *O. volvulus* include cross-reactivity with other filarial parasite species and non-filarial helminth infections. While being a highly sensitive tool (Table 1), antibodies persist in persons who are no longer infected with living parasites. This limitation restricts the use of a number of immunodiagnostic tests largely to people coming into an area from a non-endemic area and are therefore be presumed to be seronegative. It is not yet in use as a surveillance tool on a large scale by control programs.

Detection of Parasite Antibody in Body Fluids

These tests detect antibody bound to a parasite extract and can be visualized using a secondary antibody conjugated to a radioisotope (radioimmunoassay) or an enzyme (ELISA test).

Antigen Detection Tests

A difficulty with antigen detection tests is that antigens from filarial helminths are commonly cross-reactive and therefore of low specificity (Cabrera and Parkhouse 1986) necessitating need for extracts of the parasite that are species specific. ELISA-based assays are more sensitive than the skin snip and may therefore be useful for detecting early infections in young children born after control has taken place and could also serve as a warning sign for recrudescence.

Monoclonal antibodies have been used to define onchocercal specific antigens for diagnostic purposes. Promising results have been obtained but such tests are not yet available in a suitable form for field use. The use of monoclonal antibodies provides one advantage as they can be reliably produced in sufficient quantities with reproducible quality. The advent of recombinant DNA technology allows cloned antigens to be produced in sufficient quantities to overcome these problems.

Recombinant Antigens

Recombinant DNA technology may make the use of recombinant antigens more feasible for diagnosis of onchocerciasis; however, the difficulty of distinguishing between past and current infections remains a big challenge.

Detection of Parasite Antigen in Body Fluids

The detection of parasite products in the circulation or other body fluids such as urine provides conclusive evidence of an ongoing infection. The development of successful antigen detection assays for onchocerciasis has however proven technically difficult.

Immunodiagnosis

Diagnostic tests using recombinant filarial antigens have recently been developed, but their usefulness is limited by their inability to distinguish between current and past infections with sufficient reliability. Immunodiagnostic tests that are capable of detecting early infections have also been developed to identify new infections previously in areas under vector control in the OCP area, but they are considered as a tool for onchocerciasis surveillance (Lipner et al. 2006). The polymerase chain reaction (PCR) seems the most useful for operational large-scale control.

Polymerase Chain Reaction (PCR) Tests

Definitive diagnosis of *O. volvulus* infection requires the identification of the parasite in either the skin or subcutaneous nodules, but the gold standard parasitological method of examination of skin biopsies has the limitation of poor sensitivity (see Table 1). The polymerase chain reaction-based (PCR) assay is significantly more sensitive than skin snips and nodule palpation (Lustigman and Abraham 2009) and overcomes many deficiencies of parasitological and serological methods in diagnosing active disease conditions. The PCR technique uses species-specific probes for the "Oncho-150" repeat to diagnose *O. volvulus* infection by detecting parasite DNA in routine skin snips (Lustigman and Abraham 2009). It increases the sensitivity of DNA tests and the detection of low-level infections compared to the classic skin snip examination. The PCR assay is also used for pool screening of blackflies for surveillance of control measures, by identifying *O. volvulus* infections in the blackfly or the human host (Pischke et al. 2002; Rodriguez-Perez et al. 2006). By amplifying the DNA, PCR assays can be sensitive enough to allow a single infective larva or microfilaria to be identified using DNA probes (Meredith et al. 1991). The PCR assay is limited by its (a) lack of quantification of skin microfilariae and (b) requirement for considerable laboratory infrastructure too complex for routine use.

Ov16 ELISA

The Ov16 ELISA assay has high specificity and throughput (Table 1). This assay uses a recombinant antigen of *O. volvulus* to measure the prevalence of immunoglobulin G4 (IgG4) antibodies (Lobos et al. 1991a, b). The test is applied to a population sample of children less than 10 years old, born after the control measures commenced and presumably have not been infected. This test is designed to exclude a prevalence of 0.1 % based on assumptions and calculations described by Diawara et al. (2009).

The OV16 antigen has been used for this purpose in Sudan (Higazi et al. 2013) and Uganda. Although a previously described antibody test using a recombinant *O. volvulus* protein – Ov16 – is effective, it fundamentally cannot make a distinction between current and historical infections.

PATH in collaboration with APOC and funding from Bill and Melinda Gates Foundation is developing a rapid test for onchocerciasis. The technique relies on the detection of antibodies to the parasite antigen Ov16 in whole blood specimen. The test prototypes developed have passed performance evaluation in the USA. The researchers incorporated users' feedback into the design of next prototype. PATH has advanced the evaluation of the Ov16 rapid test in collaboration with APOC and researchers. The expected advantages of the Ov16 rapid test over other diagnostic tools include low cost, rapid results, ability to detect early infections, minimum training requirements, and only finger pricks needed to collect blood samples for analysis. If the current effort is successful, the Ov16 rapid test will be very useful for post-elimination monitoring of communities treated with ivermectin for many years and monitoring recrudescence of onchocerciasis infection.

DNA Tests

Among the more recent developments has been progress made toward producing probes for the detection of parasite DNA. DNA probe-based assays rely on the detection of specific sequences in the parasite's genome and not the host's response to the presence of the parasite. This means that a DNA probe-based assay cannot be used for some important applications for which an antibody-based assay is well suited, such as in detecting prepatent infections.

DNA Diagnosis of Individual Patients

Detection of parasite DNA in routine skin snips by PCR amplification of O-150, an *O. volvulus*-specific 150-bp repeated genomic DNA family, is one of the most sensitive techniques for detecting low-level infections in individual patients. A challenge with DNA probes as with other molecular techniques is to produce tests suitable for field use, as at present these tests are only suitable for research use in laboratories. There are also questions regarding the persistence and distribution of parasite DNA in the skin after ivermectin treatment has been used or after the natural death of that adult worm as this could limit the usefulness of the test.

Challenges for Appropriate Diagnostic Tools

Though onchocerciasis has a relatively well-defined distribution, there are overlapping clinical symptoms with other filarial parasites such as *Mansonella streptocerca*, *Mansonella perstans*, *M. ozzardi*, and *Loa loa* that it may be coendemic with. Differentiating onchocercomas from lipomas, fibromas, lymph nodes, cysticerci, dermoid cysts, foreign body granulomas, and ganglia can therefore be challenging.

In some areas, onchocercal chorioretinitis needs to be differentiated from choroiditis due to tuberculosis, optic neuropathy caused by primary glaucoma, or nutritional optic atrophy. For these reasons and because of overlaps, a reliable differential diagnostic technique is required for making clinical distinctions with other conditions. While antigen tests could provide effective differential diagnosis, they are not yet sufficiently sensitive or easily used under field conditions.

Establishing new tools capable of identifying presence of recrudescence is another challenge especially in the OCP countries. The (DEC) patch skin test has shown promising results and is currently being developed to replace the skin snip in former OCP areas. A rapid antigen detection test, similar to that used for diagnosis of lymphatic filariasis, would be preferable as it would detect active infections (Richards et al. 2001).

The challenges regarding diagnostics for onchocerciasis at present include the need for a field-accessible, specific, and sensitive diagnostic tool for detecting current infections; a diagnostic tool that can be used to assess the elimination status in transmission zones by monitoring the interruption of transmission.

Treatment

The management of onchocerciasis posed a considerable challenge in the past when the only drugs available for use were suramin and diethylcarbamazine. Suramin is a macrofilaricide (Ashburn et al. 1949) which has to be given by injection for several weeks. It is also toxic, causing damage to the kidneys. Although it has been used in limited mass treatment (Dawood 1978; Rougemont et al. 1980, 1984), there is hardly any place, presently, for its use in the treatment of onchocerciasis (Awadzi et al. 1995). The piperazine derivative diethylcarbamazine (DEC), however, has only a microfilaricidal action. This drug was used before not only for treatment but also to aid individual diagnosis – the so-called Mazzotti reaction (Mazzotti 1948b). The intense pruritus and severe reactions ("Mazzotti reaction") of fever, headache, rash, and edema and the possibility of causing advance onchocercal eye disease which could lead to irreversible ocular damage also limited the use of DEC in the individual and on a large scale (Awadzi and Gilles 1980). These two drugs are therefore no longer recommended for the treatment of onchocerciasis (WHO 2001a, 1995a).

Ivermectin (Mectizan®)

Ivermectin (Mectizan®, Merck & Co.) is currently the drug of choice for the treatment of onchocerciasis. It is a semisynthetic macrocyclic lactone derived from *Streptomyces avermitilis* which was registered for the treatment of human onchocerciasis in October 1987 in France. Ivermectin is safe and effective when given orally at the standard dose of 150 mcg/kg body weight (Brown and Neu 1990). A single dose provides long-lasting suppression of microfilaridermia (Greene et al. 1985) making it suitable for community-based distribution. It is also currently the only microfilaricide which is

suitable for large-scale onchocerciasis treatment (Awadzi et al. 1985; De Sole et al. 1989; Remme et al. 1989; Prodhon et al. 1991; Witworth et al. 1991; Collins et al. 1992). Ivermectin has mild adverse effects which are non-ocular (Brown and Neu 1990).

Effect of Ivermectin on the *Onchocerca* Parasite

As a microfilaricide ivermectin helps to suppress the skin microfilaria. What seems to be generally accepted is that ivermectin blocks the adult female uterus therefore affecting reproduction of mfs. Plaisier et al. (1995) suggest an irreversible decline in female adult worm microfilaria production by about 30 % per treatment. Although this assertion is up for argument and discussion (Turner et al. 2013), it would suggest that if this is the case, then repeated treatment may ultimately sterilize the adult worms provided there are no new infections. Gardon et al. (2002) report from their study that persistent three monthly treatments with ivermectin would seem to kill more worms than annual treatments. Current findings (Diawara et al. 2009) also suggest that long-term repeat ivermectin treatment seems to have eliminated the infection from certain foci.

Given that ivermectin is currently the only suitable drug for large-scale treatment of onchocerciasis, it is only prudent that other drugs that could replace and/or serve as adjunct to ivermectin be explored: (a) in the event of ivermectin resistance developing and (b) a macrofilaricide which could eliminate the adult worm, help reduce the duration of treatment, and facilitate the prospects for the elimination of onchocerciasis. Currently no macrofilaricidal drugs with efficacy after one or two doses are available for use against onchocerciasis (Mackenzie and Geary 2011). Doxycycline when given in a daily dose regimen over several weeks sterilizes and kills adult stages of onchocerciasis, but the practicality of routine field use of such a drug remains a concern. Additionally, doxycycline is contraindicated in children under 8 years old and in pregnant and breastfeeding women who could limit its use on a large scale.

Other drugs that are receiving attention for the treatment of onchocerciasis are moxidectin, a macrocyclic lactone, which is currently in clinical trials for onchocerciasis and flubendazole, an injectable benzimidazole drug which is known to be effective against onchocerciasis. More research is called for an oral and more acceptable formulation of flubendazole to make it amenable for large-scale use in onchocerciasis control.

Doxycycline and Other Antibiotics

Wolbachia endobacteria which are symbionts of arthropods and filarial nematodes including onchocerciasis seem to be essential for the fertility of *O. volvulus*. Studies that were carried out in Ghana by Hoerauf et al. (2000, 2001) showed that treatment of *O. volvulus*-infected individuals with doxycycline at 100 mg daily for 6 weeks resulted in an almost complete depletion of *Wolbachia* by the 11th month. The study also showed the inhibition of embryogenesis in female *O. volvulus* resulting in an apparent permanent elimination of skin mfs. These encouraging results have

generated enthusiasm for considering *Wolbachia* endobacteria as targets for the treatment of onchocerciasis. The question of the feasibility of use of doxycycline in the field condition given the long duration (6 weeks) for treatment with the drug has been explored in one study by Wanji et al. (2009) where it was shown that community distributors of doxycycline obtained good coverage and compliance in areas endemic for both onchocerciasis and loiasis.

Discovery of additional drugs (antibiotics) which are active against *Wolbachia* without the contraindications in the use of doxycylines or other products with a shorter course of treatment is a priority.

Moxidectin

Moxidectin, a milbemycin compound, has a similar chemical structure to ivermectin. Although it has not been proven to be macrofilaricidal, studies by Trees et al. (2000) have shown that it can induce sustained abrogation of embryogenesis in filarial animal models. The attraction to moxidectin stems from the suggestion that when given as a single dose, it may have a similar but longer duration of action than ivermectin with a prospect of being useful in interrupting transmission. The drug is already in use in animal health and is currently undergoing clinical trials for possible use in humans for onchocerciasis treatment. Research still needs to be carried out to ascertain if it will have advantages relative to ivermectin for onchocerciasis control. Although moxidectin has been used successfully in animal health when there has been ivermectin resistance, it is unclear if moxidectin will be effective against onchocerciasis in the event of ivermectin resistance in humans.

Vaccines

Although ivermectin has been used very successfully and effectively against onchocerciasis, it has been mainly microfilaricidal and requires to be given for a long time. A search for a macrofilaricide which could eliminate the adult worm and subsequently reduce the duration of treatment is required. However, an effective vaccine in the arsenal against onchocerciasis would be an important addition given that effective vaccines are still the most economical and efficient tools to control infectious diseases. An effective vaccine could also greatly assist with the realization of the goal to eliminate onchocerciasis. Development of an effective vaccine against onchocerciasis has been the focus of a research program that was supported by the Edna McConnell Clark Foundation from 1985 to 1999 (Lustigman et al. 2002), and three recombinant antigens capable of inducing protective immunity to *O. volvulus* have been identified (Abraham et al. 2001). A lot of emphasis has been put on the effort to find a macrofilaricide against onchocerciasis; however, the interest in vaccine development against onchocerciasis has been rekindled lately, and a further support of these activities will be in order (Lustigman and Abraham 2009).

Interventions in Onchocerciasis in Africa

Efforts to eliminate onchocerciasis as a disease of public health importance have been through vector control (1974–2002) and drug treatment (1987 till the present). More recently, there is a growing evidence that with the available drug (ivermectin) treatment, it has been possible to eliminate onchocerciasis altogether in the Colombia focus in Latin America with a push to achieve elimination in all the foci in that region. In Africa a similar picture of possible elimination of onchocerciasis in some foci is emerging. In 2012, Uganda and Sudan announced they had interrupted river blindness transmission in key endemic area. The findings of Diawara et al. (2009) (in the West Africa focus) and the growing evidence of elimination from several other foci (APOC) give much optimism that given the right approach in the use of the current tool, elimination of onchocerciasis from a large part of Africa could be a reality.

The two approaches that have been used for the control of onchocerciasis in Africa are vector control (through larviciding) and drug treatment (mass drug administration).

Vector Control (Historical Control Efforts)

Many efforts have been used in the past both in Africa and Latin America to control onchocerciasis through an attack on the vector. A catalogue of such efforts is:

- In the Chiapas focus in Mexico, this involved clearing vegetation and applying plant extracts, Paris green, and creosote to the vector breeding sites. This attempt was unsuccessful.
- In Africa, *S. neavei* and onchocerciasis were successfully eradicated from a very small focus, Riana focus, in Kenya by simply clearing riverine forest.
- Wide availability of DDT ushered in new campaigns against blackflies that succeeded in eradicating *S. neavei* from the Kodera Valley in Kenya.
- Ghana started vector control on a small scale beginning in the Upper East Region of the country in the Black Volta valley and later in the Lower Volta valley in the south, the latter to protect the workers at the Akosombo hydroelectric dam construction site.
- During the 1960s, the Institut français de Recherche scientifique pour le Développement en Coopération (ORSTOM), previously, Office de Recherche scientifique et technique Outre-Mer, and the Organisation de Coordination et de Coopération pour la Lutte contre les Grandes Endémies (OCCGE) carried out a series of vector control studies in Ivory Coast, Burkina Faso, and Mali.
- Other early control efforts took place on the Comoé River in Burkina Faso and the Farako area of southeast Mali.

Ground Larviciding

Ground larviciding is effective in small, easy to reach river basins and is less costly than aerial larviciding for control. This was tried with DDT in a limited area (200 km^2) in Guatemala, but although the larvae of the fly were eliminated in the treated streams, the impact on the fly population was disappointing. Similarly, in Mexico, ground larviciding was practiced for about 6 years and then abandoned because it was deemed rather labor intensive. In Africa, *S. neavei* was successfully eradicated from the Kodera valley in Kenya through wide ground application of DDT. Ground larviciding has also been used successfully in small river basins for nuisance control and for the protection for personnel in the agricultural industry. More recently, ground larviciding has been used successfully in Uganda through the auspices of APOC and the Ugandan government. In very small foci and where the vector has been confirmed to be *S. neavei*, it would be profitable to undertake ground larviciding. This approach will eliminate the vector in such a focus within a short time (2–3 years) and the disease altogether in a time frame, shorter than drug treatment will.

Aerial Larviciding (Large-Scale Vector Control)

The most comprehensive and extensive approach to the control of onchocerciasis and its elimination as a disease of public health importance in West Africa was by the Onchocerciasis Control Programme of West Africa (OCP) which was launched in 1974. This initially covered seven countries, Benin, Ghana, Côte d'Ivoire, Mali, Niger, Togo, and Burkina Faso, which later included the so-called extension areas of Guinea-Conakry, Guinea-Bissau, Senegal, and Sierra Leone. The program ran from 1974 to 2002 using larviciding (both ground and aerial) to control the vector. The objective of vector control was to interrupt transmission of the parasite, *Onchocerca volvulus*, for sufficiently long period of time to allow the human reservoir of the parasite to die out. Weekly aerial larviciding and where feasible ground larviciding were used in the river courses at which the *Simulium* vector was attacked at the larval stage. Larvicides that were used included temephos (AgrEvo, France), a cheap and efficient organophosphorous insecticide with insignificant impact on nontarget fauna, pyrethroids, and biological *Bacillus thuringiensis* serotype H14–*B.t. H14* and other organophosphorous. These insecticides were used in rotation taking the river flow into account (Guillet et al. 1995) to restrict emergence of insecticide resistance in vectors, to minimize adverse impact on nontarget organisms, and to have a cost-effective approach to the activity. The duration of larviciding was initially planned to last for a period of 20 years, but this period was reduced to 14 years when larviciding was combined with ivermectin treatment, a change that was informed by output from model predictions. Aerial larviciding as a mode of control however is relatively costly because of the heavy infrastructure, logistics, and insecticides that are required.

The impact of vector control in the OCP area has been well documented in several publications and reports. The salient features following vector control were (a) the rapid decline of human infection prevalence after 5–6 years into larviciding and

(b) absence of new infections in the areas concerned, indicating interruption of transmission. The effectiveness of larviciding in the OCP was assessed through periodic entomological and parasitological evaluations and the impact on morbidity (eye disease) as compared to baseline data. Vector control achieved a virtual interruption of transmission as observed in the zero annual transmission potentials (ATPs) recorded at the fly catching points. This was observed in most parts of the original OCP area with the exception of a few isolated foci. Similarly, the CMFLs declined in a linear manner reaching virtually zero after 10 years of control, followed by the predicted and accelerated fall in the prevalence of infection as predicted using the ONCHOSIM simulation model. The incidence of infection in children, a surrogate measure for new infections, was reduced by 100 %. Ocular onchocerciasis became rare in the area. Any lesions found now are in the elderly from earlier infection, and the incidence of eye lesions due to onchocerciasis is nil in children born since the program began in 1975. Other post-control indices show that (a) more than 40 million people in the 11 OCP countries are now considered free from infection and eye lesions, (b) more than 1.5 million people are no longer infected, and (c) more than 600,000 cases of blindness have been prevented. Sixteen million children born since the program began are free of onchocerciasis. The socioeconomic impact has also been dramatic: 25 million hectares of fertile land in the river valleys were made available for resettlement and agriculture (Remme et al. 2008).

To maintain the achievements of the control program, the primary objective should be effective epidemiological surveillance to detect early infection and control disease recurrence. The OCP operated almost solely as a vertical program until the control activities were devolved to the participating countries. The countries have made efforts to integrate the epidemiological surveillance activities into other ongoing activities in the countries. This strategy of integrated surveillance activities is vital for sustainability of post-control surveillance of onchocerciasis.

Current Control and Elimination Strategies

The donation of ivermectin (Mectizan®, Merck & Co), the drug of choice for the control of onchocerciasis, led to the evolution of innovative distribution mechanisms. Ivermectin mass chemotherapy was introduced following its discovery as an anti-helminthic drug and its donation by the manufacturers, Merck & Co, for as long as it is needed. At the onset (following its donation), ivermectin complemented vector control but gradually became the only cost-effective tool (Crump et al. 2012; Cheke and Garms 2013) for the control of onchocerciasis in Latin America, Yemen, and sub-Saharan Africa and has proven effective tool by the recent declaration of the elimination of onchocerciasis in Columbia (PAHO June 2013). Distribution of ivermectin in most endemic areas is annual in Africa, biannual in the Americas, and recently, a few projects in Africa have begun twice-yearly treatments to accelerate the elimination of the disease (Abiose et al. 2000; Sauerbrey 2008; WHO/APOC 2009).

Mobile Distribution

The mobile distribution method was the first strategy used when ivermectin became available for mass treatment in 1988. The mobile teams were made up of trained health workers who visited communities in a military-like fashion, called on the community leader, and informed the leader about the date for the distribution of ivermectin to eligible community members. Ivermectin distributions were carried out by the teams and they monitored for serious adverse events (Meredith et al. 2012). Mobile distribution by the OCP was very efficient and kept unrivalled good records of treatments; however, maintaining consistent high coverage was considered problematic since only members of the community available at the time of the team's visit benefited from the treatment, and inaccessible villages could be missed out. Mobile distribution method was unsustainable largely due to high personnel and logistic costs (Meredith et al. 2012).

Community-Based Treatment with Ivermectin (CBTi)

The community-based treatment with ivermectin (CBTi) was introduced to improve access of remote populations to ivermectin, coverage, cost-effectiveness, and sustainability (Remme 2004). In CBIT, health workers mobilize and inform the community of the processes of drug distribution that had to be undertaken and ensure that community members undertake the required activities under their supervision (Crump et al. 2012). Community members, selected by the community leader or the health workers, distribute the drug supervised by health workers. Ivermectin for those eligible individuals who were not available at the time of distribution is sometimes kept with the drug distributor for a limited period and given to health workers when they return. However, the communities were not allowed to make any modifications to the processes or decisions on the activities. They simply carried out what they had been instructed to do.

Community-Directed Treatment with Ivermectin (CDTi)

To address the challenges of access and coverage, in sub-Saharan Africa, where health systems lack structures in remote rural areas, the TDR Task Force for Onchocerciasis Operational Research launched a multi-country study on community-directed treatment with ivermectin (CDTi) in 1995. The search for a more sustainable and cost-effective strategy resulted in the CDTi strategy. The results showed great promise – that communities can plan and implement drug distributions – achieving and sustaining high treatment coverage (WHO/TDR 2008, 2010). The CDTi was adopted as the principal strategy for the control of onchocerciasis by the Joint Action Forum, the governing body of the African Programme for onchocerciasis control (APOC) in 1997 (Amazigo et al. 2012).

CDTi, also called community-directed intervention (CDI) strategy, is a bottom-up initiative to public health-care delivery that empowers communities to take care

of their own health. Under the community-directed intervention (CDI), health workers approach a community to discuss the health and socioeconomic consequences for an individual and community at large of a particular disease and the means of controlling it. The community is informed about the availability of donated medicines. The health workers respect the traditions of the community as well as the leadership structure and take note of important members and community groups that are likely allies in achieving community ownership of control strategies and tools.

Health workers and other partners jointly schedule visits to the communities, and trusting an old saying, the villagers "may know less, but they understand more," and provided with access to the tools and knowledge that they lack, they often exceed our expectations of them. Hence, at scheduled meetings with community leaders and members, the health workers explain the importance of building a partnership between the community and health providers; they define the roles and responsibilities of external partners. In these meetings, community members understand they have the authority to make collective decisions – selection of drug distributors, changing and appointing new distributors. The community assumes the responsibility for the planning and management of the distribution of drugs under the guidance and supervision of health professionals. The community holds meetings and decides the period and mode of distribution (house to house or distribution from a central place) and collection of drugs from the nearest health facility.

Without external interference, community members select community-directed distributors (CDDs) from among their rank. Experiences of countries have shown that when given the authority to make such decisions, communities select peers, who they trust will deliver the drugs. The health workers and NGO personnel train the CDDs on census taking of households, treatment eligibility, exclusion criteria, and storage and safety of drugs as appropriate. The drug distributors are trained also to treat minor side effects, referrals of severe adverse effects, and record keeping (WHO 2010).

During training, health workers emphasize the importance, to individual and community health, of accurate recording of the number of eligible persons treated, refusals and ineligibles, timely (Amazigo 1999) reporting back to the health staff, and the return of unused ivermectin. The community-directed distributors are retrained every year in the first 3 years, and new CDDs selected by the community are trained. This reduces the gap from attrition. The community is encouraged to take on the responsibility of reviewing the success of administration of ivermectin, motivation of distributors, and collection of drug supplies, through community self-monitoring (CSM). The CSM is carried out 1–3 months after distribution, and community report on how to improve the next treatment is provided to the health services.

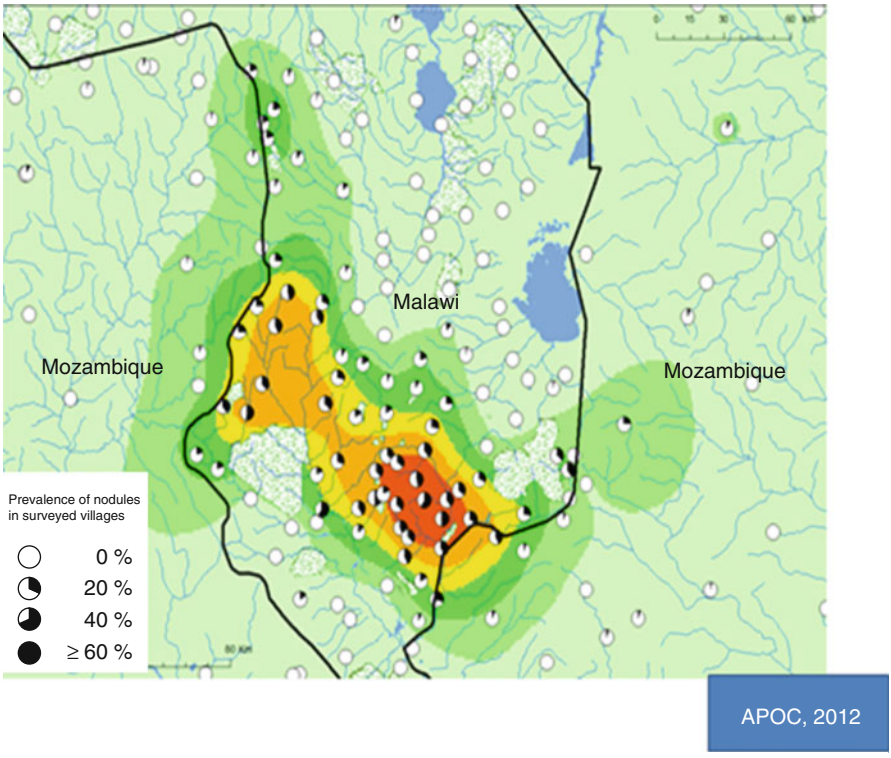
As a major contribution, CDTi has built local capacity, strengthened weak health systems, and has proven effective for the delivery of multiple health interventions such as distribution of insecticide-treated bed nets, home management of malaria and vitamin A supplementation, and distribution of other antifilarial drugs such as albendazole and Zithromax (Mutalemwa et al. 2009; Meredith et al. 2012). The CDTi empowers the communities to own, plan, and implement distribution programs that are sustainable and have been adopted by countries for the control of other neglected tropical diseases. The CDTi strategy has been shown to be a feasible and cost-effective approach for sustained ivermectin delivery (WHO/APOC 2010).

The major challenge with this strategy is that it is not a "quick fix." The implementation of efficient CDTi requires patience, time, and resources at the onset when the community and health services have to be provided with the needed capacity to run the program. The initial periods of intensive community mobilization and capacity development costs are high, especially in conflict-torn countries (Amazigo et al. 2002). However, after an initial 2–3 years when the community health system support structures are in place, ivermectin distribution runs with minimal inputs from outside partners.

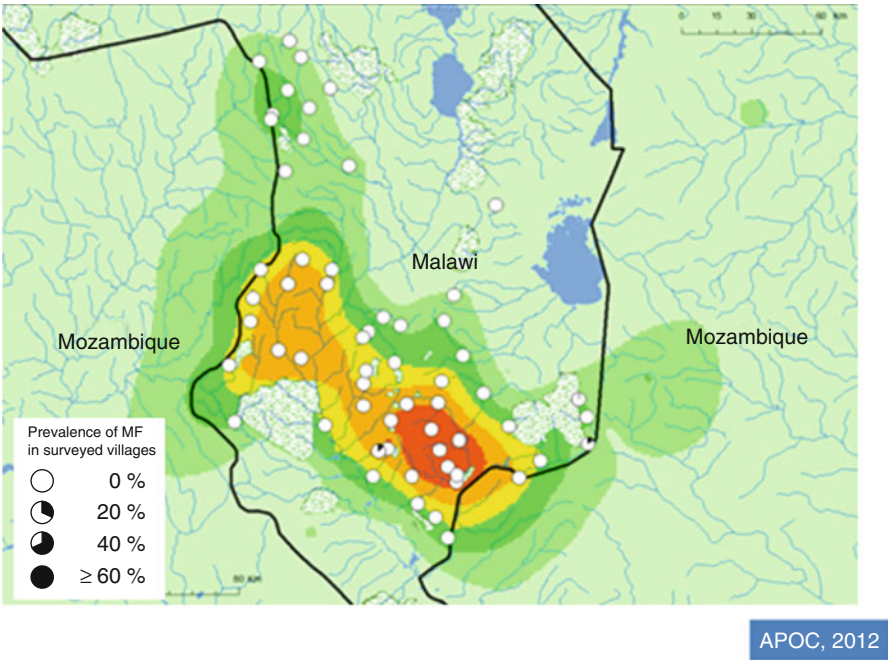
Through the CDTi approach, APOC has enabled the partner countries to place well over 97 million people from 180,000 communities on ivermectin treatment in the APOC endemic countries. Maps 2 and 3 show one example of the impact of the treatment on the prevalence of onchocerciasis.

Elimination of Onchocerciasis in Africa

Both OCP and APOC were conceived primarily as control programs with the principal goal to eliminate onchocerciasis as a disease of public health importance in Africa. OCP used a vector control strategy in the effort to interrupt transmission for



Map 2 Pre-control prevalence of nodules in Malawi



Map 3 Nodule prevalence after 12–15 years of CDTi

long enough periods so that the adult worm parasite would die out from the infected population. APOC approached the control through the establishment of a sustainable drug delivery system; however, in the light of recent findings in Latin America (Gustavsen et al. 2011) and in Africa (Traore et al. 2012), APOC has reviewed and modified its approach to include elimination of the disease.

Given the geographical limitations of vector control in eliminating the infection and the disease altogether and the fact that ivermectin which is the drug of choice would have to be given for an undefined period, total elimination of the disease was not seriously considered an immediate option. The elimination of onchocerciasis in Africa had not been considered possible using the current tools alone.

The OEPA has used only drug treatment strategy against onchocerciasis and has in the last 3 years been reporting successes with interruption of transmission in several foci in the Americas. Colombia declared elimination of the disease in 2012, while four out of the six of the endemic countries in the Americas report having broken transmission of the disease nationwide. There have also been reports of interruption of transmission in certain foci (Diawara et al. 2009) in Uganda and Sudan and several isolated foci in some of the APOC countries (Table 2). All these findings suggested that it is possible to interrupt transmission of onchocerciasis with drug treatment alone. The common factor in all these areas that have obtained interruption of transmission with ivermectin has been excellent and consistent treatment coverage. In addition, the treatment has gone on for a considerable length of time – over 5–10 years at most of the foci; and in the case of the Americas, treatment has been on twice a year basis.

Table 2 Results of epidemiological evaluations in 2008–2012

Conclusion of evaluation	Number of sites	Number of projects	Population (million)
Elimination probably already achieved	20	12	17.6
Close to elimination	8	6	4.2
On track but still some years to go	12	11	17.4
Total satisfactory progress	40	29	39.2
Unsatisfactory progress	5	5	5.4
Total evaluated	45	34	44.7

APOC (2012)

With the prospects of possible elimination of onchocerciasis with drug use, there is now a paradigm shift from just controlling the disease to thinking of eliminating the disease altogether. This is likely to be achieved in Africa provided coverage is optimum and there is further extension of the treatment to other areas that have not been included in the current treatment, e.g., some areas where there is coendemicity of onchocerciasis and *Loa loa* and onchocerciasis hypoendemic areas.

Ivermectin "Resistance"

Ivermectin was registered for treatment against onchocerciasis in October 1987. Since then, millions of the tablets have been used on a large-scale treatment of onchocerciasis covering a period of about 25 years. As for the case of any drug which is used in large quantities over a long period, there has been concern of the possibility of the emergence of resistance to ivermectin. Taylor and Green (1989) suggest, however, that resistance is unlikely because of the ineffective transmission of resistance through a vector-dependent life cycle of *O. volvulus*. Hitherto, no drug resistance to ivermectin had been seen after years of intensive veterinary usage of the drug as prophylaxis against dog heartworm (*Dirofilaria immitis*). Recent reports (Bowman 2012), however, suggest that there might be evidence of the development of resistance by (*Dirofilaria immitis*) to macrocyclic lactones. Additionally, reports from Ghana have shown persistent *O. volvulus* microfilaridemias in several subjects following multiple treatments with ivermectin (Awadzi et al. 2004a, b; Osei-Atweneboana et al. 2007). Remme et al. (2007) have, however, attributed the persistence of microfilaria in the skin in the Ghana subjects to the presence of new infections in the area concerned. Other studies (Bourguinat et al. 2007, 2008; Eng and Prichard 2005; Eng et al. 2006; Ardelli et al. 2006) have reported genetic selection by ivermectin on the genome of *O. volvulus*.

The question of whether or not there is (a) a possibility of the development of ivermectin resistance, (b) an already present ivermectin resistance in humans, (c) emerging resistance, and (d) mere nonresponsiveness or atypical or suboptimal

response of the adult worm to ivermectin has not yet been adequately answered. This calls for further work and vigilance given that ivermectin is at present the sole available and recommended drug for the treatment of onchocerciasis.

Further Research for Control

The Onchocerciasis Control Programme in West Africa (OCP) and the African Programme for Onchocerciasis Control (APOC) have both been recognized to have made excellent progress and telling impact in the control of onchocerciasis. The common goal of the two programs has been to ensure that onchocerciasis is eliminated as an important public health problem throughout sub-Saharan Africa (SSA). The OCP largely achieved its objective including making sure that the participating countries were in a position to put a post-control surveillance in place to detect recrudescence of (outbreaks of) new infections before they reach levels at which stopping transmission becomes impossible. With APOC the initial object was to support the establishment of a sustainable drug distribution in the participating countries with the ultimate aim of controlling the disease. Recent findings suggest that APOC would extend its objectives to cover elimination of onchocerciasis in as many areas as possible. Such areas would need post-elimination surveillance. Despite all these achievements, research, both basic and operational, which played a central role in helping to optimize and innovate control in the two Programmes (Remme et al. 2008), is still needed in certain areas such as (i) intervention tools, (ii) diagnostics, (iii) revised strategies, and (iv) monitoring and evaluation techniques not only to sustain the achievements of the programs but also to improve the intervention strategies still in operation.

The WHO Technical Report Series 972 (2012) on Research Priorities for helminth infections aptly sets out some of the areas that require research in onchocerciasis. Table 3 is an adaptation from the Annex 5 of the research priorities listed as the "top ten research priority areas for helminthiases" recommended by the Disease Reference Group on helminths (TDR).

Although there is as yet no conclusive evidence of ivermectin resistance, there is the need for vigilance to be able to detect such a phenomenon if and when it occurs. Attention should therefore be paid to research in (a) detection of ivermectin resistance, (b) field applicable methods for its detection, and (c) modeling to predict the impact and optimal scenarios of control of ivermectin resistance on the elimination program.

Good geographical and therapeutic coverage is key to the success of the drug distribution program to control or eliminate onchocerciasis. Research to understand compliance, noncompliance, and systematic noncompliance (where individuals persistently do not take the treatment) will be necessary to help overcome low coverages.

Community empowerment and ownership have been key in the CDTi strategy for onchocerciasis control. As elimination becomes more and more of an option, there is need for research on the best ways to improve on community empowerment, participation, and ownership.

Table 3 Top ten research priority areas for helminthiases

Area for research	Specifics of research
Diagnostic	Improve available diagnostic tests, specifically their sensitivity, specificity, and ability to measure infection intensity and detect drug resistance
	Sensitivity and specificity are mostly important to enable diagnosis of infection at low prevalence in elimination settings
Intervention tools	Optimize existing intervention tools to maximize impact
	Develop novel control tools to improve impact and sustainability
	The tools include pharmaceuticals and vaccines, the search for new or existing antibiotics to be used against *Wolbachia*, and the clinical trials and studies on moxidectin and flubendazole, respectively
Modeling	Develop and refine models to investigate the relationships between infection and morbidities to aid programs aiming to reduce the burden of disease (elimination of public health problem)
	Increase the use and application of epidemiological models to aid monitoring and evaluation (M&E) and surveillance, the design of cost-effective sampling protocols, and the monitoring of intervention efficacy including drug resistance
Monitoring and evaluation	Standardize and validate methodologies and cost-effective protocols for monitoring and evaluation (M&E) settings
Host–parasite interactions	Investigate modulation of host–parasite interactions at population and within-host levels, including impact on host immune response of concurrent infection, impact of parasite control interventions on such host–parasite interactions, and host's ability to seroconvert upon vaccination
Biology	Elucidate the effect of ivermectin on *O. volvulus* reproductive biology and quantify the patterns of coverage and compliance in treated communities

The CDTi strategy has been very appropriate in getting large quantities of ivermectin to vast areas that need it. Research will be needed to find yet other ways of distribution of ivermectin and/or other new drugs in terms of regularity and frequency.

Diagnosis is key to the control of onchocerciasis. The array of many tests that are currently available and yet not optimum for the diagnosis of onchocerciasis especially for the situation toward the "end game" suggests the dire need to look yet again through research for the ideal diagnostic tool. With the current paradigm change from control to considering elimination of onchocerciasis in SSA, it is imperative to consider the research toward the discovery of not only very sensitive tests to detect very low infections but also specific enough to exclude other parasites.

Although ivermectin has been very effective in reducing the disease (morbidity), in bringing down transmission in large areas, and in eliminating infection completely in some localities, there are still difficulties with control in some areas that will require treatment for a prolonged period. Research is therefore needed for the discovery of a macrofilaricide – one that can either kill or sterilize the adult worm – which can be used on a large scale, in an easy to administer formulation and would not have to be given over a long time frame.

There is need to optimize the use of doxycycline, i.e., given for a shorter duration, and to search for other and new antibiotics that could similarly be used for the treatment of onchocerciasis.

With the elimination of onchocerciasis as a public health problem in some foci in the Americas and scientific evidence of the feasibility of achieving the same in some countries in Africa by 2025, research must now be intensified to protect elimination efforts.

A better understanding of the immunology in the human–parasite relationship for the development of a vaccine against onchocerciasis is an important tool to guarantee sustained elimination success.

Challenges

Post-control Surveillance

The main challenge in the OCP countries continues to be finding the best possible ways to manage the post-control surveillance that has been put in place. The activity is fraught with challenges of financing, complacency as fewer and fewer infections are detected and lack of new/fresh technical expertise as the current technical staff age and retire. This is a challenge which is also likely to be faced by APOC as control efforts wind down and post-control surveillance is established. The survival of the post-control surveillance will depend on how well this can be integrated into the national health surveillance activities.

Diagnostics

Closely linked to the surveillance activities is the challenge of finding the right tool that can detect very low infections that is affordable as well as acceptable to the population for diagnosis. The currently used method depends on parasitological diagnosis based on the skin snip. The skin snip method of diagnosis is not sensitive in areas of low infection. Besides, this method is expensive to operate, may not be easily acceptable to the population, and therefore may lead to refusals to participate in surveys.

Additionally, there is a pressing need for a tool to detect reinfection rapidly in an area where control strategies have broken down or after ivermectin distribution has been stopped either because LF has been eliminated or the endpoint for onchocerciasis treatment has been reached. In these situations, it is urgent to have an assay capable of detecting either prepatent infection or exposure to the parasite. In countries with the widespread use of ivermectin and high treatment coverage of more than 15 years, the detection of microfilariae is no longer possible in some foci. For the above reasons, the detection of specific antibody or preferably antigen in sera is a great need.

Frequency of Ivermectin Distribution

Currently ivermectin treatment is based on once a year treatment in many places in the control program. There is evidence that giving ivermectin twice a year may accelerate the march toward eliminating onchocerciasis. In the event of extension of the onchocerciasis control activities to elimination in the endemic areas, there will be a need for change of paradigm as larger volumes of ivermectin supplies have to be managed, and twice a year ivermectin distribution will have to be introduced into the existing areas as well as in new areas.

Extension of Treatment for Elimination and to Hypoendemic Areas

Ivermectin treatment through the CDTi approach has been applied to hyperendemic and mesoendemic areas in the APOC countries. The hypoendemic areas have not received any treatment in most areas although some countries have started to extend their treatment to such places. The decision to extend ivermectin treatment to hypoendemic areas is not a light one as extending treatment to such areas will mean increasing the geographical coverage and with it the therapeutic coverage for treatment. The challenge here is ensuring that medicines are procured and delivered to endemic communities in a timely and regular manner and swallowed by those eligible for treatment. Other challenges would include the training of community-drug distributors and finding the resources for training frontline health workers and community implementers for the control of activities. Although the supply of ivermectin is assured for the populations, other challenges of logistics, supply chain to the communities, and financing will need attention.

In areas where onchocerciasis is coendemic with *Loa loa*, there is the possibility of serious adverse events that may occur with ivermectin treatment in *loa*-carrying patients, and special attention and precautions must be put in place to manage these patients quickly and effectively in the event of such an occurrence.

Compliance

A good coverage – the minimum has been set at 65 % – is key to attaining the objective of eliminating morbidity due to onchocerciasis and in reducing transmission. Most areas in the control program have attained coverages that surpass this minimum level with values well above coverage of 75 %. There are, however, some areas that still have had difficulty attaining the right coverage consistently. There are several reasons for this, but noncompliance appears to be an important concern in such areas. The challenge here is to find the right approach and advocacy to convince the population to adhere to the treatment, bearing in mind that for treatment that has to be taken for this length of time, population fatigue cannot be ruled out.

The Future

The two regional onchocerciasis control programs started off with the main objective to ensure that onchocerciasis is eliminated as an important public health problem throughout Africa. This has largely been achieved in large tracts of the affected areas. Given the encouraging results of possible elimination of onchocerciasis as a disease and infection in some localities, this provides optimism for possible elimination of onchocerciasis altogether from SSA. Several conditions will, however, have to be met for this to happen. These include finding the right answers to some of the research areas underlined above, and provided no ivermectin resistance occurs before an alternative means of treatment-, right regimen for antibiotic, macrofilaricide, and vaccine use- is found. It can be envisaged that with a policy of onchocerciasis elimination from SSA, emphasizing efforts toward an integrated approach for onchocerciasis and lymphatic filariasis elimination would be more cost-effective and of mutual benefit to the elimination of both diseases.

Conclusion

The control of onchocerciasis by OCP and APOC has been largely successful in the endemic areas, but onchocerciasis remains a major parasitic disease in some of the endemic countries in Africa. It therefore still requires attention. The distribution of the disease in SSA is changing as there is "shrinkage" of the onchocerciasis map as a result of the erstwhile vector control activities of the OCP and the very wide and large volumes of distribution of ivermectin through the auspices of APOC and its partners. There is a growing optimism that onchocerciasis may and can after all be eliminated altogether with the current means of treatment given the encouraging result from the Americas and the growing trend in the APOC area. But it is also realized that to be able to achieve elimination, several challenges have to be overcome. Some of the challenges include maintaining good surveillance, finding the appropriate diagnostic tools, improving compliance to treatment, finding new drugs notably a macrofilaricide, and obtaining the resources and funds for activities. Research which has played a central role in the two programs in the past needs to be continued in the areas of basic biology, host–parasite interactions, diagnostics, intervention tools, modeling, and monitoring and evaluation.

References

Abiose A et al (2000) Onchocerciasis control strategies. Lancet 356(9240):1523

Abraham D, Leon O, Leon S, Lustigman S (2001) Development of a recombinant antigen vaccine against infection with the filarial worm *Onchocerca volvulus*. Infect Immun 69(1):262–270

Amazigo U (1999) Community selection of ivermectin distributors. Community Eye Health 12(31):39–40

Amazigo UV et al (2002) The challenges of community-directed treatment with ivermectin (CDTI) within the African Programme for Onchocerciasis Control (APOC). Ann Trop Med Parasitol 96:41–58

Amazigo UV et al (2012) Community-driven interventions can revolutionise control of neglected tropical diseases. Trends Parasitol 28(6):231–238

Anderson J, Fuglsang H, De C Marshall TF (1976) Studies on onchocerciasis in the United Cameroon Republic III. A four year follow-up of six forest and six savannah villages. The incidence of ocular lesions. Trans Trop Med Hyg 79:362–373

Ardelli BF, Guerriero SB, Prichard RK (2006) Ivermectin imposes selection pressure on P-glycoprotein from *Onchocerca volvulus*: linkage disequilibrium and genotype diversity. Parasitology 132(3):375–386

Ashburn LL, Burch TA, Brady FJ (1949) Pathologic effects of suramin, hetrazan and arsenamide on adult Onchocerca volvulus. Bol Oficina Sanit Panam 28:1107–1117

Ault SK (2007) Pan American Health Organization's Regional Strategic Framework for addressing neglected diseases in neglected populations in Latin America and the Caribbean. Mem Inst Oswaldo Cruz 102(Suppl 1):99–107

Awadzi K, Dadzie KY, Schulz-Key H, Haddock DRW (1985) The chemotherapy of onchocerciasis. X. Assessment of four single dose treatment regimes of MK-933 (ivermectin) in human onchocerciasis. Ann Trop Med Parasitol 79:63–78

Awadzi K, Gilles HM (1980) The chemotherapy of onchocerciasis. III. A comparative study of DEC and metrifonate. Ann Trop Med Parasitol 79:199–210

Awadzi K, Hero M, Opoku NO, Addy ET, Büttner DW, Ginger CD (1995) The chemotherapy of onchocerciasis. XVIII. Aspects of treatment with Suramin. Trop Med Parasitol 46:19–26

Awadzi K, Attah SK, Addy ET, Opoku NO et al (2004a) Thirty-month follow-up of sub-optimal responders to multiple treatments with ivermectin, in two onchocerciasis-endemic foci in Ghana. Ann Trop Med Parasitol 98(4):359–370

Awadzi K, Boakye DA, Edwards G, Opoku NO et al (2004b) An investigation of persistent microfilaridermias despite multiple treatments with ivermectin, in two onchocerciasis-endemic foci in Ghana. Ann Trop Med Parasitol 98(3):231–249

Ayong LS, Tume CB, Wembe FE, Simo G, Asonganyi T, Lando G, Ngu JL (2005) Development and evaluation of an antigen detection dipstick assay for the diagnosis of human onchocerciasis. Trop Med Int Health 10(3):228–233

Basanez MG, Pion SD, Churcher TS, Breitling LP, Little MP, Boussinesq M (2006) River blindness: a success story under threat? PLoS Med 3(9):e371

Blacklock BD (1926) The development of onchocerca volvulus in Simulium damnosum. Ann Trop Med Parasitol 20:1–48

Boatin BA, Toe L, Alley ES, Nagelkerke NJD, Borsboom G, Habbema JDF (2002) Detection of *Onchocerca volvulus* infection in low prevalence areas: a comparison of three diagnostic methods. Parasitology 125:545–532

Borsboom GJJM, Boatin BA, Naglekerke NJD, Agoua H, Akpoboua KLB, Soumbey EW et al (2003) Impact of ivermectin treatment on onchocerciasis transmission: Assessing the empirical evidence that repeated ivermectin mass treatments may lead to elimination/eradication in West Africa. Filaria J 2(8) Online doi:10.1186/1475-2883-2-8

Bourguinat C et al (2007) Genetic selection of low fertile *Onchocerca volvulus* by ivermectin treatment. PLoS Negl Trop Dis 1(1):e72

Bourguinat C et al (2008) P-glycoprotein-like protein, a possible genetic marker for ivermectin resistance selection in *Onchocerca volvulus*. Mol Biochem Parasitol 158(2):101–111

Bowman DB (2012) Heartworms, macrocyclic lactones, and the specter of resistance to prevention in the United States. Parasit Vectors 5:138

Brieger WR, Awedoba AK, Eneanya CI, Hagan M, Ogbuagu KF, Okello DO, Ososanya OO, Ovuga EB, Noma M, Kale OO, Burnham GM, Remme JH (1998) The effects of ivermectin on onchocercal skin disease and severe itching: results of a multicentre trial. Trop Med Int Health 3:951–961

Brown KR, Neu DC (1990) Ivermectin -clinical trials and treatment schedules in onchocerciasis. Rev Acta Leidensia 59:169–175

Bryceson AD, van Veen KS, Oduloju AJ, Duke BO (1976) Antigenic diversity among *Onchocerca volvulus* in Nigeria, and immunological differences between onchocerciasis in the savanna and forest of Cameroon. Clin Exp Immunol 24(10):168–176

Cabrera Z, Parkhouse RM (1986) Identification of antigens of *Onchocerca volvulus* and *Onchocerca gibsoni* for diagnostic use. Mol Biochem Parasitol 20(3):225–231

Cheke RA, Garms R (2013) Indices of onchocerciasis transmission by different members of the Simulium damnosum complex conflict with the paradigm of forest and savanna parasite strains. Acta Trop 125:43–52

Cianchi R, Karam M, Henry MC, Villani F, Kumlien S, Bullini L (1985) Preliminary data on the genetic differentiation of *Onchocerca volvulus* in Africa (Nematoda: filaroidea). Acta Trop 42:341–351

Collins RC, Gonzales-Peralta C, Castro J et al (1992) Ivermectin: reduction in prevalence and infection intensity of *Onchocerca volvulus* following bi-annual treatment in five Guatemalan communities. Am J Trop Med Hyg 47:156–169

Crosskey RW (1990) The natural history of blackflies. Wiley, Chichester

Crump A, Morel CM, Omura S (2012) The onchocerciasis chronicle: from the beginning to the end? Trends Parasitol 28:280–288. S1471-4922(12)00069-4 doi:10.1016/j.pt.2012.04.005. PMID: 22633470

Dadzie KY, Remme J, Rolland A, Thylefors B (1986) The effect of 7–8 years of vector control on the evolution of ocular onchocerciasis in West African savannah. Trop Med Parasitol 37:263–270

Dadzie KY, Remme J, Rolland A, Thylefors B (1989) Ocular onchocerciasis an intensity of infection in the community; II West African rain-forest foci of the vector Simulium yahense. Trop Med Parasitol 40:348–354

Dadzie KY, Remme J, Baker RHA, Rolland A, Thylefors B (1990) Ocular onchocerciasis and intensity of infection in the community. III. West African rain-forest foci of the vector Simulium sanctipauli. Trop Med Parasitol 41:376–382

Dawood MS (1978) Field treatment of onchocerciasis in the Sudan with Suramin preparations and Banocide. World Health Organization, Alexandra

De Sole G, Remme J, Awadzi K, Accorsi S, Alley E, Ba O, Dadzie K, Giese J, Karam M, Keita F (1989) Adverse reactions after mass treatment of onchocerciasis with ivermectin. Combined results from eight community trials. Bull World Health Organ 67:707–719

Denery JR, Nunes AA et al (2010) Neglected tropical disease research and development. The World Health Organization's 2010 report dedicated to neglected tropical diseases … and open source collaboration methods for drugs

Diawara L, Traoré MO, Badji A, Bissan Y, Doumbia K, Goita SF, Konaté L, Mounkoro K, Sarr MD, Seck AF, Toé L, Tourée S, Remme JH (2009) Feasibility of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: first evidence from studies in Mali and Senegal. PLoS Negl Trop Dis 3:e497

Duke BOL (1981) The six diseases of WHO. Onchocerciasis. Br Med J (Clin Res Ed) 283(6297):961–962. doi:10.1136/bmj.283.6297.961

Duke BOL, Zea-Flores G, Castro J, Cupp EW, Muñoz B (1991) Comparison of the effects of a single dose and of four six-monthly doses of ivermectin on adult *Onchocerca volvulus*. Am J Trop Med Hyg 45:132–137 [PubMed]

Druet-Cabanac M, Preux PM, Bouteille B, Bernet-Bernady P, Hopkins AD (1999) Onchocerciasis and epilepsy. : a matched case-control study in the Central African Republic. Am J Epidemiol 149(6):565–570

Edungbola LD, Alabi TO, Oni GA et al (1987) 'Leopard skin' as a rapid diagnostic index for estimating the endemicity of African onchocerciasis. Int J Epidemiol 16(590):594

Elson LH, Calvopiña M, Paredes W, Araujo E, Bradley JE et al (1995) Immunity to onchocerciasis: putative immune persons produce a Th1-like response to Onchocerca volvulus. J Infect Dis 171(3):652–658 [PubMed]

Eng JK, Prichard RK (2005) A comparison of genetic polymorphism in populations of *Onchocerca volvulus* from untreated- and ivermectin-treated patients. Mol Biochem Parasitol 142(2): 193–202

Eng JK et al (2006) Ivermectin selection on beta-tubulin: evidence in *Onchocerca volvulus* and *Haemonchus contortus*. Mol Biochem Parasitol 150(2):229–235

Enk CD (2006) Onchocerciasis – river blindness. Clin Dermatol 24:176–180

Gardon J, Boussinesq M, Kamgno J et al (2002) Effects of standard and high doses of ivermectin on adult worms of *Onchocerca volvulus*: a randomized controlled trial. Lancet 360:203–210

Gemade EI, Jiya JY, Nwoke BE, Ogunba EO, Edeghere H, Akoh JI, Omojola A (1998) Human onchocerciasis: current assessment of the disease burden in Nigeria by rapid epidemiological mapping. Ann Trop Med Parasitol 92(Suppl 1):79–83

Greene BM, Taylor HR, Cupp EW, Murphy RP, White AT, Schulz-key H, D'Anna SA, Newland HS, Goldsmith LP, Auer C, Hanson AP, Freeman SV, Reber EW, Williams PN (1985) Comparison of ivermectin and diethylcarbamazine in the treatment of onchocerciasis. N Engl J Med 313:133–138

Guillet P, Seketeli A, Alley ES et al (1995) Impact of combined large-scale ivermectin distribution and vector control on transmission of onchocerca volvulus in the Niger basin, Guinea. Bull World Health Org 73(2):199–205

Gustavsen K et al (2011) Onchocerciasis in the Americas: from arrival to (near) elimination. Parasit Vectors 4(1):205. doi:10.1186/1756-3305-4-205

Hagan M (1998) Onchocercal dermatitis: clinical impact. Ann Trop Med Parasitol 92(Suppl No 1):S85–S96

Hall LR, Pearlman E (1999) Pathogenesis of onchocercal keratitis (river blindness). Clin Microbiol Rev 12:445–453

Higazi TB, Zarroug IMA, Mohamed HA, ElMubarak WA, Deran TCM, Aziz N, Katabarwa M, Hassan HK, Unnasch TR, Mackenzie CD, Richards F, Hashim K (2013) Interruption of *Onchocerca volvulus* transmission in the Abu Hamed Focus, Sudan. Am J Trop Med Hyg Online 89:51–57

Hoerauf A, Volkman L, Hamelmann C, Hamelmann C, Adjei O, Autenrieth IB, Fleischer B, Büttner DW (2000) Endosymbiotic bacteria in worms as targets for a novel chemotherapy in filariasis. Lancet 355:1242–1243

Hoerauf A, Mand S, Adjei O, Fleischer B, Büttner DW (2001) Depletion of Wolbachia endobacteria in Onchocerca volvulus by doxycycline and microfilaridermia after ivermectin treatment. Lancet 357:1415–1416

Hoerauf A, Specht S, Buttner M (2008) *Wolbachia* endobacteria depletion by doxycycline as antifilarial therapy has macrofilaricidal activity in onchocerciasis: a randomized placebo-controlled study. Med Microbiol Immun 197(3):295–311

Homeida M, Mackenzie C, Williams H, Ghalib H (1986) The detection of onchocercal nodules by ultrasound technique. Trans Roy Soc Trop Med Hyg 80:570–571

Joint African Forum Ministerial meeting, Communique (2011) Kuwait City Dec 20, African Programme for Onchocerciasis Control Meeting Report 11

Kale O (1978) Small-scale trials of six drugs against *Onchocerca volvulus*. Tropenmed Parasitol 29(2):163–167

Kipp W, Burnham G, Bamuhiiga J, Leichsenring M (1996) The Nakalanga Syndrome in Kabarole District, Western Uganda. Am J Trop Med Hyg 54(1):80–83

Lewalen S, Courtright P (2001) Blindness in Africa: present situation and future needs. Br J Ophthalmol 85:897–903

Lipner EM, Dembele N, Souleymane S, Alley WS, Prevots DR, Toe L, Boatin B, Weil GJ, Nutman TB (2006) Field applicability of a rapid-format anti-Ov-16 antibody test for the assessment of onchocerciasis control measures in regions of endemicity. J Infect Dis 194(2):216–221

Little MP, Breitling LP, Basanez MG, Alley ES, Boatin BA (2004) Association between microfilarial load and excess mortality in onchocerciasis: an epidemiological study. Lancet 363(9420):1514–1521

Lobos E, Weiss N (1985) Immunochemical comparison between worm extracts of *Onchocerca volvulus* from savanna and rain forest. Parasite Immunol 7(3):333–347

Lobos E, Weiss N, Karam M, Taylor HR, Ottesen EA, Nutman TB (1991a) An immunogenic *Onchocerca volvulus* antigen: a specific and early marker of infection. Science 25:1603–1605

Lobos E, Weiss N, Karam M, Taylor RH, Ottesen EA (1991b) An immunogenic Onchocerca volvulus antigen: a specific and early marker of infection. Science 251(5001):1603–1605
Lustigman S, Abraham D (2009) Onchocerciasis (Chapter 67). In: Barrett AT, Stanberry LR (eds) Vaccines for biodefense and emerging and neglected diseases. Academic Press, London, pp 1379–1400. ISBN 10: 0123694086
Lustigman S, James ER, Tawe W, Abraham D (2002) Towards a recombinant antigen vaccine against Onchocerca volvulus. Trends Parasitol 18(3):135–141
Mace J-M, Boussinesq M, Ngoumou P et al (1977) Country-wide rapid epidemiological mapping of onchocerciasis (REMO) in Cameroon. Ann Trop Med Parasitol 91(4):379–391
Mackenzie CD, Geary TG (2011) Flubendazole: a candidate macrofilaricide for lymphatic filariasis and onchocerciasis field programs. Expert Rev Anti Infect Ther 9(5):497–501
Mas J, Ascaso C et al (2006) Reduction in the prevalence and intensity of infection in *Onchocerca volvulus* microfilariae according to ethnicity and community after 8 years of ivermectin treatment on the island of Bioko, Equatorial Guinea. Trop Med Int Health 11(7):1082–1091
Mazzotti L (1948a) The feasibility of using the allergic reactions which follow the administration of hetrazan as an auxiliary means of diagnosis of onchocerciasis. Rev Inst Salud Enferm Trop Mex 9:935
Mazzotti L (1948b) Posibilidad de utilizar como medio diagnostico auxiliar en la onchocercosis, las reacciones alérgicas consecutivas a la administración del 'Hetrazan'. Rev Inst Salubridad Enfermedadas Tropicales 38:235–237
Meredith SE, Lando G, Gbakima AA, Zimmerman PA, Unnasch TR (1991) *Onchocerca volvulus*: application of the polymerase chain reaction to identification and strain differentiation of the parasite. Exp Parasitol 73:335–344
Meredith S, Cross C, Amazigo U (2012) Empowering communities in combating river blindness and the role of NGOs: case studies from Cameroon, Mali, Nigeria, and Uganda. Health Res Policy Syst 10:16. doi:10.1186/1478-4505-10-16, Published online 2012 May 10
Murdoch ME, Hay RJ, Mackenzie CD, Williams JF, Ghalib HW, Cousens S et al (1993) A clinical classification and grading system of the cutaneous changes in onchocerciasis. Br J Dermatol 129(3):260–269
Murdoch ME (2010) Onchodermatitis. Curr Opin Infect Dis 23(2):124–131
Murdoch ME, Asuzu MC, Hagan M et al (2002) Onchocerciasis: the clinical and epidemiological burden of skin disease in Africa. Ann Trop Med Parasitol 96(3):283–296
Mutalemwa P et al (2009) Community directed approach beyond ivermectin in Tanzania: a promising mechanism for the delivery of complex health interventions. Tanzan J Health Res 11(3):116–125
Ngoumou P, Walsh JF, Mace JM (1994) A rapid mapping technique for the prevalence and distribution of onchocerciasis: a Cameroon case study. Ann Trop Med Parasitol 88(5): 463–474
Noma M, Nwoke BEB, Nutall I, Tambala PA, Enyong P, Namsenmo A, Remme J, Amazigo UV, Kale OO, Seketeli A (2002) Rapid epidemiological monitoring of Onchocerciasis (REMO): its application by the African Programme for Onchocerciasis Control (APOC). Ann Trop Med Parasit 96(Suppl No 1):S29–S40
Osei-Atweneboana MY, Eng JK, Boakye DA, Gyapong JO, Prichard RK (2007) Prevalence and intensity of Onchocerca volvulus infection and efficacy of ivermectin in endemic communities in Ghana: a two-phase epidemiological study. The Lancet 369(9578):2021–2029
Ottesen EA (1995) Immune responsiveness and the pathogenesis of human onchocerciasis. J Infect Dis 171(3):659–671
Ozoh G, Boussinesq M, Zoung-Kanyi Bissek AC et al (2007) Evaluation of the valuation of the diethylcarbamazine patch to evaluate onchocerciasis endemicity in Central Africa. Trop Med Int Health 12(1):123–129
PAHO (2013) Global Health Observatory (GHO) data. Onchocerciasis. www.who.int/entity/gho/neglected_diseases/onchocerciasis
Pearlman E, Hall LR (2000) Immune mechanisms in Onchocerca volvulus- mediated corneal disease (river Blindness). Parasite Immunol 22:625–631

Pion SDS, Kaiser C, Boutros-Toni F, Cournil A, Taylor MM et al (2009) Epilepsy in onchocerciasis endemic areas: systematic review and meta-analysis of population-based surveys. PLoSNegl Trop Dis 3(6):e461

Pischke S, Butter DW, Liebau E, Fischer P (2002) An internal control for the detection o Onchocerca volvulus DNA by PCR-ELISA and rapid detection of specific PCR products by DNA detection test strips. Trop Med Int Health 7(6):526–531

Plaisier AP, Van Oortmarssen GJ, Remme J, Habbemma JD (1991) The reproductive lifespan of Onchocerca volvulus in West African savanna. Acta Trop 48:271–284

Plaisier AP, Alley ES, Boatin BA, Van Oortmarssen GJ, Remme H, De Vlas SJ, Bonneux L, Habbema JD (1995) Irreversible effects of ivermectin on adult parasites in onchocerciasis patients in the Onchocerciasis Control Programme in West Africa. J Infect Dis 172(1):204–210

Poltera AA, Reyna O, Zea Flores G et al (1987) Detection of skin nodules in onchocerciasis by ultrasound scans. Lancet 329(8531):505

Prod'hon J, Boussinesq M, Fobi G, Prod'hum JM, Enyong P, Lafluer C, Quillévéré (1991) Lutte contre onchocercose par ivermectin; résultats d'une campagne de masse au Nord- Cameroun. Bull World Health Organ 69:443–450

Remme J, Baker RHA, De Sole G, Dadzie KY, Adams MA, Alley ES, Avissey HSK, Walsh JF (1989) A community trial of ivermectin in the onchocerciasis focus of Asubende, Ghana.I. Effect on the microfilarial reservoir and the transmission of Onchocerca volvulus. Trop Med Parasitol 40:367–374

Remme JHF, Feenstra P, Lever PR, Medici AC, Morel CM, Noma M, Ramaiah KD, Richards F, Seketeli A, Schmunis G, Van Brakel WH, Vassall A (2006) Tropical diseases targeted for elimination: chagas disease, lymphatic filariasis, onchocerciasis and leprosy. In: Jamison DT, Breman JG, Measham AR (eds) Disease control priorities in developing countries, 2nd edn. Oxford University Press, New York

Remme JHF (2004) Research for control: the onchocerciasis experience. Trop Med Int Health 9(2):243–254. doi:10.1046/j.1365-3156.2003.01192.x[PubMed]

Remme JHF, Dadzie KY, Karam M et al (1986) The effects of 11 years of simulium control in OCP on ABR's, ATP's, prevalence and intensity of *O.volvulus* infections and on the incidence and prevalence of eye. Parasitic Diseases Programme. World Health Organization, Geneva

Remme JH, Amazigo U, Engels D, Barryson A, Yameogo L (2007) Efficacy of ivermectin against Onchocerca volvulus in Ghana. Lancet 370(9593):1123–1124

Remme JHF, Boatin B, Boussinesq M (2008) Helminthic diseases: onchocerciasis and loiasis. In: International encyclopedia of public health, vol 3, 1st edn. Academic, San Diego, pp 339–351

Richards FO, Boatin B, Sauerbrey M, Sékétéli A (2001) Control of onchocerciasis today: status and challenges. Trends Parasitol 17(12):558–563

Rodriguez-Perez MA, Lugo-Rodriguez L, Lizarazo-Ortega C, Unnasch TR (2006) Entomological and serological assessment of Onchocerca volvulus transmission in the northern Chiapas focus (Mexico). Acta Entomologica Serbica 11(Suppl):51–59

Rougemont A, Thylefors B, Ducan M, Prost A, Ranque PH (1980) Traitement de l'onchocercose par la Suramin à faibles doses progressive dans les collectivités hyperendémiques d'Afrique occidentale. 1. Résultats parasitologique et surveillance opthalmologique en zone de transmission non interrompue. Bull World Health Org 58:919–122

Rougemont A, Hien M, Thylefors B, Prost A, Rolland A (1984) Traitement de l'onchocercose par la Suramin à faibles doses progressive dans les collectivités hyperendémiques d'Afrique occidentale. 2. Résultats cliniques, parasitologiques et opthalmologique en de transmission contrôlée. Bull World Health Organ 62:261–269

Saint Andre A, Blackwell NM, Hall LR, Hoerauf A, Brattig NW, Volkmann L, Lustigman S, James ER, Tawe W, Abraham D (2002) Towards a recombinant antigen vaccine against *Onchocerca volvulus*. Trends Parasitol 18(3):135–141

Sauerbrey M (2008) The Onchocerciasis Elimination Program for the Americas (OEPA). Ann Trop Med Parasitol 102(Suppl 1):25–29

Soboslay P, Geiger SM, Weiss N et al (1997) The diverse expression of immunity in humans at distinct states of Onchocerca volvulus infection. Immunology 90:592–599

Stingl P, Ross M, Gibson DW et al (1984) A diagnostic patch test for onchocerciasis using topical diethylcarbamazine. Trans R Soc Trop Med Hyg 78:254–258
Taylor MJ (2003) Wolbachia in the inflammatory pathogenesis of human filariasis. Ann N Y Acad Sci 990:444–449
Taylor HR, Green BM (1989) The status of ivermectin in the treatment of human onchocerciasis. Am J Trop Med Hyg 41:460–466
Taylor MJ, Hoerauf A (1999) *Wolbachia* bacteria of filarial nematodes. Parasitol Today 15:437–442
Taylor MJ, Ford L, Hise AG, Lass JH, Diaconu E, Pearlman E (2002) The role of endosymbiotic Wolbachia bacteria in the pathogenesis of river blindness. Science 295:1892–1895
Taylor MJ, Bandi C, Hoerauf A (2005) *Wolbachia* bacterial endosymbionts of filarial nematodes. Adv Parasitol 60:245–284
Tekle* AH, Elhassan E, Isiyaku S, Amazigo UV, Bush S, Noma M, Cousens S, Abiose A, Remme JH (2012) Impact of long-term treatment of onchocerciasis with ivermectin in Kaduna State, Nigeria: first evidence of the potential for elimination in the operational area of the African Programme for Onchocerciasis Control. Parasites Vectors 5:28
Thylefors B, Negrel AD, Pararajasegaram R, Dadzie KY (1995) Global data on blindness. Bull World Health Organ 73:115–121
Toe L, Adjami AG, Boatin BA et al (2000) Topical application of diethylcarbamazine to detect onchocerciasis recrudescence in west Africa. Trans R Soc Trop Med Hyg 94:519–525. doi:10.1016/S0035-9203(00)90073-7 [PubMed]
Traoré MO, Sarr MD, Badji A, Bissan Y et al (2012) Proof-of-principle of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: final results of a study in Mali and Senegal. PLoS Negl Trop Dis 6:e1825 [PMC free article] [PubMed]
Trees AJ, Graham SP, Renz A, Bianco AE, Tanya V (2000) *Onchocerca ochengi* infections in cattle as a model for human onchocerciasis: recent developments. Parasitology 120(Suppl): S133–S134
Turner HC, Churcher TS, Walker M, Turner HC, Churcher TS, Walker M, Osei-Atweneboana MY, Prichard RK, Basanez M'a-G (2013) Uncertainty surrounding projections of the long-term impact of ivermectin treatment on human onchocerciasis. PLOS Negl Trop 7(4):e2169
Udall DN (2007) Recent updates on onchocerciasis: diagnosis and treatment. Clin Infect Dis 44:53–60
Vincent JA, Lustigman S, Zhang S, Weil GJ (2000) A comparison of newer tests for the diagnosis of onchocerciasis. Ann Trop Med Parasitol 94(3):253–258
Wanji S, Tendongfor N, Nji T et al (2009) Community-directed delivery of doxycycline for the treatment of onchocerciasis in areas of co-endemicity with loiasis in Cameroon. Parasit Vectors 2(1):39. doi:10.1186/1756-3305-2-39
Whitword JAG, Gemade E II (1999) Independent evaluation of onchocerciasis rapid assessment methods in Benue State, Nigeria. Trop Med Int Health 4(1):26–30
Whitworth JAG, Gilbert CE, Mabey DM, Maude GH, Morgan D, Taylor DW (1991) Effects of repeated doses of ivermectin on ocular onchocerciasis community- based trial I Sierra Leone. Lancet ii:1110–1103
WHO JAF (2011) Seventeenth Session of the Joint Action Forum-JAF17: The World Health Organisation Year 2011 Progress Report, 1st Septmber 2010 -31st August 2011
WHO/TDR (2008) CDI report for major problems in Africa. World Health Organisation, Geneva, Switzerland
World Health Organization (1987) WHO expert committee on onchocerciasis: third report. Technical series No 852. WHO, Geneva. www.who.int/entity/tdr/publications/documents/cdi_report_08.pdf
WHO/TDR (2010) Community-directed interventions for priority health problems in Africa: results of a multicountry study. Bull World Health Organ 88(7):509–518
World Health Organization (1995a) Expert Committee on onchocerciasis control, Technical Report Series no. 852. WHO, Geneva

World Health Organization (1995b) The importance of onchocercal skin disease: report of the Pan-African Study Group on Onchocercal Skin Disease, Document TDR/AFR/RP/95. WHO, Geneva

World Health Organization (2001) Criteria for certification of interruption of transmission/elimination of human onchocerciasis. World Health Organization, Geneva, Document No: WHO/CDS/CEE/2001.18a

World Health Organization/African Programme for Onchocerciasis Control (2009) Informal consultation on elimination of onchocerciasis transmission with current tools in Africa – "Shrinking the Map", Ouagadougou

Zimmeman PA, Dadzie KY, De Sole G, Remme J, Alley ES, Unnasch TR (1992) Onchocerca volvulus DNA probe classification correlates with epidemiologic patterns of blindness. J Infect Dis 165:964–968

Zouré HGM, Noma M, Tekle AH et al (2014) The Geographical distribution of onchocerciasis in the 20 participating countries of the African Programme for Onchocerciasis Control: (2) pre-control endemicity levels and estimated number infected. Parasit Vectors 7:326

Podoconiosis: Endemic Non-filarial Elephantiasis

Kebede Deribe, Fasil Tekola-Ayele, and Gail Davey

Contents

Abstract Podoconiosis is an endemic, non-filarial lymphoedema of the lower limb which needs to be differentiated from filarial elephantiasis, lymphoedema of systemic disease and leprotic lymphoedema. The disease (affecting genetically susceptible individuals who go barefoot) is linked to long-term exposure to red clay soil. Interactions between genetic and environmental factors trigger an inflammatory response that leads to lymphoedema and fibrosis. Patients with podoconiosis develop signs and symptoms in the second and third decades of life with the disease being common up to the sixth decade. The disease is bilateral but asymmetrical and almost

K. Deribe (✉) • G. Davey
Brighton & Sussex Medical School, University of Sussex, Falmer, Brighton BN1 9PX, UK
e-mail: kebededeka@yahoo.com

F. Tekola-Ayele
Center for Research on Genomics and Global Health, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892, USA

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_10

always limited to below the knees. Globally, there are about four million people with podoconiosis, mainly in tropical Africa, central and South America and Southeast Asia. Tropical African countries bear the highest disease burden with about one million people living with podoconiosis in Ethiopia and a further 500,000 in Cameroon. The key strategies for podoconiosis control are prevention of contact with irritant soil (primary prevention) and lymphoedema morbidity management (secondary and tertiary prevention). The main challenge faced in podoconiosis is lack of awareness that the condition exists and that it is different from lymphatic filariasis and other main cause of lymphoedema in the tropics. This lack of awareness and diagnostic confusion with lymphatic filariasis has led to podoconiosis-affected communities being treated with DEC and albendazole. Research directed at the mapping of podoconiosis will have important consequences in planning the control and future elimination of the disease. Mapping of the disease burden of podoconiosis will help target resources, monitor control progress and advocate for investment in podoconiosis prevention, control and ultimately elimination. Mapping of disease must be accompanied by development of endemicity classifications and criteria for disease elimination before policies can be finalised. Controlling podoconiosis is achievable because no biological agent or vector involved in podoconiosis has been identified, the global scale of the problem is relatively small, the means for podoconiosis prevention and control are safe and additional strategies for prioritisation of resources such as the use of family health history and risk maps can be implemented.

Introduction

Podoconiosis is the lesser-known of the two major forms of tropical lymphoedema. An endemic, non-filarial lymphoedema of the lower limb, podoconiosis is linked to long-term exposure to red clay soil (Davey et al. 2007a). The disease affects genetically susceptible individuals who often go barefoot (Price 1990; Tekola Ayele et al. 2012a). It causes bilateral, often below-knee lymphoedema of the lower limb. The term podoconiosis was coined from the two Greek words *podos* and *konos,* which mean foot and dust, respectively, and imply that the disease is caused by exposure of the feet to irritant clay soil (Price 1990; Davey et al. 2007b).

Epidemiology

Distribution and Burden

Globally, it is estimated that there are four million people with podoconiosis, mainly in tropical Africa, central and South America and Southeast Asia. Tropical African countries bear the highest disease burden. Recent estimates suggest that there are one

Fig. 1 Countries where podoconiosis is endemic or has been described (Adapted from WHO website)

million people living with podoconiosis in Ethiopia and a further 500,000 in Cameroon (Davey 2009). In Africa, the disease has been reported from Burundi, Cameroon, Cape Verde, Equatorial Guinea, Ethiopia, Kenya, Rwanda, Sao Tome and Principe, North Sudan, Tanzania and Uganda (Price 1990; Davey et al. 2007b). Podoconiosis was reported in the Central American highlands in Mexico and Guatemala south to Ecuador, Brazil, Suriname and French Guiana in the coast of South America (Davey 2010). In Asia although filarial elephantiasis predominates in India, podoconiosis has been reported from north-west India, Sri Lanka and Indonesia (Fig. 1).

Based on market counts, prevalence of podoconiosis was found to be highly variable within a given country. In Burundi in 1975, a market survey in nine districts demonstrated a prevalence of 1.0 %, ranging from 0 to 2.07 %, while in Rwanda, the same market survey generated a prevalence of 0.63 %, ranging from 0.1 to 1.7 % (Price 1976b). A more recent study in eastern Uganda documented prevalence of 4.5 % among individuals ≥10 years old and 8.2 % among individuals ≥20 years old (Onapa et al. 2001). In a study conducted in the North West province of Cameroon, a prevalence of 8.1 % was documented among individuals ≥15 years old (Wanji et al. 2008).

Ethiopia is where most studies on podoconiosis have been conducted. Studies conducted in 1960 and 1970 reported widespread occurrence of podoconiosis in Ethiopia (Price 1974a). Studies over the past 10 years have documented that the prevalence of podoconiosis ranges from 2.8 to 7.4 % in endemic areas (Kloos et al. 1992; Desta et al. 2003; Alemu et al. 2011; Geshere Oli et al. 2012; Tekola Ayele et al. 2013).

Prevalence studies are summarised in Table 1.

Table 1 Prevalence of podoconiosis – studies in sub-Saharan Africa

Country	Source	Year	*N*	Prevalence	Comments
Burundi	Price (1976b)	1975	6156	1.0 %	Market counts
Rwanda	Price (1976b)	1975	20,446	0.63 %	Market counts
Uganda	Onapa et al. (2001)	2001	884	4.5 %	Village survey, age ≥10 years
Cameroon	Wanji et al. (2008)	2008	834	8.1 %	Village survey, age ≥15 years
Ethiopia	Oomen (1969)	1969	247,908	2.72 %	Market counts
	Price (1974a)	1974	43,573	4.09 %	Market counts
	Kloos et al. (1992)	1992	416	7.5 %	Village survey, age ≥5 years
	Desta et al. (2003)	2003	33,678	5.5 %	Community survey, all ages
	Alemu et al. (2011)	2011	69,465	2.8 %	Community survey, all ages
	Geshere Oli et al. (2012)	2012	5590	7.4 %	Community survey, age ≥14 years
	Molla et al. (2012a)	2012	51,017	3.3 %	Community survey, age ≥15 years
	Tekola Ayele et al. (2013)	2013	6710	5.6 %	Community survey, age ≥10 years

Podoconiosis is common among barefoot subsistence farmers, who are exposed to red clay soil due to their work. The onset of the disease is more common in the second and third decades of life with the disease being common up to the sixth decade (Davey et al. 2007b). The prevalence in the first decade is almost zero. A study from Uganda reported no cases among <10 years old (Onapa et al. 2001), and in southern Ethiopia, only 6.8 % of the patients were ≤15 years old (Desta et al. 2003).

There are inconsistent findings about the gender ratio in podoconiosis distribution. A study conducted in southern Ethiopia found a male: female ratio among podoconiosis sufferers of 1:0.98. This was not significantly different from the zonal gender ratio (1:1.02) (Desta et al. 2003). A study conducted in northern Ethiopia recorded a gender ratio of 0.98:1 (Molla et al. 2012a). Two studies conducted in western Ethiopia documented gender ratios of 0.7:1 (Tekola-Ayele et al. 2013) and 0.5:1 (Alemu et al. 2011). A study conducted in central Ethiopia indicated a gender ratio of 1.2:1 (Geshere Oli et al. 2012). Another study conducted in Cameroon recorded 0.5:1 gender ratio (Wanji et al. 2008), while a study in Uganda (Onapa et al. 2001) indicated 1:1 gender ratio. In addition, some studies suggested that mild forms of the disease were more common among women than men, which could be due to differences in treatment-seeking behaviour (Geshere Oli et al. 2012).

The distribution of podoconiosis shows associations with the distribution of red clay soil derived from volcanic rocks. Previous observations documented high prevalence of podoconiosis in areas with red clay soil (Price 1976a). A recent study which linked historical data with GIS identified significant associations between high prevalence of podoconiosis and average annual land surface temperature

(between 19 and 21 °C), average annual rainfall (greater than 1500 mm), slope of the land and fine soil texture (most of these variables contribute to weathering of base rock to soil) (Deribe et al. 2013a).

Public Health Impact

In addition to the health impacts described below, podoconiosis has severe social and economic consequences (Tekola et al. 2006). According to a study in southern Ethiopia in an area with 1.7 million residents, the annual economic cost of podoconiosis was more than 16 million USD per year, which when extrapolated to the country as a whole suggests cost of more than 200 million USD per annum for Ethiopia. People with podoconiosis were found to be half as productive as those without podoconiosis but with the same occupations. Podoconiosis patients lose 45 % of their economically productive time because of morbidity associated with the disease (Tekola et al. 2006). Total direct costs of podoconiosis amounted to the equivalent of US$ 143 per patient per year.

Studies have documented that 77.4–97 % of patients have experienced acute dermatolymphangioadenitis (ADLA) at least once per year (Alemu et al. 2011; Molla et al. 2012a; Tekola Ayele et al. 2013). Acute dermatolymphangioadenitis (or simply an 'acute attack') is a recurrent inflammatory swelling of lymphoedematous legs that may be triggered by bacterial, viral or fungal superinfection. It is characterised by hot, painful and reddened swelling which leads to loss of productivity. People with podoconiosis become bedridden during acute attacks. On average, most patients have five or more episodes of acute dermatolymphangioadenitis and hence lose 25 productive days per year.

The social impact of podoconiosis is also significant. Qualitative studies in southern Ethiopia have shown that podoconiosis is considered the most stigmatising health problem in endemic areas (Gebrehanna 2005; Tora et al. 2011). Social stigma against people with podoconiosis is rife, patients being excluded from school; denied participation in local meetings, churches and mosques; and excluded from marriage with unaffected individuals (Gebrehanna 2005; Yakob et al. 2008; Tekola et al. 2009; Tora et al. 2011; Molla et al. 2012b). In a study conducted in northern Ethiopia, 13 % of patients mentioned that they had experienced one or more forms of social stigmatisation at school or church or in the market place (Molla et al. 2012b). In southern Ethiopia, 55.8 % of community members showed stigmatising attitudes towards social interactions with podoconiosis patients (Yakob et al. 2008). Widespread misconceptions about the causes, prevention and treatment of podoconiosis have contributed to this stigma and discrimination. The misconception that podoconiosis is caused by hereditary factors and is unrelated to environmental factors leads to the assumption that it cannot be avoided (Ayode et al. 2012). In addition, there is a widespread belief that podoconiosis cannot be prevented nor treated (Yakob et al. 2010). These misconceptions prevail even among healthcare providers. In a recent study among people with podoconiosis and healthy neighbourhood controls, the healthy controls had

much higher quality of life scores than podoconiosis-affected individuals in all domains of quality of life. Overall, patients had almost seven times the risk of lower than average quality of life scores than controls. Patients' quality of life was worse than that of patients with other neglected tropical diseases (NTDs) such as soil-transmitted helminths (Mousley et al. 2013). Using a validated stigma scale (Franklin et al. 2013), a quantitative study in northern Ethiopia showed that the mean felt stigma was 21.7 (range 0–45) and mean enacted (experienced) stigma, 9 (range 0–51) (Deribe et al. 2013a). This baseline study will be useful to evaluate the impact of podoconiosis intervention programmes in reducing felt and enacted stigma over time.

Basic Biology

Gene-Environment Interactions

The pathogenesis of podoconiosis is not yet clearly understood. Based on existing evidence, the most accepted cause of podoconiosis is that of mineral particle-induced inflammation on a background of genetic susceptibility (Davey et al. 2007a). Interactions between genetic and environmental factors trigger an inflammatory response that leads to lymphoedema and fibrosis (Davey et al. 2007a). It is hypothesised that mineral particles that penetrate bare skin are engulfed by macrophages in the lower limb lymphatics and induce an inflammatory response in the lymphatic vessels. This is followed by fibrosis and obstruction of the vessel lumen leading to oedema of the lower leg, which progresses to elephantiasis (Price1972b). Below, we describe the pathogenesis of podoconiosis using the gene-environment interaction model.

Genetics

Not all barefoot people who live in areas of red clay soil develop podoconiosis. In the early 1970s, Price reported familial aggregation of podoconiosis in Ethiopia, Rwanda and Burundi (Price 1976b). These observations and subsequent epidemiological studies in Ethiopia hinted at high heritability of podoconiosis. Reportedly a third to one-half of patients have other podoconiosis-affected close relatives or family members: 48 % in Illubabor resettlement schemes, western Ethiopia (Kloos et al. 1992); 38 % in East and West Gojjam Zones, northern Ethiopia (Molla et al. 2012b); 34 % in Bedele Zuria, western Ethiopia (Tekola-Ayele et al. 2013); and 30 % in Midakegn, central Ethiopia (Geshere Oli et al. 2012). These figures may be underestimates because patients may not disclose the presence of podoconiosis in blood relatives to protect their family from social stigmatisation.

Price performed segregation analysis on 80 families with more than one affected child. The study suggested the possibility of a genetic factor with an autosomal recessive mode of inheritance and an estimated risk genotype frequency of 15–40 % (Price 1972a). Price also hypothesised that individual differences in the tissue handling of absorbed minerals play a role in development of full-blown podoconiosis (Price 1990).

A pedigree study conducted in 2005 in 59 multigenerational families with multiple affected members in southern Ethiopia presented evidence for a genetic basis to podoconiosis. The sibling recurrence risk ratio was 5.07 (i.e. the sibling of an affected person is at five times increased risk of developing podoconiosis when compared to a person in the general population), and the heritability of podoconiosis was estimated to be 63 % (SE 0.069, $p = 1 \times 10^{-7}$) (i.e. 63 % of the variance in occurrence or nonoccurrence of podoconiosis is accounted for by genetics). Segregation analysis showed the most parsimonious model to be that of an autosomal codominant major gene, with age and history of use of footwear as significant environmental covariates. The study illustrated that both genetic and environmental factors contribute to the pathophysiology of podoconiosis (Davey et al. 2007a).

A genome-wide comparison of the frequency of genetic variants between podoconiosis cases and unaffected controls from southern Ethiopia revealed that genetic variants in the HLA locus (a genomic region on chromosome 6) confer susceptibility to podoconiosis. Specifically, variants in or near the class II HLA genes, namely, *HLA-DQA1*, *HLA-DRB1* and *HLA-DQB1*, were found to be associated with increased susceptibility to podoconiosis. The study findings were further corroborated with a family-based association test. Subsequent high-resolution sequence-based HLA typing showed that HLA-DRB1*0701 and HLA-DQA1*0201 are risk variants for podoconiosis. The study suggested that podoconiosis is a T-cell-mediated inflammatory condition (Tekola Ayele et al. 2012a).

Environment

Some of the environmental factors that facilitate formation of the red clay soils containing the putative inorganic particles that trigger the inflammatory response leading to podoconiosis have been described. Podoconiosis-endemic areas have characteristic red clay soils, elevation >1000 m above sea level and annual rainfall >1000 mm (Price 1974b).

The exact causal agent in red clay soil areas has not yet been identified. A range of studies has suggested that mineral particles present in red clay soils play a role in the pathogenesis of podoconiosis (Price 1972b, 1976a, 1990; Fyfe and Price 1985; Frommel et al. 1993; Abrahams 2002). Electron microscopy microanalysis examination of lower limb lymphatic tissues of barefoot people from Ethiopia indicated the presence of microparticles containing the elements found in clays with some difference in the amount between affected and unaffected individuals (Price and Henderson 1978). Moreover, podoconiosis-endemic areas were free of filariasis; footwear had a protective effect; birefringent silica particles were found in the lymph node macrophages; and the dermal content of silicon, aluminium, iron and trace metals was consistent with local soils, leading to the postulation that podoconiosis was a soil-induced disease (Price 1972b, 1976a, 1990). Price suggested that silicate particles cause subendothelial oedema, endolymphangitis, collagenisation and obliteration of the lymphatic lumen (Price 1976a). Ongoing studies involving geological, spatial and soil chemical analyses are expected to assist in defining the causative environmental agent(s) of podoconiosis.

Disease Presentation

The clinical presentation of podoconiosis varies depending on the time at which healthcare is sought during the course of the disease progression. The majority of patients develop signs and symptoms of podoconiosis in the second and third decades of life. Disease is bilateral but asymmetrical and almost always limited to below the knees (Davey et al. 2007b; Alemu et al. 2011; Geshere Oli et al. 2012; Molla et al. 2012a; Tekola Ayele et al. 2013).

A system for grading the clinical stages of podoconiosis has been developed and validated. The system has five stages, with the first two stages defining disease presentation that can easily be reversed with currently implemented treatment packages. The system has been implemented in podoconiosis treatment and control programmes in Ethiopia to monitor treatment outcomes (Tekola et al. 2008).

Prodromal symptoms of podoconiosis include a burning sensation in the leg, itching and knocking of the big toes while walking. The key early signs of podoconiosis are splaying of the forefoot, transient plantar and lower leg oedema that disappears after overnight rest, thickening of the skin over the anterior and posterior dorsum of the foot and rough, warty and papillomatous growths that look like moss on the anterior one-third and sole of the foot (Price 1983, 1984, 1990) Fig. 2.

The stratum corneum of the lower leg and foot of patients with podoconiosis is significantly less hydrated than that of unaffected controls (Ferguson et al. 2013). With time, the swelling becomes soft and ('water-bag type', Fig. 3) or nodular and fibrotic ('leathery type', Fig. 4).

Late stage disease is characterised by fusion of the interdigital spaces and ankylosis of the inter-phalangeal and ankle joints (Fig. 5) (Cohen 1960; Price 1983, 1984, 1990). Little is known of the molecular pathogenesis of podoconiosis, but early evidence suggests that transforming growth factor β-1 (TGF β-1) may play a

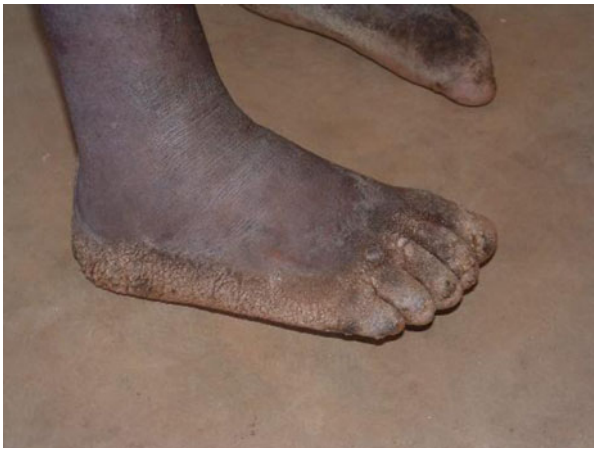


Fig. 2 Slipper distribution of mossy papillomatous changes

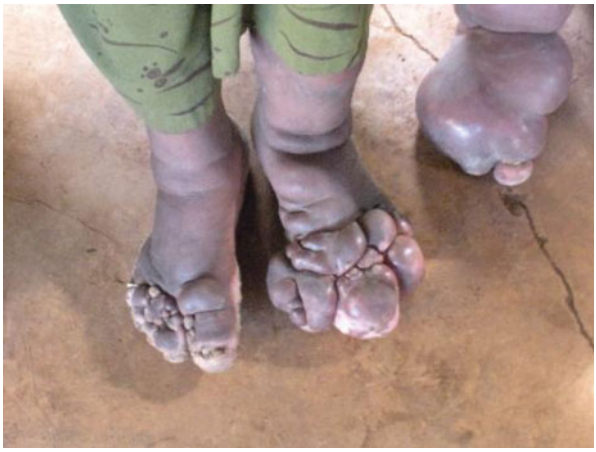


Fig. 3 Extensive soft swelling of both feet

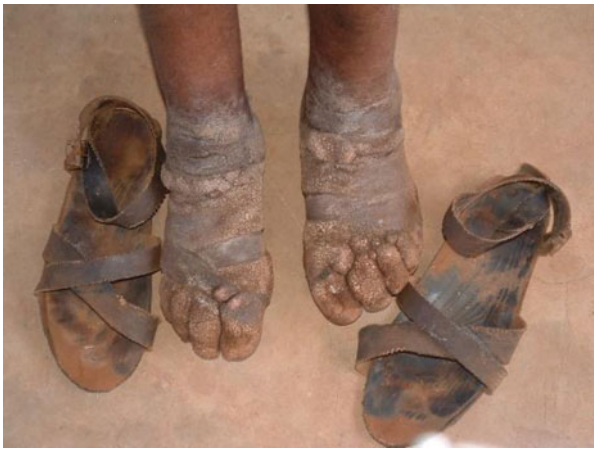


Fig. 4 Nodular, fibrotic swelling of both feet

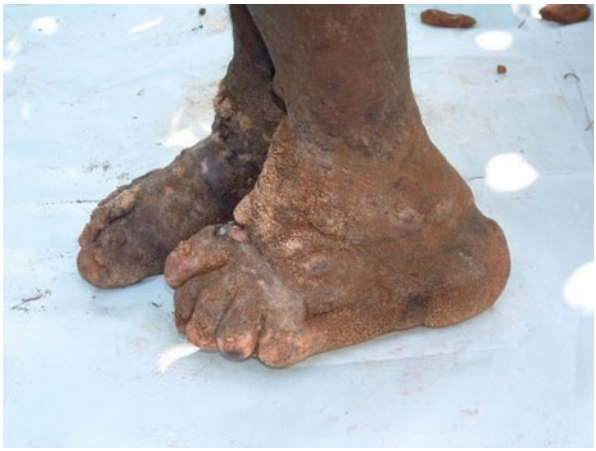


Fig. 5 Late stage (stage 5) podoconiosis in both feet

role (Addisu et al. 2010). The impact of acute dermatolymphangioadenitis (ADLA), a common clinical presentation and frequent cause of morbidity in podoconiosis is described in section "Public health impact" above.

Diagnosis

There is no point-of-care diagnostic tool for podoconiosis. Currently, podoconiosis is a diagnosis of clinical exclusion based on history, physical examination and certain disease-specific tests to exclude common differential diagnoses. Several studies have shown that 30–40 % of podoconiosis patients report having affected blood relatives (Kloos et al. 1992; Geshere Oli et al. 2012b; Molla et al. 2012b; Tekola Ayele et al. 2013). Therefore, enquiring about family history may also assist as a pointer towards the diagnosis of podoconiosis.

The common differential diagnoses of podoconiosis are filarial elephantiasis, lymphoedema of systemic disease and leprotic lymphoedema. Although there are point-of-care diagnostic tests for lymphatic filariasis infection, these are not very sensitive in established filarial infection among advanced cases. The differentiation of podoconiosis from filarial elephantiasis uses a panel approach, including clinical history, physical examination, antigen and antibody tests. The swelling of podoconiosis starts in the foot and progresses upwards (Price 1990), whereas the swelling in filarial elephantiasis starts elsewhere in the leg. Podoconiosis lymphoedema is bilateral, asymmetric, usually confined to below the level of the knees and unlikely to involve the groin (Davey et al. 2007b). In contrast, filarial elephantiasis is commonly unilateral and extends above the knee, usually with groin involvement. In addition to the clinical history and physical examination, an antigen-based ICT test (the Binax©Now Filariasis ICT) can also help to further distinguish between the two lymphoedemas, although the majority of filarial elephantiasis patients are also negative for the antigen-based test. Studies suggest that antibody-based tests such as the Wb123 test may help define the filaria transmission status of a community in areas where few and possibly outlying cases of lymphoedema are found and may help to reduce misclassification of patients.

The other important differential diagnosis is leprotic lymphoedema. In podoconiosis patients, sensory perception of the peripheral nerves is intact in the toes and forefoot, and there are no neurotrophic ulcers or thickened nerves (Davey et al. 2007b). Onchocerciasis has clear clinical features which can easily be distinguished from podoconiosis. Systemic causes of lymphoedema can be ruled out by examination of other organ systems. Some hereditary lymphoedemas can be excluded since they occur at birth or immediately after birth, whereas podoconiosis requires extended exposure to red clay soil.

The lack of a diagnostic tool for podoconiosis is a significant problem. There is a need for an evidence base to identify important clinical features of podoconiosis and the predictive value of each in ascertaining the diagnosis of podoconiosis. Although the panel approach of excluding other causes may be used in research settings, it may not be practical or cost-effective in routine clinical practice or disease surveillance. A recent study has found that clinical examination of patients with

lymphoedema in endemic communities has strong predictive value for podoconiosis and is an adequate means of diagnosing the disease within these communities (Desta et al. 2007; Geshere Oli et al. 2012).

Developing a point-of-care diagnostic tool is vital for future control of podoconiosis, but it is still a distant prospect. Ongoing biomedical studies hope to provide information from which a diagnostic tool might be developed. Since LF and podoconiosis are the major causes of tropical lymphoedema, working with the LF community to produce a highly sensitive test for filarial elephantiasis might also have the spin-off of developing a test that better excludes podoconiosis.

Control Tools and Strategies

The key strategies for podoconiosis control are prevention of contact with irritant soil (primary prevention) and lymphoedema morbidity management (secondary and tertiary prevention).

Primary Prevention of Podoconiosis

Prevention of contact with the (still uncharacterised) mineral trigger encompasses:

- Behavioural measures (using footwear, daily foot washing)
- Environmental measures (replacing earth floors with concrete, paving roads)
- Lifestyle changes (shift from subsistence farming to alternative income-generating activities).

These measures are all predicated on the assumptions that the trigger(s) of podoconiosis are only found in certain irritant volcanic soils, that prolonged contact between bare feet and these soils is necessary for disease pathogenesis and that passage of the trigger through the skin of the feet can be prevented using standard footwear. The evidence for each of these assumptions will be briefly discussed.

Extensive work by EW Price in the 1970s showed fine soil particles to be closely associated with disease prevalence in southern Ethiopia. The prevalence of podoconiosis among people living on ‘tropical red soil’ averaged 5.38 %, which decreased to 2.83 % at the limits of this soil and further to 0.79 % among people living 25 km away from the edge of the soil (Price 1974b). Similar observations relating disease prevalence to soil type were made in Kenya, Rwanda, Burundi and north-west Tanzania (Price 1976a).

Evidence that prolonged contact between bare feet and irritant soils comes from studies in which age of onset is recorded. In community surveys, Kloos et al. noted that most patients reported disease onset in their teens and early twenties (Kloos et al. 1992), while Molla et al. and Alemu et al. found only 0.7 % and 0.6 % of patients to be aged less than 15 years, respectively (Alemu et al. 2011; Molla et al. 2012a).

There is no direct information on the effect of shoes in preventing passage of mineral particles through the skin of the feet. Indirect ecological evidence comes from areas such as the Canary Islands in which podoconiosis was documented in 1867 but no longer exists. No specific disease control programme has been responsible for these changes, which are ascribed by Price to secular changes in shoe-wearing habits (Price 1990).

Evidence for the effectiveness of the behavioural, environmental and lifestyle measures listed above is not yet available. The fact that interest in podoconiosis has only been rekindled in the past decade, together with the long latent period of podoconiosis has meant that long-term follow-up studies of prevention have not been launched. However, given that the preventive intervention (shoe distribution) is low-risk, several podoconiosis projects distribute shoes donated by TOMS, a US-based shoe company with a commitment to match every pair of shoes purchased with a pair of new shoes for a child in need.

However, recent behavioural research has explored the relationship between beliefs about cause of disease and preventive behaviours (Ayode et al. 2012) in endemic communities in Ethiopia. This study demonstrates that people with a nuanced view of the causes of podoconiosis (who are able to consider heritability as a necessary but not sufficient cause) are more likely to perceive themselves as being able to control the disease and are also more likely to espouse positive preventive behaviours, including shoe use and foot washing. Research more closely focussed on barriers to use of shoes revealed disease-specific barriers (fit of shoe, fear of labelling) and more general, structural level barriers related to poverty (price and shoe quality) (Ayode et al. 2013). Taken together, these studies suggest that culturally tailored education programmes that explain the gene x environment basis of podoconiosis may positively influence preventive behaviours. Combining such programmes with broader infrastructural changes to increase accessibility of shoes appears likely to enhance preventive shoe use and foot hygiene behaviours. This hypothesis is currently under test in a trial in southern Ethiopia.

Secondary and Tertiary Prevention of Podoconiosis

Secondary and tertiary prevention of podoconiosis is currently based on lymphoedema management (foot hygiene, compression, exercises and elevation) and use of shoes to reduce exposure to irritant soil. The foot hygiene ‘package’ has evolved independently in several sites in Ethiopia, and while the basic elements at each site are similar, local variations exist. The fundamental elements are:

- Soaking the feet in water
- Washing with soap
- Drying
- Use of an emollient oil, cream or ointment

Antiseptic (Savlon, dilute bleach, salt or *neem* tree [*Azadirachter indica*] extract) may be added to the soaking basin. In some sites, the soap is made with *neem*

extract. Once dry, Vaseline or Whitfield's ointment, cooking oil or *neem*-infused oil may be used. There is as yet no evidence to support the efficacy of one alternative over another.

Pilot evidence for the effectiveness of lymphoedema management comprising soaking with dilute bleach, use of Whitfield's ointment, bandages, exercises and elevation was obtained from an uncontrolled study that followed 30 patients over the course of 1 year (Sikorski et al. 2010). This demonstrated modest clinical improvements (reduction in mean leg circumference and disease stage) and substantial increases in quality of life measurements. While this study did not provide definitive evidence for the lymphoedema management regimen, it offered 'proof of concept' for the design of a much larger randomised controlled trial. The results of this trial, in which the main outcome is frequency of acute dermatolymphangioadenitis (ADLA) and which will include measures of economic impact, are expected in 2016.

There are many similarities between lymphoedema morbidity management for podoconiosis and for filarial lymphoedema, making 'generic' lymphoedema management (which does not distinguish the cause) attractive in countries such as Cameroon, Uganda and Ethiopia in which both NTDs are found. At present, the main differences between management regimes for the two types of lymphoedema are that bandaging is recommended in podoconiosis (where it is particularly effective in soft 'water-bag'-type swelling) but is not in filarial lymphoedema, due to safety concerns. Anecdotally, podoconiosis patients can be trained to bandage their legs safely, and formal assessment will be carried out in the context of the lymphoedema management trial described above.

Programmatic Aspects

Many features of morbidity management for podoconiosis mean that most treatment can be carried out by patients themselves, with little intervention from healthcare professionals. Expert patients (patients who have been trained to successfully manage their condition and assist others in doing so) can be trained to identify patients in endemic areas (Desta et al. 2007) and to guide treatment for uncomplicated lymphoedema (Davey and Burridge 2009). Health professional input is important in cases of diagnostic uncertainty, to manage ADLA, to evaluate for nodulectomy if prominent nodules prevent shoe wearing and to identify coexisting pathologies including jiggers, chromoblastomycosis and carcinoma.

Recent content analysis based on a new podoconiosis programme in northern Ethiopia identified 16 key steps to establishment of a sustainable, community-led programme (Tomczyk et al. 2012). These steps (grouped into six domains) included gathering initial data, sensitisation, development of infrastructure, initiation of treatment activities, awareness raising and follow-up. Few health professional curricula include information on podoconiosis; thus, training of health professionals and other stakeholders was identified as important in the early stages of programme initiation.

Challenges of Programme Implementation

Intervention is still so new in podoconiosis that challenges exist chiefly in programme initiation rather than implementation. The key challenge faced is lack of awareness that the condition exists and is different from lymphatic filariasis, the other main cause of lymphoedema in the tropics. This lack of awareness is evident among health professionals, academics and Ministry of Health and World Health Organization staff. There appears to be many reasons for the lack of awareness of podoconiosis, including lack of a positive diagnostic test (see section "Basic biology"), a phenotype very similar to filarial lymphoedema and lack of understanding of simple prevention and treatment strategies. Diagnostic confusion with lymphatic filariasis has led to podoconiosis-affected communities in Cameroon and Burundi mistakenly being given DEC and albendazole.

As for most neglected tropical diseases, podoconiosis primarily affects remote, rural populations. These populations are commonly underserved in terms of health facilities and personnel and have little voice at regional or national level. In addition, access to both water and shoes (necessary for disease prevention and treatment) is lower in these communities. A qualitative study of factors influencing attendance at clinic for continued treatment showed that distance, worries about stigma, illness and misconceptions about treatment were all challenges for patients' continuing attendance at clinics to attend (Tora et al. 2012).

Finally, although a global voice for podoconiosis now exists (Foot*work*, the International Podoconiosis Initiative (Davey et al. 2012), this organisation is still young and relatively small. Given that there are still few individuals worldwide with expertise in podoconiosis, Foot*work* aims to draw in complementary experience from the more established NTDs as it grows and develops.

Further Research for Policy and Control

Mapping of NTDs is a rapidly evolving science that combines geographic, epidemiological and statistical methods. The development of rapid mapping methods for lymphatic filariasis and onchocerciasis has enabled expansion of the respective elimination programmes. Adaption of these methods to podoconiosis mapping will have important consequences in planning the control and future elimination of the disease. Mapping of the disease burden of podoconiosis will help target resources, monitor control progress and advocate for investment in podoconiosis prevention, control and ultimately elimination. Ethiopia and Rwanda are the two countries currently doing nationwide mapping of podoconiosis. Such mapping activities will generate important information on the distribution of podoconiosis, population at risk and treatment and prevention needs, and enable cost estimates of podoconiosis control to be generated. Mapping of disease must be accompanied by development of endemicity classifications and criteria for disease elimination before policies can be finalised.

The widespread misconception that podoconiosis is inevitable because it is hereditary may aggravate stigma against people with podoconiosis if precautions are not taken to communicate the gene x environment message clearly. Qualitative research into the links between beliefs about heredity and preventive behaviours (Ayode et al. 2012), has led to the development of community-wide and household education approaches currently under trial (McBride et al. 2015). Should these approaches prove effective, further research on scaling up delivery of these interventions will be necessary.

Once the results of the trial of lymphoedema management (Negussie et al. 2015) are known, further smaller trials will be necessary to test the effectiveness and cost-effectiveness of local adaptations (e.g. type of soap or antiseptic, duration of supervised treatment). It will also be important to provide stronger evidence of effectiveness of shoes in prevention of disease, at the least from observational studies comparing incidence of disease in sites in which shoes have been distributed for a number of years with that in sites lacking shoe distribution.

Diagnosis of podoconiosis is a continued challenge. Until point-of-care diagnostic tests are designed, standardising clinical diagnosis will be important, and would involve establishing the predictive value of signs and symptoms of podoconiosis. Previous studies have indicated that clinical diagnosis is an accurate and workable approach in podoconiosis-endemic settings (Desta et al. 2007). Similar studies must be conducted in settings in which lymphatic filariasis and podoconiosis potentially overlap. In addition, the ability of the algorithm to exclude other causes of lymphoedemas must be formally evaluated.

Finally, a costing tool for prevention and management of podoconiosis is an important area of future research. Such a tool will help programme planers to accurately estimate programme costs and facilitate proper implementation, and will help advocacy and resource mobilisation.

The combination of understanding the distribution of podoconiosis, and optimising treatment and prevention activities will help to guide policy and practice in endemic countries and ultimately the elimination of podoconiosis.

Outlook for the Next Decade

The past 10 years have been marked by changes in the way podoconiosis is viewed by endemic country policy makers, global funding organisations and researchers. In February 2011, the World Health Organization included podoconiosis in its list of NTDs (http://www.who.int/neglected_diseases/diseases/podoconiosis/en/). In 2013, the Ethiopian Ministry of Health included podoconiosis in the National Master Plan for NTDs and in modules for the upgrading of Health Extension Workers. New initiatives including Footwork, the International Podoconiosis Initiative and the Ethiopian National Podoconiosis Action Network have been formed with the shared vision of a world free of podoconiosis. The UK Wellcome Trust, the UK Medical Research Council and the US National Institutes of Health have funded research on

genetics, geospatial, behavioural and morbidity management aspects of podoconiosis in Ethiopia and Cameroon. The past decade has also witnessed small-scale, yet successful, podoconiosis prevention and treatment programmes that can be adopted and scaled up (Tomczyk et al. 2012). These achievements have created bright prospects for the global community and the achievement of a podoconiosis-free world is foreseeable.

Controlling podoconiosis is achievable because no biological agent or vector involved in podoconiosis has been identified, the global scale of the problem is relatively small, the means for podoconiosis prevention and control are safe and additional strategies for prioritisation of resources such as use of family health history (Tekola Ayele et al. 2012b) and risk maps can be implemented.

Realisation of these plans over the next decade needs a renewed model as part of the global movement to eradicate other NTDs. The currently uncoordinated efforts by small-scale programmes on podoconiosis must be integrated into a framework led by endemic country governments. This must be backed by robust public health policies, by sustainable resource allocation and by inclusion of podoconiosis in the formal education curricula of health professionals at all levels. Government support is only one step. Public-private partnerships must be strengthened and should match public resources (of government and research institutions) with private financial investments. Treatment of podoconiosis should be integrated with other forms of lymphoedema and skin problems, and services should be widely accessible to patients in primary healthcare facilities.

Basic science and applied research should continue to drive and improve upon existing prevention and treatment modalities. For example, despite the effectiveness of lymphoedema management against early clinical disease, no effective treatment is available to reverse debilitating, advanced stage disease. Given the fact that many patients present with advanced disease, investment in cutting-edge therapeutic solutions is crucial and may be responsible in the future for considerable improvements in quality of life of patients and in the overall social capital and economy. Finally, global-level advocacy and funding will play key roles in shaping the pathway towards a world free of podoconiosis.

Conclusion

- Podoconiosis is a preventable, treatable, non-infectious form of tropical lymphoedema.
- Prevalence >1 % has been documented in several countries in sub-Saharan Africa.
- The condition appears to arise from mineral particle-induced inflammation on a background of genetic susceptibility.
- No diagnostic tool for podoconiosis is available, so differentiation from the lymphoedema of lymphatic filariasis is based on clinical examination and exclusion of microfilariae.

- Prevention of disease is through protection of the feet from exposure to irritant clay soils.
- Simple foot washing, use of emollients and bandaging appears to reverse lymphoedema in early stage disease.

Acknowledgement KD and GD are supported by a Wellcome Trust PHATIC Training Fellowship (099876) and a Wellcome Trust University Award (091956), respectively.

References

Abrahams PW (2002) Soils: their implications to human health. Sci Total Environ 291(1–3):1–32

Addisu S, El-Metwally TH, Davey G, Worku Y, Titheradge MA (2010) The role of transforming growth factor-beta1 and oxidative stress in podoconiosis pathogenesis. Br J Dermatol 162(5):998–1003

Alemu G, Tekola Ayele F, Daniel T, Ahrens C, Davey G (2011) Burden of podoconiosis in poor rural communities in Gulliso woreda, West Ethiopia. PLoS Negl Trop Dis 5(6):e1184

Ayode D, McBride C, de Heer H, Watanabe E, Gebreyesus T, Tadele G, Tora A, Davey G (2012) The association of beliefs about heredity with preventive and interpersonal behaviors in communities affected by podoconiosis in rural Ethiopia. Am J Trop Med Hyg 87(4):623–630

Ayode D, McBride CM, de Heer HD, Watanabe E, Gebreyesus T, Tora A, Tadele G, Davey G (2013) A qualitative study exploring barriers related to use of footwear in rural highland Ethiopia: implications for neglected tropical disease control. PLoS Negl Trop Dis 7(4):e2199

Cohen LB (1960) Idiopathic lymphoedema of Ethiopia and Kenya. East Afr Med J 37:53–74, 37: 53–74

Davey G (2009) Recent advances in podoconiosis. Ann Trop Med Parasitol 103(5):377–382

Davey G (2010) Podoconiosis, non-filarial elephantiasis, and lymphology. Lymphology 43(4):168–177

Davey G, Burridge E (2009) Community-based control of a neglected tropical disease: the mossy foot treatment & prevention association. PLoS Negl Trop Dis 3(5):e424

Davey G, GebreHanna E, Adeyemo A, Rotimi C, Newport M, Desta K (2007a) Podoconiosis: a tropical model for gene-environment interactions? Trans R Soc Trop Med Hyg 101(1):91–96

Davey G, Tekola F, Newport MJ (2007b) Podoconiosis: non-infectious geochemical elephantiasis. Trans R Soc Trop Med Hyg 101(12):1175–1180

Davey G, Bockarie M, Wanji S, Fuller C, Fox L, Mycoskie M, Gruin M, Tsegaye A, Ayele FT, Newport M (2012) Launch of the international podoconiosis initiative. Lancet 379(9820):1004

Deribe K, Brooker SJ, Pullan RL, Hailu A, Enquselassie F, Reithinger R, Newport M, Davey G (2013a) Spatial distribution of podoconiosis in relation to environmental factors in Ethiopia: a historical review. PLoS One 8(7):e68330

Deribe K, Tomczyk S, Mousley E, Tamiru A, Davey G (2013b) Stigma towards a neglected tropical disease: felt and enacted stigma scores among podoconiosis patients in northern Ethiopia. BMC Public Health 13:1178

Desta K, Ashine M, Davey G (2003) Prevalence of podoconiosis (endemic non-filarial elephantiasis) in Wolaitta, Southern Ethiopia. Trop Doct 32:217–220

Desta K, Ashine M, Davey G (2007) Predictive value of clinical assessment of patients with podoconiosis in an endemic community setting. Trans R Soc Trop Med Hyg 101:621–623

Ferguson JS, Yeshanehe WE, Matts PJ, Davey G, Mortimer PS, Fuller LC (2013) Assessment of skin barrier function in podoconiosis: measurement of stratum corneum hydration and transepidermal water loss. Br J Dermatol 168(3):550–5544

Franklin H, Tora A, Deribe K, Reda AA, Davey G (2013) Development of a scale to measure stigma related to podoconiosis in Southern Ethiopia. BMC Public Health 13(1):1178

Frommel D, Ayranci B, Pfeifer HR, Sanchez A, Frommel A, Mengistu G (1993) Podoconiosis in the Ethiopian rift valley. Role of beryllium and zirconium. Trop Geogr Med 45(4):165–167

Fyfe NC, Price EW (1985) The effects of silica on lymph nodes and vessels – a possible mechanism in the pathogenesis of non-filarial endemic elephantiasis. Trans R Soc Trop Med Hyg 79(5):645–651

Gebrehanna E (2005) The social burden of podoconiosis in Wolaita zone. MPH thesis, Addis Ababa University, Addis Ababa

Geshere Oli G, Tekola Ayele F, Petros B (2012) Parasitological, serological, and clinical evidence for high prevalence of podoconiosis (non-filarial elephantiasis) in Midakegn district, central Ethiopia. Trop Med Int Health 17(6):722–726

Kloos H, Kello AB, Addus A (1992) Podoconiosis (endemic non-filarial elephantiasis) in two resettlement schemes in western Ethiopia. Trop Doct 22:109–112

McBride CM, Price CS, Ayode D, Tora A, Farrell D, Davey G. A cluster randomized intervention trial to promote shoe use by children at high risk for podoconiosis. International Journal of Health Sciences and Research 2015; 5(6):518–28

Molla YB, Tomczyk S, Amberbir T, Tamiru A, Davey G (2012a) Podoconiosis in East and west gojam zones, northern ethiopia. PLoS Negl Trop Dis 6(7):e1744

Molla YB, Tomczyk S, Amberbir T, Tamiru A, Davey G (2012b) Patients' perceptions of podoconiosis causes, prevention and consequences in East and West Gojam, Northern Ethiopia. BMC Public Health 12:828

Mousley E, Deribe K, Tamiru A, Davey G (2013) The impact of podoconiosis on quality of life in Northern Ethiopia. Health Qual Life Outcomes 11:122

Negussie H, Kassahun MM, Fegan G, et al (2015) Podoconiosis treatment in northern Ethiopia (GoLBet): study protocol for a randomised controlled trial. Trials 16:307. doi: 10.1186/s13063-015-0818-7

Onapa AW, Simonsen PE, Pedersen EM (2001) Non-filarial elephantiasis in the Mt. Elgon area (Kapchorwa District) of Uganda. Acta Trop 78(2):171–176

Oomen AP (1969) Studies on elephantiasis of the legs in Ethiopia. Trop Geogr Med 21:3

Price EW (1972a) A possible genetic factor in non-filarial elephantiasis of the lower legs. Ethiop Med J 10(3):87–93

Price EW (1972b) The pathology of non-filarial elephantiasis of the lower legs. Trans R Soc Trop Med Hyg 66(1):150–159

Price EW (1974a) Endemic elephantiasis of the lower legs in Ethiopia an epidemiological survey. Ethiop Med J 12(2):77–90

Price EW (1974b) The relationship between endemic elephantiasis of the lower legs and the local soils and climate. Trop Geogr Med 26(3):225–230

Price E (1976a) The association of endemic elephantiasis of the lower legs in East Africa with soil derived from volcanic rocks. Trans R Soc Trop Med Hyg 4:288–295

Price EW (1976b) Endemic elephantiasis of the lower legs in Rwanda and Burundi. Trop Geogr Med 28:283–290

Price EW (1983) Endemic elephantiasis: early signs and symptoms, and control. Ethiop Med J 21(4):243–253

Price EW (1984) Pre-elephantiasic stage of endemic nonfilarial elephantiasis of lower legs: 'podoconiosis'. Trop Doct 14(3):115–119

Price E (1990) Podoconiosis: non-filarial Elephantiasis. Oxford Medical publications, Oxford

Price EW, Henderson WJ (1978) The elemental content of lymphatic tissues of barefooted people in Ethiopia, with reference to endemic elephantiasis of the lower legs. Trans R Soc Trop Med Hyg 72(2):132–136

Sikorski C, Ashine M, Zeleke Z, Davey G (2010) Effectiveness of a simple lymphoedema treatment regimen in podoconiosis management in southern Ethiopia: one year follow-up. PLoS Negl Trop Dis 4(11):e902

Tekola Ayele F, Adeyemo A, Finan C, Hailu E, Sinnott P, Burlinson ND, Aseffa A, Rotimi CN, Newport MJ, Davey G (2012a) HLA class II locus and susceptibility to podoconiosis. N Engl J Med 366(13):1200–1208

Tekola Ayele F, Adeyemo A, Rotimi CN (2012b) Using a "genomics tool" to develop disease prevention strategy in a low-income setting: lessons from the podoconiosis research project. J Community Genet 3(4):303–309

Tekola Ayele F, Alemu G, Davey G, Ahrens C (2013) Community-based survey of podoconiosis in Bedele Zuria woreda, southwest Ethiopia. Int Health 5(2):119–125

Tekola F, Mariam DH, Davey G (2006) Economic costs of endemic non-filarial elephantiasis in Wolaita Zone, Ethiopia. Trop Med Int Health 11(7):1136–1144

Tekola F, Ayele Z, Mariam DH, Fuller C, Davey G (2008) Development and testing of a de novo clinical staging system for podoconiosis (endemic non-filarial elephantiasis). Trop Med Int Health 13(10):1277–1283

Tekola F, Bull S, Farsides B, Newport MJ, Adeyemo A, Rotimi CN, Davey G (2009) Impact of social stigma on the process of obtaining informed consent for genetic research on podoconiosis: a qualitative study. BMC Med Ethics 10:13(13)

Tomczyk S, Tamiru A, Davey G (2012) Addressing the neglected tropical disease podoconiosis in Northern Ethiopia: lessons learned from a new community podoconiosis program. PLoS Negl Trop Dis 6(3):e1560

Tora A, Davey G, Tadele G (2011) A qualitative study on stigma and coping strategies of patients with podoconiosis in Wolaita zone, Southern Ethiopia. Int Health 3(3):176–181

Tora A, Davey G, Tadele G (2012) Factors related to discontinued clinic attendance by patients with podoconiosis in southern ethiopia: a qualitative study. BMC Public Health 12:902

Wanji S, Tendongfor N, Esum M, Che JN, Mand S, Tanga Mbi C, Enyong P, Hoerauf A (2008) Elephantiasis of non-filarial origin (podoconiosis) in the highlands of north-western Cameroon. Ann Trop Med Parasitol 102(6):529–540

Yakob B, Deribe K, Davey G (2008) High levels of misconceptions and stigma in a community highly endemic for podoconiosis in southern Ethiopia. Trans R Soc Trop Med Hyg 102(5):439–444

Yakob B, Deribe K, Davey G (2010) Health professionals' attitudes and misconceptions regarding podoconiosis: potential impact on integration of care in southern Ethiopia. Trans R Soc Trop Med Hyg 104(1):42–47

Schistosomiasis

Tony Danso-Appiah

Contents

T. Danso-Appiah
Department of Epidemiology and Disease Control, School of Public Health, College of Health Sciences, University of Ghana, P. O. Box LG 13, Legon, Ghana
e-mail: tdappiah@yahoo.co.uk

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_11

Abstract Schistosomiasis, a neglected tropical disease, is caused by the blood fluke that resides in the blood vessels in the human hosts. It presents as an acute, but mostly chronic, illness and is commonly found in the least developed countries with poor healthcare systems. Forty countries in Africa were endemic for schistosomiasis in sub-Saharan Africa (SSA) in 2010. Of the five species, *Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, *S. intercalatum* and *S. mekongi*, that can infect humans, it is *S. haematobium* which causes urogenital schistosomiasis and *S. mansoni* and *S. japonicum* which cause intestinal schistosomiasis, which have public health importance, being responsible for most of the disease in SSA. Children, women and farmers in rural communities who depend on water contact for recreational, domestic or occupational activities are most vulnerable to the infection. Cross-border movements from unstable and conflict zones in SSA have contributed to the spread of the disease to previously non-endemic foci, and emigration from rural areas into the cities for economic opportunities has introduced the disease into some urban areas. Schistosomiasis causes around 4.5 million DALYs annually, with around 90 % of the burden of disease concentrated in SSA. Annual loss from disability due to schistosomiasis in Africa was estimated to be nearly half a billion US dollars approximately 70 % of the global cost. The life cycle involves an intermediate planorbid freshwater snail hosts – *Bulinus truncatus and Biomphalaria pfeifferi* – in the transmission of the infection with sexual and asexual stages. Man is the definitive host. Pathology and clinical morbidity of schistosomiasis are caused by eggs trapped in tissues and symptoms and signs of the disease present among other things, as haematuria in urinary schistosomiasis and abdominal pain, diarrhoea which can be bloody and blood in stool in intestinal schistosomiasis. Long-term complications from schistosomiasis include urinary tract infections, bladder calcification, hydronephrosis/hydroureter, kidney failure, lesions of the liver, portal vein, and spleen, leading to periportal fibrosis, hepatomegaly, splenomegaly, pipe-stem portal fibrosis, ascites, nodules in the vulva and bladder cancer. Microscopic examination for parasite eggs in the urine or stool is considered definitive for the diagnosis of the infection. Control of schistosomiasis is by transmission and morbidity control using health education, safe water supply, molluscicding, environmental management, chemotherapy praziquantel (PZQ) as drug of choice or combination of these measures. Whether or not schistosomiasis can only be controlled or can be eliminated using the current MDA with anthelminthes is an ongoing debate.

Keywords Urinary/urogenital • *S. mansoni*/intestinal schistosomiasis • *S. haematobium*/urinary/urogenital schistosomiasis drug/medicine/treatment

Epidemiology of the Disease

Geographic Distribution

Schistosomiasis is mostly a tropical disease caused by the blood fluke, a group of flat worms that reside in the blood vessels in the human hosts. It presents as an acute, but mostly chronic illness. Due to its geographic and demographic distribution, the disease is listed as one of the neglected tropical diseases (NTDs). It is commonly found in countries among the least developed whose health systems face difficulties to provide basic care at the primary health level (Chitsulo et al. 2000). Five species, namely, *Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, *S. intercalatum* and *S. mekongi*, can infect humans, but the three with public health importance are *S. haematobium* (mostly endemic in Africa and the Middle East), *S. mansoni* (common in the tropics and subtropics) and *S. japonicum* (mainly found in the People's Republic of China and the Philippines) (WHO 2012). *S. haematobium* causes urogenital schistosomiasis, while *S. mansoni* and *S. japonicum* cause intestinal schistosomiasis. According to WHO AFRO Regional Report, 40 countries were endemic for schistosomiasis in sub-Saharan Africa (SSA) in 2010 with the most severely affected countries being Angola, Central African Republic, Chad, Ghana, Madagascar, Malawi, Mali, Mozambique, Nigeria, Senegal, Uganda, The United Republic of Tanzania, Zambia and Zimbabwe (Fig. 1).

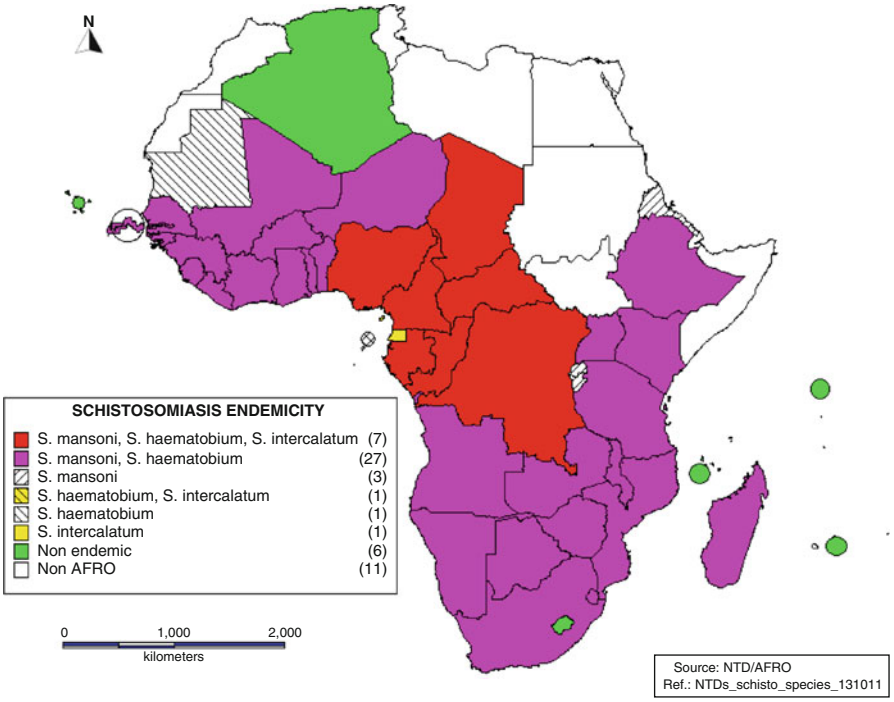


Fig. 1 Schistosomiasis endemic countries in Africa (Source: WHO AFRO)

Demographic Distribution

A major feature of the infection is that it shows a characteristic aggregated distribution and overdispersion of worms. In a typical endemic setting, it has been estimated that 20 % of the population usually carry approximately 80 % of the total infection; the remaining 80 % of the population harbour few worms that constitute only about 20 % of the overall population of worm load (Anderson and May 1992; Woolhouse et al. 1991). The infection also displays age-intensity profile that is typically convex, with prevalence and intensity of infection rising in childhood, peaking in adolescence and decreasing in adulthood to a relatively stable phase (King et al. 1988; Mitchell et al. 2008). Children, women and farmers in disadvantaged rural communities without access to adequate sanitation or clean water and who depend on water contact for recreational, domestic or occupational activities are most vulnerable to the infection. Poverty is a major determinant of schistosomiasis but attempts to improve the livelihood of poor farmers through the creation of water-related economic schemes have in turn led to the promotion of transmission of the infection (Chitsulo et al. 2000; Poda et al. 2004; Steinmann et al. 2006).

Urogenital schistosomiasis and intestinal schistosomiasis are responsible for most of the disease in SSA. In some countries, there is an overlap in distribution, resulting in mixed infection in majority of the infected persons. *S. intercalatum* which causes another form of intestinal schistosomiasis is endemic in six countries in Central and West Africa, namely, Democratic Republic of Congo, Gabon, Cameroon, Central African Republic, Chad and Sao Tome. It has recently been reported in travellers returning from Mali, West Africa, but this is yet to be officially confirmed. This chapter focuses on the two common schistosome types in SSA, namely, *S. haematobium* and *S. mansoni*, with reference to the other species where necessary.

Impact of Conflict, Migration and Tourism on Spread of the Disease

Cross-border movements from unstable and conflict zones in SSA have contributed to the spread of the disease to previously non-endemic foci (Chitsulo et al. 2000). As the economy of most of these countries is concentrated in the urban centres and cities, there has been a trend of emigration from rural areas into the cities for economic opportunities. The rural-to-urban migration has introduced the disease into some urban areas. In non-endemic countries in Europe, such as Denmark, England, Germany, Netherlands, Spain and Switzerland, the prevalence of imported schistosomiasis is rising, partly because of an increase in travelling to endemic areas and partly to emigration from these areas. The rise in the number of imported cases of schistosomiasis is creating a new diagnostic and management challenge to the health systems of these countries (Grobusch et al. 2003; Bierman et al. 2005;

Helleberg and Thybo 2010). Travellers embarking on ecotourism and diving tours in endemic destinations in Africa are the most at risk (Schwartz et al. 2005; Kinkel et al. 2012). However, records show that in 2005, two thirds of all imported cases of schistosomiasis to Europe were mostly immigrants and refugees who had fled conflicts and wars in some parts of SSA (Hatz 2005).

Life Cycle and Mode of Transmission

Schistosomiasis has a complex life cycle that involves an intermediate snail host and sexual and asexual stages (Fig. 2). Man is the definitive host and some species of the planorbid freshwater snails are the intermediate hosts in the transmission of the infection: *Bulinus truncatus* for *S. haematobium* and *Biomphalaria pfeifferi* for *S. mansoni*. The asexual reproduction occurs in the snail, whereas the sexual reproduction takes place in the human host (Hoffmann and Dunne 2003). The worms do not multiply in the human host. People infected with *S. haematobium* worms excrete the parasite eggs in their urine and *S. mansoni* eggs in faeces. Under optimal conditions, the eggs hatch to release miracidia (larvae) which swim to locate and penetrate a specific freshwater snail, the intermediate host. Within the snail, the miracidia undergo a two-staged developmental process to produce the infective larvae called

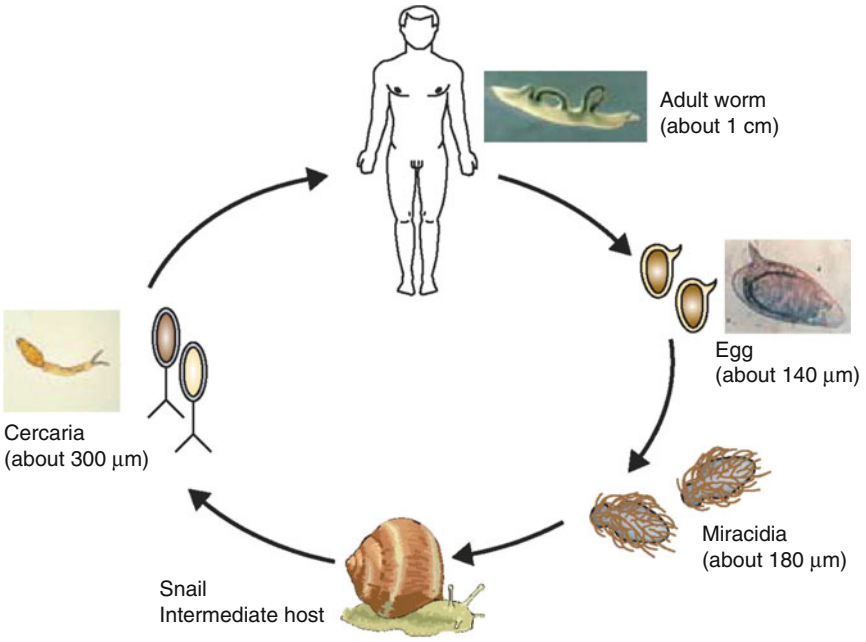


Fig. 2 Life cycle of schistosome worm and mode of transmission of schistosomiasis (Courtesy: Hoffmann and Dunne *Genome Biology* 2003)

cercariae within 4–6 weeks. Cercariae are phototropic and their release from the snail is triggered by sunlight, mostly around midday, in the tropics which tends to coincide with the peak hours of water contact activities by children and women. It has been reported that a snail infected by one miracidium can release thousands of cercariae every day for months (Gryseels et al. 2006). Upon release into the water, the cercariae can swim for up to 72 h when they must locate and penetrate the skin of the human host. Their infectivity potential slows and plateaus around nine hours post-release (Whitfield et al. 2003). The infection is acquired when the infective cercariae penetrate a person's skin upon contact with contaminated water bodies. Upon entering the skin of the human host, the cercariae shed their tail and become schistosomulae which remain in the skin for up to 2 days before locating a post-capillary venule, migrate through the venous system, the right chamber of the heart, the lungs, the mesenteric arteries and the liver via the portal vein.

Eight to 10 days post-penetration of the host's skin, the worm migrates to the liver sinusoids, develops an oral sucker and begins to feed on red blood cells. Schistosomes undergo developmental processes throughout their migratory phases until finally locating and residing in the venous plexus of the urinary bladder (*S. haematobium* worms) or superior mesenteric veins draining the large intestine (*S. mansoni* worms). A schistosome worm reaches maturity in 6–8 weeks when a male and a female worm pair up in a groove formed by the male called the gynaecophoric channel. Here, the male worm holds the longer and slender female where mating takes place and the female worms begin to produce a large number of eggs ($\approx$ 300 eggs per day) (Davis 2009). An adult worm usually lives for 3–5 years, but some can live up to 30 years (Warren 1982) and produce up to 600 billion schistosomes during their lifetime (Gryseels et al. 2006). Schistosome eggs can survive for up to 7 days.

Pathology and Disease Presentation

Pathology and clinical morbidity of schistosomiasis are caused by eggs trapped in tissues but not the worms themselves, and symptoms and signs of the disease are location specific. Within the human body, eggs produced by the worms are moved progressively across the walls of blood vessels towards the lumen of the bladder and ureters for excretion with the urine (*S. haematobium*) or the intestine to be excreted with the faeces (*S. mansoni*). In the process, a substantial number, up to half, of the eggs released by the worm become trapped in tissues and initiate immune-induced inflammatory reactions that lead to pathology and morbidity (Richter 2003; King and Dangerfield-Cha 2008). Although most individuals with few schistosome worms, especially adults, remain asymptomatic, about 80 % of infected children present with one or more symptoms of the disease in the early stages of the infection (Mott et al. 1983; Gryseels and Polderman 1987; Olds and Dasarathy 2000). The main signs and symptoms related to schistosomiasis are summarised in Table 1.

Table 1 Schistosomiasis-related pathology and clinical presentation

Stage of symptom	*S. haematobium*	*S. mansoni*	Both (non-specific)
Katayama syndrome[a]	Itchy skin	Itchy skin	Fever
	Nephropathy	Abdominal pain	Fatigue
		Diarrhoea (with or without blood)	Muscle ache
		Nephropathy	Non-productive cough
			Lymphadenopathy
			Eosinophilia
Early[b]	Haematuria	Diarrhoea	Anaemia
	Dysuria	Blood in stool/bloody diarrhoea	Fatigue
		Abdominal pain	
		Gastrointestinal bleeding	
		Hepatomegaly	
		Splenomegaly	
Late stage[c]	Bladder wall thickening	Colonic polyps	Anaemia
	Bladder wall calcification	Cirrhosis of the liver	Fatigue
	Bladder stones	Pipe-stem portal fibrosis	Nutritional deficiencies
	Secondary bacterial infection	Portal hypertension	Poor growth
	Higher risk for ectopic pregnancies	Varicose veins	Memory loss
	Infertility	Haematemesis	Slower reaction time
	Bladder abnormal pyelon dilation	Haemorrhage from rupturing varicose veins	Lower scores in cognitive ability
	Distal ureter hydronephrosis	Haemorrhagic shock	Low birth weight
	Pyelonephritis	Gallbladder cancer	
	Anuria	Liver cancer	
	Hydroureter		
	Kidney failure		
	Squamous cell carcinoma		

Source: Adapted from Danso-Appiah (2009)
Haematuria (blood in urine), dysuria (painful urination), hepatomegaly (enlargement of the liver), splenomegaly (enlargement of the spleen), anuria (no urine excretion)
[a]Occurs a few days or weeks after exposure to the infection
[b]May occur a few weeks or months after the infection
[c]Insidious and may take a long time depending on the intensity of infection

Katayama Syndrome

The acquisition of cercariae may be followed by an initial rash or itchy skin at the site of penetration. This may be followed by an acute illness called Katayama's syndrome within 4–8 weeks following exposure to the infection that may result in a systemic hypersensitivity reaction characterised by fever, fatigue, muscle aches, abdominal pain, diarrhoea, non-productive cough, lymphadenopathy and eosinophilia. There may also be pain in the upper right part of the abdomen just below the rib cage. Katayama syndrome is most common with *S. mansoni* and *S. japonicum* infections. It mainly occurs following primary infection in individuals with low or no protective immunity, such as tourists visiting an endemic area for the first time. Katayama syndrome is thought to be triggered by maturation and migration of schistosomula within the host (Zuidema 1981; Istre et al. 1984). The patient recovers spontaneously after 2–10 weeks, but some develop persistent and more serious disease. If symptoms do not abort, it can lead to other complications such as weight loss, dyspnoea, diarrhoea, diffuse abdominal pain, widespread rash, hepatosplenomegaly and toxaemia.

Early Symptoms of an Established Disease

The main early symptom of established infection with *S. haematobium* is blood in the urine (haematuria) or terminal blood after urination, appearing 10–12 weeks after the infection. This may be accompanied by painful urination (dysuria). There is evidence that parasite-induced pathological changes of the bladder and abnormal pyelon dilation of at least one of the kidneys are common in children in the early stages of the infection (Brouwer et al. 2003). This suggests that development of pathology begins far earlier in children than previously thought. For intestinal schistosomiasis due to *S. mansoni*, the early symptoms are non-specific but usually include abdominal pain, diarrhoea (which can be bloody) and blood in stool (Gryseels et al. 1992; Lengeler et al. 2002). These symptoms are caused by cellular granulomatous inflammatory reactions around eggs trapped in the intestinal tissues. In spite of the fact that a large number of eggs are deposited in the small intestine, most severe infection-related lesions such as colonic polyps occur in the large intestine (Cheever et al. 1978). It is commonly accepted that intensity and duration of infection determine severity of the disease, but some recent studies have challenged this assumption and suggested that the mere presence of the infection and not necessarily intensity determines morbidity (King and Dangerfield-Cha 2008), although further evidence is warranted to confirm or refute this. Inflammatory reactions in the liver lead to hepatosplenic schistosomiasis, which can manifest as hepatomegaly and splenomegaly within a couple of months from heavy infections or many years

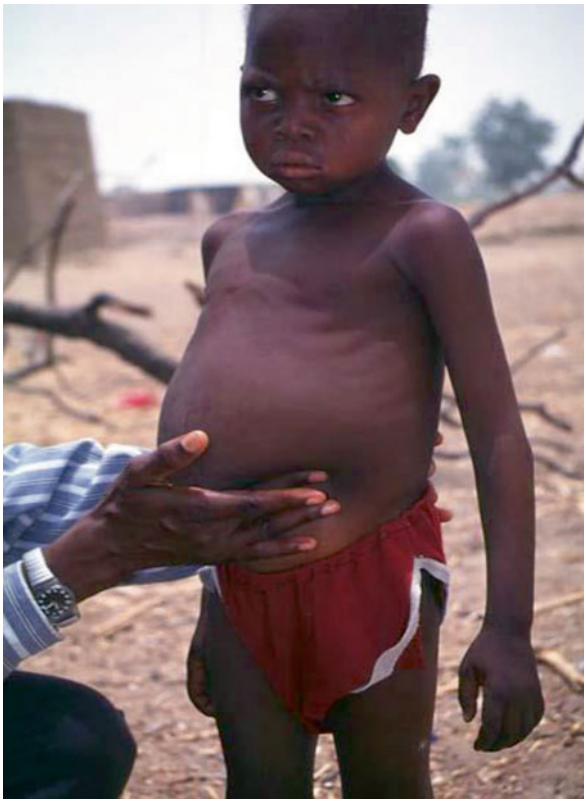


Fig. 3 Hepatosplenomegaly in schistosomiasis patient

after light infections (Fig. 3). It should be noted that chronic schistosomiasis affects mainly individuals with long-standing or repeated infections.

Late-Stage Symptoms and Complications

Long-term complications caused by schistosomiasis are mostly insidious. For *S. haematobium* infection, granulomatous changes and ulcers of the bladder wall and ureter can lead to bladder obstruction, dilatation, secondary urinary tract infections and subsequent bladder calcification. Photomicrography of the bladder in *S. haematobium* infection may show clusters of the parasite eggs with intense eosinophilia (Fig. 4). Diffused or localised wall thickening of the bladder and distal ureter hydronephrosis or hydroureter may eventually lead to kidney failure (Kardorff and Doehring 2001; WHO 2002a). In females, genital lesions resulting from the infection may present with vaginal bleeding, pain during sexual intercourse and nodules

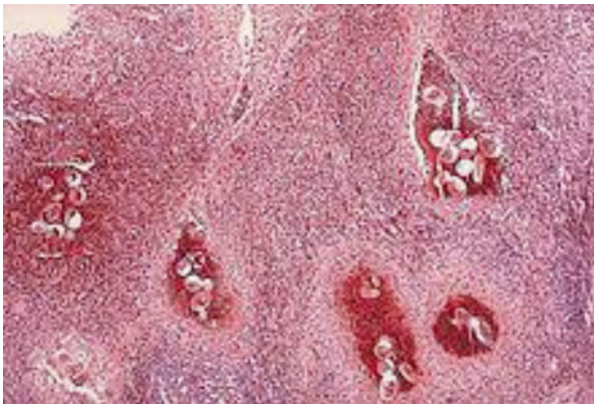


Fig. 4 Photomicrography of the bladder in *S. haematobium* infection, showing clusters of the parasite eggs with intense eosinophilia (Source: Centre for Disease Control (CDC))

in the vulva. In men, urogenital schistosomiasis can induce pathology of the seminal vesicles, prostate and other organs that may decrease male vitality and fertility. Urogenital schistosomiasis is also associated with increased risk of bladder cancer. A review on this topic showed that bladder carcinoma is ranked seventh on the list of most common cancers worldwide in men with the highest incidence occurring among men in Egypt (Murta-Nascimento et al. 2007), which may be related to *S. haematobium* infection (Jordan 2000).

Structural changes or damage resulting from complications of the infection may allow intravascular shift of worms between locations. The superior mesenteric veins have numerous anastomoses with the veins draining the internal genital organs and the vulval area towards the inferior vena cava. The structural damage to valves allows unrestricted migration of worms to the genital organs where they deposit eggs to initiate genital organ pathology (Poggensee and Feldmeier 2001). There are also communications between the spermatic ducts with the superior and inferior mesenteric veins allowing eggs to move into the semen (Arean 1956). In females, the linkage between the ovarian and uterine plexus through anastomoses allows free movement of eggs to the cervix and the vagina thereby affecting the female reproductive organs (Arean 1956; Camara 1959). In recent studies, evidence has emerged that urogenital schistosomiasis is a potential risk factor for HIV infection, especially in women with schistosomiasis-related lesions (WHO 2010a; Mbabazi et al. 2011). There is also an increased risk of hepatocellular carcinoma and mortality from co-infection of schistosomiasis and hepatitis and HIV or malaria.

The late-stage complications commonly associated with *S. mansoni* infection include lesions of the liver, portal vein and spleen, leading to periportal fibrosis, hepatomegaly, splenomegaly, pipe-stem portal fibrosis and ascites (Hatz 2001; Richter 2003). The fibrotic lesions in turn lead to liver cirrhosis that progressively occludes the portal system giving rise to Symmers' pipe-stem periportal fibrosis and portal hypertension. The portal hypertension eventually causes enlargement of the hepatic arteries that leads to varicose veins (oesophageal varices). These may rupture and cause heavy blood loss, haemorrhagic shock and finally death. The patient

may also suffer repeated episodes of variceal bleeding, the primary cause of death in hepatic schistosomiasis (Anderson and Chung 2007).

Public Health Impact of the Disease

Risk of Infection, Morbidity and Mortality Estimates

Schistosomiasis is mostly recurrent and a person may be reinfected repeatedly even when regular treatment is provided, creating long-lasting public health, social and economic burden in endemic populations (WHO 2002b; King and Dangerfield-Cha 2008). Although most individuals with schistosomiasis show few or no early symptoms, significant morbidity can develop if untreated. Current statistics suggest that the burden due to schistosomiasis may even be comparable to that of malaria (Hotez et al. 2009). Globally, it is estimated that around 800 million people are at risk of acquiring the infection and 207 million people are already infected (Hotez et al. 2006; Steinmann et al. 2006). Of those with infection, 120 million are estimated to manifest symptoms and signs of the disease while 20 million experience long-term infection-related complications (WHO 2002a). The statistics are staggering as it shows that around 580 million (~72 %) of the global total estimate of people are at risk of acquiring the infection live in SSA; over 130 million are school-age children.

From mathematical modelling, it was predicted that the two schistosome worms commonly found in SSA may contribute to the deaths of more than a quarter of a million people annually from disease-specific or infection-related complications (van der Werf et al. 2003). However, given that it is uncommon for schistosomiasis to directly result in the death of the infected person, mortality estimates provide only little insight about the public health impact of the disease. Measures such as disability-adjusted life years (DALYs) are considered to provide a better picture of the burden of disease due to schistosomiasis.

Disability-Adjusted Life Years (DALYs)

Using the DALYs approach, it has been estimated that schistosomiasis causes around 4.5 million DALYs annually, with around 90 % of the burden of disease concentrated in SSA (Hotez et al. 2006; Steinmann et al. 2006). Other analyses have challenged this value arguing that the burden of the disease has been significantly underestimated (King et al. 2005; Engels and Savioli 2006; WHO 2012), given the difficulty in establishing and quantifying cause-specific deaths due to schistosomiasis. For example, exposure to the infection usually takes place in childhood but severe-chronic disease occurs later in adulthood making it difficult to

establish the link between infection and long-term complications. Another reason for the underestimation of the burden of the disease is a limitation inherent in the DALYs approach itself, as the DALYs systematically undervalue chronic diseases, including schistosomiasis (King and Bertino 2008; Utzinger et al. 2009). Researchers and public health practitioners disagree on the current morbidity and mortality assessment methods used for the estimation of burden attributable to schistosomiasis.

Subtle Morbidity and Other Schistosomiasis-Related Complications

Heavy infection in schoolchildren may be associated with short-term memory loss, slower reaction time, lower scores in some tests of cognitive ability and poor growth (WHO 2002b). Iron deficiency anaemia and other nutritional deficiencies have been linked with heavy infection (Awasthi et al. 2003). The social and economic implications of schistosomiasis are thought to be even greater (Wright 1972; WHO 2012). In Brazil, Egypt, Sudan and Tanzania, researchers found substantial reduction in labour productivity of working adults and high school absenteeism of children suffering from schistosomiasis. For example, a substantial drop in labour output by as much as 35 % of adults infected with schistosomiasis has been reported in Egypt (Salehe and Hassan 2012). Similar results have been reported from studies investigating adults working in sugar plantations in Tanzania and Sudan that showed a decrease in work output by up to 15 % in workers infected with schistosomiasis (Salehe and Hassan 2012). Further studies from Tanzania showed that apart from spending more time in seeking treatment and hence having fewer working hours per month, irrigation rice farmers suffering from schistosomiasis also spent much more money from their harvest on seeking health care (Salehe and Hassan 2012). A group of researchers from Nigeria found similar findings with reduced worker productivity, cash income, rates of land clearing and farm size of those with the disease (Umeh et al. 2004). Generally, individuals suffering from schistosomiasis in rural areas show severely impaired work capacity and performance due to lethargy (WHO 2002b).

For schistosomiasis-related complications, evidence is also emerging from recent research that urogenital schistosomiasis may pose a significant risk for HIV infection, especially in women with schistosomiasis-related lesions (WHO 2010a, b; Mbabazi et al. 2011). Co-infection of schistosomiasis and hepatitis and HIV or malaria can increase the risk of hepatocellular carcinoma and risk of mortality. Genital lesions resulting from the infection may present with vaginal bleeding, pain during sexual intercourse and nodules in the vulva. In men, urogenital schistosomiasis can induce pathology of the seminal vesicles, prostate and other organs that may decrease male vitality and fertility.

Economic Implications of Schistosomiasis

In the early 1970s, some staggering results from analyses of the economic impact of schistosomiasis in terms of disability and loss of work capacity were published in the Bulletin of the WHO (Wright 1972). The main objective of the analysis was to quantify resource loss attributable to reduced productivity. The analysis estimated the total global annual loss to be greater than 600 million US dollars (US $641, 790, 130) excluding the cost of public health programmes, medical care or compensation for illness (Wright 1972). Annual loss from complete and partial disability due to schistosomiasis in Africa alone was estimated to be nearly half a billion US dollars (US $445, 866, 945), constituting approximately 70 % of the global cost. This value excluded Mauritius with an estimated cost of US $755, 480. Southeast Asia accounted for US $16, 527, 275, Southwest Asia US $118, 143, 675 and the Americas US $60, 496, 755. These costs estimates were based on an estimated 124, 905, 800 prevalence of the infection in those days. The authors acknowledged that the data were based on prevalence estimates obtained from less sensitive diagnosis of a single stool (for intestinal schistosomiasis) or single urine (for urogenital schistosomiasis) examinations which could lead to serious underestimation of the actual number of cases. With current estimates well over 200 million people having the infection, far higher than estimates used in this calculation (around 124 million), it is expected that the cost will be far higher.

Diagnosis of the Infection and Disease

Parasitological Diagnosis

Microscopic examination for parasite eggs in the urine (for urogenital schistosomiasis) or stool (for intestinal schistosomiasis) is considered definitive for the diagnosis of the infection. For urinary schistosomiasis, the diagnostic technique involves a Nucleopore membrane of a standard 10 ml volume of urine. This method can quantify egg count and very useful in epidemiological investigations. For *S. mansoni* infection, the use of the Kato-Katz technique (Katz et al. 1972) to examine a single or multiple stool specimens remains the gold standard. The Kato-Katz technique is both specific and sensitive and able to quantify eggs into different intensity levels. It also has low operational cost and can be used in settings with minimal infrastructure (Rabello 1992). However, sensitivity of parasitological diagnosis by microscopy decreases considerably when egg excretion is low, particularly in low endemicity areas or after chemotherapy.

Rectal biopsy for all schistosome species and biopsy of the bladder for *S. haematobium* are more sensitive and occasionally done when repeated stool or urine

examinations are negative for schistosome eggs (Rabello 1992). Rectal biopsies are particularly useful when conducting clinical trials into new treatments when it is necessary to observe egg morphology in tissues. The disadvantage is that biopsies are invasive and cumbersome to perform and not recommended for mass field application (Allan 2001).

Immunological Diagnosis

Monoclonal antibody-based technique to detect schistosome specific by-products is gaining prominence in the diagnosis of the infection (Bosompem et al. 1996, 2004; Polman et al. 2001, 2002). Reagent strips are applied for the detection of schistosomiasis-related blood and proteins released in the urine, but this technique is unable to quantify the infection. Recent studies on monoclonal antibody-based dipsticks have shown promising results (Legesse and Erko 2007, 2008; Caulibaly et al. 2011). Polymerase chain reaction (PCR) is increasingly being used in some reference laboratories in Europe, and it is hoped that this can be assessed for evidence of test accuracy and cost-effectiveness for application in endemic settings (Sandoval et al. 2006; Cnops et al. 2012; Enk et al. 2012). More recently, the FLOTAC has evolved as a novel technique for the detection and quantification of *S. mansoni* eggs in stools (Glinz et al. 2010; Cringoli et al. 2013).

Clinical Diagnosis

Clinically, schistosomiasis is diagnosed on the basis of blood in the urine of the patient (for *S. haematobium* infection) and blood in stool, diarrhoea and abdominal pain (for *S. mansoni* infection). Diagnosis based on presence of blood in urine is reliable in children but less so in adults where blood in the urine may be caused by other diseases than urogenital schistosomiasis, for example, sexually transmitted diseases. For intestinal schistosomiasis, diarrhoea, abdominal pain and splenohepatomegaly are non-specific and could be due to other causes such as malaria. Also, blood in stool can be caused by dysentery but not necessarily schistosomiasis.

Mass Screening

For mass or field control, questionnaires have been suggested as operationally cost-effective for rapid screening of the infection in high-endemic communities. Questionnaire-based assessment relies on self-reporting of symptoms; it is not reliable as recall bias can be high. For urogenital schistosomiasis, blood in urine and painful urination show moderate-to-high sensitivity, depending on age and

prevalence of the infection (Bogoch et al. 2012). In high-prevalence areas, sensitivity and specificity tend to be high, whereas in areas with low prevalence of the infection, sensitivity and specificity of this method are low. For intestinal schistosomiasis, the main signs and symptoms (blood in stool, diarrhoea and abdominal pain) are neither sensitive nor specific (Danso-Appiah et al. 2004, 2010), and questionnaire-based diagnosis is less encouraging (Raso et al. 2005). Another major challenge is that questionnaire application is influenced by age and gender of the infected person.

Control Strategies and Challenges of Implementation

The goal of schistosomiasis control, like any infectious disease, is to prevent new infections or transmission of the infection, usually by interrupting the parasites' life cycle. As this has been difficult to achieve, control guidelines have changed several times over the years. Historically, schistosomiasis control measures implemented across SSA have centred around two main strategies, namely, (i) transmission control and (ii) morbidity control, using one or more of the following measures: health education, safe water supply, molluscicding, environmental management, chemotherapy or combination of measures.

Transmission Control

Molluscicding

The application of molluscicide formed the primary control option prior to the introduction of safe and effective antischistosomal drugs in the 1970s (WHO 1985; Sturrock 2001). The objective was to interrupt transmission of the infection by targeting the intermediate snail host. Mass application of molluscicide has been conducted in various settings in SSA, particularly where outbreaks of schistosomiasis have occurred as a result of the creation of dams (Shiff et al. 1973; Chu 1978). In Ghana, for example, control measures adopted following the outbreaks of schistosomiasis after the construction of the Akosombo Dam focused primarily on chemical (molluscide) control targeting the intermediate host snails. Generally, large-scale molluscicide control proved to be very expensive and impractical in the long term and also raised a number of operational and health concerns (Chu 1978; Sturrock 2001).

Environmental Management

Environmental management attempts to reduce the snail population and thereby transmission of the infection. It has generally not been used as one of the approaches undertaken in SSA due to the high cost and paucity of information about the exact

areas where this can be implemented. Positive experiences with this have been mainly documented in Morocco and Egypt, outside SSA. There is the need for identification of areas where environmental management for snail control can be intensified in the SSA to improve effort towards control of the infection.

Health Education

Health education focuses on promoting good hygiene and sanitation, especially among school-age children and caregivers, discouraging practices such as bathing in streams and indiscriminate disposal of refuse that underpin spread of the infection. The main objective of this strategy is to decrease the number of eggs reaching and contaminating bodies thereby force of transmission and acquisition of the infection in endemic communities. The impact of most health education programmes appears to be encouraging in the short term (Asaolu and Ofoezie 2003; Mascie-Taylor et al. 2003; Guo et al. 2005; Minamoto et al. 2012), but are unsustainable in the long run (Minamoto et al. 2012). A systematic review that pooled data to evaluate the effect of health education showed that health education helps to sustain the benefits of other control measures such as chemotherapy (Asaolu and Ofoezie 2003). The review also found that health education is effective, easy and cheap to deliver and will remain the only tool for creating enabling environment for both chemotherapy and sanitation to succeed.

Safe Water Supply

The goal of safe water supply is to reduce frequency of water contact by poor rural inhabitants. However, in some settings in SSA, water contact may not be avoidable as this is the only means rural inhabitants can conduct their domestic activities such as washing clothing or fetching water for drinking, as well as children swimming in streams infested with the intermediate host snails responsible for transmission of the infection. A study examining the impact of improved water supply and sanitation facilities on schistosomiasis and other NTDs by analysing 144 independent studies and calculating disease-specific median reduction levels of the infection found marked reductions in diarrhoea (26 %), trachoma (27 %) and ascariasis (29 %) (Esrey et al. 1991). The median reduction of new infection with schistosomiasis was 77 % and dracunculiasis 78 %, with overall child mortality decreasing by 55 % (Esrey et al. 1991). The authors concluded that properly maintained water supply alone was highly effective for controlling NTDs. Investigating the value of individual household water supplies in curtailing the transmission of schistosomiasis in Saint Lucia, households in five villages were provided with their own water supply, as well as community laundry shower units between 1970 and 1975 (Jordan et al. 1982). Evaluation of the impact of water supply showed a marked reduction in the incidence of *S. mansoni* infections. Chemotherapy was introduced thereafter for 3 years (1975–1977) with oxamniquine to all the infected persons. The results

showed a further reduction in the transmission of the infection to a very low level which remained low for over 4 years, with no sign of an increase in infection rates in spite of reservoirs of the infection and poor level of sanitation in the villages remaining unchanged after the treatment (Jordan et al. 1982). The authors concluded that properly maintained water supply alone appeared to be effective in keeping transmission of infection low and that effectiveness improved further when safe water supply was combined with chemotherapy.

Drug Treatment

Chemotherapy focuses on the human host and aims at killing the worms residing in the human body thereby reducing the worm burden and infection-related pathology and morbidity. Various medicines have been tried and abandoned because of poor effect or adverse events. Egypt was the first country in Africa to use the Antimonies, one of the earliest antischistosomal medicines developed after the First World War around 1918. However, the low compliance associated with the long course of administration, pain from the injections and the serious side effects meant that the antimonies were limited to only hospital patients (Shekhar 1991; Cioli et al. 1995; Wu and Halim 2000). Treatment-associated death rates were very high, estimated at 3 per 1000 patients treated (Jordan 2000; Sturrock 2001). Ghana too tried the Antimonies in the 1960s when schistosomiasis became a big public health problem following the construction of the Akosombo Dam across the Volta River, but discontinued its use few years later because of serious adverse events (Wolfe et al. 1966).

The 1970s marked the turning point in schistosomiasis control when safe and effective medicines were introduced onto the market shifting control emphasis to chemotherapy of the human host (Cioli et al. 1995). Praziquantel (PZQ), a broad-spectrum, safe and easy-to-administer medicine immediately became the treatment of choice for schistosomiasis. The WHO endorsed selective treatment (i.e. identification of high-prevalence communities, screening the people and treating those identified to have the infection) as a more cost-effective option (WHO 1985). PZQ was delivered through small-to-medium, or large-scale selective programmes across endemic countries in SSA, funded by foreign donor organisations. The objective was to reduce or interrupt transmission of the infection; morbidity was a secondary objective.

Selective treatment programmes were implemented mainly as ‘vertical’ strategies where control decisions were mainly the responsibility of the donor agencies and expatriate experts. The outcome of this approach showed short-term promise in reducing prevalence of the infection. It was expected that any initial gains would lead to a takeover of the maintenance phase by national health authorities (Bruun et al. 2008), but transmission and reinfection rates usually remained unchanged in most treated areas. Lack of sustainability after withdrawal of donor funds and the expatriates at the end of a project was a major problem (Chitsulo et al. 2000; Engels et al. 2002). The high cost of PZQ at the time before expiry of its patent made universal coverage impossible.

Morbidity Control

Realising the minimal impact and lack of sustainability of selective treatment, WHO issued a guideline endorsing morbidity control as a new and cost-effective approach (WHO 1985). This approach was to limit coverage to symptomatic individuals or those with heavy worm load and likely to suffer complications from the infection. Morbidity control was delivered mainly through 'vertical' strategies. After about 10 years of its adoption, the WHO Expert Committee reviewed the strategy in the early 1990s and agreed that morbidity control was feasible and effective (WHO 1993). However, the Expert Committee identified that a leading role of the existing health service was necessary for its success and sustainability. It was acknowledged that if the patients themselves recognise signs and symptoms of the disease and self-report to a clinic or hospital ('passive case finding') for appropriate treatment, most severe infection-related pathology and complications may be averted. Passive case finding by local clinics looks promising because it is based on the primary healthcare concept already embraced by many endemic countries in Africa (Danso-Appiah et al. 2004, 2010).

Other potential success signs of passive case finding are that (1) control within the regular health service will strengthen the local health services including material and human resource; (2) related activities can be easily combined in an integrated concept, for example, the control of schistosomiasis can be combined with other helminthiases of public health relevance such as soil-transmitted helminths (STHs) or malaria as these diseases tend to coexist and (3) many parts of Africa where the highest burden of the disease is concentrated did not benefit from the donor-supported vertical control programmes (WHO 1998).

The morbidity control strategy was reviewed in 1998 by programme managers, scientists and public health experts from various endemic countries who reset the agenda for future control activities (WHO 1998). The Expert Committee recognised the leading role of the WHO in developing control strategies since its establishment after the Second World War but acknowledged that in SSA only a few countries had ongoing schistosomiasis control programmes as at 1990 (WHO 1998). It noted that PZQ was often not available at the peripheral health facilities where it is needed most. At the same time, major challenges were identified: (1) how to make PZQ widely available to communities where the medicine is needed most at an affordable cost; (2) how to organise and finance the distribution of PZQ to those who need it in a sustainable way and (3) how to adjust control measures to the varying distribution pattern and public health relevance of schistosomiasis in different communities.

It was also felt that drug supply from a strong centralised purchasing system with distribution through the existing health services according to local needs would facilitate decentralised planning and implementation of control strategies (WHO 1998). However, paucity of information on whether availability of PZQ alone in health facilities would influence rate of hospital uptake was a worry to policy makers. Therefore, the Expert Committee recommended the need to build local capacity and strengthen existing health systems, with main emphasis on

integration of control and decentralised decision-making and service delivery. Schistosomiasis is a focal problem and often its importance is diluted when control activities are planned and managed at the national centralised level.

Schistosomiasis was not acknowledged as a serious problem in preschool children until recently. Therefore, children under 5 years have been excluded from mass population treatment programmes (Stothard and Gabrielli 2007; WHO 2012). A major reason for their exclusion is that there is limited information about the safety of PZQ in this age group. Also, the dose pole used for determining the dose of PZQ, recommended by the WHO and used in these control programmes, only works for those over 94 cm in height. There are also no readily available syrup or paediatric formulations of PZQ.

A WHO-sponsored meeting that reviewed the results of studies on the treatment of schistosomiasis in preschool-age children in several countries in Africa (WHO 2010b) confirmed results from earlier publications (Bosompem et al. 2004; Odogwu et al. 2006; Johansen et al. 2007; Stothard and Gabrielli 2007) that (i) schistosomiasis can represent a significant public health problem in children aged less than 5 years; (ii) preschool-age children living in areas where endemicity for schistosomiasis is high, levels of infection are comparable with those of school-age children; (iii) prevalence of the infection may exceed 50 % and pathological lesions may be detectable by ultrasonography and (iv) administration of PZQ to preschool-age children is acceptable, safe and efficacious in the context of individual case management and in group settings, such as reported in the studies reported (WHO 2012).

Based on the above considerations, a series of recommendations were formulated. Among these, it was recommended that preschool-age children should be regarded as a high-risk group in areas endemic for schistosomiasis and that WHO should consider formally recommending the use of PZQ in preschool-age children in areas where schistosomiasis is endemic. However, the studies reviewed in this report had some limitations in design and methodology. Recognising the existence of knowledge, operational, regulatory and evidence gaps in existing data, it was re-emphasised that (i) treatment of this age group should be within an appropriate healthcare setting (WHO 2012), (ii) systematic review(s) involving preschool-age children, or well-designed multi-country randomised controlled trials (RCTs) using a standard protocol are warranted to contribute further evidence and (iii) a pharmacokinetic study investigating PZQ is warranted (WHO 2011). The case for health facility-based passive case reporting is strengthened given that this is the only way for preschoolers to benefit from treatment of their infection.

Chemotherapy

At present, chemotherapy is the cornerstone of schistosomiasis control and applied in endemic countries in SSA. PZQ remains the only drug for control and treatment programmes of schistosomiasis. Pressure on this drug is growing, and it is expected that this will increase exponentially given the endorsement of the implementation of

mass drug administration (MDA) in endemic countries across SSA. The risk of PZQ resistance remains a big threat and its prevention requires adequate and continued monitoring. A well-designed systematic review and meta-analysis of clinical and laboratory evidence are highly warranted to inform on the drug's performance, dynamics and resistance.

Metrifonate

Metrifonate is an effective antischistosomal drug introduced around 1952, initially as an insecticide (Lorenz et al. 1955) before it was approved for use in humans in the 1960s (Snellen 1981). It is one of only few treatments where clinical trials were initiated before detailed testing in animals were concluded (Aldridge and Holmstedt 1981). It has been used extensively giving at a dose of 7.5–10 mg/kg three times at 14-day intervals (Feldmeier and Doehring 1987). The only limitation is that it is active against only *S. haematobium*. Adverse effects are mainly associated with cholinergic stimulation and include fatigue, muscular weakness, tremor, sweating, salivation, fainting, abdominal colic, diarrhoea, nausea, vomiting and bronchospasm. Its use was limited after the publication that it was inferior clinically, economically and operationally to PZQ (Feldmeier and Chitsulo 1999). The chemistry, pharmacological properties and therapeutic efficacy as well as adverse events in clinical human use have been discussed in detail elsewhere (Cioli 2000; Utzinger and Keiser 2004).

Oxamniquine

Oxamniquine belongs to the same group of drugs as hycanthone with activity against only *S. mansoni*. It was introduced onto the market for clinical use in the early 1970s and has since been used widely with good effect, particularly in Brazil where it has been a major component of the national schistosomiasis control programme (NSCP). It acts by dislodging the worms from the mesenteric veins to the liver and destroying the male worms. Although oxamniquine allows the female worms to return to the mesentery, they are made sterile and are no longer able to produce eggs. In South America (mainly Brazil) and West Africa, a single lower dose of 15 mg/kg is given to adults and 20 mg/kg to children. In other countries of Africa and the Arabian Peninsula, higher doses are given, the total dose varying from 30 to 60 mg/kg (Foster 1987). Differences in the susceptibility of parasites to the drug seem to account for the variation in dosage. Adverse events are mild and transient and include dizziness with or without drowsiness, headache and gastrointestinal effects such as nausea, vomiting and diarrhoea. Few serious events such as seizures have been reported but all were associated with higher doses. Oxamniquine's use has declined considerably in favour of PZQ, even in Brazil, where it has long been preferred to PZQ.

Praziquantel

Praziquantel is a broad-spectrum antischistosomal drug effective against all schistosome worms. PZQ is distributed mainly as 600 mg tablet, with two or three grooves for ease of breaking. In China, it is distributed as 200 mg pills while some manufacturers provide syrup formulation containing 600 mg/5 ml (e.g. epiquentel from EIPICO). The shelf life of PZQ is usually 4 years in temperate climates and 3 years in hot humid environments. When administered orally, the drug is rapidly and almost completely absorbed, appearing in the blood within 15 min and attaining peak concentration 1–2 h after treatment (Valencia et al. 1994). Approximately 80 % of the drug is cleared within 24 h of treatment mainly through urine (Cioli et al. 1995). There are many brands and generic forms in the system including Distocide manufactured by Shin Poong in Korea, Bilharzid from Egypt and Prazitel from Kenya (Cioli and Pica-Mattoccia 2003). There are other brands produced in the Netherlands and Malta. PZQ is administered orally at a standard single dose of 40 mg/kg body weight and well tolerated. Most common adverse events are mild and transient, mostly related to the gastrointestinal tract: abdominal pain, nausea, vomiting, anorexia and diarrhoea. Currently, it is the only drug on the WHO Model List of Essential Medicines for treating schistosomiasis. Although its effectiveness is unequivocal, PZQ is less effective against immature schistosome worms (Sabah et al. 1986). Therefore, it has been suggested that a combination therapy with drugs of unrelated mechanisms of action and targeting the different developmental stages of the schistosomes may improve therapeutic efficacy and slow the development of resistance. Drugs with potential for combination with PZQ include the artemisinin derivatives, metrifonate and oxamniquine.

Other Medicines

Several drugs have been tried for the treatment of schistosomiasis and later abandoned because of poor effect or adverse events. These include the *antimonials*, *niridazole*, *lucanthone*, *hycanthone*, *oltipraz*, *cyclosporin A* and *levamisole*, extensively reviewed by Cioli et al. (1995). More recently, the efficacy of *myrrh* (*Mirazid*) in the treatment of intestinal schistosomiasis was tested in Egypt at a single daily dose of 300 mg for 3 days, and virtually no activity was observed as almost all the treated participants failed treatment at 3–6 weeks (Barakat et al. 2005; Botros et al. 2005).

Status of Medicines Used for Treating Schistosomiasis

In the late 1990s, amidst the argument that metrifonate acts against only *S. haematobium* coupled with clinical, economic and operational suitability when compared with PZQ (Feldmeier and Chitsulo 1999), this medicine was withdrawn from the

WHO Model List of Essential Medicines. The application of oxamniquine (which acts against only *S. mansoni*) infection has declined considerably, and in areas where it was formally used as the drug of choice, it is being replaced with PZQ (Cioli 2000; Beck et al. 2001; Reich and Fenwick 2001; Utzinger and Keiser 2004; WHO 2012). Oxamniquine has subsequently been removed from the WHO Model List of Essential Medicines.

At present, there is no effective and acceptable antischistosomal vaccine (Utzinger et al. 2007; Bergquist et al. 2008), and evidence on the artemisinins are inconclusive (Utzinger et al. 2007; Utzinger et al. 2010; Liu et al. 2011; del Villar et al. 2012; Wikman-Jorgensen et al. 2012; Danso-Appiah et al. 2013). Therefore, PZQ remains the only drug available for the treatment of millions of persons suffering from schistosomiasis. At the same time, PZQ use in SSA has increased enormously following the endorsement of Resolution 54.19 at World health Assembly (WHA) in the early millennium. Endemic countries in SSA have been encouraged to adopt MDA as their national control strategy. PZQ distribution is expected to increase exponentially, raising fears about potential resistance emerging against this medicine. Given aforementioned, it is critical to find and appraise available data for evidence on resistance against PZQ.

Resistance to Praziquantel

In the early 1990s, PZQ treatment in Senegal (West Africa) resulted in unacceptably low cure rates, raising concerns about possible emergence of resistance against PZQ (Gryseels et al. 1994; Stelma et al. 1995). Meanwhile, analysis of *S. mansoni* strains obtained from patients treated with PZQ but not cured in the areas where low cure rates had been registered in Senegal, also Egypt, yielded isolates less susceptible to higher doses of the drug. Around the same time, laboratory experiments in mice yielded isolates of *S. mansoni* strains from Senegal that were less sensitive to PZQ (Fallon et al. 1995). The development of resistance against PZQ was cited as one of the main reasons for the observed low drug performance. Other reasons given were the very high pretreatment intensity of infection observed in Senegal, presence of immature worms less susceptible to PZQ and rapid acquisition of a large number of new infections immediately following treatment. This prompted the European Commission to set up the European Commission-Concerted Action on PZQ in the late 1990s (Renganathan and Cioli 1998) to review reports of low efficacy of trials from Senegal and Egypt. However, it was difficult to distinguish between normal performance and failure of PZQ as it was not possible to analyse data quantitatively. Notwithstanding, the EC-Concerted Action on PZQ advocated continued monitoring and evaluation of resistance to PZQ.

In order to ascertain the availability of evidence on clinical resistance against PZQ, various electronic databases and sources were searched for systematic reviews and meta-analysis. The search retried only one meta-analysis of observational studies that has assessed this question quantitatively (Danso-Appiah and De Vlas 2002). The meta-analysis used robust Bayesian approach of evidence synthesis, accounting for various

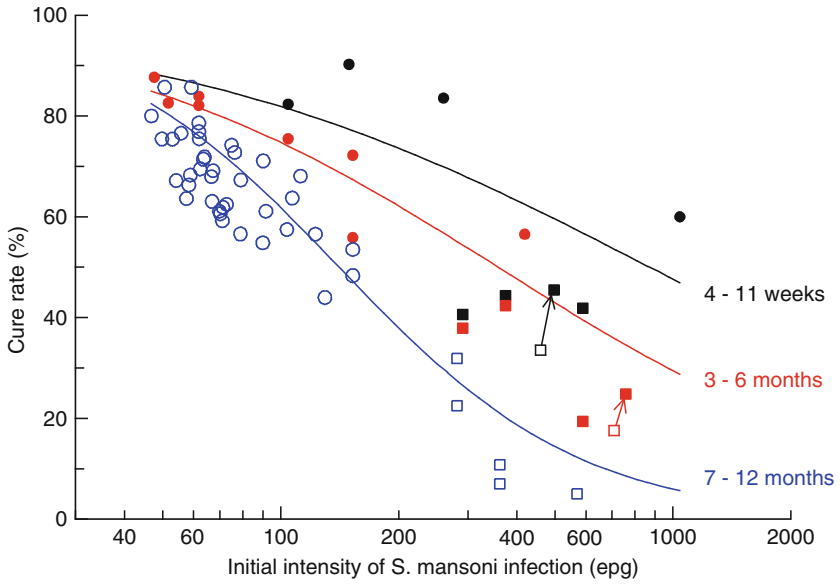


Fig. 5 The impact of pretreatment intensity of *Schistosoma mansoni* infection, diagnostic sensitivity and follow-up time on cure rate using the standard PZQ dose of 40 mg/kg body weight in population-based, selective chemotherapy. Intensity of infection (logarithmic scale) is the geometric mean of egg count per gram of faeces (epg) for individuals positive for *S. mansoni* eggs. Cure rate denotes percentage of treated subjects who appeared negative for *S. mansoni* eggs at follow-up. The dots represent different follow-up time categories: 4–11 weeks; 3–6 months; 7–12 months. Data points located on same vertical axis indicate successive follow-ups of a treatment in the same community. *Squares* represent observations from Senegal; *circles*, studies from other locations. *Arrows* illustrate shifts from published observations from Senegal based on duplicate stool specimens (*open squares*) to the corresponding cure rate and intensity from a single stool specimen. For the three follow-up time categories, curves give best fitting associations of *cure rate* and *ln epg* through cure rate = $100/(1+e^{-Lp})$, where $Lp = \alpha + \beta \ln epg$.. α and β coefficient values are 4.7 and −0.70 (4–11 weeks follow-up); 5.0 and −0.85 (3–6 months); 6.9 and −1.40 (7–12 months). Coefficients α and β are estimated by generalised linear mixed modelling (GLMM). Out of the 13 data points from Senegal, 12 are located below the respective lines. Thus, even when initial intensity, follow-up time and sensitivity of diagnosis are accounted for, cure rates from Senegal are consistently lower than expected (Reproduced from Danso-Appiah and De Vlas (2002), *Trends in Parasitology*)

risks of biases and confounding effects. Although no formal quality assessment of the included studies was conducted, rigorous standardisation measures were used to ensure comparability across studies and that biases and errors were minimised.

The results showed that the low cure rates observed in Senegal was largely the result of high pretreatment intensity of infection in persons treated there. The relatively sensitive diagnostic technique used in the studies from Senegal to some extent contributed to the observed low cure rates.

However, after correcting for pretreatment intensity and sensitivity of diagnosis, cure rates from Senegal remained somewhat lower than expected (Fig. 5). Various

studies on biological and methodological aspects were reviewed to help explain the Senegal situation (Geerts and Gryseels 2001; Gryseels et al. 2001; Cioli 2000; Doenhoff 1998).

The meta-analysis concluded that although high pretreatment intensity of infection, sensitive diagnostic methods and presence of high baseline numbers of immature worms in treated patients explained most of the low performance of PZQ in Senegal, the suspicion about resistance could not be ruled out completely. This is because tools and methods for assessing resistance were not adequate or unavailable.

Combination Therapy

As far as it is known, no new medicines are being developed although some scientists suggest that the combination of PZQ and metrifonate or PZQ and oxamniquine would be potentially cost-effective treatment. The rationale is that PZQ and metrifonate or PZQ and oxamniquine are independently effective against *S. haematobium* and *S. mansoni* infections that their targets of action in the parasite are not linked. Therefore, combination may improve therapeutic efficacy and slow or prevent the development of drug resistance. However, both oxamniquine and metrifonate are active against single schistosome species, while in most endemic settings in SSA, there is an overlap of *S. haematobium* and *S. mansoni*. As it is operationally less suitable within the MDA PC strategy, pharmaceutical companies may be less motivated to invest in the development of these combination therapies.

Amoscanate

Another potentially useful drug is amoscanate, a broad-spectrum anthelminthic medicine with activity against all the major schistosome species (Striebel 1976). It was discovered before the 1970s and showed effect against some systemic parasites including filariae and gastrointestinal nematodes such as the hookworms. It was tested extensively in China from locally produced brand called 'nithiocyaminum' (Bueding et al. 1976; Striebel 1976). Toxicity was low in animal models but mutagenicity tests in bacteria gave positive results. Also, mutagenic metabolites were constantly found in the urine of mammals administered this treatment (Batzinger and Bueding 1977). Coupled with concerns about liver toxicity, amoscanate was abandoned when PZQ became available (Cioli 1995). Given its broad-spectrum schistosomicidal properties, new and well-designed research that will investigate structural modifications of the chemical structure to decrease liver toxicity is warranted (Cioli et al. 1995).

Artemisinin Derivatives

The artemisinins act against immature schistosomes (schistosomulae) that are less sensitive to PZQ (Le et al. 1982, 1983; Utzinger et al. 2003, 2007); the invasive and adult worms are less susceptible to the artemisinins. Adverse effects are minor and last for less than 24 h. The combination of artemisinin with existing drugs effective against other stages of the parasite such as PZQ may improve efficacy and slow or prevent the development of resistance against PZQ. Therefore, combination therapy with the artemisinins should be pursued vigorously given that current evidence is inconclusive.

Supportive Evidence for Diagnostic Tools and Treatment

In order to investigate whether application of diagnostic tests and techniques in sub-Saharan Africa is supported by systematic reviews and other forms of evidence synthesis, relevant electronic databases including MEDLINE, LILACS, DARE and the Cochrane Collaboration Databases were searched in September 2013. The reference lists of published studies were also searched, and experts in the field of schistosomiasis were contacted for additional or unpublished systematic reviews that might have been missed through the search. The search identified only one published systematic review protocol which intends to assess rapid screening and diagnostic tests for schistosomiasis in endemic areas, but data are not yet available (Ochodo et al. 2012) and six published systematic reviews of varying qualities assessed treatment options and effects (Danso-Appiah et al. 2008, 2013; Liu et al. 2011; del Villar et al. 2012; Wikman-Jorgensen et al. 2012; Stothard et al. 2013).

Given that the search did not retrieve any systematic review or carefully synthesised evidence on diagnostic accuracy, it is not possible to establish whether available evidence supports the use of current diagnostic tools and methods used in SSA. The WHO recently commissioned a systematic review and meta-analysis to assess the circulating cathodic antigen (CCA) test in the diagnosis of schistosome infections which may provide valuable information (Danso-Appiah et al. submitted). The six systematic reviews on treatment options and effects retrieved are of variable quality and thus reliability. Detailed assessment as to whether they support current treatment options and policies in SSA is beyond the remit of this study. Therefore, a new and well-designed study is warranted to examine this.

The Millennium Control Strategies

With the exceptions of Egypt and Morocco, hardly any observable progress was made in the control of schistosomiasis in the African continent up to the 1990s (Utzinger et al. 2009). The reasons for this were attributed to the absence of safe and

easy-to-apply medicines prior to the 1970s and high price of available medicines after their introduction onto the market. The expiry of patency of PZQ in the early 1990s allowed the production of brands leading to a sharp fall in the price of this medicine from about US$1 at 1990 to less than UD$ 0.06 per tablet in the early millennium. PZQ use has since increased considerably. One other major reason for the surge in PZQ distribution may be due to evidence that dispelled fears about the likelihood of resistance against PZQ (Doenhoff 1998; Cioli 2000; Gryseels et al. 2001; Danso-Appiah and De Vlas 2002) together with increased advocacy for control of NTDs (Hotez et al. 2007; Fenwick et al. 2009; Garba et al. 2009; Utzinger et al. 2011).

The adoption of Resolution WHA54.19 in 2001 urged member states to treat at least 75 % of schoolchildren infected with schistosomiasis and high-risk individuals or entire 'at-risk' populations (e.g. school-age children) through mass distribution of PZQ, usually without prior diagnosis – an approach termed 'preventive chemotherapy' (PC). This is the millennium control strategy endorsed by WHO and applied in many endemic countries. Usually, PZQ at a standard single oral dose of 40 mg/kg is used.

In 2002, WHO convened an Expert Committee meeting to develop operational guidelines to translate the recommendations of WHA54.19 into concrete action with emphasis on morbidity control (WHO 2002b). The strategy had a goal of control of morbidity to be achieved through large-scale distribution of PZQ to populations at risk, using defined thresholds of prevalence as criteria for selecting the appropriate interval of retreatment. Schools were identified as the most efficient delivery entry point. On the other hand, if school enrolment is low, community-based interventions are to be implemented to reach out to children not attending school. The adoption of Resolution WHA54.19 has led to thousands of school-age children in countries in SSA to receive multiple doses of PZQ initially through the Schistosomiasis Control Initiative (SCI) which started in 2003 and funded by the Bill and Melinda Gates Foundation (Fenwick et al. 2006, 2009; Linehan et al. 2011) and more recently through the integrated control approach of NTDs supported by the United States Agency for International Development (USAID), the British Department for International Development (DFID) and the Global Network for NTDs and its partners (Hotez 2009, 2011).

New evidence that emerged that morbidity is not necessarily determined by the intensity of infection led to a revised version of the operational details of PC in 2006 (WHO 2006a, b). The target population was expanded to include all adults in high-risk areas where prevalence of infection in school-age children is 50 %, as well as special-risk groups such as people occupationally exposed to risk of infection. The targets for moderate and low-risk areas were also revised (Table 2).

With new evidence that preschool-age children in endemic areas may be at a similar risk of infection and morbidity (WHO 2011), the recommendation is that children aged up to 5 years who are excluded from population-based mass chemotherapy should be treated in health facilities as part of national control programmes. The 2006 guidelines came out with additional component about coordinated use of anthelminthic medicines to control and eliminate four main helminth infections,

Table 2 Recommended treatment strategy for schistosomiasis

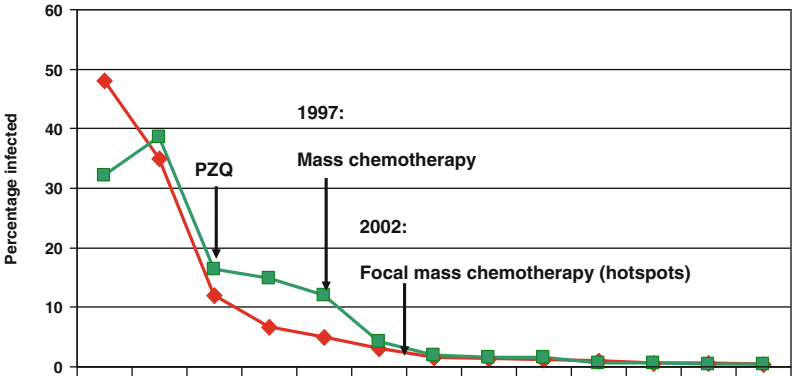
Category	Baseline prevalence among school-age children	Action to be taken	
High-risk community	50 % by parasitological methods (both) or 30 % by questionnaire for history of haematuria (for urinary schistosomiasis)	Treat all school-age children (enrolled and not enrolled) once a year	Also treat adults considered to be at risk (from special groups to entire communities living in endemic areas)
Moderate-risk community	10 % but <50 % by parasitological methods (both), or <30 % by questionnaire for history of haematuria (for urinary schistosomiasis)	Treat all school-age children (enrolled and not enrolled) once every 2 years	Also treat adults considered to be at risk (special groups only)
Low-risk community	<10 % by parasitological methods (for both urinary and intestinal schistosomiasis)	Treat all school-age children (enrolled and not enrolled) twice during their primary schooling age (e.g. once on entry and once on exit)	Praziquantel should be available in dispensaries and clinics for treatment of suspected cases

Adapted from WHO (2012)

namely, lymphatic filariasis, onchocerciasis, schistosomiasis and soil-transmitted helminths (STHs) which usually coexist and for which the medicines used for their treatment can safely be co-administered (Utzinger and Keiser 2004; Olsen 2007; Hotez 2009).

Political Will, Functional Health Service and Sustainable Control

Most countries that have been successful in schistosomiasis control have used multifaceted approach combining various control measures together with political will. For example, Japan, China, Iran, Laos, Mauritius, Morocco, Saudi Arabia, Tunisia, the endemic Caribbean Islands, Brazil and Venezuela have been successful in their control effort because they made functional health services key component of the control of schistosomiasis. Also, their governments showed political will and commitment. Therefore, an adequately resourced or functional health service can play a crucial role as control is far more effective when placed in the context of a general health system (WHO 2002b). Although in terms of cost-effectiveness and sustainability the concept which underpins this strategy is sound, the process has been slow in SSA due to lack of material and human resource and political will. The experiences of schistosomiasis control from Egypt and Uganda have been presented to



	1935	1983	1988	1993	1996	2000	2004	2005	2006	2007	2008	2009	2010
S.haematobium	48	35	11.9	6.6	5	3	1.6	1.4	1.2	0.9	0.6	0.5	0.4
S.mansoni	32	38.6	16.4	14.8	11.9	4.2	1.9	1.6	1.5	0.6	0.6	0.4	0.3

Fig. 6 The impact of mass chemotherapy with praziquantel on schistosomiasis control in Egypt (Adapted from WHO (2012). Schistosomiasis: progress report 2001–2011 and strategic plan 2012–2020)

highlight the importance of multifaceted approach as a way to successful and sustainable control.

Egypt is endemic for both urinary and intestinal schistosomiasis. Implementation of a National Schistosomiasis Control Program started in 1977, through the primary healthcare system. First, pilot projects were implemented using either snail control or chemotherapy with little success. From 1988, PZQ was made available free of charge for all diagnosed cases of schistosomiasis in all governmental health facilities. Then from 1997 to 2002, mass treatment campaigns without prior diagnosis in communities with a prevalence of infection above 20 % were actively embarked on. As the programme progressed and the disease prevalence decreased, the threshold for mass chemotherapy was changed. As the infection levels went down, the 1997 threshold of prevalence for mass treatment was reduced to >10 % in 1999, 5 % in 2000 and >3.5 % in 2002, to >3 % in 2003. Since 2003, mass chemotherapy has been applied only in hotspots (micro-focal control).

Available statistics show that before the mass chemotherapy campaigns in 1996 (Fig. 6), there were 168 villages with prevalence >30 %, 324 villages with prevalence 20–30 % and 654 villages with schistosomiasis prevalence of 10–20 %. However, during the programme evaluation by the end of 2010, only 20 villages in the whole country had prevalence more than 3–5 %, and none had prevalence >10 %. The prevalence of both *S. mansoni* and *S. haematobium* has consistently decreased under sustained treatment effort supported by political will.

Tracing Egypt's success story, the prevalence of the two species was 38.6 % and 35 %, respectively, in 1983, reduced to 11.9 % and 5 % in 1996 and to 2.7 % and 1.9 % in 2002. Mass chemotherapy began to be targeted on "hotspot" areas in 2003 when the prevalence of *S. mansoni* was 2.6 % and that of *S. haematobium* was 1.7 %, but by 2010, these were 0.3 % and 0.4 %, respectively (WHO 2011).

The achievements in Egypt were made possible after treating a total of 38.8 million and a further nine million people with PZQ. In parallel to the national programme and functional health service as a key component, attention was also focused on snail control, universal access to potable water to almost every household and significant increase in access to adequate sanitation.

SCI and other partners began the support to Uganda from 2003. Like Egypt, control began with a pilot phase in 2003, in one subregion in each of the 18 most affected districts, mainly mass treatment and health education. Activities included planning, advocacy, training of teachers and supervisors, selection and training of community drug distributors, health education, supervision, monitoring of treatment side effects, reporting of treatment coverage and drug accountability.

During the pilot phase, 400,000 people were treated and this increased to 1.4 million in 2004, 3 million in 2005. Annual meetings were held regularly at national level to review constraints and plan the way forward. In 2006, two million people were treated in 27 of the 38 endemic districts. In addition health centre-based treatment was conducted alongside mass chemotherapy in 11 of the districts. The main aspects monitored were programme performance and the impact of treatment campaigns, severe adverse events and drug utilisation and efficacy. The impact of yearly mass treatment with PZQ on infection status and morbidity of *S. mansoni* infection in school-age children was evident in several ways. Anaemia was also reduced. In adults, yearly treatment significantly reduced both the prevalence and the intensity of *S. mansoni* infection between 2003 and 2006, as well as the incidence and severity of fibrosis (WHO 2011).

Similar success stories have been reported from countries selected and supported for mass PZQ distribution as part of the SCI (2003).

Control or Elimination

From a recent survey for NTD disease-specific experts' opinions on the role of MDA for the elimination of lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminths (STHs) and trachoma, most experts in lymphatic filariasis, onchocerciasis and trachoma thought elimination was the appropriate goal of treatment programmes with MDAs. For schistosomiasis and STHs, the majority of experts thought that MDA programmes were intended to control (Keenan et al. 2013) and that MDA plus other control measures would be required for their elimination.

In a debate in PLoS Medicine titled '*Which new approaches to tackling NTDs show promise*?' (Spiegel et al. 2010), while some experts held the view that there has been too much focus on the biomedical mechanisms and drug development for NTDs at the expense of attention to the social determinants of disease and that the weak health systems and poor socio-environmental conditions that cause and/or perpetuate NTDs have largely been ignored, others argue that the best return on investment will continue to be MDA for NTDs.

In the same paper, one school of thought suggested that the designation of a set of tropical diseases as 'neglected' has indeed provoked interest in strategies for their control and research on new tools for alleviation of their burden. This initiative, however, has also exposed the over-medicalisation of contemporary tropical disease control strategies. A primary example is the emphasis on drug administration alone to alleviate the burden of schistosomiasis and STHs, two groups of disease that would benefit more from a combination of MDA and other control methods. Others of contrary views advance the points that in terms of both health impact and cost-effectiveness, few other interventions can rival MDA for NTDs, particularly schistosomiasis. Furthermore, MDA increasingly is being recognised for its beneficial effects on strengthening health systems, improving economic development and achieving the Millennium Development Goals (Spiegel et al. 2010). The successful control of blindness in SSA through free community-directed treatments with ivermectin of the Onchocerciasis Control Program (OCP) and the African Programme for Onchocerciasis Control (APOC) is cited as positive examples. Furthermore, there is considerable epidemiological overlap of NTDs, and in more than 75 % of countries in SSA at least six of the seven these diseases coexist in the same community and that there is ample evidence about the cost-effectiveness of simultaneous MDA to tackle these diseases.

Outlook of Control in the Next Decade

Schistosomiasis is widely recognised as a disease that is socially determined but most programmes have ignored the key issues about understanding the social and behavioural factors that underpin transmission and control of the disease. Therefore, social determinants of schistosomiasis should be considered as vital in designing strategies and policies for prevention and control (Bruun et al. 2008). Given the lack of suitable and appropriate water supplies in rural areas, the rural folk have no alternative but to be in constant contact with schistosomiasis infested water bodies for their daily use. There is therefore, the suggestion that preventive programmes could be updated and made relevant to real-life situations in remote rural areas by using insights from social scientists including medical anthropologists, health geographers, sociologists and others whose skills enable them to explore the social context of schistosomiasis transmission and control at the micro level, in the setting in which the infection is transmitted and where efforts are made to control it (Bruun et al. 2008).

Mass distribution of PZQ to endemic countries in SSA as set out in The WHA Resolution 54.19 has been adopted by the endemic countries. Caution is, however, called for in (i) what is a solely large-scale anthelminthic drug administration to the exclusion of preventive strategies for control which include access to clean water, improved sanitation and hygiene in an integrated and sustainable disease control

programmes (Utzinger et al. 2003) and (ii) the disconnection between engineering projects and community-led initiatives in the developing world on clean water and sanitation and the vertical 'drugs only' programmes (Singer and Castro 2007; Utzinger et al. 2009).

Utzinger et al. (2009) predict PZQ treatment needs in SSA and estimate that approximately 128 million school-age children would need to be given PZQ. This amounts to 384 million tablets of PZQ every year for treatment in Africa alone. Although PZQ has now been made available free of charge by multilateral collaboration between donor organisations and pharmaceutical companies to poor endemic countries in SSA, issues of supplies, cost, whether or not free PZQ alone will be enough to achieve the objectives of schistosomiasis control and elimination, and possible drug resistance need to be kept in mind and addressed effectively.

Experiences from schistosomiasis control as, for example, in Burundi and Mali where the German Technical Cooperation (GTZ) funded large-scale vertical control programmes with PZQ show that these programmes were not sustainable in the long run. Usually, gains in prevalence reductions were offset by rapid reinfection after withdrawal of external funds and technical capacity at the end of the programmes given practical and operational problems which resurface in the absence of adequate funding. These operational problems are not unique to Burundi and Mali. They exist in many of the endemic countries presently and will need further attention in the future. These include availability of material, human resource, operational funds and infrastructure, political will to sustain the benefit achieved with chemotherapy, availability of reliable data and adequate technical capacity for delivery, monitoring and evaluation of national control programmes. Any one of these or a combination of some of them has led to the situation where after nearly 10 years of MDA campaign only 18 countries were yet to start MDAs as at 2010, and just over half (23) of the 42 schistosomiasis endemic countries in SSA had national control programmes, mostly of limited scale. Only about five countries had reached all their at-risk populations, but prevalence rates were still 100 % in some endemic settings. In some conflict and post-conflict areas, e.g. the Democratic Republic of Congo, the actual schistosomiasis problem situation is still unknown. The next decade should see an amelioration of some of these challenges given the current goodwill and enthusiasm of ministries of health, partners and donors to eliminate several of the NTDs including schistosomiasis.

The current WHO monitoring guideline which has not been specific on how parasitological and morbidity monitoring should be conducted should see updating together with the production of guidelines on how to assess drug sensitivity and timely detection of emergence of resistance.

Very few partners provide financial support for research and development; despite the devastating public health impact of NTDs and their effect on development (Hotez et al. 2009; Manderson et al. 2009; McCoy et al. 2009; Hotez and Pecoul 2010), there is however, a cautious optimism that such a situation could change in the coming decade (Hotez and Pecoul 2010).

References

Aldridge WN, Holmstedt B (1981) Metrifonate and dichlorvos: theoretical and practical aspects. History and scope of the conference. Acta Pharmacol Toxicol (Copenh) 49(Suppl 5):3–6

Allan RW (2001) The Johns Hopkins Hospital, Department of pathology. Johns Hopkins Microbiol Newsl 20:30

Anderson RM, May RM (1992) Infectious diseases of humans: dynamics and control. Oxford University Press, Oxford

Andersson KL, Chung RT (2007) Hepatic schistosomiasis: current treatment options. Gastroenterology 10(6):504–512

Arean VM (1956) Lesions caused by Schistosoma mansoni in the genitourinary tract of men. Am J Clin Pathol 26(9):1010–1021

Asaolu SO, Ofoezie IE (2003) The role of health education and sanitation in the control of helminth infections. Acta Trop 86(2–3):283–294

Awasthi S, Bundy DAP, Savioli L (2003) Helminthic infections. BMJ 327:431–433

Barakat R, Elmorshedy H, Fenwick A (2005) Efficacy of myrrh in the treatment of human schistosomiasis mansoni. Am J Trop Med Hyg 73(2):365–367

Batzinger RP, Bueding E (1977) Mutagenic activities in vitro and in vivo of five antischistosomal compounds. J Pharmacol Exp Ther 200(1):1–9

Beck L, Favre TC, Pieri OS, Zani LC, Domas GG, Barbosa CS (2001) Replacing oxamniquine by praziquantel against Schistosoma mansoni infection in a rural community from the sugar-cane zone of Northeast Brazil: an epidemiological follow-up. Mem Inst Oswaldo Cruz 96(Suppl):165–167

Bergquist R, Utzinger J, McManus DP (2008) Trick or treat: the role of vaccines in integrated schistosomiasis control. PLoS Negl Trop Dis 2(6):e244

Bierman WF, Wetsteyn JC, van Gool T (2005) Presentation and diagnosis of imported schistosomiasis: relevance of eosinophilia, microscopy for ova, and serology. J Travel Med 12(1): 9–13

Bogoch II, Andrews JR, Dadzie ERK, Utzinger J (2012) Simple questionnaire and urine reagent strips compared to microscopy for the diagnosis of *Schistosoma haematobium* in a community in northern Ghana. Trop Med Int Health 17(10):1217–1221

Bosompem KM, Ayi I, Anyan WK, Nkrumah FK, Kojima S (1996) Limited field evaluation of a rapid monoclonal antibody-based dipstick assay for urinary schistosomiasis. Hybridoma 15: 443–447

Bosompem KM, Owusu O, Okanla EO, Kojima S (2004a) Applicability of a monoclonal antibody-based dipstick in diagnosis of urinary schistosomiasis in the Central Region of Ghana. Trop Med Int Health 9(9):991–996

Bosompem KM, Bentum IA, Otchere J, Anyan WK, Brown CA et al (2004b) Infant schistosomiasis in Ghana: a survey in an irrigation community. Trop Med Int Health 9(8):917–922

Botros S, Sayed H, El-Dusoki H, Sabry H, Rabie I, El-Ghannam M et al (2005) Efficacy of mirazid in comparison with praziquantel in Egyptian *Schistosoma mansoni*-infected school children and households. Am J Trop Med Hyg 72(2):119–123

Brouwer KC, Ndhlovu PD, Wagatsuma Y, Munatsi A, Shiff CJ (2003) Epidemiological assessment of Schistosoma haematobium-induced kidney and bladder pathology in rural Zimbabwe. Acta Trop 85(3):339–347

Bruun B, Aagaard-Hansen J, Watts S (2008) The social context of schistosomiasis and its control. An introduction and annotated bibliography. Special Programme for Research & Training in Tropical Diseases (TDR) sponsored by UNICEF/UNDP/World Bank/WHO

Bueding E, Batzinger R, Petterson G (1976) Antischistosomal and some toxicological properties of a nitrodiphenylaminoisothiocyanate (C9333-Go/CGP 4540). Experientia 32(5):604–606

Camara A (1959) Female genital schistosomiasis. Rev Ginecol Obstet (Sao Paulo) 105:271–280

Cheever AW, Kamel IA, Elwi AM, Mosimann JE, Danner R, Sippel JE (1978) *Schistosoma mansoni* and *S. haematobium* infections in Egypt. III. Extrahepatic pathology. Am J Trop Med Hyg 27(1 Pt 1):55–75

Chitsulo L, Engels D, Montresor A, Savioli L (2000) The global status of schistosomiasis and its control. Acta Trop 77:41–51

Chu KY (1978) Trials of ecological and chemical measures for the control of *Schistosoma haematobium* transmission in a Volta Lake village. Bull World Health Organ 56(2):313–322

Cioli D, Pica-Mattoccia L, Archer S (1995) Antischistosomal drugs: past, present … and future? Pharmacology 68:35–85

Cioli D (2000) Praziquantel: is there real resistance and are there alternatives? Curr Opin Infect Dis 13(6):659–663

Cioli D, Pica-Mattoccia L (2003) Praziquantel. Parasitol Res 90(Supp 1):S3–S9

Cnops L, Tannich E, Polman K, Clerinx J, Van Esbroeck M (2012) Schistosoma real-time PCR as diagnostic tool for international travellers and migrants. Trop Med Int Health 17(10): 1208–1216

Coulibaly JT, Knopp S, N'Guessan NA, Silué KD, Fürst T et al (2011) Accuracy of urine circulating cathodic antigen (CCA) test for Schistosoma mansoni diagnosis in different settings of Côte d'Ivoire. PLoS Negl Trop Dis 5(11):e1384. doi:10.1371/journal.pntd.0001384

Cringoli G, Rinaldi L, Albonico M, Bergquist R, Utzinger J (2013) Geospatial (s)tools: integration of advanced epidemiological sampling and novel diagnostics. Geospatial Health 7(2): 399–404

Danso-Appiah A, De Vlas SJ (2002) Interpreting low praziquantel cure rates of Schistosoma mansoni infections in Senegal. Trends Parasitol 18(3):125–129

Danso-Appiah A, De Vlas SJ, Bosompem KM, Habbema JD (2004) Determinants of health-seeking behaviour for schistosomiasis-related symptoms in the context of integrating schistosomiasis control within the regular health services in Ghana. Trop Med Int Health 9(7): 784–794

Danso-Appiah A, Utzinger J, Liu J, Olliaro P (2008) Drugs for treating urinary schistosomiasis. Cochrane Database Syst Rev 16(3):CD000053. doi:10.1002/14651858.CD000053.pub2

Danso-Appiah A (2009) Treatment effects and integrated morbidity control of schistosomiasis. Ipskamp Publishers, Enschede 1–202

Danso-Appiah A, Stolk WA, Bosompem KM, Otchere J, Looman CW et al (2010) Health seeking behaviour and utilization of health facilities for schistosomiasis-related symptoms in Ghana. PLoS Negl Trop Dis 4(11):e867. doi:10.1371/journal.pntd.0000867

Danso-Appiah A, Olliaro PL, Donegan S, Sinclair D, Utzinger J (2013) Drugs for treating Schistosoma mansoni infection. Cochrane Database Syst Rev 2:CD000528. doi:10.1002/14651858.CD000528.pub2

Danso-Appiah et al (2014) Systematic review and meta-analysis of the circulating cathodic antigen (CCA) test in the diagnosis of schistosome infection (Submitted)

Davis A (2009) Schistosomiasis In: Cook GC, Zumla AI (eds) Manson's tropical diseases, Section 11, Chapter 82, 22nd edn. Saunders Elsevier, pp 1431–1469. International edition. Printed in China

del Villar PL, Burguillo FJ, López-Abán J, Muro A (2012) Systematic review and meta-analysis of artemisinin based therapies for the treatment and prevention of schistosomiasis. PLoS ONE 7(9):e45867. doi:10.1371/journal.pone.0045867

Doenhoff MJ (1998) Is Schistosomicidal chemotherapy sub-curative? Implications for drug resistance. Parasitol Today 14(10):434–435

Engels D, Savioli L (2006) Reconsidering the underestimated burden caused by neglected tropical diseases. Trends Parasitol 22(8):363–366

Engels D, Chitsulo L, Montresor A, Savioli L (2002) The global epidemiological situation of schistosomiasis and new approaches to control and research. Acta Trop 82(2):139–146

Enk MJ, Silva OG, Rodrigues NB (2012) Diagnostic accuracy and applicability of a PCR system for the detection of Schistosoma mansoni DNA in human urine samples from an endemic area. PLoS ONE 7(6):e38947. doi:10.1371/journal.pone.0038947

Esrey SA, Potash JB, Roberts L, Shiff C (1991) Effects of improved water supply and sanitation on ascariasis, diarrhoea, dracunculiasis, hookworm infection, schistosomiasis, and trachoma. Bull World Health Organ 69(5):609–621

Fallon PG, Sturrock RF, Niang AC, Doenhoff MJ (1995) Diminished susceptibility to praziquantel in a Senegalese isolate of Schistosoma mansoni. Am J Trop Med Hyg 53:61–62
Feldmeier H, Chitsulo L (1999) Therapeutic and operational profiles of metrifonate and praziquantel in *Schistosoma haematobium* infection. Arzneimittelforschung 49(7):557–565
Feldmeier H, Doehring E (1987) Clinical experience with metrifonate. Review with emphasis on its use in endemic areas. Acta Trop 44(3):357–368
Fenwick A, Rollinson D, Southgate V (2006) Implementation of human schistosomiasis control: challenges and prospects. Adv Parasitol 61:567–622
Fenwick A, Webster JP, Bosque-Oliva E, Blair L, Fleming FM et al (2009) The Schistosomiasis Control Initiative (SCI): rationale, development and implementation from 2002–2008. Parasitology 136(13):1719–1730
Foster R (1987) A review of clinical experience with oxamniquine. Trans R Soc Trop Med Hyg 81(1):55–59
Garba A, Touré S, Dembelé R, Boisier P, Tohon Z et al (2009) Present and future schistosomiasis control activities with support from the Schistosomiasis Control Initiative in West Africa. Parasitology 136(13):1731–1737
Geerts S, Gryseels B (2001) Anthelmintic resistance in human helminths: a review. Trop Med Int Health 6(11):915–921
Glinz D, Silué KD, Knopp S, Lohourignon LK, Yao KP et al (2010) Comparing diagnostic accuracy of Kato-Katz, Koga agar plate, ether-concentration, and FLOTAC for Schistosoma mansoni and soil-transmitted helminths. PLoS Negl Trop Dis 4(7):e754. doi:10.1371/journal.pntd.0000754
Grobusch MP, Mühlberger N, Jelinek T, Bisoffi Z, Corachán M et al (2003) Imported Schistosomiasis in Europe: sentinel surveillance data from Trop Net Europe. J Travel Med 10(3):164–169
Gryseels B, Polderman AM (1987) The morbidity of schistosomiasis mansoni in Maniema (Zaire). Trans R Soc Trop Med Hyg 81(2):202–209
Gryseels B, Polderman AM, Engels D (1992) Experiences with the control of schistosomiasis mansoni in two foci in central Africa. Mem Inst Oswaldo Cruz 87(Suppl 4):187–194
Gryseels B, Nkulikyinka L, Engels D (1994) Impact of repeated community-based selective chemotherapy on morbidity due to schistosomiasis mansoni. Am J Trop Med Hyg 51:634–641
Gryseels B, Mbaye A, De Vlas SJ, Stelma FF, Guissé F et al (2001) Are poor responses to praziquantel for the treatment of Schistosoma mansoni infections in Senegal due to resistance? An overview of the evidence. Trop Med Int Health 6(11):864–873
Gryseels B, Polman K, Clerinx J, Kestens L (2006) Human schistosomiasis. Lancet 368(9541): 1106–1118
Guo JG, Cao CL, Hu GH, Lin H, Li D, Zhu R, Xu J (2005) The role of 'passive chemotherapy' plus health education for schistosomiasis control in China during maintenance and consolidation phase. Acta Trop 96(2–3):177–183
Hatz CF (2001) The use of ultrasound in schistosomiasis. Adv Parasitol 48:225–284
Hatz CF (2005) Schistosomiasis: an underestimated problem in industrialized countries? J Travel Med 12(1):1–2
Helleberg M, Thybo S (2010) High rate of failure in treatment of imported schistosomiasis. J Travel Med 17(2):94–99
Hoffmann KF, Dunne DW (2003) Characterization of the *Schistosoma* transcriptome opens up the world of helminth genomics. Genome Biol 5:203
Hotez PJ (2009) Mass drug administration and integrated control for the world's high-prevalence neglected tropical diseases. Clin Pharmacol Ther 85:659–664
Hotez P (2011) Enlarging the "Audacious Goal": elimination of the world's high prevalence neglected tropical diseases. Vaccine 29(Suppl 4):D104–D110. doi:10.1016/j.vaccine.2011.06.024
Hotez PJ, Pecoul B (2010) "Manifesto" for advancing the control and elimination of neglected tropical diseases. PLoS Negl Trop Dis 4(5):e718. doi:10.1371/journal.pntd.0000718
Hotez PJ, Molyneux DH, Fenwick A, Ottesen E, Ehrlich Sachs S, Sachs JD (2006) Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria. PLoS Med 3:e102

Hotez P, Raff S, Fenwick A, Richards F Jr, Molyneux DH (2007) Recent progress in integrated neglected tropical disease control. Trends Parasitol 23(11):511–514
Hotez PJ, Fenwick A, Savioli L, Molyneux DH (2009) Rescuing the bottom billion through control of neglected tropical diseases. Lancet 373:1570–1575
Istre GR, Fontaine RE, Tarr J, Hopkins RS (1984) Acute schistosomiasis among Americans rafting the Omo River Ethiopia. JAMA 251:508–510
Johansen MV, Sacko M, Vennervald BJ, Kabatereine NB (2007) Leave children untreated and sustain inequity! Trends Parasitol 23(12):568–569
Jordan P (2000) From katayama to the Dakhla Oasis: the beginning of epidemiology and control of bilharzia. Acta Trop 77(1):9–40
Jordan P, Unrau GO, Bartholomew RK, Cook JA, Grist E (1982) Value of individual household water supplies in the maintenance phase of a schistosomiasis control programme in Saint Lucia, after chemotherapy. Bull World Health Organ 60(4):583–588
Kardorff R, Dohring E (2001) Ultrasound diagnosis of bilharziasis. Ultraschall Med 22(3): 107–115
Katz N, Chaves A, Pellegrino J (1972) A simple device for quantitative stool thick-smear technique in Schistosomiasis mansoni. Rev Inst Med Trop Sao Paulo 14(6):397–400
Keenan JD, Hotez PJ, Amza A, Stoller NE, Gaynor BD et al (2013) Elimination and eradication of neglected tropical diseases with mass drug administrations: a survey of experts. PLoS Negl Trop Dis 7(12):e2562
King CH, Bertino A-M (2008) Asymmetries of poverty: why global burden of disease valuations underestimate the burden of neglected tropical diseases. PLoS Negl Trop Dis 2(3):1–10
King CH, Dangerfield-Cha M (2008) The unacknowledged impact of chronic schistosomiasis. Chron Illn 4(1):65–79
King CH, Keating CE, Muruka JF, Ouma JH, Houser H et al (1988) Urinary tract morbidity in schistosomiasis haematobia: associations with age and intensity of infection in an endemic area of Coast Province. Kenya Am J Trop Med Hyg 39(4):361–368
King CH, Dickman K, Tisch DJ (2005) Reassessment of the cost of chronic helminthic infection: a meta-analysis of disability-related outcomes in endemic schistosomiasis. Lancet 365(9470):1561–1569
Kinkel HF, Dittrich S, Bäumer B, Weitzel T (2012) Evaluation of eight serological tests for diagnosis of imported schistosomiasis. Clin Vaccine Immunol 19(6):948–953
Le WJ, You JQ, Yang YQ, Mei JY, Guo HF, Yang HZ et al (1982) Studies on the efficacy of artemether in experimental schistosomiasis. YaoXue Xue Bao 17(3):187–193
Le WJ, You JQ, Mei JY (1983) Chemotherapeutic effect of artesunate in experimental schistosomiasis. YaoXue Xue Bao 18(8):619–621
Legesse M, Erko B (2007) Field-based evaluation of a reagent strip test for diagnosis of *Schistosoma mansoni* by detecting circulating cathodic antigen in urine before and after chemotherapy. Trans R Soc Trop Med Hyg 101(7):668–673
Legesse M, Erko B (2008) Field-based evaluation of a reagent strip test for diagnosis of schistosomiasis mansoni by detecting circulating cathodic antigen (CCA) in urine in low endemic area in Ethiopia. Parasite 15(2):151–155
Lengeler C, Utzinger J, Tanner M (2002) Questionnaires for rapid screening of schistosomiasis in sub-Saharan Africa. Bull World Health Organ. 80(3):235–42
Linehan M, Hanson C, Weaver A, Baker M, Kabore A et al (2011) Integrated implementation of programs targeting neglected tropical diseases through preventive chemotherapy: proving the feasibility at national scale. Am J Trop Med Hyg 84(1):5–14
Liu R, Dong HF, Guo Y, Zhao QP, Jiang MS (2011) Efficacy of praziquantel and artemisinin derivatives for the treatment and prevention of human schistosomiasis: a systematic review and meta-analysis. Parasitol Vectors 4:201. doi:10.1186/1756-3305-4-201
Lorenz W, Henglein A, Schrader G (1955) The new insecticide 0.0-dimethyl-2,2,2-trichloro-1-hydroxyethyl phosphate. J Am Chem Soc 77:2554
Manderson L, Aagaard-Hansen J, Allotey P, Gyapong M, Sommerfeld J (2009) Social research on neglected diseases of poverty: continuing and emerging themes. PLoS Negl Trop Dis 3:e332. doi:10.1371/journal.pntd.0000332

Mascie-Taylor CGN, Karim R, Karim E, Akhtar S, Ahmed T et al (2003) The cost-effectiveness of health education in improving knowledge and awareness about intestinal parasites in rural Bangladesh. Econ Hum Biol 1(3):321–330

Mbabazi PS, Andan O, Fitzgerald DW, Chitsulo L, Engels D, Downs JA (2011) Examining the relationship between urogenital schistosomiasis and HIV infection. PLoS Negl Trop Dis 5(12):e1396. doi:10.1371/journal.pntd.0001396

McCoy D, Kembhavi G, Patel J, Luintel A (2009) The Bill & Melinda Gates Foundation's grant-making programme for global health. Lancet 373:1645–1653

Minamoto K, Mascie-Taylor CGN, Karim E, Moji K, Rahman M (2012) Short- and long-term impact of health education in improving water supply, sanitation and knowledge about intestinal helminths in rural Bangladesh. Public Health 126(5):437–440

Mitchell KM, Mutapi F, Woolhouse ME (2008) The predicted impact of immunosuppression upon population age- intensity profiles for schistosomiasis. Parasite Immunol 30(9):462–470

Mott KE, Dixon H, Osei-Tutu E, England EC (1983) Relation between intensity of *Schistosoma haematobium* infection and clinical haematuria and proteinuria. Lancet 1(8332):1005–1008

Murta-Nascimento C, Schmitz-Drager BJ, Zeegers MP, Steineck G, Kogevinas M, Real FX et al (2007) Epidemiology of urinary bladder cancer: from tumor development to patient's death. World J Urol 25(3):285–295

Ochodo EA, Spek B, Reitsma JB, Van Lieshout L, Polman K et al (2012) Rapid screening and diagnostic tests for human schistosomiasis in endemic areas. Cochrane Database Syst Rev (2):CD009579. doi:10.1002/14651858.CD009579

Odogwu SE, Ramamurthy NK, Kabatereine NB, Kazibwe F, Tukahebwa E, Webster JP, Fenwick A, Stothard JR (2006) Schistosoma mansoni in infants (aged <3 years) along the Ugandan shoreline of Lake Victoria. Ann Trop Med Parasitol 100(4):315–326

Olds GR, Dasarathy S (2000) Schistosomiasis. Curr Treat Options Infect Dis 2:88–99

Olsen A (2007) Efficacy and safety of drug combinations in the treatment of schistosomiasis, soil-transmitted helminthiasis, lymphatic filariasis and onchocerciasis. Trans R Soc Trop Med Hyg 101(8):747–758

Poda JN, Wango SP, Sorgho H, Dianou D (2004) Recent evolution of schistosomiasis in the water project of Sourou in Burkina Faso. Bull Soc Pathol Exot 97(1):15–18

Poggensee G, Feldmeier H (2001) Female genital schistosomiasis: facts and hypotheses. Acta Trop 79(3):193–210

Polman K, Stelma FF, De Vlas SJ, Sow S, Fathers L et al (2001) Dynamics of egg counts and circulating antigen levels in a recent *Schistosoma mansoni* focus in northern Senegal. Trop Med Int Health 6:538–544

Polman K, Stelma FF, Le Cessie S, De Vlas SJ, Falcao-Ferreira ST et al (2002) B. Evaluation of the patterns of Schistosoma mansoni infection and re-infection in Senegal, from faecal egg counts and serum concentrations of circulating anodic antigen. Ann Trop Med Parasitol 96:679–689

Rabello AL (1992) Parasitological diagnosis of schistosomiasis mansoni: faecal examination and rectal biopsy. Mem Inst Oswaldo Cruz 87(Suppl 4):325–331

Raso G, Utzinger J, Silué KD, Ouattara M, Yapi A et al (2005) Disparities in parasitic infections, perceived ill health and access to health care among poorer and less poor schoolchildren of rural Côte d'Ivoire. Trop Med Int Health 10:42–57

Reich MR, Fenwick A (2001) Schistosoma haematobium. N Engl J Med 344(15):1170

Renganathan E, Cioli D (1998) An international initiative on praziquantel use. Parasitol Today 14(10):390–391

Richter J (2003) The impact of chemotherapy on morbidity due to schistosomiasis. Acta Trop 86(2–3):161–183

Sabah AA, Fletcher C, Webbe G, Doenhoff MJ (1986) *Schistosoma mansoni*: chemotherapy of infections of different ages. Exp Parasitol 61:294–303

Salehe FS, Hassan SN (2012) Socio-economic effects of Schistosomiasis on. Irrigation rice growers in Morogoro, Tanzania. J Exp Agric 2(3):395–406

Sandoval N, Siles-Lucas M, Pérez-Arellano JL, Carranza C, Puente S et al (2006) A new PCR-based approach for the specific amplification of DNA from different Schistosoma species applicable to human urine samples. Parasitology 133(Pt 5):581–587

Schwartz E, Kozarsky P, Wilson M, Cetron M (2005) Schistosome infection among river rafters on Omo River Ethiopia. J Travel Med 12:3–8
Shekhar KC (1991) Schistosomiasis drug therapy and treatment considerations. Drugs 42(3): 379–405
Shiff CJ, de Clarke V, Evans AC, Barnish G (1973) Molluscicide for the control of schistosomiasis in irrigation schemes. A study in Southern Rhodesia. Bull World Health Organ 48:299–307
Singer BH, Castro MC (2007) Bridges to sustainable tropical health. Proc Natl Acad Sci U S A 104:16038–16043
Snellen WM (1981) Therapeutic properties of metrifonate. Acta Pharmacol Toxicol (Copenh) 49(Suppl V 5):114–117
Spiegel JM, Dharamsi S, Wasan KM, Yassi A, Singer B, Hotez PJ et al (2010) Which new approaches to tackling neglected tropical diseases show promise? PLoS Med 7(5):e1000255. doi:10.1371/journal.pmed.1000255
Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J (2006) Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. Lancet Infect Dis 6:411–425
Stelma FF, Talla I, Sow S, Kongs A, Niang M et al (1995) Efficacy and side effects of praziquantel in an endemic focus of Schistosoma mansoni. Am J Trop Med Hyg 53:167–170
Stothard JR, Gabrielli AF (2007) Schistosomiasis in African infants and preschool children: to treat or not to treat? Trends Parasitol 23:83–86
Stothard JR, Sousa-Figueiredo JC, Navaratnam AM (2013) Advocacy, policies and practicalities of preventive chemotherapy campaigns for African children with schistosomiasis. Expert Rev Anti-Infect Ther 11(7):733–752
Striebel HP (1976) 4-Isothiocyanato-4′-nitrodiphenylamine (C 9333-Go/CGP 4540), an anthelminthic with an unusual spectrum of activity against intestinal nematodes, filariae and schistosomes. Experientia 32(4):457–458
Sturrock RF (2001) Schistosomiasis epidemiology and control: how did we get here and where should we go? Mem Inst Oswaldo Cruz 96(Suppl):17–27
Umeh JC, Amali O, Umeh EU (2004) The socio-economic effects of tropical diseases in Nigeria. Econ Hum Biol 2:245–263
Utzinger J, Keiser J (2004) Schistosomiasis and soil-transmitted helminthiasis: common drugs for treatment and control. Expert Opin Pharmacother 5(2):263–285
Utzinger J, Keiser J, Xiao SH, Tanner M, Singer BH (2003a) Combination chemotherapy of schistosomiasis in laboratory studies and clinical trials. Antimicrob Agents Chemother 47: 1487–1495
Utzinger J, Bergquist R, Xiao SH, Singer BH, Tanner M (2003b) Sustainable schistosomiasis control – the way forward. Lancet 362:1932–1934
Utzinger J, Xiao SH, Tanner M, Keiser J (2007) Artemisinins for schistosomiasis and beyond. Curr Opin Invest Drugs 8(2):105–116
Utzinger J, Raso G, Brooker S, De Savigny D, Tanner M et al (2009) Schistosomiasis and neglected tropical diseases: towards integrated and sustainable control and a word of caution. Parasitology 136(13):1859–1874
Utzinger J, N'goran EK, Caffrey CR, Keiser J (2010) From innovation to application: social-ecological context, diagnostics, drugs and integrated control of schistosomiasis. Acta Trop 120 Suppl 1:S121–37
Utzinger J, N'goran EK, Caffrey CR, Keiser J (2011) From innovation to application: social-ecological context, diagnostics, drugs and integrated control of schistosomiasis. Acta Trop 120(Suppl 1):S121–S137
Valencia CI, Catto BA, Webster LT Jr, Barcelon E, Ofendo-Reyes R (1994) Concentration time course of praziquantel in Filipinos with mild Schistosoma japonicum infection. Southeast Asian J Trop Med Public Health 25(2):409–414
van der Werf MJ, de Vlas SJ, Brooker S, Looman CW, Nagelkerke NJ, Habbema JD et al (2003) Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. Acta Trop 86(2–3):125–139
Warren KS (1982) Schistosomiasis: host-pathogen biology. Infect Dis 4(4):771–775

Whitfield PJ, Bartlett A, Khammo N, Clothier RH (2003) Age-dependent survival and infectivity of Schistosoma mansoni cercariae. Parasitology 127(Pt 1):29–35
WHO (1985) The control of Schistosomiasis: report of WHO expert committee. Technical Report Series No. 728, Geneva
WHO (1998) Report of the WHO Informal Consultation on schistosomiasis control, Geneva 2–4 Dec, 1–44
WHO (2002a) Death and DALY estimates for 2004 by cause for WHO Member States: persons, all ages. World Health Organization. Retrieved 2009-11-12
WHO (2002b) Prevention and control of schistosomiasis and soil-transmitted helminthiasis, Geneva, World Health Organization, (WHO Technical Report Series, No. 912):1–57
WHO (2006a) Preventive chemotherapy in human helminthiasis. World Health Organization, Geneva, Also available from http://whqlibdoc.who.int/publications/2006/9241547103_eng.pdf
WHO (2006b) Preventive chemotherapy in human helminthiasis. Coordinated use of anthelmintic drugs in control interventions: a manual for health professionals and programme managers. World Health Organization, Geneva
WHO (2010a) Schistosomiasis, Fact Sheet No 115; February. World Health Organization Available at http://www.who.int/mediacentre/facesheets/fs115/en/index.html. Accessed 5 Oct 2010
WHO (2010b) Report of a Meeting to Review the Results of Studies on the treatment of Schistosomiasis in Preschool age Children, Geneva, 13–14 Sept. WHO/HTM/NTD/PCT/2011.7
WHO (2011) Report of an informal Consultation on schistosomiasis control, Geneva, 30 March – 1 April 2011
WHO (2012) Schistosomiasis: progress report 2001–2011 and strategic plan 2012–2020. World Health Organization, 1–82
WHO. World Health Organization (1993) The control of schistosomiasis. Second report of the WHO Expert Committee. WHO Tech Rep Ser 830:1–86
WHO. World Health Organization (2002) Prevention and control of schistosomiasis and soil-transmitted helminthiasis. Report of a WHO Expert Committee. WHO Tech Rep Ser 912:1–57
Wikman-Jorgensen PE, Henríquez-Camacho CA, Serrano-Villar S, Pérez-Molina JA (2012) The role of artesunate for the treatment of urinary schistosomiasis in schoolchildren: a systematic review and meta-analysis. Pathog Glob Health 106(7):397–404
Wolfe MS, Quansah FO, Agbemadzo F (1966) Suppressive management of urinary schistosomiasis with antimony dimercaptosuccinate (TWSb) in Ghana. J Trop Med Hyg 69(10):217–223
Woolhouse M, Taylor P, Matanhire D, Chandiwana SK (1991) Acquired immunity and epidemiology of *Schistosoma haematobium*. Nature 351:757–759
Wright WH (1972) A consideration of economic impact of schistosomiasis. Bull World Health Organ 47(5):559–565
Wu GY, Halim MH (2000) Schistosomiasis: progress and problems. World J Gastroenterol 6(1):12–19
Zuidema PJ (1981) The Katayama syndrome: an outbreak in Dutch tourists to the Omo National Park. Ethiopia Trop Geogr Med 33:30–35

Soil-Transmitted Helminthiasis

Michael D. Wilson, Dziedzom K. de Souza, and Irene Ayi

Contents

Abstract The human burden of soil-transmitted helminthiasis is highest in sub-Saharan Africa (SSA) than in other parts of the planet. The major parasites that contribute to the global burden, *Ascaris*, *Trichuris*, hookworm, schistosomes, and *Strongyloides*, and even less known ones such as *Oesophagostomum bifurcum* and *Ternidens deminutus* (a.k.a. "false hookworm") all occur in SSA. In this chapter, the symptoms and consequences of infection by these parasites including retarded growth, reduced work capacity, poor school performance, adverse cognitive development, and nutritional and reproductive health problems are described for each parasite. The most at-risk groups for the diseases they cause are also specified. Why then is SSA carrying the highest burden? The answer is the diseases' association with ignorance or lack of awareness, poor personal and environmental hygiene, poverty, impoverished health services, and economic development. These factors

M.D. Wilson (✉) • D.K. de Souza • I. Ayi
Department of Parasitology, Noguchi Memorial Institute for Medical Research, University of Ghana, LG 581, Legon, Ghana
e-mail: MWilson@noguchi.ug.edu.gh

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_12

are common to these helminths' infections and also explain to a large degree the skewed high prevalence of the diseases in rural African communities. The parasites all share similar basics of the life cycle except for *Strongyloides stercoralis* which in addition is also capable of autoinfection (i.e., multiplication) in human and of existing as free living and productive adults in the environment, attributes which make it difficult to control. Treatment and challenges with mass drug administration (MDA) with antihelminthics and the urgent need for more sensitive diagnostic tools than the existing ones for scenarios of low-intensity infections and the likelihood of resistance developing with the MDA are highlighted. There are opportunities arising from recent technological advancements such as the availability of genome data of 22 helminth species to be exploited for novel drugs and vaccine design and of IT tools, remote sensing data, and global resource platforms for disease mapping, ecology and epidemiology studies, operational research, and implementation of control programs. What it entailed in conducting a successful and sustainable STH control in a hitherto deprived community in Ghana is presented as a case study.

Introduction

Helminthiases are generally infections by intestinal nematodes, of which the roundworm (*Ascaris lumbricoides*), the whipworm (*Trichuris trichiura*), and the hookworms (*Ancylostoma duodenale* and *Necator americanus*) are the most widespread species (Bethony et al. 2006; Brooker et al. 2006a). There are other helminth infections such as *Strongyloides stercoralis* and the even less known *Oesophagostomum bifurcum* and *Ternidens deminutus* [the "false hookworm"] (Hotez and Kamath 2009). The World Health Organization estimates that more than 1.5 billion people, or 24 % of the world's population, are infected with soil-transmitted helminthiasis (STH), with the greatest numbers occurring in sub-Saharan Africa, the Americas, China, and East Asia (WHO 2013). The high prevalence of these infections is closely associated with poverty, poor environmental hygiene, and impoverished health services.

Children and pregnant women are particularly vulnerable to STH infection which decreases work capacity (Crompton and Stephenson 1990) and fitness, and especially in the case of children, it influences their nutritional status, causing growth retardation (Adams et al. 1994) and reduced learning ability (Nokes et al. 1992).

Helminth infections produce a wide range of symptoms including intestinal manifestations (diarrhea, abdominal pain), general malaise, and weakness that may affect working and learning capacities and impair physical growth. Hookworms cause chronic intestinal blood loss that result in iron-deficiency anemia. Some other features of helminth infections include growth stunting, rectal prolapse, and chronic dysentery. These parasitic infections can also adversely affect cognitive development in childhood (Crompton and Nesheim 2002).

Infection intensity is a key factor in understanding the morbidity of STH; although light infections are often asymptomatic, heavy infections cause an array of morbidities, including dietary deficiencies and delayed physical and cognitive development.

Additionally, hookworm and *T. trichiura* infections contribute to iron-deficiency anemia (Bethony et al. 2006; Brooker et al. 2006a; Zimmermann and Hurrell 2007).

According to the 2010 estimates, the global burden due to STH ranges between 43 and 128 disability-adjusted life-years (DALYs) per 100,000 populations (Murray et al. 2012). These diseases are predominant in rural areas and also in some poor urban areas in sub-Saharan Africa, Asia, and Latin America which are rated as low-income countries. Long-term disability and poverty can result from any of these neglected tropical diseases (Hotez et al. 2006; Molyneux et al. 2005; Lammie et al. 2006).

Globally, it is estimated that more than 1.5 billion people, or 24 % of the world's population, are infected with soil-transmitted helminth infections (WHO 2013). As many as 1.2 billion individuals might be infected with *A. lumbricoides*, close to 800 million with *T. trichiura*, and more than 700 million with hookworm (Bethony et al. 2006; Lammie et al. 2006). The actual prevalence of *Strongyloides* infections are not known due to the difficulty in diagnosis, but it is estimated that 30–100 million people may be infected worldwide (Hotez and Kamath 2009; Olsen et al. 2009). It is estimated that 270 million preschool-aged children and over 600 million school-aged children reside in areas where these parasites are intensively transmitted and are in need of treatment and preventive interventions (WHO 2013).

About one-third of the world's population is infected with either one or more species of STH (Warren et al. 1993), and this is a major concern for nutritional health workers since these infections impair children's growth and development. Several studies have shown associations between helminth infection and undernutrition, iron-deficiency anemia, stunted growth, poor school attendance, and poor performance in cognition tests (Simeon et al. 1994; Savioli et al. 1992; Nokes and Bundy 1994; Evans and Guyatt 1995).

The relationship between parasitic infections and malnutrition is one of the factors emphasized in the 1993 World Development Report (World Bank 1993). According to the World Health Organization, globally, there is an increasing trend in helminth infections particularly among people living in developing countries (WHO 2002). Children are more susceptible to the ill effects of parasitic attacks, at the age when their need for nutrients is high. In young children, physical and mental development may be affected by malabsorption, blood and protein loss, and diarrhea generated often by the presence of several types of worms in the gut. Many parasites interfere with the process of intestinal absorption of nutrients. They feed on the nutrients, depriving the child of its sources of nutrition. The child is thus thrown into a state of acute and chronic malnutrition.

Morbidity due to STH and schistosomiasis is relatively easy to control with simple intervention measures. Better sanitation practices reduce transmission to a minimum. However, another approach called preventive chemotherapy is to treat children or whole populations at risk on a regular basis to reduce infection rates (WHO 2013). The targeted STH diseases are ascariasis, trichuriasis, and schistosomiasis.

Helminth infections affect millions of people, and the prevalence and intensity of *T. trichiura* and *A. lumbricoides* are also greatest in school-aged children (Bundy and Cooper 1989). For these reasons and safety, coupled with the cost-effectiveness of anthelminthic delivery to children in this age group, most research and investiga-

tions are targeted at school-aged children (Anderson 1980). It has been argued that targeting delivery of antihelminthics to school-aged children by taking advantage of the existing education infrastructure and administrative system can be one of the most cost-effective approaches in minimizing the intensity of infections with both major intestinal nematodes and urinary schistosomes in many developing countries.

While school-based approach to control of STH may be cost-effective, the challenge is with the treatment of non-enrolled children. Non-enrolled children form a significant proportion of rural communities in sub-Saharan Africa, and they are potentially sources of reinfection of STH and schistosomiasis to their enrolled counterparts, who benefit from the school-based interventions. The enrolment rate in Africa has been estimated to be approximately 68 % and variations between countries exist (Bundy and Guyatt 1995). Although the enrolment ratios are expected to have increased since 1995, the number of non-enrolled children still remains high. Therefore a sizeable number of children are not covered by school-based interventions. In some communities in Ghana, for example, enrolment of children aged 6–15 years in 1999 was estimated to be 37 % (Fentiman et al. 1999). This, however, may have increased substantially with the introduction of the capitation grant policy and National School Feeding Program in 2005 (Osei-Fosu 2011). The capitation grant covers the extra cost and levies (such as examination, facilities, management, security charges, games, and sports) parents usually pay as "school fees" in public schools.

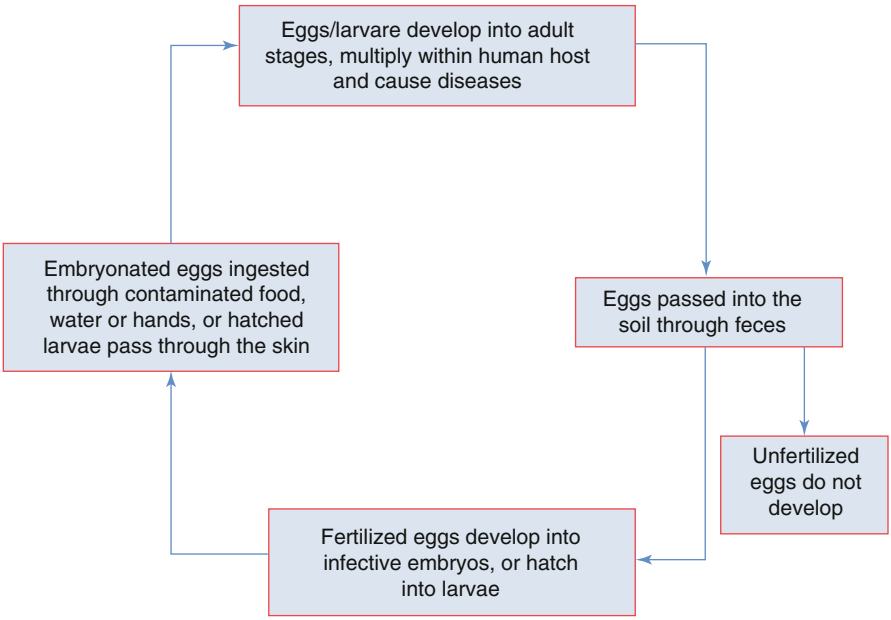


Fig. 1 A generalized transmission cycle of STHs

Basic Biology, Life Cycle, and Disease Presentation

The STHs share a basic biology and life cycle represented in the simplified diagram below (Fig. 1). The adult worms in the human shed many eggs which are passed into the environment through the feces. The eggs develop into infective embryo, which are ingested with contaminated food, water, or hands. From the stomach, they develop into adults and lay more eggs.

Roundworms

Ascaris lumbricoides is the largest nematode parasite of humans. Adult females can grow up to 20–35 cm, while adult males can measure up to 15–30 cm (Fig. 2). Adult worms live in the lumen of the small intestine. A female may produce approximately 200,000 eggs per day, which are passed with the feces. Unfertilized eggs may be ingested but are not infective. The eggs develop into embryos and become infective after 18 days to several weeks, depending on the environmental conditions (optimum: moisture, temperature, and shaded soil). The infective eggs usually enter the body through contaminated water or food or on fingers placed in the mouth after the hands have touched a contaminated object. After infective eggs are swallowed, the larvae hatch, invade the intestinal mucosa, and are carried via the portal and then systemic circulation to the lungs. In the lungs, they mature further after 10–14 days. They then penetrate the alveolar walls, ascend the bronchial tree to the throat, and are swallowed. They develop into adult worms in the small intestine. A typical life cycle (Fig. 3) takes between 2 and 3 months; from ingestion of the infective eggs to oviposition by the adult female. Adult worms can live for 1–2 years.

Ascariasis usually results in no symptoms. Symptoms, however, may present in the form of light abdominal discomfort. Heavy parasite loads can cause intestinal blockage and growth retardation in children. Other symptoms such as cough may be present and are due to migration of the worms through the body.

The life cycle of *S. stercoralis* (Fig. 4) is rather more complex than that of other nematodes, in that it has a free-living stage and a parasitic stage. In addition to this,

Fig. 2 *Left*/*Right*: fertilized eggs of *A. lumbricoides* in unstained wet mounts of stool. *Center*: adult female *A. lumbricoides*. Credit: DPDx. http://www.cdc.gov/parasites/ascariasis/index.html

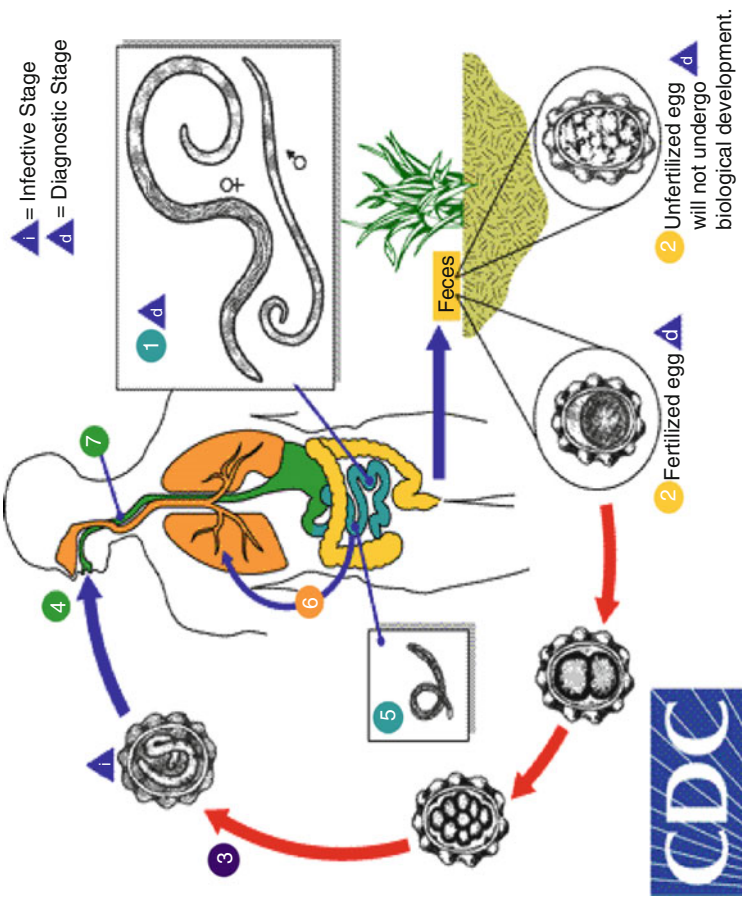


Fig. 3 Life cycle of *Ascaris lumbricoides*

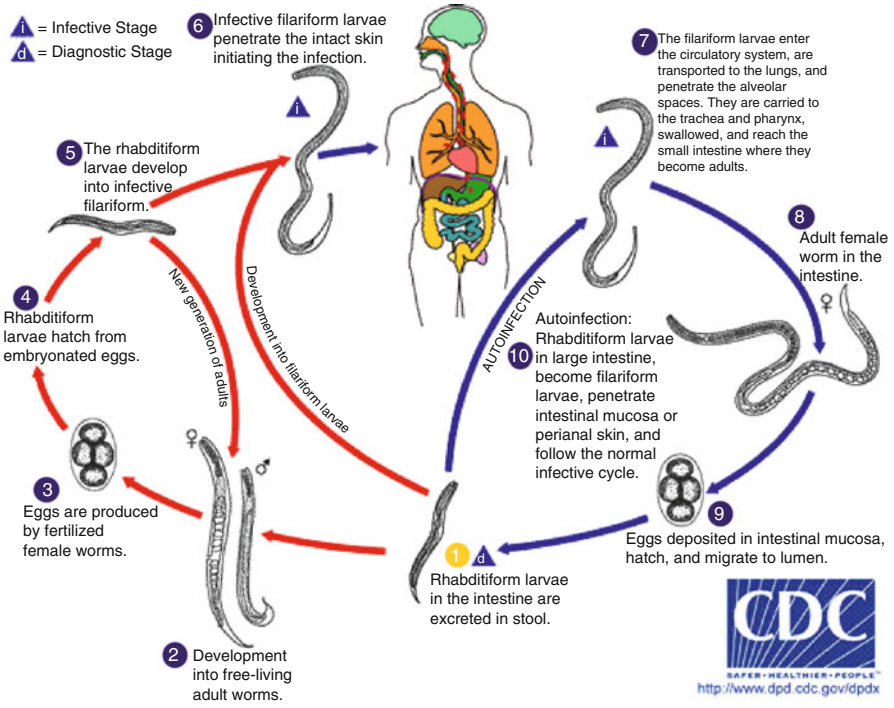


Fig. 4 Life cycle of *Strongyloides stercoralis*

it has the potential for autoinfection and multiplication within the host. In the free-living cycle, the rhabditiform larvae passed in the stool follow one of two cycles. In

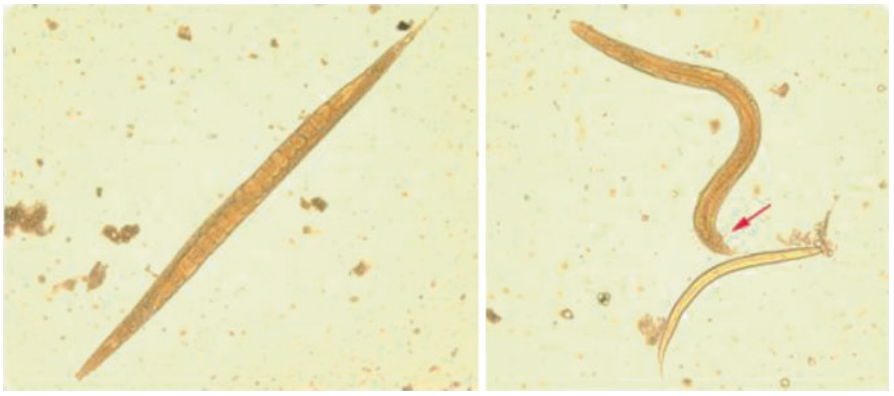


Fig. 5 *Left*: adult free-living female *S. stercoralis*. Notice the row of eggs within the female's body. *Right*: free-living adult male *S. stercoralis*, showing a spicule (*red arrow*). A smaller, rhabditiform larva lies adjacent to the adult male. Credit: DPDx. http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/Strongyloidiasis_il.htm

the first cycle, they molt twice and become infective filariform larvae. In the second cycle, they molt four times and become free-living adult males and females. Males grow to only about 0.9 mm (0.04 in.) in length, and females can grow from 2.0 to 2.5 mm. The males and females (Fig. 5) mate and produce eggs from which rhabditiform larvae hatch. The hatched rhabditiform larvae develop either into a new generation of free-living adults or into infective filariform larvae.

In the parasitic cycle, the filariform larvae in contaminated soil penetrate through the skin and are transported to the lungs. From there, they enter the alveolar spaces and are carried through the bronchial tree to the pharynx, swallowed, and then reach the small intestine. In the small intestine, they molt twice and become adult female worms. The adult females live in the epithelium of the small intestine and produce eggs by parthenogenesis. The eggs hatch into rhabditiform larvae, which either can be passed in the stool or can cause autoinfection. In autoinfection, the rhabditiform larvae become infective filariform larvae, which can penetrate either the intestinal mucosa (internal autoinfection) or the skin of the perianal area (external autoinfection); in either case, the filariform larvae may follow the previously described route, being carried successively to the lungs, the bronchial tree, the pharynx, and the small intestine where they mature into adults, or they may disseminate widely in the body.

Whipworm

Trichuris trichiura, also called the human whipworm, is another species of roundworm. The adult whipworms measure approximately 4 cm in length (Fig. 6). The whipworm life cycle is depicted in Fig. 7. They live permanently in the cecum and ascending colon. The female sheds 3,000–20,000 eggs a day. These are passed with the stool, into the soil, where they embryonate and become infective in 15–30 days. When ingested through soil-contaminated hands or food, the eggs hatch in the small intestine. The larvae mature and establish themselves as adults in the colon, with the anterior portions threaded into the mucosa. The females begin to oviposit 60–70 days after infection. The life span of the adults is about 1 year.

The presentation of symptoms as a result of whipworm infection may depend on the parasite load. Light infections usually have no symptoms. However, heavy infec-

Fig. 6 Egg of *T. trichiura* in an iodine-stained wet mount. *Right*: egg of *T. trichiura* in an unstained wet mount. *Center*: micrograph of an adult female *Trichuris* human whipworm that is approximately 4 cm long. Credit: DPDx, PHIL. http://www.cdc.gov/parasites/whipworm/

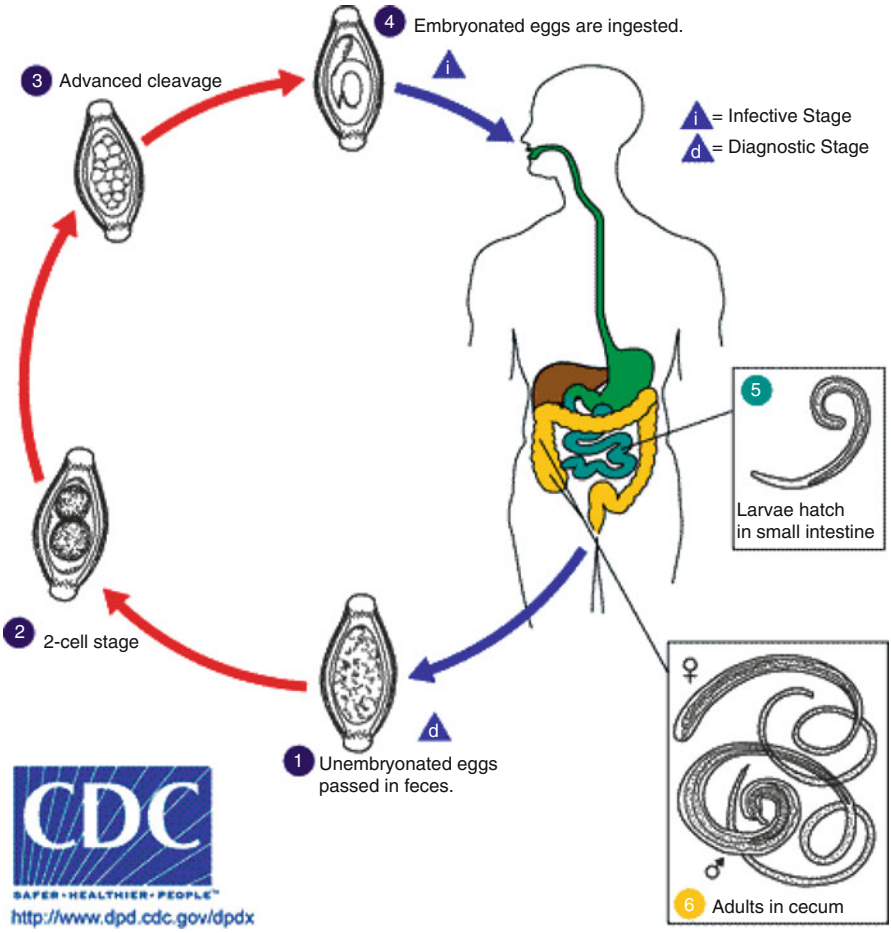


Fig. 7 Life cycle of *Trichuris trichiura*

tions can result in frequent, painful passage of stool, containing a mixture of mucus, water, and blood. Rectal prolapse can also occur. Heavy infection in children results in severe anemia, growth retardation, and impaired cognitive development.

Hookworms

The human hookworm infections are the second most common helminth infections after ascariasis. They are usually due to the nematode species, *Ancylostoma duodenale* and *Necator americanus*. The life cycle of the hookworms differs from the other intestinal helminths, in their mode of transmission (Fig. 8). Adult worms live in the lumen of the small intestine. They produce eggs that are passed in the stool. Within

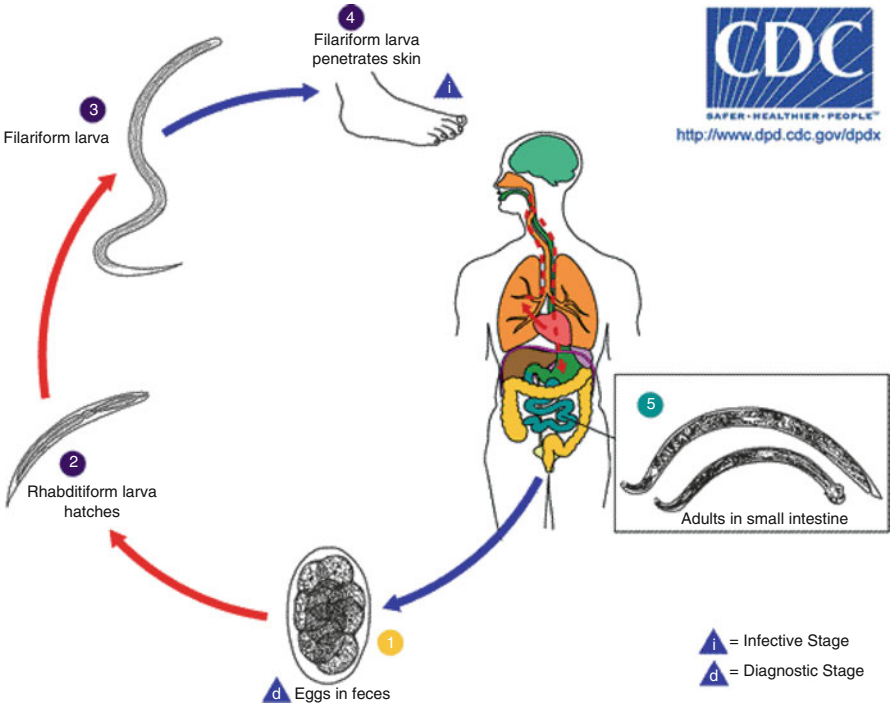


Fig. 8 Life cycle of *Ancylostoma duodenale* and *Necator americanus*

1–2 days, and under favorable environmental conditions, the eggs hatch into rhabditiform (first-stage) larvae (Fig. 9). The larvae grow in the feces and/or the soil and become infective filariform (third-stage) larvae, after 5–10 days. These infective larvae can survive 3–4 weeks in favorable environmental conditions. On contact with the human host, the larvae break through the skin and are carried through the blood vessels to the heart and then to the lungs. They enter into the pulmonary alveoli, up the bronchial tree, and to the pharynx and are swallowed. The larvae reach the small intestine, where they reside and mature into adults. They attach to the intestinal wall with resultant blood loss by the host. The life span of most adult worms is 1–2 years

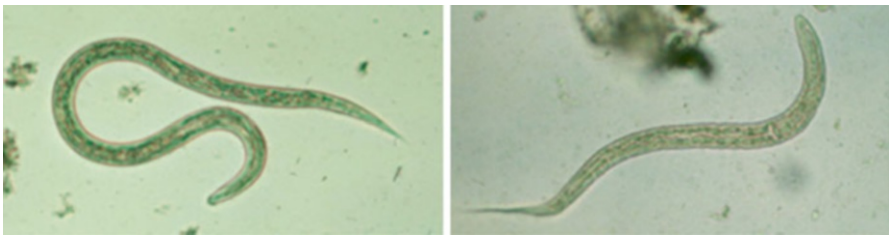


Fig. 9 *Left*: filariform (L3) hookworm larva in a wet mount. *Right*: hookworm rhabditiform larva (wet preparation). Credit: DPDx. http://www.cdc.gov/parasites/hookworm/

but may reach several years. Some *A. duodenal* larvae, following penetration of the host skin, can become dormant (in the intestine or muscle). In addition, infection by *A. duodenale* may probably also occur by the oral and transmammary route. *Necator americanus*, however, requires a transpulmonary migration phase.

The disease presentation is primarily iron-deficiency anemia (a result of blood loss at the site of intestinal attachment of the adult worms), in addition to gastrointestinal and nutritional/metabolic symptoms. Cardiac complications and respiratory symptoms can be observed during the cardiac and pulmonary migration of the larvae. In addition, local skin manifestations ("ground itch") can occur during penetration by the filariform (L3) larvae.

Epidemiology of Soil-Transmitted Helminths in Sub-Saharan Africa

The transmission of STHs is closely linked to poverty and poor personal hygiene and sanitation. The geographic distribution of roundworms, whipworms, and hookworms is worldwide, in areas with warm, moist climates, and is widely overlapping. Infection occurs worldwide and is most common in tropical and subtropical areas where sanitation and hygiene are poor. Hookworm species are worldwide in distribution, mostly in areas with moist, warm climate. Both *N. americanus* and *A. duodenale* are found in Africa, Asia, and the Americas. *Necator americanus* predominates in the Americas and Australia, while only *A. duodenale* is found in the Middle East, North Africa, and southern Europe. STH infections are usually a result of ingestion of parasite eggs through contaminated food or hands or the active penetration on the skin by larvae in the soil. While STH infections occur predominantly in rural areas, with the absence of proper human waste disposal systems, the social and environmental conditions in many unplanned urban slums in developing countries provide ideal conditions for their transmission (Crompton and Savioli 1993). Helminth infections disproportionately affect marginalized, low-income, and resource-constrained regions of the world (Lustigman et al. 2012a). An equilibrium state exists between parasitic populations, host populations, and the environment. STHs are overdispersed or aggregated in human populations such that the majority of people in a community will have either light-intensity infections while only a small number will have heavy-intensity infections (Schad and Anderson 1985). Individuals with heavy infections suffer most of the clinical consequences of STHs and are the major source of infection for the rest of the community (WHO 2002), although their proportion in the community may be small. If environmental and/or behavioral conditions are not changed at the same time that chemotherapy program is being implemented, the prevalence and intensity of infection will tend to return to original pretreatment levels through reinfection.

The epidemiology of helminth infections is influenced by several factors, including environmental and social ecology, age, parasite population structure and composition, geographic and household clustering, multiple parasite infections, chemotherapeutic factors, and current diagnostic abilities (Hotez et al. 2008; Lustigman et al. 2012a). There is considerable geographical variation in the occurrence of infections (Brooker et al. 2009). The intensity of infection also varies with age. *A. lumbricoides* and *T. trichiura* are among the heaviest and most frequent infections in children aged 5–15 years, with a decline in intensity and frequency in adulthood (Gillies 1996). On the other hand, hookworm infections show a steady increase in intensity with age, peaking in adulthood (Bethony et al. 2002). Individuals infected with STHs have also been shown to cluster at the household levels (Forrester et al. 1988), especially with regard to familial predisposition to heavy infection with *A. lumbricoides* and *T. trichiura* (Forrester et al. 1990).

Morbidity due to STH infections is a result of worm burden (number of eggs per gram of feces). Thus disease prevalence is commonly combined with the intensity of infection to assess the epidemiological situation for STH infections and to classify communities into transmission categories. This enables the determination of the appropriate strategies for treatment and control (WHO 2006).

Poor Sanitation, Overcrowding, and Helminth Infections

In common with many other parasitic infections, STH infections flourish in impoverished areas characterized by inadequate sanitation and overcrowding. It is commonly assumed that *A. lumbricoides* and *T. trichiura* are more prevalent in urban areas whereas hookworm is more often found in rural areas (Crompton and Savioli 1993). However, comparable data on STH infections in urban and rural settings are remarkably few, and those that do exist indicate a more complicated picture. Studies which surveyed similar age groups and socioeconomic areas indicate that the prevalence of *A. lumbricoides* and *T. trichiura* differs between urban and rural communities but in no systematic manner. By contrast, hookworm appears to be equally prevalent in both urban and rural settings. The precise reasons for the urban-rural dichotomies for *A. lumbricoides* and *T. trichiura* are as yet unclear. Differences in prevalence of *A. lumbricoides* and *T. trichiura* in urban and rural areas may reflect differences in sanitation or population density. Socioeconomic differences will also play an important role. It is clear that further work is needed to resolve these issues.

The parasites that cause helminth infections are naturally present in the environment. However, the high prevalence of intestinal parasite infections in certain parts of the world is closely correlated with poverty and poor environmental hygiene, namely, (a) the lack of safe water supply, (b) contamination of the environment by human waste, (c) lack of shoes, and (d) poor environmental or personal hygiene.

Unlike viruses, bacteria, fungi, and protozoa, these parasites do not multiply in the human host. Reinfection can therefore occur only as a result of new contact with the contaminated environment. The World Health Organization asserts that school-aged children are an important group in areas where STHs are prevalent, children are disproportionately infected, and the "worm load" in infected children is often greater than in adults (WHO 1997). Also, children with heavy worm infections are more likely to contaminate the environment and thereby increase the risk of infection to others.

Helminth Infections, Anemia, and Undernutrition

Iron-deficiency anemia is the most prevalent nutritional deficiency worldwide (Stoltzfus et al. 1997; Viteri 1994; Zetterstrom 2004; Van den Broek 2003; Stephenson et al. 2000). More than 90 % of affected individuals live in the developing world, where helminth infections are highly prevalent and the parasites are endemic (Stephenson et al. 2000). Helminths are known to be significant contributors to the overall anemia burden in the developing world (Stephenson et al. 2000; Traore' et al. 1998). The health effects associated with anemia are most pronounced in children and women of reproductive age (Viteri 1994; Crompton and Whitehead 1993). In addition to the morbidity in these groups, anemia generates profound physiological and economic costs in the general population (Stephenson et al. 2000). The amount of blood loss that results from iron-deficiency anemia depends on the degree of infection (Stephenson et al. 1985; Stoltzfus et al. 1996), as well as the dietary intake of iron (Roche and Layrisse 1966; Tatala et al. 1998), and also the presence of other parasitic infections that can cause blood loss or hemolysis, such as malaria and *T. trichiura* infection (Stoltzfus et al. 1997; Robertson et al. 1992; Olsen et al. 1998). School-aged children are most vulnerable to iron-deficiency anemia caused by parasitic infection because they tend to harbor the heaviest worm loads in communities (Bundy 1988). STH infections are associated with decreased appetite and low food intake (Stephenson et al. 1993), resulting in decreased growth rate, poor fitness, decreased activity, and poor cognitive function. Micronutrient losses and nutrient malabsorption due to ascariasis and blood loss due to trichuriasis can lead to iron deficiency, iron-deficiency anemia, and poor growth rate (Stephenson et al. 1993, 2000). An analysis of the association between hookworm and anemia in school-aged children in Zanzibar showed that 25 % of all anemia cases, 35 % of iron-deficiency anemia cases, and 73 % of severe anemia cases could be attributed to hookworm infection (Stoltzfus et al. 1997). It has been observed that hookworm contributes more than schistosomiasis or malaria to iron-deficiency anemia in school-aged children (Stephenson et al. 1985; Stephenson 1987). Similarly, other studies in sub-Saharan African countries have revealed similar trends between STH infections, anemia, and malnutrition (Osazuwa et al. 2011; Brooker et al. 1999).

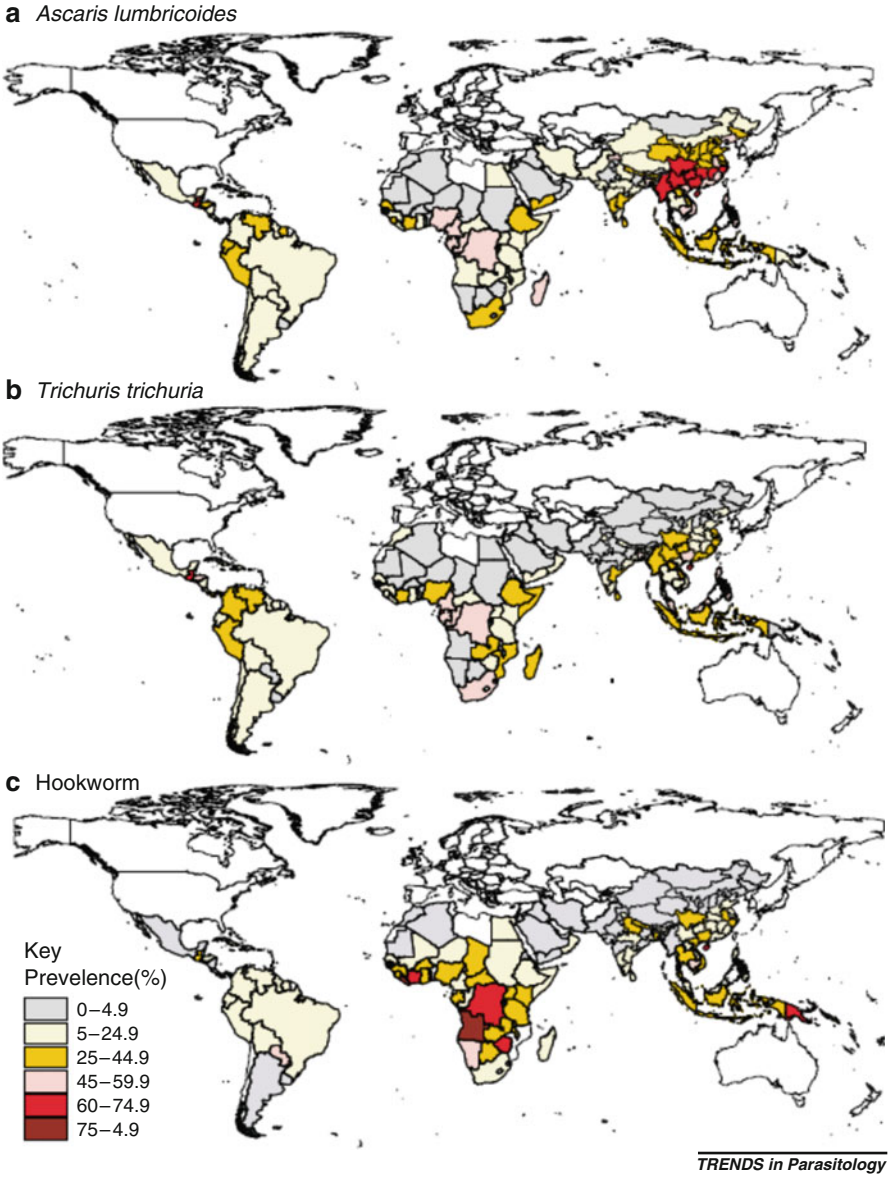


Fig. 10 The global distribution of (**a**) *Ascaris lumbricoides*, (**b**) *Trichuris trichiura*, and (**c**) hookworm (From de Silva et al. 2003)

Burden of Disease and Distribution in Sub-Saharan Africa

Figure 10 shows the global distribution of STHs. In Africa STH infections are prevalent in 50 countries, and it is estimated that 173 million people are infected with *A. lumbricoides*, 162 million with *T. trichiura*, and another 193 million with the

Table 1a Estimates of prevalence and the number of cases of STHs in SSA

Population (millions)			Infection prevalence (%)	Estimated no. of infections (millions)				
				Age groups (years)				Total
	Total	At risk		0–4	5–9	10–14	>15	
Ascariasis	683	571	25	28	28	25	92	173
Trichuriasis	683	561	24	26	27	23	86	162
Hookworm	683	646	29	9	18	29	142	198

Extracted from de Silva et al. (2003)

hookworms (de Silva et al. 2003), in 42 countries. 24 % of the African population is in need of preventive chemotherapy. Tables 1a and 1b summarizes the STH infections in SSA by their estimated prevalence, the percentage of the population infected, the percentage of the world's cases found in the region, and the disease burden.

It is estimated that between one-quarter and one-third of SSA's population is affected by one or more STH infections (Stephenson et al. 1990). Children, especially school-aged children, are the most infected, with half (89 million) of the estimated population of school-aged children infected with hookworm, ascariasis, trichuriasis, or some combination of these STH infections (Brooker et al. 2006a; Hotez and Kamath 2009). The high infection intensities observed in children accounts for the physical and mental deficits, reduced school performance, and the high disease burden in SSA (Hotez and Kamath 2009; Stephenson et al. 1990; Miguel and Kremer 2003).

The morbidity associated with STH infections is primarily the effect on nutritional status and nutrient deficiencies in infected people (Hall et al. 2008). In children, STHs result in cognitive impairment. In severe cases, surgical interventions for intestinal and biliary obstructions are required. The specific signs associated with STH infections are intestinal bleeding and anemia (Stoltzfus et al. 1996), malabsorption of nutrients (Cropmton and Nesheim 2002; Solomons 1993), competition for micronutrients (Curtale et al. 1993), impaired growth (Taren et al. 1987), loss of appetite and reduction of food intake (Stephenson et al. 1993), diarrhea (Callender et al. 1998), reduction in fluency and memory (Nokes et al. 1992; Kvalsvig et al. 1991), intestinal and biliary obstructions (de Silva et al. 1997), and rectal prolapse (Montresor et al. 2002).

Table 1b Prevalence, distribution, and burden of the three major STHs in SSA

Disease	Estimated population infected in SSA (million)	Estimated % of SSA population infected (%)	Estimated % global disease burden in SSA (%)	Estimated global disease burden in DALYs (million)	Estimated % disease burden in SSA (%)	Estimated SSA disease burden in DALYs (million)
Ascariasis	173	25	21	1.8–10.5	21	0.4–2.2
Trichuriasis	162	24	27	1.8–6.4	27	0.5–1.7
Hookworm	198	29	34	1.5–22.1	34	0.5–7.5

Extracted from Hotez and Kamath (2009)

Hookworms are the most common STH infections and the most common NTD in SSA, accounting for up to one-third of the total burden from NTDs in SSA (Hotez and Kamath 2009). It is estimated that 29 % of SSA's population (198 million) are infected with hookworm, including 40–50 million school-aged children (Brooker et al. 2006a, b). Nearly one-third of the world's hookworm infections occur in SSA, with the greatest number of cases occurring in Nigeria (38 million) and the Democratic Republic of the Congo (31 million), followed by Angola, Ethiopia, and Côte d'Ivoire (10–11 million) (Hotez and Kamath 2009). The distribution of hookworm in SSA reveals a high prevalence and intensity, particularly in the coastal regions (Mabaso et al. 2004) and areas of extremely high temperatures (where land surface temperatures exceed 37–40 °C) (Behnke et al. 2000; Brooker and Michael 2000; Brooker et al. 2000, 2002). In SSA, both *N. americanus* and *A. duodenale* are endemic, with *N. americanus* being the predominant species (Albonico et al. 2008). Iron-deficiency anemia in school-aged and preschool-aged children is a principal symptom of hookworm infection (Stoltzfus et al. 1997; Albonico et al. 1998; Brooker et al. 1999; Hotez et al. 2004). It has been estimated that 35 % of iron-deficiency anemia and 73 % of severe anemia in school-aged children in Zanzibar were attributable to hookworm (Stoltzfus et al. 1997). In addition to its effects in children, hookworms have also been recognized as an important cause of anemia and morbidity in women of reproductive age in SSA, especially among pregnant women (Hotez et al. 2004; Crompton 2000). At any given time, almost seven million pregnant women in SSA (up to one-third of pregnant women in the region) are infected with hookworm (Brooker et al. 2008), thus reflecting the importance of hookworm infections as a cause of maternal and child anemia (Hotez and Kamath 2009).

Similar to hookworm infections, the highest prevalence and intensity of *Ascaris* and *Trichuris* infections occur in school-aged children (Brooker et al. 2006a), with an estimated 173 million and 162 million people being infected in SSA with *Ascaris* and *Trichuris*, respectively. Of these, 36 million school-aged children are infected with ascariasis and 44 million with trichuriasis. For both infections, the largest number of cases occurs in Nigeria (being the most populous African country), where coinfections with hookworm are common (Dada-Adegbola et al. 2005). Tens of millions of cases are also found in Ethiopia, DRC, and South Africa (Hotez and Kamath 2009). The distribution of *Ascaris* and *Trichuris* infections in SSA is patchy, with the highest prevalence occurring in equatorial Central and West Africa, eastern Madagascar, and southeast Africa (Brooker et al. 2006a). High prevalence rates of ascariasis and trichuriasis are also found in urban areas compared with rural areas (Brooker et al. 2006a); thus it has been suggested that increased urbanization in SSA may promote the emergence of ascariasis and trichuriasis in the future (Hotez and Kamath 2009).

Available Tools and Control Strategies

The control of STHs requires, principally, the need for assessing the prevalence, intensity, and distribution of infections and the use of chemotherapy to reduce and clear parasite load in infected individuals or the whole community. These approaches

are based on different tools and strategies that have been tested and implemented over the years.

In assessing the prevalence and intensity of STHs, the most widely used approach is the Kato-Katz (K-K) technique (Katz et al. 1972), which has been recommended by the World Health Organization (Montresor et al. 1998). Worm burden is commonly measured by the number of eggs per gram (EPG) of feces (Montresor et al. 1998). The estimated prevalence and intensity of infections are then used to classify communities into low-risk (<20 %), moderate-risk (≥20 % but <50 %), and high-risk (>50 %) transmission categories, which enable the determination of the appropriate treatment strategy for a community (WHO 2006). The K-K method has however been shown to lack sensitivity if only a single stool sample is examined and especially in areas with high proportions of light-intensity infections (Booth et al. 2003). A small number of helminths' eggs, unequally excreted over days and patchily distributed in stool, can occasionally not be detected in the small amount of stool examined with the K-K (i.e., 41.7 mg), hence negatively impacting on the method's sensitivity (Knopp et al. 2008). Thus, for more accurate estimations of parasite intensity (especially in areas with light-intensity infections), examination of multiple stool samples instead of a single one is advocated, in combination with other diagnostic methods (Knopp et al. 2008). These other tools for STH diagnosis include the McMaster test (Levecke et al. 2011), the Koga agar plate (KAP) method (Koga et al. 1991), FLOTAC method (Knopp et al. 2009; Cringoli 2006), and the molecular methods (Verweij et al. 2007).

In addition to determining the prevalence and intensity of infections, tools such as the geographical information system (GIS) and remote sensing (RS) have been used to better understand helminth ecology and epidemiology, and to develop low-cost ways to identify target populations for treatment. GIS and RS have been used to develop the Global Atlas of Helminth Infections (GAHI), and to estimate the number of infections in school-aged children in sub-Saharan Africa (Brooker et al. 2000, 2009; Brooker and Michael 2000). The GAHI provides a global information resource on the distribution of STH and schistosomiasis and can be accessed at http://www.thiswormyworld.org/. The information in the database enables users to visualize the following: (i) survey data maps showing the prevalence of infection based on survey data; (ii) a predictive risk map showing the probability that infection prevalence warrants MDA, according to recommended WHO thresholds; and (iii) a control planning map showing which districts require MDA treatment or where further surveys would be helpful in defining risk (Brooker et al. 2010). Coupled with mathematical modeling for helminth infections (Basanez et al. 2012), it is expected that data collection efforts will take advantage of the current opportunities to integrate multidimensional data, providing a more scientific input into programmatic activities and improving the decision-making in STH control.

Interventions for the control of STHs require the treatment of whole communities through mass drug administration (MDA) and/or individual chemotherapy, supplemented with improved sanitation, environmental conditions, and education (Prichard et al. 2012). MDA programs for STHs are most often targeted at school-aged children who are most at risk of acquiring heavy infection and developing associated morbidity. They are also most accessible for intervention through school-based

programs. Thus, the World Health Assembly resolution WHA54.19, passed in 2001, set the global target of treating by the year 2010 at least 75 % of all school-aged children at risk of morbidity from STHs and schistosomiasis (Lustigman et al. 2012a). The current strategic plan aims at eliminating STHs as a public health problem in children, by the year 2020 (WHO 2012). In highly endemic areas, MDA programs may also be directed at whole communities. The focus of MDA programs for STHs is to achieve long-term reduction in infection prevalence and intensity, and consequently of the associated morbidity, rather than aiming for the elimination of infection (Prichard et al. 2012). The health outcomes aimed for in STH programs and other NTDs are closely related to those of the health-related Millennium Development Goals 1, 2, and 6 of poverty reduction, improvements in education, combating diseases, respectively (Molyneux and Malecela 2011; Lustigman et al. 2012a).

Challenges of Program Implementation

The STH control program is not without challenges. A challenge to program implementation is the lack of resources required to effectively carry out diagnosis, mapping, treatment, monitoring, and evaluation. While albendazole and mebendazole for STH control are donated by GlaxoSmithKline and Johnson & Johnson, respectively (Prichard et al. 2012), MDA still requires the costly prerequisite for mass screening and diagnosis. Very little funding, through the financial support from foundations, government, and agencies, is available to support the operational costs of control programs, and these are directed at short-term objectives (Lustigman et al. 2012a). Integrating various programs therefore has the advantage of reducing the operational costs associated with MDA.

Another important challenge is in monitoring and evaluation of the control programs, especially in the light of the level of sensitivity of various diagnostic tools at low-intensity infections. There are major deficiencies in intervention and diagnostic tools that are appropriate to the changing requirements of large-scale preventative chemotherapy strategies (Boatin et al. 2012). Various diagnostic tools have their usefulness and drawbacks, and their use should be determined by the needs, requirements, and resources available. For instance, the FLOTAC method is more sensitive than the K-K particularly for hookworm eggs but requires a centrifuge and is relatively low throughput (McCarthy et al. 2012). The McMaster test on the other hand is not suitable for community studies where intestinal schistosomiasis is coendemic (McCarthy et al. 2012). Molecular methods can only determine parasite presence and genetic markers for anthelminthic resistance (Schwenkenbecher et al. 2007; Diawara et al. 2009), but they cannot determine parasite intensity. The K-K method, which has become the gold standard in STH diagnosis, lacks sensitivity if only single stool samples are examined, especially in areas with high proportions of light-intensity infections (Booth et al. 2003; Nikolay et al. 2014). A small number of helminth eggs, unequally excreted over days and patchily distributed in stool, can occasionally not be detected in the small amount of stool examined with the K-K

(i.e., 41.7 mg), hence negatively impacting on the method's sensitivity (Knopp et al. 2008). Thus, for more accurate estimations of parasite intensity (especially in areas with light-intensity infections), examination of multiple stool samples instead of a single one is advocated (Knopp et al. 2008). The programmatic implications of this therefore lead to more manpower and time that must be used toward the tail end of STH control programs.

There are also limitations to MDA programs based on single-dose anthelmintic monotherapy for STHs (Keiser and Utzinger 2008). Single-dose therapy with either albendazole (ABZ) or mebendazole (MBZ) is currently highly effective against *A. lumbricoides*; this is not the case for hookworms and whipworms (Prichard et al. 2012). Research is therefore needed to optimize the dose regimes of existing drugs used for the treatment of STHs (Geary et al. 2010). Another limitation to the MDA programs is the identification of genetic polymorphisms in β-tubulin, the marker for benzimidazole resistance in livestock parasites *T. trichiura* and *N. americanus* (Prichard et al. 2012). This partly explains the low/variable efficacy of ABZ or MBZ in *T. trichiura* and *N. americanus* may be due to benzimidazole-resistant genotypes in these parasites in some populations (Diawara et al. 2009). This development, if not properly understood, may threaten the sustainability of control efforts against STHs. Thus, routine monitoring and evaluation should be essential components for STH control programs. Unfortunately most health-care systems do not yet prioritize surveillance of NTDs. Thus, outreach is needed to extend to and involve cooperating health services, health professionals, environmental health officers, and communities that can organize themselves for surveillance (Lustigman et al. 2012a). In addition, modeling tools may help forecast the change in prevalence of soil-transmitted helminths during control programs (Montresor et al. 2013).

Mass treatments further face the challenges of sustainability. Noncompliance and "patient fatigue" to MDA programs have been reported for lymphatic filariasis control programs (Boyd et al. 2010; El-Setouhy et al. 2007). Community involvement and ownership of control activities are also crucial for successful programs (Lustigman et al. 2012a). There may be further "donor fatigue" to sustained funding, if initial successes are not maintained (Lustigman et al. 2012a). Finally, there are many social, political, and environmental factors affecting STH control (Gazinelli et al. 2012). Control programs must be supplemented by improvements in the availability of potable water, sanitation, and hygiene (WASH); improved socioeconomic development; and environmental sustainability, through multidisciplinary studies encompassing the various stakeholders. These must principally be accompanied with behavior change, if the gains made are to be sustainable.

Further Research for Control

The Disease Reference Group on Helminth Infections (DRG4), established in 2009 by the Special Programme for Research and Training in Tropical Diseases (TDR), has outlined the research priorities and gaps associated with the control of helminth

infections. Basic helminth research has been hampered by the need for operational control activities which attract most of the funding available (Lustigman et al. 2012a; Moran et al. 2009). It has been suggested that research into helminth genomics and the use of bioinformatics tools may enhance the functional analysis of genes and the proteins they encode and the identification of candidate antigens for vaccine development (Lustigman et al. 2012a).

The drugs used for helminth control are limited. In the case of STHs, there are four main antihelminthics on the World Health Organization model list of essential medicines for the treatment and control of STH, and these include albendazole, mebendazole, levamisole, and pyrantel pamoate (Utzinger and Keiser 2004; WHO 2006)). However, albendazole and mebendazole are the main drugs used, because of their efficacy (Prichard et al. 2012). In Kenya, for example, it was found that the antihelminthic drug levamisole was highly effective against *A. lumbricoides* but ineffective against hookworms and *T. trichiura*; hence levamisole was exchanged with albendazole (Magnussen et al. 1997).

The rather small number of drugs against STH infections poses concerns should there be development of anthelminthic resistance following years of treatment (Olliaro et al. 2011; Vercruysse et al. 2011), and in view of the fact that despite the benefits to treated populations, helminth infections have been resilient and persistent in their host populations (Prichard et al. 2012). Currently, single-dose treatment with albendazole and mebendazole is effective against *A. lumbricoides*, but not hookworms and whipworms (Prichard et al. 2012). In many endemic areas, STH infections are coendemic and polyparasitism is not uncommon. Thus, the use of single-dose treatments with suboptimal responses against some parasites may pose challenges to control programs. Furthermore, genetic polymorphisms in the benzimidazole drug resistance marker (β-tubulin) have been detected in *T. trichiura* and *N. americanus* (Diawara et al. 2009, 2013). Thus, one priority research need is to undertake well-designed dose-finding studies to optimize the dose regimes of existing drugs used for the treatment of STHs (Geary et al. 2010). Another research need is to investigate the development of resistance to benzimidazole, for monitoring and evaluation purposes. Recently, molecular assays have been developed to detect putative resistance genetic changes in *A. lumbricoides*, *T. trichiura*, and hookworms (Diawara et al. 2013). However, these new assays need to be validated. A third research need is the formulation of new drug combinations, novel drugs, and vaccines. The use of new drug combinations will help increase the spectrum, effectiveness, and convenience of drug administration while reducing the development of resistance. Currently, new antihelminthics for STHs (e.g., tribendimidine, nitazoxanide, monepantel) do exist, but these lack in efficacy compared to current drugs (Prichard et al. 2012; Hu et al. 2009). It has also been suggested that new veterinary antihelminthics (e.g., emodepside, derquantel) should be evaluated for potential use against helminth parasites of humans (Prichard et al. 2012; Olliaro et al. 2011; Keiser and Utzinger 2010). Similarly, there have been some advances in vaccine development against hookworm and some other helminth infections (Prichard et al. 2012).

Being principally diseases of the poor, there are many social, cultural, political, and environmental factors that affect the success of STH control programs (Gazzinelli et al. 2012). While chemotherapy is considered the most effective control tool by far, it is recommended that a more holistic, integrated approach be used. Research is thus needed to understand the range of social, cultural, and environmental factors and conditions involved in helminth transmission, spread, persistence, and control, such as the role of poverty, environmental and climatic change, and active and broadly based community participation, intersect oral collaboration, and equitable access to health services. All of these must be considered in developing and scaling up acceptable, cost-effective, and sustainable control and elimination programs.

Finally, there is the need for establishing capacity in disease-endemic countries (DECs), in order to undertake the various research needs facing the national and global helminth control programs. The research infrastructure in DECs is at the mercy of international donor agencies, major funding bodies, and academic institutions from the developed world, who contribute to the creation of (not always equitable) North-South "partnerships" (Osei-Atweneboana et al. 2012). Thus, while most funding for control implementation programs go to DECs, most funding for research and development remain in developed countries. Furthermore, there is an outflow of trained personnel to developed countries, as a result of low salaries, unattractive work conditions and enabling environments, and low government support for research activities. Thus, comprehensive approaches to human resource management as well as a systemic approach to capacity building, including recognition of the importance of developing a strong research culture in DECs, are needed.

Outlook for the Next Decade

The London Declaration on Neglected Tropical Diseases (Uniting to Combat NTDs 2012) in January 2012 has led to increased commitment on the part of the international community to provide support for the global efforts to control or eliminate several NTDs. The global partners committed to:

- Sustain, expand and extend programmes that ensure the necessary supply of drugs and other interventions to help eradicate Guinea worm disease, and help eliminate by 2020 lymphatic filariasis, leprosy, sleeping sickness (human African trypanosomiasis) and blinding trachoma.
    - Sustain, expand and extend drug access programmes to ensure the necessary supply of drugs and other interventions to help control by 2020 schistosomiasis, soil-transmitted helminthes, Chagas disease, visceral leishmaniasis and river blindness (onchocerciasis).
    - Advance R&D through partnerships and provision of funding to find next-generation treatments and interventions for neglected diseases.
    - Enhance collaboration and coordination on NTDs at national and international levels through public and private multilateral organisations to work more efficiently and effectively together.

- Enable adequate funding with endemic countries to implement NTD programmes necessary to achieve these goals, supported by strong and committed health systems at the national level.
- Provide technical support, tools and resources to support NTD-endemic countries to evaluate and monitor NTD programmes.
- Provide regular updates on the progress in reaching the 2020 goals and identify remaining gaps.

These goals will determine the global agenda for the control of STH infections and other NTDs, for the next decade. The pharmaceutical companies providing the drugs used for NTDs have pledged to donate drugs for as long as they are needed. The UK's Department for International Development (DFID) announced a fivefold increase in their aid for NTDs (http://endtheneglect.org/2012/01/uk-announces-five-fold-increase-in-funding-for-ntds/). Similarly, there has been an increase in funding from other sources such as the USAID (http://www.neglecteddiseases.gov/funding/index.html) and the Bill & Melinda Gates Foundation (http://www.gatesfoundation.org/Media-Center/Press-Releases/2009/01/Bill-and-Melinda-Gates-Urge-Global-Leaders-to-Maintain-Foreign-Aid), all in the effort to help control and greatly reduce the burden of the most prevalent neglected diseases that affect the world's poorest populations by 2020. Given these commitments toward NTDs, it is expected that there will be expanded programs for the control of STH infections in many DECs.

Currently, many sub-Saharan African countries have completed or in the process of completing the STH mapping exercise. Thus, expanded programs for STH control should be in their full state within the next couple of years and especially with regard to current approaches aiming at integrating the control of coendemic NTDs. The improvements in the cartography of helminth infections and updated estimates of the public health burden of STH (Pullan et al. 2014) coupled with the scale-up of control efforts and the free donation of drugs by pharmaceutical companies should result in significant reductions of STH infections. High levels of coverage will be required if MDA is to drive the parasite below the breakpoint under which transmission will be eliminated (Anderson et al. 2014). Further, the addition of long-term measures such as WASH interventions is believed to contribute to lowering the basic reproductive number and facilitate the ability of MDA to interrupt transmission (Anderson et al. 2014). However, further research is warranted to determine the magnitude of benefit from WASH interventions for STH control, through multisectorial, integrated intervention packages that are tailored to social-ecological contexts (Strunz et al. 2014).

Given the advanced state of helminth genomics and the mapping of the genome sequences of 22 species of helminths, including most or all of the significant STHs (Brindley et al. 2009), it is expected that the search for novel drugs and vaccines will be intensified. These advances will also lead to a better understanding of the human-parasite immune interactions. For example, higher infection burden, as a result of reinfection, has been reported in some areas where previous MDA campaigns have not resulted in transmission interruption (Narain et al. 2004). Thus, a better understanding of host-parasite immune relationships at play at the molecular level and at different life cycle stages within the host is important not only to make more precise predictions about the eventual success of the specific elimination efforts but also for monitoring and evaluation purposes, alerting MDA programs of potential challenges that might arise from altered immunity in treated communities (Lustigman et al. 2012b).

References

Adams EJ, Stephenson LS, Latham MC, Kinoti SN (1994) Physical activity and growth of Kenyan school children with hookworms, *Trichuris trichiura* and *Ascaris lumbricoides* infections are improved after treatment with albendazole. J Nutr 124:1199–1206

Albonico M, Stoltzfus RJ, Savioli L, Tielsch JM, Chwaya HM, Ercole E, Cancrini G (1998) Epidemiological evidence for a differential effect of hookworm species, Ancylostoma duodenale or Necator americanus, on iron status of children. Int J Epidemiol 27:530–537

Albonico M, Allen H, Chitsulo L, Engels D, Gabrielli AF, Savioli L (2008) Controlling soil-transmitted helminthiasis in pre-school-age children through preventive chemotherapy. PLoS Negl Trop Dis 2:e126

Anderson RM (1980) The dynamics and control of direct life cycle helminth parasites. Biomathematics 39:278–322

Anderson R, Truscott J, Hollingsworth TD (2014) The coverage and frequency of mass drug administration required to eliminate persistent transmission of soil-transmitted helminths. Phil Trans R Soc B: Biol Sci 369:20130435

Basanez MG, Mccarthy JS, French MD, Yang GJ, Walker M, Gambhir M, Prichard RK, Churcher TS (2012) A research agenda for helminth diseases of humans: modelling for control and elimination. PLoS Negl Trop Dis 6:e1548

Behnke JM, De Clercq D, Sacko M, Gilbert FS, Ouattara DB, Vercruysse J (2000) The epidemiology of human hookworm infections in the southern region of Mali. Trop Med Int Health 5:343–354

Bethony J, Chen J, Lin S, Xiao S, Zhan B, Li S, Xue H, Xing F, Humphries D, Yan W, Chen G, Foster V, Hawdon JM, Hotez PJ (2002) Emerging patterns of hookworm infection: influence of aging on the intensity of Necator infection in Hainan Province. People's Republic of China. Clin Infect Dis 35:1336–1344

Bethony J, Brooker S, Albonico M, Geiger M, Loukas A, Diemert D, Hotez PJ (2006) Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet 367:1521–1532

Boatin BA, Basanez MG, Prichard RK, Awadzi K, Barakat RM, García HH, Gazzinelli A, Grant WN, McCarthy JS, N'Goran EK, Osei-Atweneboana MY, Sripa B, Yang GJ, Lustigman S (2012) A research agenda for helminth diseases of humans: towards control and elimination. PLoS Negl Trop Dis 6:e1547

Booth M, Vounatsou P, N'goran EK, Tanner M, Utzinger J (2003) The influence of sampling effort and the performance of the Kato-Katz technique in diagnosing Schistosoma mansoni and hookworm co-infections in rural Côte d'Ivoire. Parasitology 127:525–531

Boyd A, Won KY, Mcclintock SK, Donovan CV, Laney SJ, Williams SA, Pilotte N, Streit TG, Beau De Rochars MVE, Lammie PJ (2010) A community-based study of factors associated with continuing transmission of lymphatic filariasis in Leogane, Haiti. PLoS Negl Trop Dis 4:e640

Brindley PJ, Mitreva M, Ghedin E, Lustigman S (2009) Helminth genomics: the implications for human health. PLoS Negl Trop Dis 3:e538

Brooker S, Michael E (2000) The potential of geographical information systems and remote sensing in the epidemiology and control of human helminth infections. Adv Parasitol 47:245–288

Brooker S, Peshu N, Warn PA, Mosobo M, Guyatt HL, Marsh K, Snow RW (1999) The epidemiology of hookworm infection and its contribution to anemia among pre-school children on the Kenya coast. Trans R Soc Trop Med Hyg 93:240–246

Brooker S, Rowlands M, Haller L, Savioli L, Bundy DAP (2000) Towards an atlas of human helminth infection in sub-Saharan Africa: the use of geographical information systems (GIS). Parasitol Today 16:303–307

Brooker S, Beasley M, Ndinaromtan M, Madjiouroum EM, Baboguel M, Djenguinabe E, Hay SI, Bundy DA (2002) Use of remote sensing and a geographical information system in a national helminth control programme in Chad. Bull World Health Organ 80:783–789

Brooker S, Clements AC, Bundy DA (2006a) Global epidemiology, ecology and control of soil-transmitted helminth infections. Adv Parasitol 62:221–261

Brooker S, Clements AC, Hotez PJ, Hay SI, Tatem AJ, Bundy DAP, Snow RW (2006b) The co-distribution of plasmodium falciparum and hookworm among African schoolchildren. Malar J 5:99

Brooker S, Hotez PJ, Bundy DA (2008) Hookworm-related anaemia among pregnant women: a systematic review. PLoS Negl Trop Dis 2:e291

Brooker S, Kabatereine NB, Smith JL, Mupfasoni D, Mwanje MT, Ndayishimiye O, Lwambo NJ, Mbotha D, Karanja P, Mwandawiro C, Muchiri E, Clements AC, Bundy DA, Snow RW (2009) An updated atlas of human helminth infections: the example of East Africa. Int J Health Geogr 8:42

Brooker S, Hotez PJ, Bundy DAP (2010) The global atlas of helminth infection: mapping the way forward in neglected tropical disease control. PLoS Negl Trop Dis 4:e779

Bundy DAP (1988) Population ecology of intestinal helminth infections in human communities. Philos Trans R Soc Lond: B 321:405–420

Bundy D, Cooper E (1989) Trichuris and trichuriasis in humans. Adv Parasitol 28:107–173

Bundy DAP, Guyatt HL (1995) The health of school-age children; report of a workshop. Parasitol Today 11:166–167

Callender JE, Walker SP, Grantham-Mcgregor SM, Cooper ES (1998) Growth and development four years after treatment for the trichuris dysentery syndrome. Acta Paediatr 87:1247–1249

Cringoli G (2006) FLOTAC, a novel apparatus for a multivalent faecal egg count technique. Parassitologia 48:381–384

Crompton DW (2000) The public health importance of hookworm disease. Parasitology 121(Suppl):S39–S50

Crompton DW, Nesheim MC (2002) Nutritional impact of intestinal helminthiasis during the human life cycle. Annu Rev Nutr 22:35–59

Crompton DW, Savioli L (1993) Intestinal parasitic infections and urbanization. Bull World Health Organ 71:1–7

Crompton DWT, Stephenson LS (1990) Hookworm infections, nutritional status and productivity. In: Schad GA, Warren KS (eds) Hookworm disease. Taylor and Francis Ltd., London

Crompton DW, Whitehead RR (1993) Hookworm infections and human iron metabolism. Parasitology 107(Suppl):S137–S145

Curtale F, Tilden R, Muhilal, Vaidya Y, Pokhrel RP, Guerra R (1993) Intestinal helminths and risk of anaemia among Nepalese children. Panminerva Med 35:159–166

Dada-Adegbola HO, Oluwatoba AO, Falade CO (2005) Prevalence of multiple intestinal helminths among children in a rural community. Afr J Med Med Sci 34:263–267

De Silva NR, Guyatt HL, Bundy DAP (1997) Worm burden in intestinal obstruction caused by Ascaris lumbricoides. Trop Med Int Health 2:189–190

De Silva NR, Brooker S, Hotez PJ, Montresor A, Engels D, Savioli L (2003) Soil-transmitted helminth infections: updating the global picture. Trends Parasitol 19:547–551

Diawara A, Drake LJ, Suswillo RR, Kihara J, Bundy DA, Scott ME, Halpenny C, Stothard JR, Prichard RK (2009) Assays to detect beta-tubulin codon 200 polymorphism in Trichuris trichiura and Ascaris lumbricoides. PLoS Negl Trop Dis 3:e397

Diawara A, Schwenkenbecher JM, Kaplan RM, Prichard RK (2013) Molecular and biological diagnostic tests for monitoring benzimidazole resistance in human soil-transmitted helminths. Am J Trop Med Hyg 88:1052–1061

El-Setouhy M, Abd Elaziz KM, Helmy H, Farid HA, Kamal HA, Ramzy RMR, Shannon WD, Weil GJ (2007) The effect of compliance on the impact of mass drug administration for elimination of lymphatic filariasis in Egypt. Am J Trop Med Hyg 77:1069–1073

Evans DB, Guyatt HL (1995) The cost-effectiveness of mass drug therapy for intestinal helminths. Pharmacoeconomics 8:14–22

Fentiman A, Hall A, Bundy D (1999) School enrolment patterns in rural Ghana: a comparative study of the impact of location, gender, age and health on children's access to basic schooling. Comp Educ 35:331–349

Forrester JE, Scott ME, Bundy DA, Golden MH (1988) Clustering of *Ascaris lumbricoides* and *Trichuris trichiura* infections within households. Trans R Soc Trop Med Hyg 82:282–288

Forrester JE, Scott ME, Bundy DAP, Golden MHN (1990) Predisposition of individuals and families in Mexico to heavy infection with *Ascaris lumbricoides* and *Trichuris trichiura*. Trans R Soc Trop Med Hyg 84:272–276

Gazzinelli A, Correa-Oliveira R, Yang GJ, Boatin BA, Kloos H (2012) A research agenda for helminth diseases of humans: social ecology, environmental determinants, and health systems. PLoS Negl Trop Dis 6:e1603

Geary TG, Woo K, Mccarthy JS, Mackenzie CD, Horton J, Prichard RK, De Silva NR, Olliaro PL, Lazdins-Helds JK, Engels DA, Bundy DA (2010) Unresolved issues in anthelmintic pharmacology for helminthiases of humans. Int J Parasitol 40:1–13

Gilles HM (1996) Soil-transmitted helminths (geohelminths). In: COOK GC (ed) Manson's tropical diseases. Saunders, London

Hall A, Hewitt G, Tuffrey V, De Silva N (2008) A review and meta-analysis of the impact of intestinal worms on child growth and nutrition. Matern Child Nutr 4:118–236

Hotez PJ, Kamath A (2009) Neglected tropical diseases in sub-Saharan Africa: review of their prevalence, distribution, and disease burden. PLoS Negl Trop Dis 3:e412

Hotez PJ, Brooker S, Bethony JM, Bottazzi ME, Loukas A, Xiao S (2004) Hookworm infection. N Engl J Med 351:799–807

Hotez PJ, Bundy DAP, Beegle K, Brooker S, Drake L, De Silva N, Montresor A, Engels D, Jukes M, Chitsulo L, Chow J, Laxminarayan R, Michaud C, Bethony J, Correa-Oliveira R, Shuhua X, Fenwick A, Savioli L (2006) Helminth infections: soil-transmitted helminth infections and schistosomiasis. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, Jha P, Mills A, Musgrove P (eds) Disease control priorities in developing countries. The International Bank for Reconstruction and Development/The World Bank Group, Washington, DC

Hotez PJ, Brindley PJ, Bethony JM, King CH, Pearce EJ, Jacobson J (2008) Helminth infections: the great neglected tropical diseases. J Clin Investig 118:1311–1321

Hu Y, Xiao SH, Aroian RV (2009) The new anthelmintic tribendimidine is an L-type (levamisole and pyrantel) nicotinic acetylcholine receptor agonist. PLoS Negl Trop Dis 3:e499

Katz N, Chaves A, Pellegrino J (1972) A simple device for quantitative stool thick smear technique in Schistosomiasis mansoni. Rev Inst Med Trop Sao Paulo 14:397–400

Keiser J, Utzinger J (2008) Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. JAMA 299:1937–1948

Keiser J, Utzinger J (2010) The drugs we have and the drugs we need against major helminth infections. Adv Parasitol 73:197–230

Knopp S, Mgeni AF, Khamis IS, Steinmann P, Stothard JR, Rollinson D, Marti H, Utzinger J (2008) Diagnosis of soil-transmitted helminths in the era of preventive chemotherapy: effect of multiple stool sampling and use of different diagnostic techniques. PLoS Negl Trop Dis 2:e331

Knopp S, Glinz D, Rinaldi L, Mohammed KA, N'goran EK, Stothard JR, Marti H, Cringoli G, Rollinson D, Utzinger J (2009) FLOTAC: a promising technique for detecting helminth eggs in human faeces. Trans R Soc Trop Med Hyg 103:1190–1194

Koga K, Kasuya S, Khamboonruang C, Sukhavat K, Ieda M, Takatsuka N, Kita K, Ohtomo H (1991) A modified agar plate method for detection of Strongyloides stercoralis. Am J Trop Med Hyg 45:518–521

Kvalsvig JD, Cooppan RM, Connolly KJ (1991) The effects of parasite infections on cognitive processes in children. Ann Trop Med Parasitol 85:551–568

Lammie PJ, Fenwick A, Utzinger J (2006) A blueprint for success: integration of neglected tropical disease control programmes. Trends Parasitol 22:313–321

Levecke B, Behnke JM, Ajjampur SS, Albonico M, Ame SM, Charlier J, Geiger SM, Hoa NT, Kamwa Ngassam RI, Kotze AC, Mccarthy JS, Montresor A, Periago MV, Roy S, Tchuem Tchuente LA, Thach DT, Vercruysse J (2011) A comparison of the sensitivity and fecal egg counts of the McMaster egg counting and Kato-Katz thick smear methods for soil-transmitted helminths. PLoS Negl Trop Dis 5:e1201

Lustigman S, Geldhof P, Grant WN, Osei-Atweneboana MY, Sripa B, Basanez MG (2012a) A research agenda for helminth diseases of humans: basic research and enabling technologies to support control and elimination of helminthiases. PLoS Negl Trop Dis 6:e1445

Lustigman S, Prichard RK, Gazzinelli A, Grant WN, Boatin BA, Mccarthy JS, Basanez MG (2012b) A research agenda for helminth diseases of humans: the problem of helminthiases. PLoS Negl Trop Dis 6:e1582

Mabaso ML, Appleton CC, Hughes JC, Gouws E (2004) Hookworm (necator americanus) transmission in inland areas of sandy soils in KwaZulu-natal, South Africa. Trop Med Int Health 9:471–476

Magnussen P, Muchiri E, Mungai P, Ndzovu M, Ouma J, Tosha S (1997) A school-based approach to the control of urinary schistosomiasis and intestinal helminth infections in children in Matuga, Kenya: impact of a two year chemotherapy programme on prevalence and intensity of infections. Trop Med Int Health 2:825–831

Mccarthy JS, Lustigman S, Yang GJ, Barakat RM, Garcia, HH Sripa B, Willingham AL, Prichard RK, Basáñez MG (2012) A research agenda for helminth diseases of humans: diagnostics for control and elimination programmes. PLoS Negl Trop Dis 6:e1601

Miguel EA, Kremer M (2003) Worms: identifying impacts on education and health in the presence of treatment externalities. Econometrica 72:159–217

Molyneux DH, Malecela MN (2011) Neglected tropical diseases and the millennium development goals – why the "other diseases" matter: reality versus rhetoric. Parasite Vectors 4:234

Molyneux DH, Hotez PJ, Fenwick A (2005) "Rapid-impact interventions": how a policy of integrated control for Africa's neglected tropical diseases could benefit the poor. PLoS Med 2:e336

Montresor A, Crompton DWT, Hall A, Bundy DAP, Savioli L (1998) Guidelines for the evaluation of soil-transmitted helminthiasis and schistosomiasis at community level. A guide for managers of control programmes. World Health Organization, Geneva

Montresor A, Crompton DWT, Gyorkos TW, Savioli L (2002) Helminth control in school-age children: a guide for managers of control programmes. World Health Organization, Geneva

Montresor A, Gabrielli AF, Yajima A, Lethanh N, Biggs BA, Casey GJ, Tinh TT, Engels D, Savioli L (2013) Markov model to forecast the change in prevalence of soil-transmitted helminths during a control programme: a case study in Vietnam. Trans R Soc Trop Med Hyg 107:313–318

Moran M, Guzman J, Ropars AL, Mcdonald A, Jameson N, Omune B, Ryan S, Wu L (2009) Neglected disease research and development: how much are we really spending? PLoS Med 6:e1000030

Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Almazroa MA, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basáñez M-G, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabé E, Bhalla K, Bhandari B, Bikbov B, Abdulhak AB, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F, Chen H, Cheng AT-A, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, De Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N, Damsere-Derry J, Danaei G, Davis A, Leo DD, Degenhardt L, Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC et al (2012) Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990? 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2197–2223

Narain K, Medhi GK, Rajguru SK, Mahanta J (2004) Cure and reinfection patterns of geohelminthic infections after treatment in communities inhabiting the tropical rainforest of Assam, India. Southeast Asian J Trop Med Public Health 35:512–517

Nikolay B, Brooker SJ, Pullan RL (2014) Sensitivity of diagnostic tests for human soil-transmitted helminth infections: a meta-analysis in the absence of a true gold standard. Int J Parasitol 44:765–774

Nokes C, Bundy D (1994) Does helminth infection affect mental processing and educational achievement? Parasitol Today 10:14–18
Nokes C, Grantham-Mcgregor SM, Sawyer AW, Cooper ES, Bundy DAP (1992) Parasitic helminth infection and cognitive function in school children. Proc R Soc Lond 247:77–81
Olliaro P, Seiler J, Kuesel A, Horton J, Clark JN, Don R, Keiser J (2011) Potential drug development candidates for human soil-transmitted helminthiases. PLoS Negl Trop Dis 5:e1138
Olsen A, Magnussen P, Ouma JH, Andreassen J, Friis H (1998) The contribution of hookworm and other parasitic infection to haemoglobin and iron status among children and adults in western Kenya. Trans R Soc Trop Med Hyg 92:643–649
Olsen A, Van Lieshout L, Marti H, Polderman T, Polman K, Steinmann P, Stothard R, Thybo S, Verweij JJ, Magnussen P (2009) Strongyloidiasis – the most neglected of the neglected tropical diseases? Trans R Soc Trop Med Hyg 103:967–972
Osazuwa F, Ayo OM, Imade P (2011) A significant association between intestinal helminth infection and anaemia burden in children in rural communities of Edo state, Nigeria. N Am J Med Sci 3:30–34
Osei-Atweneboana MY, Lustigman S, Prichard RK, Boatin BA, Basanez MG (2012) A research agenda for helminth diseases of humans: health research and capacity building in disease-endemic countries for helminthiases control. PLoS Negl Trop Dis 6:e1602
Osei-Fosu AK (2011) Evaluating the impact of the capitation grant and the school feeding programme on enrollment, attendance and retention in schools: the case of Weweso Circuit. J Sci Technol 31:55–64
Prichard RK, Basanez MG, Boatin BA, Mccarthy JS, Garcia HH, Yang GJ, Sripa B, Lustigman S (2012) A research agenda for helminth diseases of humans: intervention for control and elimination. PLoS Negl Trop Dis 6:e1549
Pullan R, Smith J, Jasrasaria R, Brooker S (2014) Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasite Vectors 7:37
Robertson LJ, Crompton DW, Sanjur D, Nesheim MC (1992) Haemoglobin concentrations and concomitant infections of hookworm and Trichuris trichiura in Panamanian primary school children. Trans R Soc Trop Med Hyg 86:654–656
Roche M, Layrisse M (1966) The nature and causes of hookworm anaemia. Am J Trop Med Hyg 15:1031–1110
Savioli L, Bundy DAP, Tomkins A (1992) Intestinal parasitic infections a soluble public health problem. Trans R Soc Trop Med Hyg 86:353–354
Schad GA, Anderson RM (1985) Predisposition to hookworm infection in humans. Science 228:1537–1540
Schwenkenbecher JM, Albonico M, Bickle Q, Kaplan RM (2007) Characterization of beta-tubulin genes in hookworms and investigation of resistance associated mutations using real-time PCR. Mol Biochem Parasitol 156:167–174
Simeon D, Callender J, Wong M, Grantham-Mcgregor S, Ramdath DD (1994) School performance, nutritional status and trichuriasis in Jamaican schoolchildren. Acta Paediatr 83:1188–1193
Solomons NW (1993) Pathways to the impairment of human nutritional status by gastrointestinal pathogens. Parasitol Int 107:S19–S35
Stephenson LS (1987) Impact of helminth infection in human nutrition. Taylor & Francis, New York
Stephenson LS, Latham MC, Kurz KM, Kinoti SN, Oduori ML, Crompton DWT (1985) Relationships of Schistosoma haematobium, hookworm and malaria infections and metrifonate treatment to haemoglobin levels in Kenyan school children. Am J Trop Med Hyg 34:519–528
Stephenson LS, Latham MC, Kinoti SN, Kurz KM, Brigham H (1990) Improvements in physical fitness of Kenyan schoolboys infected with hookworm, Trichuris trichiura and Ascaris lumbricoides following a single dose of albendazole. Trans R Soc Trop Med Hyg 84:277–282
Stephenson LS, Latham MC, Adam EJ, Kinoti SN, Pertet A (1993) Physical fitness, growth and appetite of Kenyan school boys with Hookworm, Trichuris trichiura and Ascaris lumbricoides

infections are improved four months after a single dose of albendazole. J Nutr 123:1036–1046
Stephenson LS, Latham MC, Ottesen EA (2000) Malnutrition and parasitic helminth infections. Parasitology 121:S23–S28
Stoltzfus RJ, Albonico M, Chwaya HM, Savioli L, Tielsch J, Schulze K, Yip R (1996) Hemoquant determination of hookworm-related blood loss and its role in iron deficiency in African children. Am J Trop Med Hyg 55:399–404
Stoltzfus RJ, Chwaya HM, Tielsch JM, Schulze KJ, Albonico M, Savioli L (1997) Epidemiology of iron deficiency anemia in Zanzibari school children: the importance of hookworms. Am J Trop Med Hyg 65:153–159
Strunz EC, Addiss DG, Stocks ME, Ogden S, Utzinger J, Freeman MC (2014) Water, sanitation, hygiene, and soil-transmitted helminth infection: a systematic review and meta-analysis. PLoS Med 11:e1001620
Taren DL, Nesheim MC, Crompton DWT, Holland CV, Barbeau I, Rivera G, Sanjur D, Tiffany J, Tucker K (1987) Contribution of ascariasis to poor nutritional status of children from Chiriqui Province, Republic of Panama. Parasitology 95:603–613
Tatala S, Svanberg U, Mduma B (1998) Low dietary iron availability is a major cause of anaemia: a nutritional survey in Lindi District of Tanzania. Am J Clin Nutr 68:171–178
Traore' M, Traore' H, Kardorff R, Diarra A, Landoure A (1998) The public health significance of urinary schistosomiasis as a cause of morbidity in two districts in Mali. Am J Trop Med Hyg 59:407–413
Uniting To Combat Ntds (2012) The London declaration on neglected tropical diseases 2012. Available:http://unitingtocombatntds.org/downloads/press/ntd_event_london_declaration_on_ntds.pdf. [Online]. Available: http://unitingtocombatntds.org/downloads/press/ntd_event_london_declaration_on_ntds.pdf. Accessed 28 Dec 2013
Utzinger J, Keiser J (2004) Schistosomiasis and soil soil-transmitted helminthiasis: common drugs for treatment and control. Expert Opin Pharmacother 5:263–285
Van Den Broek N (2003) Anaemia and micronutrient deficiencies. Br Med Bull 67:149–160
Vercruysse J, Behnke JM, Albonico M, Ame SM, Angebault C, Bethony JM, Engels D, Guillard B, Nguyen TV, Kang G, Kattula D, Kotze AC, Mccarthy JS, Mekonnen Z, Montresor A, Periago MV, Sumo L, Tchuente LA, Dang TC, Zeynudin A, Levecke B (2011) Assessment of the anthelmintic efficacy of albendazole in school children in seven countries where soil-transmitted helminths are endemic. PLoS Negl Trop Dis 5:e948
Verweij JJ, Brienen EA, Ziem J, Yelifari L, Polderman AM, Van Lieshout L (2007) Simultaneous detection and quantification of Ancylostoma duodenale, Necator americanus, and Oesophagostomum bifurcum in fecal samples using multiplex real-time PCR. Am J Trop Med Hyg 77:685–690
Viteri FE (1994) The consequences of iron deficiency and anaemia in pregnancy on maternal health, the foetus and the infant. SCN News 11:14–18
Warren K, Bundy D, Anderson R, Davis A, Henderson D, Jamison D, Prescott N, Senf A (1993) Helminth infection. In: Jamison D, Mosley W, Measham A, Bibadilla J (eds) Disease control priorities in developing countries. Oxford Publishing, Oxford
WHO (1997) Information series on school health – document 1. Strengthening interventions to reduce helminth infections: an entry point for the development of health-promoting schools. World Health Organization, Geneva
WHO (2002) Prevention and control of schistosomiasis and soil-transmitted helminthiasis, vol 912, WHO Technical Report Series. World Health Organization, Geneva
WHO (2006) Preventive chemotherapy in human helminthiasis: coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers. World Health Organization, Geneva
WHO (2012) Soil-transmitted helminthiases: eliminating soil-transmitted helminthiases as a public health problem in children: progress report 2001–2010 and strategic plan 2011–2020. World Health Organization, Geneva

WHO (2013) Soil-transmitted helminth infections. Fact sheet N°366. World Health Organization, Geneva
World Bank (1993) World development report: investing in health. Oxford University Press, New York
Zetterstrom R (2004) Iron deficiency and iron deficiency anaemia during infancy and childhood. Acta Paediatr 93:436–439
Zimmermann MB, Hurrell RF (2007) Nutritional iron deficiency. Lancet Infect Dis 370:511–520

Trachoma

Teshome Gebre

Contents

Abstract Trachoma is the leading infectious cause of blindness worldwide and the eighth commonest blinding disease. Blinding trachoma is hyperendemic in many of the poorest and most remote rural areas in 53 countries. Africa alone harbors about 44 % of the global total cases. Caused by the obligate intracellular bacterium *C. trachomatis* of the four ocular serovars (A, B, Ba, and C), the recurrent episodes of conjunctival infection, and the associated chronic inflammation it causes, initiate a scarring process that ultimately leads to irreversible blindness. The genital serovars (D to K) of *C. trachomatis* can infect the conjunctiva causing either ophthalmia neonatorum in infants or inclusion conjunctivitis in adults. Infection is probably usually acquired through living in close physical proximity to an infected person, with the family as the principle unit for transmission. Trachoma has two major phases: active or inflammatory trachoma, the key sign of which is the "trachoma follicle," that is lymphoid follicles or germinal centers in the superior tarsal conjunctiva and cicatricial or late trachoma, marked by structural change in the lid with

T. Gebre
International Trachoma Initiative, The Task Force for Global Health,
Ethio-China Friendship Road, Dire Dawa Building, 5th Floor, Room 301, 10001, Addis Ababa, Ethiopia
e-mail: tgebre@taskforce.org

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_13

tarsal scarring and trichiasis. In hyperendemic settings, infection may be acquired in early infancy, whereas in meso-endemic and hypo-endemic regions, it is probably on average later. Active trachoma is predominantly seen in young children, becoming less frequent and of shorter duration with increasing age, while trichiasis and corneal opacity are more common in women than men. Control of trachoma is based on the SAFE strategy, which is composed of Surgery for trichiasis cases, Antibiotics to treat the community pool of infection, Face washing, and Environmental improvement to reduce transmission. The major challenges in national trachoma control programs have been the generation of baseline data, conducting baseline surveys, and scaling up of program interventions due to inadequate funds. The prevailing insecurity and inaccessibility in some of the endemic countries are another critical impediment to effective implementation. More research is required in diagnostics, use of photography for trachoma grading, Mass Drug Administration and especially alternative treatment strategies, determination of threshold level at which infection disappears without MDA, monitoring and evaluation, and defining the endgame strategies. The outlook for the fight against trachoma in next decade is bright given all the various parameters that have been put in place with the hope that nobody would go blind from trachoma after the elimination target date, 2020.

Introduction

Blinding trachoma, the leading infectious cause of blindness worldwide and the eighth commonest blinding disease, is hyperendemic in many of the poorest and most remote rural areas in 53 countries. Africa alone harbors about 44–48 % of about 30 million of the estimated 63 million cases of active trachoma globally. It affects all ages. While active trachoma is predominantly seen in young children, it is less frequent and of shorter duration with age with trichiasis and corneal opacity being common in women. The main etiological risk factor for corneal damage is the presence of trichiasis; however, a number of other factors probably contribute such as bacterial infection and chronic conjunctival inflammation.

The economic costs of trachoma in endemic countries are estimated at an annual productivity loss of USD 2.9 billion, based on loss of vision (Frick et al. 2003) of which approximately about one-half is attributed to SSA (Hotez 2009). The prevalent cases of visual loss are responsible for 39 million lifetime disability-adjusted life years (DALYs). In a recent WHO report (2013), the annual economic cost of trachoma in terms of lost productivity is estimated to be between US$ 2.9 billion and US$ 5.3 billion, increasing to US$ 8 billion when trichiasis is included. With the SAFE strategy of Surgery for trichiasis cases, Antibiotics to treat the community pool of infection, Face washing, and Environmental improvement to reduce transmission, positive strides have been made in the control of trachoma with the hope of full control by 2020.

Basic Biology and Disease Presentation

Trachoma is caused by the obligate intracellular bacterium *C. trachomatis*. Recurrent episodes of conjunctival infection and the associated chronic inflammation it causes initiate a scarring process that ultimately leads to irreversible blindness. Endemic trachoma is caused by the four ocular serovars of *C. trachomatis* (A, B, Ba, and C). Although the genital serovars (D to K) of *C. trachomatis* can infect the conjunctiva causing either ophthalmia neonatorum in infants or inclusion conjunctivitis in adults, these are usually isolated episodes for the individual, which do not lead to blinding sequelae (Burton et al. 2003).

For endemic trachoma, the average age of acquisition of the first episode of *C. trachomatis* infection is probably related to the prevailing level of infection in the community. In hyperendemic settings, infection may be acquired in early infancy, whereas in meso-endemic and hypo-endemic regions, it is probably on average later. Infection is probably usually acquired through living in close physical proximity to an infected person, with the family as the principle unit for transmission (Barefanger 1975). It seems universally accepted and recognized over time that, however defined, trachoma has two major phases: active or inflammatory trachoma and cicatricial or late trachoma. Active trachoma is characterized by an inflammatory response associated with the variable presence of demonstrable infection. The inflammation can vary in intensity but when severe, it leads to tarsal scarring and corneal pannus. Cicatricial trachoma is marked by structural change in the lid with tarsal scarring and trichiasis. In this case, inflammation is variable and *Chlamydia* are infrequently seen (Taylor 2008).

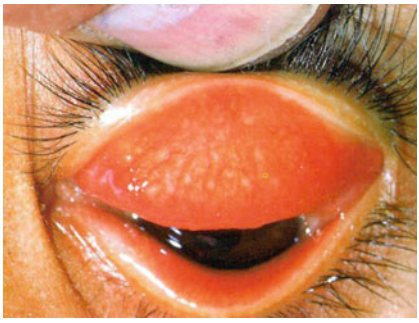
Taylor further describes that in an endemic setting, a well-established case of active trachoma can be very easy to diagnose. The key sign in active trachoma is the "trachoma follicle," that is lymphoid follicles or germinal centers in the superior tarsal conjunctiva. Although the presence of superior tarsal follicles is used as a primary diagnostic feature in the grading of active trachoma, it is the intense inflammation shown by conjunctival inflammatory thickening and papillae that reflects the critical process in the pathogenesis. The difficulty with diagnosing active inflammatory trachoma in an endemic community is not so much in making the diagnosis in established cases, but the differentiation of borderline cases from normal, or sometimes, distinguishing cases of severe inflammatory trachoma from acute bacterial or viral conjunctivitis. The detection of trichiasis only requires careful examination. However, the diagnosis of trachoma can be much more difficult to make in areas of low endemicity, although several tarsal scarring, corneal pannus with Herbert's pits, and upper lid trichiasis are almost pathognomonic (characteristic) in any setting.

Studies from trachoma-endemic communities have found that the prevalence and duration of conjunctival chlamydial infection decline with increasing age, suggesting that there is a maturation of the immune response as individuals are repeatedly exposed to infection. However, in the early vaccine trials using whole

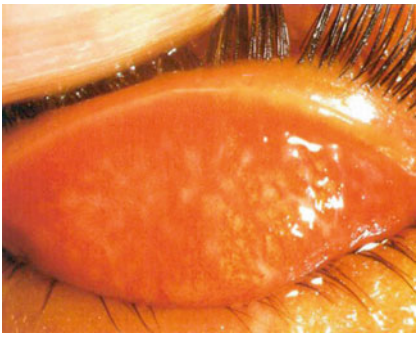
C. trachomatis organisms, the acquired immunity appeared to be strain specific and relatively short lived. As a result of the relatively ineffective immune response, repeated infection of the individual by *C. trachomatis* is common within an endemic environment. This leads to a recurrent chronic inflammation, which is associated with the development of scar tissue within the conjunctiva over many years. As the scar tissue accumulates, it also contracts, causing the eyelids to roll inward toward the eye (entropion) and the eyelashes to scratch the ocular surface (trichiasis). The degree to which conjunctival scarring develops probably depends on a complex interaction between the pressure of infection (load and frequency) and host-specific immunogenetic factors. It is possible that a failure of the immune response to adequately control the *Chlamydia* leads to prolonged infection episodes, which provokes more severe inflammation, tissue damage (through the release of proteases), and aberrant repair. The most serious disease sequela from trachoma is blinding corneal opacification. The main etiological risk factor for corneal damage is the presence of trichiasis; however, a number of other factors probably contribute such as bacterial infection and chronic conjunctival inflammation (Burton and Mabey 2009).

Staging of Trachoma

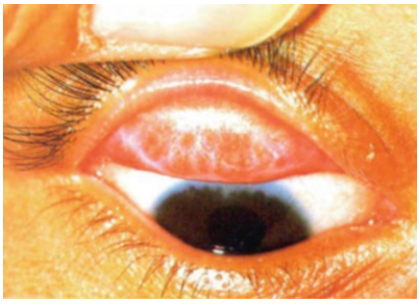
1. Trachomatous inflammation-follicular (TF)



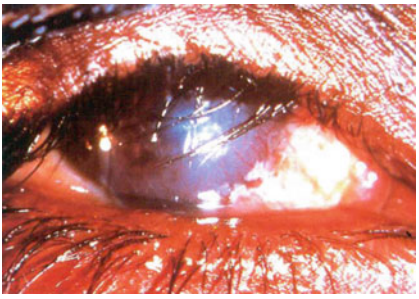
2. Trachomatous inflammation-intense (TI)



3. Trachomatous scarring, TS



4. Trachomatous trichiasis, TT



The Epidemiology of Trachoma

Trachoma is a disease of the crèche and clusters in large or small pockets. These pockets may be countries, districts or regions, villages, or household clusters within villages, but ultimately, trachoma is a disease of individual families. Epidemiology can describe where trachoma occurs but more importantly, why some are affected and others are not. It can also explain the patchiness of these pockets of infection and the basis of family clustering (Taylor 2008).

Blinding trachoma is hyperendemic in many of the poorest and most remote rural areas in 53 countries in Africa, Asia, Central America and South America, Australia, and the Middle East. Overall, Africa is the most badly affected continent with 18.2 million cases of active trachoma (85.3 % of all cases globally) and 3.2 million cases of trichiasis (44.1 % of all cases globally) occur in 29/46 countries in WHO's African Region. The highest prevalence of active trachoma has been reported from Ethiopia and South Sudan, where the infection often occurs in more than 50 % of children who are younger than 10 years; trichiasis is found in up to 19 % of adults (WHO 2013). One hundred years ago, trachoma was widespread in Europe and North America but faded away during the first half of the twentieth century as living conditions improved (Mariotti et al. 2009). The clinical manifestations of trachoma change with age. Active trachoma is predominantly seen in young children, becoming less frequent and of shorter duration with increasing age (Bailey et al. 1999). The onset of the blinding complications of trachoma can occur in children living in regions where the pressure of infection is high (Ngondi et al. 2008a). Epidemiological surveys have generally found trichiasis and corneal opacity to be more common in women than men. This difference has been attributed to the greater lifetime exposure of women to *C. trachomatis* infection, through closer contact with children, the main reservoirs of infection (West et al. 1991).

In a large risk factor analysis following a trachoma prevalence study conducted in the Amhara region of Ethiopia, Ngondi et al. (2008b) reported active trachoma prevalence in children to be independently associated with ocular discharge, nasal discharge, and proxy indicators of low socioeconomic status and increasing altitude, while trichiasis was independently associated with increasing age, female gender, increasing prevalence of active trachoma in children, and increasing altitude. Several studies in sub-Saharan Africa (SSA) have reported high prevalence of active trachoma in areas where water supply and sanitary conditions are poor (Berhane et al. 2007). The age distribution of the different signs of trachoma depends in part on the stability and endemicity of the disease in the community. In hyperendemic areas, trachomatous inflammation-follicular (TF) and trachomatous inflammation-intense (TI) are commonest in preschool children, with prevalence as high as 60–90 % (Courtright et al. 1989). The prevalence of active trachoma decreases with increasing age, with less than 5 % of the adults showing signs of active disease (West et al. 1991b). In addition to age and sex, environmental factors such as household proximity to water source, poor hygienic conditions, presence and density of eye-seeking flies, availability of functional latrine, presence of cattle

pens and cattle ownership, crowded living conditions in the family unit, and nutritional deficiencies (vitamin A) have been identified as possible risk factors for trachoma (West 2004).

Burden of Trachoma in Sub-Saharan Africa

Trachoma is the most important bacterial infection among the NTDs in SSA. Of the 63 million cases of active trachoma globally (although some estimates indicate 84 million cases worldwide), 48 % or 30 million cases occur in SSA (Hotez and Kamath 2009). In the same article, it was reported that nearly half of the global disease burden of active trachoma and a quarter of end-stage trichiasis are concentrated in ten countries alone, with six of these located in SSA. Ethiopia has the highest number of cases (10.2 million) followed by Republic of South Sudan (3.6 million) and Tanzania, Kenya, and Niger (2.0–2.1 million each). The burden of trachoma is measured not just in the prevalence, nor in the prevalence of blindness or visual loss due to trachoma. The economic costs of trachoma in endemic countries are estimated at an annual productivity loss of USD 2.9 billion, based on loss of vision (Frick et al. 2003) of which approximately about one-half is attributed to SSA (Hotez 2009). The prevalent cases of visual loss are responsible for 39 million lifetime disability-adjusted life years (DALYs). These impacts are likely to be underestimates as trichiasis, even without vision loss, is associated with disability (Frick et al. 2001). In a recent WHO report (2013), the annual economic cost of trachoma in terms of lost productivity is estimated to be between US$ 2.9 billion and US$ 5.3 billion, increasing to US$ 8 billion when trichiasis is included.

As stated above, sub-Saharan Africa is disproportionately affected by trachoma. The distribution of trachoma in SSA is shown in the map (Fig. 1). Of the 14 high-burden countries listed in the most recent publication of the International Coalition for Trachoma Control (ICTC 2011), all except one are from SSA. These countries carry 83 % of the total endemic population and 71 % of the global burden of trichiasis.

Available Control Strategies for Trachoma

Based on the current understanding of the epidemiology of trachoma and its risk factors, the WHO has endorsed what is known as the SAFE strategy for countries implementing trachoma control programs. The SAFE strategy is an innovative public health approach designed to treat and prevent trachoma. As illustrated below, this multifaceted approach is composed of four critical interventions, i.e., Surgery for trichiasis cases, Antibiotics to treat the community pool of infection, Face washing, and Environmental improvement to reduce transmission. In order for trachoma

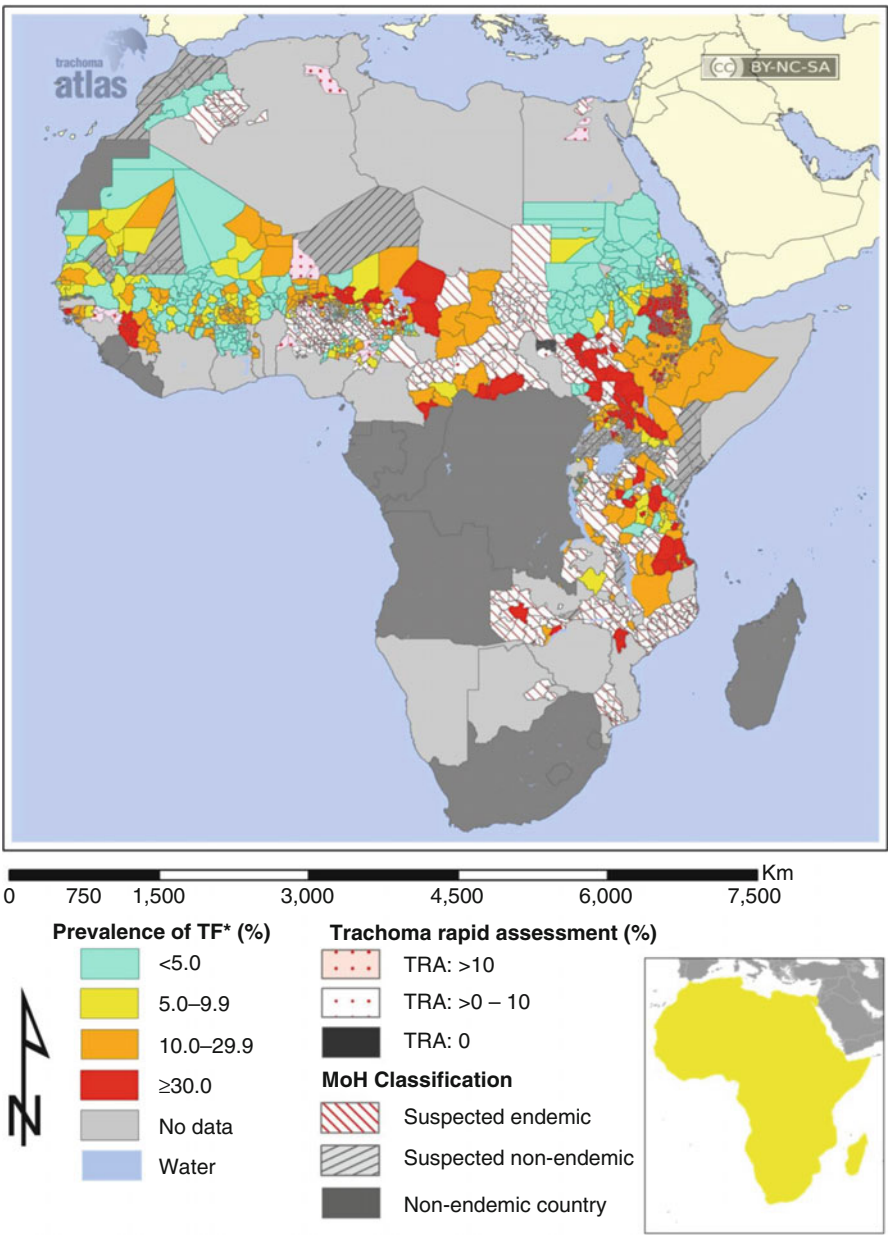


Fig. 1 Prevalence of active trachoma in Africa (Copyright: Licensed to the trachoma Atlas Project (www.trachomaatlas.com) under a Creative Commons Attribution License (http://creativecommons.org)

control programs to be successful, all these package of preventive and curative interventions should be implemented effectively and in a harmonized manner. In most national programs, there is a general tendency of leaning toward the two medical interventions of mass distribution of antibiotics (MDA) and conducting surgical camps. As a result, in some hyperendemic settings, impact evaluations conducted after 3 or 5 years of implementation of control interventions showed that the programs were unable to attain the intended level of reduction of infection to stop MDA. Although there was substantial reduction in the level of infection compared to baseline levels, continuation of control interventions was compulsory (Ngondi et al. 2008).

Components of the SAFE Strategy

The good news is that Pfizer-donated azithromycin (Zithromax®), the most expensive, highly effective, and safe antibiotic against *C. trachomatis* infection, is available freely for all endemic countries until 2020. As of 2012, a total of 280 million doses of Zithromax® have been provided to 19 endemic countries since the inception of the donation program (www.trachoma.org).

The benefits of mass treatment with azithromycin go far beyond trachoma control. Porco et al. (2009) in a randomized clinical trial found out that mass distribution with azithromycin was associated with reduced mortality in children aged 1–9 years. The safety profile of azithromycin in MDA for trachoma has also been assessed. The prevalence of any reported adverse events varied from 4.9 to 7.0 % in children aged 1–9 years and slightly higher among adults (17.0–18.7 %). Adverse events appeared to cluster among households and perhaps by village (Ayele et al. 2011).

The issue of who should be treated, how frequently, and for how long has been extensively researched over the past decade or so. Although the current WHO recommendation for trachoma-endemic communities with TF greater than 10 % is mass azithromycin treatment for the entire community, studies have indicated that frequent treatment of children (may be twice a year), who are a core group of *C. trachomatis* transmission, could eventually eliminate trachoma infection from the entire community. Herd protection is offered by repeated mass antibiotic treatments, providing a strategy for elimination of a bacterial disease when an effective vaccine is unavailable (House et al. 2009). On the other hand, a cluster-randomized clinical trial comparing annual versus twice-yearly mass azithromycin treatment for hyperendemic trachoma in Ethiopia showed no statistically significant difference in the prevalence of ocular infection with *Chlamydia* after 42 months of treatment. However, elimination of infection might have been more rapid in the groups of villages that received treatment twice-yearly (Gebre et al. 2012).

Challenges in Implementation

Generation of Baseline Data

The fact that trachoma belongs to the group of neglected tropical diseases in SSA is certainly one of the obvious challenges program coordinators and partners normally encounter nearly in all countries. Among the commonest crosscutting challenges in most national trachoma control programs has been generation of baseline data or conducting baseline surveys. Thanks to the generous funding of DFID, USAID, and other donors, this problem is being effectively addressed at the moment. It is hoped that with the current pace of the Global Trachoma Mapping Project (GTMP), nearly all countries are expected to complete the task by 2014 or in some exceptional cases by 2015.

Issues with Scaling Up

The other challenge is related to scaling up of program interventions. Generally, there are resource limitations in most endemic countries to implementing full-blown SAFE interventions. The prevailing insecurity and inaccessibility in some of the endemic countries are another critical impediment to effective implementation.

Low MDA coverage and uptake of trichiasis surgery are among the commonly reported serious challenges. A study evaluating MDA coverage and compliance in Ethiopia indicated that knowledge of trachoma and prior awareness of distribution time and place were identified as determinants of compliance for mass treatment with azithromycin (Gebre 2011). A separate KAP study in the same region identified direct and indirect costs associated with surgery, lack of

escort, and lack of time as barriers to trichiasis surgery (Rajak et al. 2012). In line with this, in a study conducted by Habtamu et al. (2011) to determine trichiasis surgeon retention and productivity in Northern Ethiopia, it was confirmed that surgeon attrition rates were high and vertical surgery campaigns were effective in treating large numbers of cases while static site service productivity was low.

It is commonly believed that widespread antibiotic use selects for community antibiotic resistance, though this has been difficult to prove in the setting of community randomized clinical trial. In Ethiopia, a cluster-randomized clinical trial by Skalet et al. (2010) demonstrated that compared to untreated control communities, nasopharyngeal pneumococcal resistance to macrolides was significantly higher in communities randomized to intensive azithromycin treatment. Mass azithromycin treatments were given more frequently than currently recommended by the World Health Organization for trachoma control program. Interestingly, azithromycin use in this setting did not select for resistance to penicillin, which remains a drug of choice for pneumococcal infections.

Further Research

The NTD Support Center at the Task Force for Global Health (TFGH) convened a meeting of trachoma experts in London on April 9, 2013, and identified several operational research priorities for trachoma. Accordingly, the group came up with a number of research topics in the area of:

(i) Trachoma diagnostics (understanding better what TF is including its correlation with infection, duration, and its relationship with TS and TT)
(ii) Using photography for trachoma grading (potentially using smartphones)
(iii) MDA implementation (testing alternative treatment strategies, e.g., focusing only on treating children; assess the safety of coadministration of azithromycin, albendazole/mebendazole, and praziquantel)
(iv) Determining the threshold level at which infection disappears without MDA
(v) Monitoring and evaluation (defining alternative methods for measuring coverage of SAFE interventions)
(vi) Defining the endgame strategies and studying behavioral factors associated with trachoma interventions (SAFE strategy implementation)

Outlook for the Next Decade

From the trachoma program standpoint, the next decade is very bright and promising. As outlined in the 2020 Insight publication (ICTC 2011), the road to GET2020 has been carefully charted. The current global trachoma situation has

been critically analyzed; the pathway to elimination and what it takes to get there has been systematically outlined. As a result, a lot of advocacy work has been done by various stakeholders at global, regional, and national levels. Bilateral and multilateral donors including private philanthropists have pledged their support. The Global Trachoma Mapping Project is underway and is on course to complete its mission by 2015. Regional and national strategic plans for elimination are being finalized. If all goes well as planned, at the minimum, the unnecessary human suffering and disability from blinding trachoma will come to an end and nobody shall go blind from trachoma anywhere in sub-Saharan Africa after 2020. The only exceptions to this could be those places and countries with civil strife and instability.

References

Ayele B, Gebre T, House JI, Zhou Z et al (2011) Adverse events after mass azithromycin treatment for trachoma in Ethiopia. Am J Trop Med Hyg 85(2):291–294

Bailey R, Duong T, Carpenter R et al (1999) The duration of human ocular *Chlamydia trachomatis* infection is age dependent. Epidemiol Infect 123:479–486

Barenfanger J (1975) Studies on the role of the family unit in the transmission of trachoma. Am J Trop Med Hyg 24:509–515

Berhane Y, Worku A, Bejiga A et al (2007) National blindness, low vision and trachoma survey in Ethiopia. Ethiop J Health Dev 21(Special Issue):183–215

Burton MJ, Mabey DCW (2009) The global burden of trachoma: a review. PLoS Negl Trop Dis 3(10):e460. doi:10.1371/journal.pntd.0000460

Courtright P, Sheppard J, Lane S et al (1989) Trachoma and blindness in the Nile Delta: current patterns and projections for the future in the rural Egyptian population. Br J Ophthalmol 73:536–540

Frick KD, Melia BM, Buhrman RR et al (2001) Trichiasis and disability in a trachoma-endemic area of Tanzania. Arch Ophthalmol 119:1839–1844

Frick KD, Basilion EV, Hanson CL et al (2003) Estimating the burden and economic impact of trachomatous visual loss. Ophthalmic Epidemiol 10:121–132

Gebre T (2011) Evaluating mass antibiotic treatment coverage and compliance for trachoma control in amhara region, Northern Ethiopia, PhD Dissertation, American Century University.

Gebre T, Ayele B, Zerihun M et al (2012) Comparison of annual versus twice-yearly mass azithromycin treatment for hyperendemic trachoma in Ethiopia: a cluster-randomized trial. Lancet 379:143–151

Habtamu E, Rajak SN, Gebre T, Zerihun M, Genet A et al (2011) Clearing the backlog: trichiasis surgeon retention & productivity in Northern Ethiopia. PLoS Negl Trop Dis 5(4):e1014. doi:10.1371/journal.pntd.00001014

Hotez PJ, Kamath A (2009) Neglected tropical diseases in Sub-Saharan Africa: review of their prevalence, distribution and disease burden. PLoS Negl Trop Dis 3(8):e412. doi:10.1371/journal.pntd.0000412

House JI, Ayele B, Porco TC et al (2009) Assessment of herd protection against trachoma due to repeated mass antibiotic distributions: a cluster-randomized trial. Lancet 373:1111–1118

International Coalition for Trachoma Control (ICTC 2011) The end in sight

Mariotti SP, Pascolini D, Rose-Nussbaumer J (2009) Trachoma: global magnitude of a preventable cause of blindness. Br J Ophthalmol 93:563–568

Ngondi J, Matthews F, Reacher M et al (2007) Prevalence of risk factors and severity of active trachoma in Southern Sudan: an ordinal analysis. Am J Trop Med Hyg 77:126–132

Ngondi J, Reacher MH, Matthews FE et al (2008a) Risk factors for trachomatous trichiasis in children: cross-sectional household surveys in Southern Sudan. Trans R Soc Trop Med Hyg 103:305–314

Ngondi J, Gebre T, Shargie EB et al (2008b) Risk factors for active trachoma in children and trichiasis in adults: a household survey in Amhara Regional State. Ethiop Trans R Soc Trop Med Hyg 102:432–438

Polack S, Brooker S, Kuper H et al (2005) Mapping the global distribution of trachoma. Bull World Health Organ 83:913–919

Porco TC, Gebre T, Ayele B et al (2009) Effect of mass distribution of azithromycin for trachoma control on the overall mortality in Ethiopian children: a randomized trial. JAMA 302(9):962–968

Rajak S, Habtamu E, Weiss H et al (2012) Why do people not attend for treatment of trachomatous trichiasis in Ethiopia? A study of barriers to surgery. PLoS Negl Trop Dis 6(8):e1766

Skalet AH, Cevallos V, Ayele B et al (2010) Antibiotic selection pressure and macrolide resistance in nasopharyngeal *Streptococcus pneumoniae*: a cluster-randomized clinical trial. PLoS Med 7(12):e1000377

Taylor HR (2008) Trachoma: a blinding scourge from the Bronze Age to the twenty-first century, 1st edn. Center for Eye Research Australia, East Melbourne

West SK (2004) Trachoma: a new assault on an ancient disease. Sci Direct Prog Retin Eye Res 23(2004):381–401

West SK, Munoz B, Turner VM et al (1991) The epidemiology of trachoma in central Tanzania. Int J Epidemiol 20:1088–1092

World Health Organization (2013) Sustaining the drive to overcome the global impact of neglected tropical diseases: second WHO report on neglected diseases, pp 37–40

Yaws

Nsiire Agana, Cynthia Kwakye-Maclean, and Earnest Njih Tabah

Contents

Abstract Yaws, a chronic skin, bone, and cartilage treponemal infection of rural tropical communities, causes mostly painless but stigmatizing lesions, some of which may become permanent disfiguring, crippling deformities. The palmar and plantar forms of yaws are, however, very painful. Yaws had clinical prevalence of 30 % or more in some communities before the mid-1960s and caused considerable rural poverty. A global eradication effort initiated by WHO in 1952 reduced the prevalence in endemic countries by over 95 % by 1965. But short of eradicating it, and given the poor health systems of endemic countries then, yaws started to resurge in the 1970s and has since been fought successfully by only Ecuador and India.

N. Agana (✉)
Disease Control and Prevention Department, Korle Bu, KB 493, Accra, Ghana
e-mail: agana.nsiire@gmail.com

C. Kwakye-Maclean
Regional Health Directorate, Greater Accra, Accra, Ghana

E.N. Tabah
National Buruli Ulcer, Leprosy, Yaws and Leishmaniasis Control Program, Ministry of Public Health, Yaoundé, Cameroon

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_14

Some sub-Saharan African (SSA) countries, Southeast Asian countries, and Pacific Ocean Islands remain endemic. Children under 15 years, the most affected by yaws, continue to suffer deformities and, possibly, stigma, resulting in family and community neglect and some "dropouts" of school. Country and global goals for poverty reduction and universal education cannot be achieved if diseases like yaws continue to be neglected despite the availability of effective tools to eradicate or at least eliminate them.

Introduction

Yaws is a neglected tropical disease. It is a contagious disease of the skin, cartilage, and bones. It causes firm swellings (bumps), ulcers, and rashes on the skin and can affect any part of the body. It may cause mild pain and tenderness, with or without swelling, in the bones and joints. Children in deprived communities in the tropics are mostly affected, but no age is spared. The infective agent is a bacterium called Treponema pallidum *pertenue*. It is transmitted by persons with yaws skin lesions to susceptibles who have breaches in the skin through which the organisms enter and set up new infection and possibly disease. The infection stimulates some antibody production, but no lasting immunity is attained. The disease is diagnosed mostly clinically and easily treated with an appropriate dose for age, using single intramuscular injection of aqueous benzathine benzyl penicillin or oral azithromycin tablets or capsules.

Yaws is known and given local names in parts of SSA. In Ghana it is called "*gyator"* generally in the middle and southern belt, *"ekli"* in the eastern border with Togo, and *"jaga"* generally in northern Ghana. Yaws was well known by endemic populations before eradication attempts wiped out a lot of the disease. Of late though, it is less known, especially among the younger generations, although it is still quite known in typically endemic communities even by children. A primary school child in the Eastern Region of Ghana was able to describe the disease accurately as "a yellow boil." Anecdotes of local treatments of yaws in the past include rubbing the painless "bumps" with rough, loofah sponges until they were scaled down and using bluestone (copper sulfate) to shrink lesions. Many children with yaws today are still not sent to clinics for treatment, and some of such children hide their lesions if possible with clothing until they disappear or grind them away with rough objects. Such neglect has cost some children their education and deformed others with gangosa and other permanent deformities.

Clinical Features of Yaws

This section describes the forms of presentation of yaws, its signs and symptoms, diagnosis, and treatment. There probably can be no more complete description of the clinical picture of yaws than that presented in *Manson's Tropical Diseases* and

by the papers of C. J. Hackett, a WHO yaws expert of the 1950s and 1960s. This section describes clinical yaws with focus on observations made particularly in Ghana and the black skin of SSA for that matter.

Yaws Presentations

The following terminologies have been associated with the clinical presentations of yaws and are defined from the onset to clarify further discussions.

Early yaws refers to lesions of the first two phases of yaws called primary and secondary yaws. Primary yaws, also called mother yaws, is the first lesion, usually a single raised bump called a papilloma, that appears in 2–6 weeks at the site of entry of yaws germs into a skin breach. This papilloma may have other primary small satellite papules or papillomas near it (Fig. 1). The primary papilloma may also be two at different positions depending on the sites initially inoculated with treponemal organisms.

In one bad case of primary yaws affecting the left eyelids, the lesion had been present for about 9 months before being seen because the child was hidden away in a room from the public eye (Fig. 2).

Secondary yaws appears in other parts of the body, earliest 2 weeks after the primary papilloma, but may take as long as 16 weeks or longer to appear. These may show as uniform lesions or a mixture of papillomas, ulcers, macules, or papules of various forms, pustules especially in the scalp where they are likely to be infected. Other forms are anhidrosis of the skin, cracks, pitting, erosions or thickenings of palms and soles, or bone and joint pain or swellings. Secondary lesions result from organisms that enter the bloodstream from the primary papillomas to set up skin, bone, or joint lesions in parts of the body other than the site of initial entry. Secondary yaws can therefore coexist with a primary yaws papilloma or its ulcerated stage which can make their distinction difficult except by careful history taking.

Late yaws, also called tertiary yaws, refers to a very small fraction of early yaws cases (less than 5 %) who progress to late forms of yaws that destroy tissues leaving permanent scars, contractures, or other bone and cartilage deformities (gangosa, gondou, sabre tibia, dactylitis, etc.) (Fig. 3).

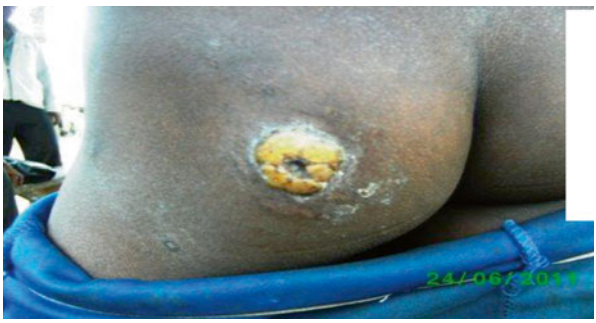


Fig. 1 Primary yaws papilloma with satellite lesions (Taken by Dr Kwakye-Maclean in 2011)

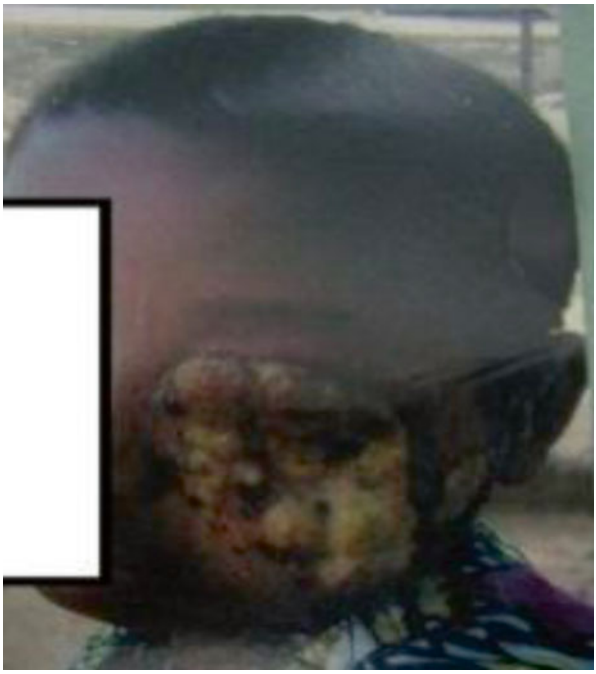


Fig. 2 Ulcerated primary yaws papilloma over left eye that healed after treatment with no affection of eye sight

Fig. 3 Gangosa in 13 year olds (Picture by Messrs. Asumeng and Dwamena 2013)

Late yaws does not normally coexist with early yaws lesions, but two 13-year-old boys from the same community reported with yaws-like lesions on the noses which progressed to permanent gangosa deformities. This is consistent with reports which suggest that gangosa and gondou can occur early in yaws infection and can be stopped with appropriate treatment or progress to permanent deformities (Perine et al. 1984). This makes it imperative to pay particular attention to lesions on the face and nose in yaws-endemic populations. Saber tibia and dactylitis may also be stopped and reversed if treated early or may progress to permanent deformities if left untreated. Late yaws is noninfectious because the body's own defense mechanisms have eliminated the organism or greatly attenuated it, though no permanent immunity is generated.

For practical purposes of yaws control, elimination, and eventual eradication, primary, secondary, and tertiary yaws have been regrouped as (i) *early yaws* which is infectious but can be controlled with drug treatment and other measures like

personal hygiene and avoiding close contact behavior and (ii) *late yaws* which is noninfectious but the lesions remain permanent features of individuals unless surgically corrected where possible or functionally improved through physiotherapy.

Infectious yaws This refers to all the skin lesions of early yaws with the potential to transmit yaws organisms to other persons. The papillomas secrete many more organisms than the other skin manifestations (macules, papules, etc.) and are therefore more infectious. Papillomas on the palms and soles are also infectious, but the palmar and plantar forms like cracks, erosions, and fissures which occur more on the soles than palms are the least infectious. This means children playing or sleeping together more easily get infected from papillomas than from the other skin forms for which closer contact (e.g., wrestling and sweating) is needed.

Noninfectious yaws The early bone and joint forms as well as all the late forms of yaws are noninfectious as they secrete no treponemes on the surface. Technically, the early bone and joint forms are still in the infectious phase as organisms from them may later show as skin lesions after latency.

Overt and latent yaws Overt yaws shows signs on the skin, cartilage, or bone and is diagnosed clinically and treated. Latent yaws is a phase during early yaws infection when all the skin, bone, and joint manifestations have disappeared without treatment or with ineffective treatment. The organisms have however not all died out but persist in the blood to manifest later with signs of early yaws on the body. Because of this, latent yaws is a crucial population in yaws eradication activities as not treating them allows transmission of the disease to persist in the population.

Contacts Yaws contacts are those who are incubating the disease (i.e. between inoculation of germs and appearance of primary papilloma(s) which on average is 2–6 weeks but can be longer). This means that one overt case can continue infecting many people and set up a continuum of new cases and incubators that will not show overt disease for weeks. These incubators will be missed out when looking for cases in facilities, schools, or communities. Contacts are therefore an important population in disease elimination and eradication strategies because if they are not treated, they will later show overt disease and continue the transmission of yaws.

Attenuated yaws This term attempts to describe the current clinical and epidemiological picture of yaws due to widespread use of antibiotics and improving sanitation which are believed to reduce the manifestation of the disease. Thus, attenuation appears in four ways: (i) reduced size of lesions (e.g., papillomas) on an individual, (ii) reduced extent or numbers of lesions on an individual, (iii) absence or near absence of late forms of yaws, and (iv) generally low prevalence in traditionally highly endemic countries or communities. While the concept of attenuated yaws may generally be acceptable whatever its value to eradication efforts, it should be stated that very large papillomas have still been observed both in children and adults. Late yaws lesions including *gangosa* have also been seen in Ghana in the recent past. High yaws prevalences have been reported in some schools in Ghana and among the pygmies by Medecins Sans Frontièr staff piloting single-dose oral

azithromycin mass drug administration in 2012 (MSF presentation, Geneva 2013). Sporadic outbreaks have also been reported in Cameroon (Tabah EN 2012) and in Ghana in a number of districts (District Outbreak Report 2009).

Clinical Features of Yaws

Constitutional symptoms are very mild in yaws. They present as mild joint and bone pain in children at night with no obvious fever. This is easily complained of by guardians in some endemic communities where the disease is called by its local name.

(i) *Early yaws* lesions may appear on any part of the skin from the scalp to the sole of the foot. The majority of the lesions however are found in the lower limbs because of the greater exposure of those parts. The bone and joint forms affect mostly the face, forearms, wrists, hands, fingers, legs, and the ankles. But nodular forms may also affect the skull. Early yaws lesions are characterized by the presence of one or more of the following:

- *Papillomas* are pale or yellowish, painless, and firm to hard chancres usually with dark tips showing points of beginning necrosis. They vary in size from less than 1 to 3 cm typically with no inflammation of the skin around them. But papillomas may also have a pale halo of macula inflammation extending a centimeter or more around them. Those on the exposed parts especially the legs tend to have surrounding skin inflammation due to bacterial infection. There may be pigmented skin around the lighter yaws lesions or a mixture of pale and pigmented surroundings. Because they are painless and stigmatizing, some children tend to hide them with their clothing or rub off those in accessible parts of their body with rough objects like sponges or even sand until they become flattened small yellowish blebs that feel rubbery soft rather than hard.
- *Ulcers*: These may occur as initial lesions or be ulcerated papillomas. They usually have raised edges, especially papillomas that necrose from the tip. The floor is dirty and crusty or yellowish and soggy. Some papillomas may not ulcerate from tip downwards but peel off the skin leaving a raw fungating surface. Both papillomas and ulcer forms attract flies because of their secretions, but there is no documented evidence of transmission by flies (Figs. 4 and 5).

– *Papules* are of the size of rice grains or smaller, pale, painless, firm, and usually discrete. The smaller forms may be patchy and itchy.
  – *Macules* are small, pale, discrete dots or patches. They may be present as mixed with other yaws lesions like papillomas and papules. The dorsum and margins of feet frequently show maculopapular rashes that may have atypical appearance due to the exposure of those parts to hazards of the physical environment.

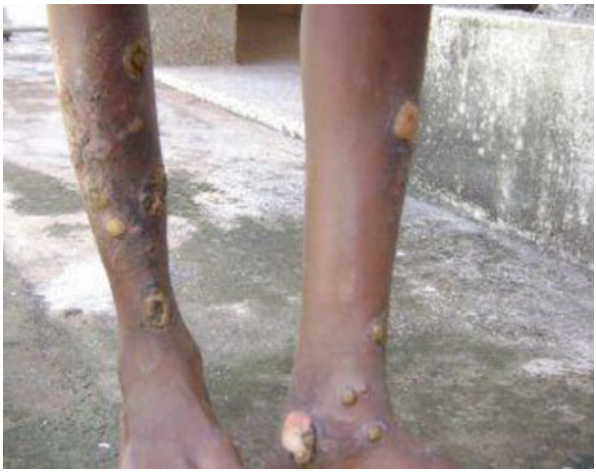


Fig. 4 Papillomata, papules, and ulcers of early yaws (Ghana Yaws Program)

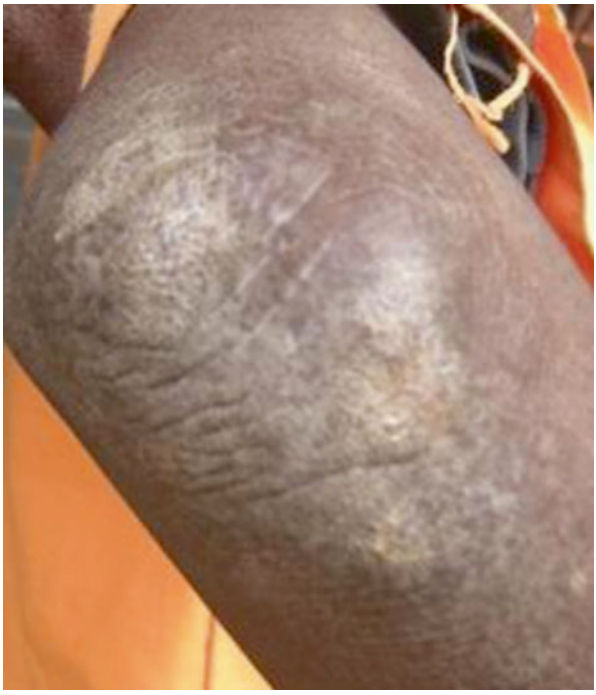


Fig. 5 Poorly developed and infected papules and macules on elbow (Ghana Yaws Program)

– *Palmar and plantar yaws* are painful lesions of the palms and soles. The palmar lesions are less painful usually showing as hyperkeratosis. Plantar yaws especially is very painful showing as cracks or fissures, erosions, pitting, or hyperkeratotic thickenings on the soles (Figs. 6 and 7). Papillomas may also occur on palms and soles and are similarly painful.

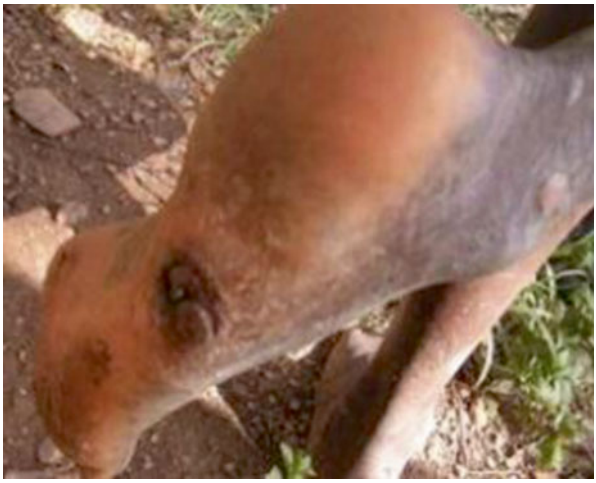


Fig. 6 Plantar yaws thickenings; very painful

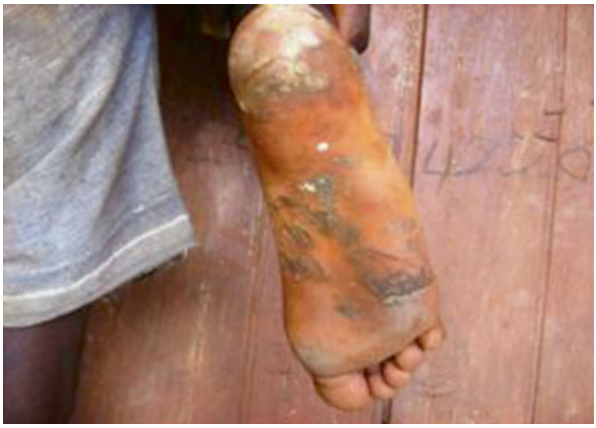


Fig. 7 Plantar yaws erosions (Dr. Kwakye-Maclean)

- *Bone and joint lesions:* Moderate swelling and tenderness affect mostly the bones and joints of the forearm, wrist, fingers, and legs. Usually one or two bones may show obvious swelling with other bones having subclinical osteitis. The early stages of tibia bowing may be seen with or without ulcerated lesions on the leg. It is not uncommon to see a pale, contiguous patch on the dorsum of a hand with one of the fingers of the same hand swollen and tender. The presence of bone and/or joint swelling together with suspicious skin rashes in a child in an endemic area should lead to a high suspicion of yaws (Figs. 8 and 9).
- *Ganglia, nodules, and enlarged lymph nodes:* These have rarely been seen in Ghana. They can occur especially near the joints and in the head. Enlarged lymph nodes have been seen in very few cases.

Yaws may present as other atypical rashes including anhidrosis and other scaly, dry, or pigmented conditions with line markings especially on the

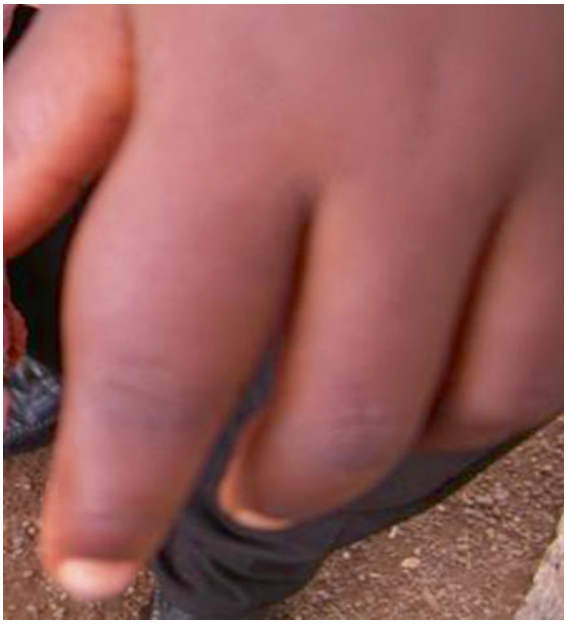


Fig. 8 Dactylitis of early yaws affection of bones (Kaitoo 2008)

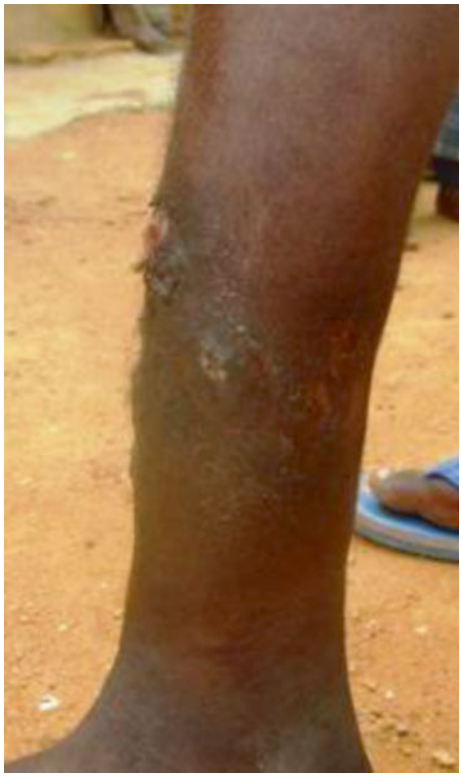


Fig. 9 Saber tibia: early yaws affection of bones (Kwakye 2011)

lower limbs. Lesions on elbows and knees tend to be mixed papules, macules, and small papillomas which usually ulcerate and look soggy, but they may also be clean macules or papules or patches of them. Generally all early yaws skin lesions are paler than the normal skin and painless except for those on the soles and palms or when secondarily infected with other bacteria. They are also frequently polymorphous – that is, many types of early lesions present together.

(ii) *Late yaws lesions* are rarely seen but have traditionally affected the face (gangosa and gondou), forearm and finger bones (polydactylitis), leg bones (sabre tibia), and the skin as ugly and permanent scars. It should be noted that bending of long bones occurs in early yaws but can be corrected with treatment. Sabre tibia is therefore used here to describe late yaws where the tibia deformity has become permanent.

Diagnosis of Yaws

Yaws is mostly diagnosed clinically from the various lesions described above. For purposes of searching for overt and latent cases and contacts in control or eradication programs, however, a case definition of yaws involves anyone with one or more of the following: papillomas, ulcers with raised edges, papules, macules, arthralgia especially in children, bone swellings with moderate tenderness especially in children, nodules or ganglia, plantar cracks, erosions or thickenings, or a history of any of these in the last 5 years. Gangosa, gondou, sabre tibia, deformed finger bones and joints, and skin gummas, active or within the recent past or any skin condition not attributable to any known cause, should be considered as yaws.

The laboratory diagnosis of yaws is based on both qualitative and quantitative serology tests. The two main types of serology used are t*reponemal* and *non-treponemal* tests. Treponemal tests detect treponemal antibodies which are present for life once a person is infected with any of the Treponemes. They are useful therefore in confirming a person's previous exposure to infection but do not confirm a current infection. Examples of treponemal tests are Treponema pallidum hemagglutination (TPHA) and Treponema pallidum passive particle agglutination (TPPA) tests. There are variants of these like *syphilis first response* used in antenatal clinics and on the field qualitatively as point-of-care tests (POCTs). Treponemal tests can also be used quantitatively to estimate the dose of antibodies in the individual.

Non-treponemal tests like rapid plasma reagin (RPR) detect active disease by the presence of nonspecific antibodies that rise with infection but peter out in a month or two. They may also be used qualitatively and quantitatively but have the drawback of cross reactivity in other conditions like malaria, typhoid, and pregnancy. In community surveys, they are probably more useful than treponemal tests in detecting latent cases and contacts who are harboring active infection.

Perhaps the best serological tests are the modern generation of dual POCTs being developed for both treponemal and non-treponemal tests on one platform.

New products, like the Chembio Dual Path Platform tests, test for treponemal and non-treponemal antibodies at the same time. Some of these have been evaluated in Ghana, Papua New Guinea, and Vanuatu and are promising for use as point-of-care rapid diagnostic tests for surveys, for confirmation of yaws in resistant lesions to treatment, and for surveillance in the eradication phase of yaws if they are cost-effective. For routine diagnosis however, and identifying endemic communities for total community treatment or total targeted treatment with azithromycin or depot penicillin, clinical diagnosis with given case definitions will continue to be the preferred tool for highest sensitivity.

Genetic tests like the polymerase chain reaction tests are being developed with primers specific for yaws. These will be the only tests to differentiate the various Treponemes. Old Venereal Diseases Research Laboratory (VDRL) tests and dark field microscopy are hardly used nowadays for the diagnosis of yaws.

Differential Diagnoses of Yaws

Common differential diagnoses are as follows:

Similar skin, bone, and cartilage lesions of the three related treponemal diseases, namely, venereal syphilis, endemic syphilis, and pinta. Pinta is however not found in SSA, and endemic syphilis affects more the mucous membranes. In venereal syphilis, there may be a chancre or history of a chancre in the genital area in a person that is sexually active, the age of onset of which is coming down and posing more differential diagnostic problems.

Scabies presents as tiny pustules that are intensely itchy, found in the finger webs and flexure areas. An itchy pustule on the penis is almost pathognomonic of scabies. Presence in other family members including adults at the same time is more frequent than with yaws.

Fungal skin infections which also occur in any part of the body including the mucous membranes. Useful distinguishing features are the ring nature of fungal infections with healing in the center and active disease at the edge of the ring. Scaling is also commoner in fungal infections. The ring forms of yaws may be heaped at the edges and not show much scaling.

Eczematous lesions and urticaria of varied causes may be differentiated from yaws by careful history and the patch test in the case of allergic or contact dermatitis. The dermatophism test may also indicate if lesions are other than yaws, though a person may have both.

Leprosy has associated thickened peripheral nerves and loss of sensation on the lesions as opposed to yaws lesions which are painless but tactile sense is not lost.

Buruli ulcer may be distinguished by undermining edges of the ulcer stage as opposed to the raised edges of most yaws ulcers. The nodule, plaque, and edematous forms of Buruli ulcer may however be difficult to distinguish except by careful history and histology. Buruli ulcers will however usually be single as opposed to the many lesions especially of secondary yaws.

Corns, niduses, plantar warts, and the cracks or fissures of soles in certain occupations like farmers and in certain seasons like the Harmattan are frequently diagnosed by inexperience as plantar yaws.

Other uncommon differential diagnoses include vitiligo which is permanent, much more paler than the normal skin, and on exactly the same plane with normal skin (you cannot see or feel the slightest elevation of the lesion), cutaneous leishmaniasis, and lichen planus distinguished by its shiny surfaces and tiny white lines (Wickham's striae), psoriasis with its characteristic shiny, reddish, and itchy plaques. Its frequent affection of the extensor aspects of the knees and elbows alone cannot be used to differentiate it from yaws which also affects those parts frequently.

Molluscum contagiosum and congenital epidermolytic hyperkeratosis are other rare conditions simulating yaws. The latter however tends to be present from birth or at least for a long, long time and is also painless.

Treatment of Yaws

Yaws was first treated in the 1950s and earlier with toxic bismuth and arsenical substances which could not be used easily for mass campaigns. These were replaced by penicillin, and luckily, yaws, like syphilis, has remained sensitive to penicillin especially in SSA. Depot forms for single intramuscular injections to keep high blood levels for long periods have included penicillin aluminum monostearate in oil (PAM) which was used for yaws eradication purposes in the 1950s and 1960s. It had the undesirable effect of leaving scars at injection sites due to the oil base. PAM was therefore replaced by aqueous benzathine benzyl penicillin which can keep blood levels high for 2–4 weeks depending on the source. The dose of depot penicillin for adult cases and children over 10 years is a single intramuscular injection of 1.2 megaunits. Half of that is given to corresponding adult and child contacts. For children 10 years and below, 0.6 megaunits is used and half of that (0.3 megaunits) for child contacts 10 years and below. Aqueous depot penicillin is however very painful and cumbersome for mass field administration for control, elimination, or eradication purposes. The Ghana and Papua New Guinea drug trials of 2010/2011 have however caused the World Health Organization (WHO) to revamp and revise the policy for yaws eradication using single oral doses of tablet or capsule azithromycin in mass drug administration. The prescribed doses are indicated in the figure below (Fig. 10).

Importance of Yaws

The importance of yaws is derived from the direct physical effects it has on the individual and the social, cultural, and economic effects or impact on individuals, families, and communities. For yaws, the direct physical effects are not death but

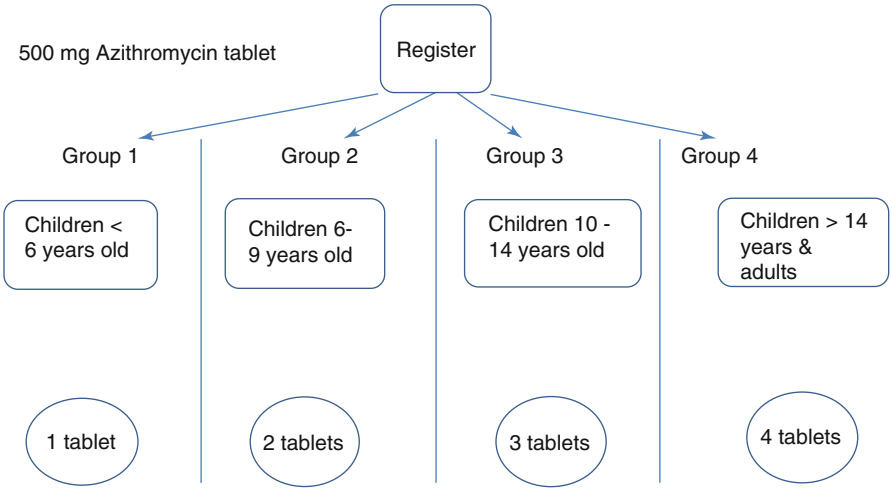


Fig. 10 Organization of yaws treatment campaigns with azithromycin 500 mg azithromycin tablet (Figure courtesy of Dr. Kingsley Asiedu, WHO Geneva)

the presence of ugly, discomforting, and sometimes painful or crippling lesions, which could be transient or permanent. Some yaws lesions, especially those on the face, leave stigmatizing effects negatively affecting social life and the education of some children. One such child in Ghana with a large papilloma covering the left eye was hidden away in the room until discovered by a philanthropist, personally attended to by one of the authors with other colleagues and returned to school. Another young girl with early bone deformities kept out of mingling with her colleagues until unearthed and treated by the health system before resuming active social life. These stigmatizing and the other painful and crippling yaws (crab yaws, dactylitis, sabre tibia, etc.) may impact negatively on individual, family, or community activities and incomes and possibly negate the millennium development goals on poverty reduction, universal education, and morbidity reduction.

Epidemiology of Yaws and Its Public Health Importance

The demographics of yaws have not changed over the years. Yaws affects all ages but mostly children under 15 years of age. Young adults are next most affected especially by plantar yaws. Boys are more affected than girls. The reasons for these lie in behavior, children, especially the boys, being usually more exposed and more contact and bruise prone which are necessary conditions for yaws transmission. Poor personal hygiene is a strong contributing factor.

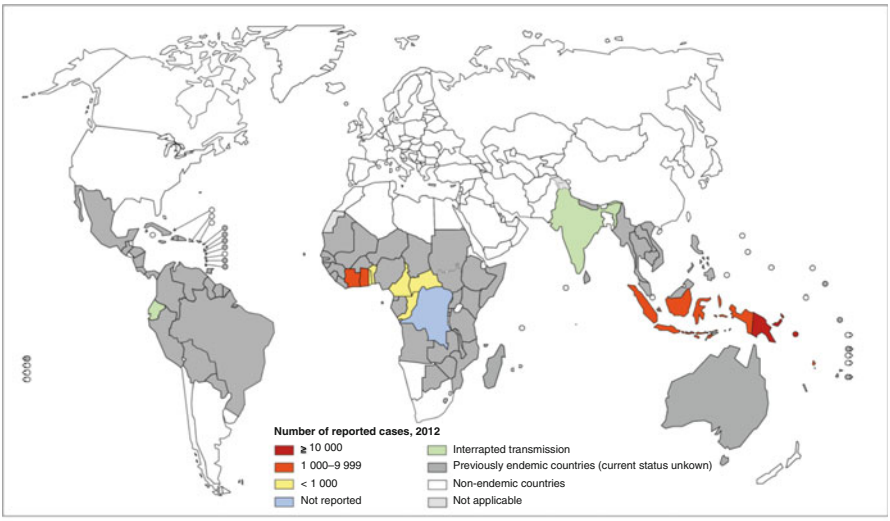
Between 1940 and 1950, 37 sub-Saharan African countries (outside South Africa) reported yaws cases to the WHO (Hackett 1953). Since 46 countries were involved in the global campaign, it means Africa formed the bulk of yaws-endemic countries

then. Today, yaws is still endemic in a number of SSA countries with wet, humid forest and/or dry, grassland areas. Generally, these countries lie within the tropics with temperatures between 20 and 40 °C and exceptionally exceeding these limits especially in East and South Africa with considerable highlands and which may lie within the southern temperate belt. Yaws or its close relation bejel therefore probably thrives in all of sub-Saharan Africa, but current WHO records indicate that only 13 of about 50 such countries have any reports or post eradication period assessments suggesting that they are yaws endemic (see map). These are Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of Congo, Ghana, Guinea, La Cote d'Ivoire, Liberia, Sierra Leone, and Togo (Edorrh et al. 1994; Sanou I, 2012). A WHO AFRO *Report of a Regional Meeting, Brazzaville, 3–6 February 1986* on "Yaws and other endemic Treponematoses" also listed additional countries to the above that reported yaws cases in 1984, namely, Burundi (102), Chad (629), Equatorial Guinea (283), Gabon (257), and Rwanda (225). The same report mentions that yaws was being reported from states like Borneo and Bauchi in Nigeria which were previously not known to be endemic. The current yaws situation on the African continent therefore really needs a reassessment. The highest prevalence remains among the pygmies of Central African countries (Cameroon, Central African Republic, Congo, and the Democratic Republic of Congo). In Ghana and other West African countries, however, the prevalence is generally low but the distribution is wide in isolated rural areas and some suburban poor communities. Surveys in Ghana suggest that yaws may be found more in children and young adults not in school than those in school (National Yaws Eradication Program Annual Report 2008, Ghana). But this is easily reversed as school enrolment improves.

Records compiled by C. J. Hackett for 37 SSA countries of the 1950s gave little information on the seasonality pattern to yaws, though few countries (Angola, Cameroon, Congo, Mozambique, and Sierra Leone) did indicate higher numbers of yaws during the warm, humid, rainy seasons (Hackett 1953; Harding 1949). Monthly returns to the national program in Ghana do not show clear seasonality. Some reports suggest however that yaws incidence may rise in the cold seasons as a behavioral outcome when children huddle together during sleep, as reported of the cold monsoons in parts of India. My personal experience is that you can find dry yaws lesions quite commonly during the cold Harmattan season in some communities in Northern Ghana.

Yaws is transmitted through skin contact between infectious yaws cases and others who sustain bruises or openings of any kind during the contact, or previously, allowing the organism (Treponeme) to enter and establish infection. The Treponeme is a slow-growing oxygen-dependent intracellular organism with a doubling rate of about 30 h (Magnuson and Eagle 1948; Norris et al. 2001). This combined with a long incubation period of up to 6 weeks or more makes yaws a not too highly infectious disease. But the very existence of long incubating contacts and latent cases makes yaws transmission intractable unless effective interventions are put in place. Apart from age and sex, other predisposing factors for yaws transmission are poor personal hygiene, especially not bathing at least once a day, poor water supply and overcrowding.

Distribution of yaws worldwide, 2012



Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

World Health Organization

Public Health Importance of Yaws

As a communicable disease, yaws remains a public health hazard to all at-risk populations, which is the totality of sub-Saharan Africa living under predisposing conditions especially as the exact situation is unknown in most countries currently. The colonial office medical department annual reports (MDARs) of the Gold Coast Government (now Ghana) point to the high burden of yaws in the pre-campaign days, and some documentations ranked yaws as highest cause of outpatient morbidity or at same level with malaria, guinea worm, and onchocerciasis (Destombes 1999; Colonial Reports – Annual No 1919, Gold Coast 1938–1939). One survey among school children in Ghana in 2013 (yet unpublished) put yaws clinical prevalence at 1.3 % and serological prevalence at 10.8 %. Surveys in other SSA countries have reported prevalences ranging between 1 and 10 % depending on the method and size of the study population (Coldiron et al. 2013; Touré et al. 2007; Toure 1985; Gerstl). Qualitative comments of the social and economic impact on rural populations are rampant in the literature, but these have never been quantified and are absent in recent research works. Anecdotal evidence and personal experience of the authors and some field workers seem to indicate that stigma and morbidity may affect children negatively in terms of their education and social life.

Surveillance of yaws after the global eradication efforts seemed to have been stopped in most African countries. In Cameroon the eradication effort ended in 1970 and, with it, surveillance on yaws (Njih Tabah 2013). After outbreaks of yaws in five districts in 2007 and 2008, the Ministry of Public Health included yaws in the Buruli ulcer, Leprosy and Leishmaniasis Control Program in 2009 and in the national master plan of 2012–2014. Between 2010 and 2011, 23 out of the 58 health districts had reported yaws cases through mass screening and passive notification. La Cote d'Ivoire similarly had no program of yaws control, though in 2010, according to routine data made available to WHO by Professor Henri Asseh of the Buruli Ulcer program, 67 out of the 90 districts reported yaws. Ghana's eradication effort ended in 1969, but Eastern and Central Regions, now the most endemic in the country, had been excluded in the campaign. Since then passive surveillance and treatment have been continuously carried out by facility-based medical field unit (now disease control unit) staff. Between 1980 and 1983, WHO, the World Bank and other partners tried a combined yaws mass treatment with immunization against yellow fever and tetanus in Ghana and neighboring countries, but it was short-lived. The current resurgence of global interest in the neglected tropical diseases coupled with new treatment and diagnostic tools have caused WHO to bring to the fore again the drive to eradicate yaws. In this respect, globally, countries have been divided into three categories: (i) Category C countries are traditionally non-endemic or have achieved and documented yaws elimination for which they will be so certified; (ii) category B countries are previously endemic countries with little or no knowledge of their current situation (they will have to carry out studies/surveys to establish their status and either join category A or C); (iii) category A countries, like Cameroon and Ghana that know that they are endemic, will carry out pilot studies with the new tools and scale up elimination activities. The WHO target for global eradication of yaws is 2020, along with elimination of ten other NTDs, but this poses the frequently asked question: should yaws or any other disease be eliminated or eradicated instead of just being controlled?

Should Yaws Be Eradicated?

This good question may be considered from both the pragmatic and philosophical viewpoints. In pragmatic terms, disease eradication is considered to be the reduction of the disease to zero (no cases at all) and removal of the causative agent from the wild where it freely moves within the population. The causative agent may be confined to a laboratory, but if all specimens are destroyed, the disease would be said to be extinct. Yaws (if the germ is the same strain) is believed to exist also among other primates like chimpanzees and gorillas (Andrea Rinaldi and Charles King 2008), so it would seem more appropriate to talk of yaws elimination (reduction of disease to below public health importance) rather than eradication, as attempts to eradicate it in other primates, like in all zoonoses, could be extremely challenging. Conceptually though, eradication of the disease rather than the

causative organism from the human population is still possible and any disease scientifically amenable to elimination or eradication from a population must be so targeted. That yaws has already been eliminated from a number of countries including big India most recently, using the tedious tool of injections, encourages us that with the newer and easier tools (azithromycin for oral treatment and point-of-care tests for surveillance), eradication globally is possible. We should therefore reengineer our social effort to achieve it. The key is in the reengineering of our collective effort toward this objective, goaded by the achievements of earlier efforts.

Conclusion

Yaws, a communicable disease transmitted by skin contact, is a nonfatal but crippling and sometimes stigmatizing disease that affects mostly children in deprived tropical communities. It is still present in a number of SSA and other countries despite previous efforts at global eradication. Earlier campaigns, however, helped many countries, some of which have unofficially declared yaws eliminated from their borders. For those countries that are still endemic with yaws, competing priorities have relegated yaws to the domain of neglected tropical diseases, though it is relatively easy to diagnose and treat.

Eradication of yaws, however, requires that contacts of yaws cases and its latent forms also be treated to remove the germ, which resides mainly in man, from the population. New and simpler treatment options and surveillance tools are available to facilitate the process as improving sanitation, water supply and personal hygiene are scaled up. What remains therefore is the collective will and effort in this direction. We must *end the neglect*.

References

Asumening M, Dwamena K. Picture of gangosa in children aged 13, taken in 2013 (not published)

Colonial Reports – Annual, No. 1919, Annual Report on the Social and Economic Progress of the People of the GOLD COAST (1938–1939) libsysdigi.library.illinois.edu/…/5530214_1938_1939_opt.pdf

Coldiron M, Obvala D, Mouniaman-Nara I, Pena J, Blondel C, Porten K (2013) The prevalence of yaws among the Aka in the Congo. Med Sante Trop 23(2):231–232 [Article in French]

Destombes J (1999) Working Paper No. 49/99, Nutrition and Economic Destitution in Northern Ghana, 1930–1957. A historical perspective on nutritional economics, eprints.lse.ac.uk/22388/1/wp49.pdf

Edorh AA, Siamevi EK, Adanlete FA, Aflagah EK, Kassankogno Y, Amouzou AB, Lodonou KG (1994) Resurgence of endemic yaws in Togo. Cause and eradication approach. Bull Soc Pathol Exot 87(1):17–18

Gerstl S, Kiwila G, Dhorda M, Lonlas S, Myatt M, Ilunga BK, Lemasson D, Szumilin E, Guerin PJ, Ferradini L (n.d.) Prevalence study of yaws in the Democratic Republic of Congo using the lot quality assurance sampling method. PLoS ONE 4(7). doi: 10.1371/journal.pone.0006338

Ghana Yaws Program. Picture of ulcerated yaws papilloma over left eye (taken in 2009, not published)
Ghana Yaws Program. Picture: Papillomas, papules and ulcers of early yaws (not published)
Ghana Yaws Program. Picture: Poorly developed and infected papules and macules on elbow (not published)
Hackett CJ (1953) Part III. Extent and nature of the yaws problem. Bull World Health Organ 8(1–3):129–182
Harding RD (1949) Trans R Soc Trop Med Hyg 42:348
http://www.who.int/yaws/epidemiology/en/: Yaws: epidemiological situation
Kaitoo E. Dactylitis of early yaws affection of bones (taken in 2008, not published)
Kwakye-Maclean C. Primary yaws papilloma with satellite lesions (taken in 2011, not published)
Kwakye-Maclean C, 2011. Picture: Plantar yaws erosions (not published)
Kwakye-Maclean C, 2011. Saber tibia: early yaws affection of bones (not published)
Magnuson HJ, Eagle H (1948) The minimal infectious inoculum of Spirochaeta pallida (Nichols strain), and a consideration of its rate of multiplication in vivo. Am J Syph 32:1–18
MSF presentation at WHO annual Yaws review meeting, Geneva, 20–22 Mar 2013
National Yaws Eradication Program Annual Report (2008) Ghana
Norris SJ, Cox DL, Weinstock GM (2001) Biology of Treponema pallidum: correlation of functional activities with genome sequence data. J Mol Microbiol Biotechnol 3(1):37–62
Organization of yaws treatment campaigns with azithromycin 500 mg azithromycin tablet (Figure courtesy of Dr. Kingsley Asiedu and captured in draft WHO Program Managers Guide for Yaws Eradication following Consultative Meeting of Experts on Yaws Eradication, held in Morges, Switzerland, 2012;5–7
Perine PL, Hopkins DR, St John RK et al (1984) Handbook of treponematoses: yaws, endemic syphilis and pinta. WHO, Geneva
Report of Yaws outbreak in the Sissala District of Ghana (2009)
Rinaldi A, King CH (eds) (2008) Yaws: a second (and maybe last?) Chance for Eradication. PLoS Negl Trop Dis Aug 2(8):e275. Published online 27 Aug 2008. doi: 10.1371/journal.pntd.0000275, PMCID: PMC2565700
Sanou I, 2012. Presentation captured in WHO's Summary Report of a consultation on the eradication of yaws, 5–7 March 2012, Morges, Geneva, Switzerland,
Tabah EN, 2012. Presentation captured in WHO's Summary Report of a consultation on the eradication of yaws, 5–7 March 2012, Morges, Geneva, Switzerland
Tabah EN, 2013. Presentation on Yaws in Cameroon at Yaws Review Meeting in Geneva, 20–22
Toure IM (1985) Endemic Trematoses in Togo and other west African States. Rev Infect Dis 7(Suppl 2):242–244
Touré B, Koffi NM, Assi KP, Ake O, Konan DJP (2007) Yaws in Côte d'Ivoire: health problem forgotten and neglected. Bull Soc Pathol Exot 100(2):130–132

The Social and Economic Impact of Neglected Tropical Diseases in Sub-Saharan Africa

Margaret Gyapong, Alexander Nartey, Enoch Oti, and Samantha Page

They are hiding their skin so that people cannot see them. I have not heard of anyone who wants others to know about it. No one will allow them to lead, and many people ignore them. They are considered dangerous. People fear contact with them. I feel sorry for them. Even me, I feared that from staying and meeting them we could get the disease … They find it hard to marry, and marriages can break because of this condition. (25-year-old Ugandan woman)

Contents

M. Gyapong (✉)
Dodowa Health Research Centre, Ghana Health Service, Dodowa, Ghana

CouNTDown Consortium, Dodowa, Ghana
e-mail: margaret.gyapong@ghsmail.org

A. Nartey • E. Oti
Dodowa Health Research Centre, Ghana Health Service, Dodowa, Ghana

S. Page
Department of International Public Health in the University of Liverpool, Liverpool School of Tropical Medicine, Merseyside, UK

CouNTDown Consortium, Dodowa, Ghana

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_15

Abstract NTDs are characterised by several factors, the most common of which is poverty. Attention needs to be given to the socio-economic impact of NTDs and the wide-reaching effects this has on the health and well-being of affected individuals and households. This impact is not uniform as NTDS are linked to poverty and other axes of inequity: vulnerable groups, e.g. gender, disability and ethnicity may become additionally vulnerable. This chapter addresses these issues whilst highlighting the need to focus on illness as well as disease.

Introduction

From Buruli ulcer to trachoma, the illustrative experience of a patient suffering from skin lesions expressed by a 25-year-old woman in an onchocerciasis-endemic village in a study by Weiss (2008) is a typical description of persons suffering from any of the parasitic, bacterial, viral and fungal infectious diseases described in the earlier chapters of this book and known as Neglected Tropical Diseases (NTDs). Together, NTDs affect about 2.7 billion people and kill more than half a million people every year (Hotez et al. 2009). These 2.7 billion are the poorest, disadvantaged and most marginalised people from Africa and some parts of Asia where poverty is high (Hotez et al. 2007a; Molyneux et al. 2005; Brooker et al. 2006; Fenwick et al. 2005, 2006; Ajanga et al. 2006). Sub-Saharan African countries bear the highest burden of NTDs with the number of people afflicted by each of the several NTDs representing up to 90 % of the world's burden for some of these diseases (Hotez et al. 2009; Zhang et al. 2010).

These diseases are characterised by several factors, the most common of which is poverty (WHO 2010a). In sub-Saharan Africa as in other countries where NTDs are present, the poorest of the poor, the most stigmatised and marginalised and those least able to demand services are affected. These often include women, children, ethnic minorities, displaced people as well as those living in remote areas with restricted access to health services.

The economic effects of disease control have been known since the early twentieth century. Research has shown that investment in disease control could rescue the "bottom billion" – those living in some of the world's poorest communities – through its effect on the four key elements of the poverty trap: health, agriculture, education and infrastructure (Sachs 2008; Bleakley 2007). However, attention needs to be given to the socio-economic effects of NTDs and the devastating impact they have on the health of infected households, leading to debilitating physical disability and disfigurement including peripheral neuropathy, cardiac disease from Chagas disease, skin lesions and ulcers from lymphatic filariasis and Buruli ulcer, loss of eyesight from trachoma and onchocerciasis and cognitive impairment from schistosomiasis resulting in a lifetime of disability (Hotez et al. 2007b; Rodrigues and Lockwood 2011). The impact of NTDs on agricultural productivity and education and the infrastructural development in affected communities are wide reaching. The impact is not uniform as NTDs are linked to poverty and other axes of inequity: vulnerable groups, e.g. gender, disability and ethnicity may become additionally vulnerable. Research has established the disability associated with NTDs to be

about 57 disability-adjusted life years (DALYS). However, Hotez (2009), Gyapong et al. (2000a), Babu (2009) and Perera et al. (2007) have noted that these DALYS may actually be higher and that the economic, social and psychological burden of these diseases put together is more extensive than previously calculated. Dr. Margaret Chan in her introduction to the first WHO NTD report succinctly summarised: "The consequences are costly for societies and for health care. Such costs include intensive care for dengue haemorrhagic fever and clinical rabies, surgery and prolonged hospital stays for Chagas disease and Buruli ulcer, and rehabilitation for leprosy and lymphatic filariasis. For some diseases, such as sleeping sickness and leishmaniasis, treatments are old, cumbersome to administer and toxic. For others, especially the diseases that cause blindness, the damage is permanent. Clinical development of rabies can be prevented through timely immunization after exposure, but access to life-saving biologicals is expensive and is not affordable in many Asian and African countries. For most of these diseases, stigma and social exclusion compound the misery, especially for women" (WHO 2010a, p. iv).

The disease-specific chapters in this book use aspects of the medical model of disability (Carson 2009; Yoko ani 2001) (an individual's disability) which views physical problems as needing to be cared for and cured by medicine, through a focus on the basic biology, life cycle, disease presentation, epidemiology and burden of disease and distribution, available control tools and strategies, challenges of programme implementation, further research for control and an outlook for the next decade of NTDs. This chapter focuses on the socio-economic impact of NTDs using aspects of the social model of disability (Yokotani 2001) (an unequal relationship within a society in which the needs of people with some form of disability are often given little or no consideration especially when they are the poorest of the poor and have no voice). It firstly highlights lay perceptions and understanding of NTDs, followed by an overview of NTDs gender as well as the stigma, the quest for therapy in the event of contracting an NTD and the economic burden of having an NTD on the individuals, households, and society. Additionally it highlights the importance of action to address female and male genital schistosomiasis, which have been neglected to date. The chapter finishes with a discussion on the cross-cutting themes with respect to the social and economic impact of NTDs and the need for further action.

Disease Versus Illness: Lay Perceptions of NTDs

The distinction between disease and illness has been well described. Whereas disease defines a pathophysiologic process, illness is defined by the complete person: physical, psychological, social and cultural (Eisenberg 1977; Helman 1981). Illness represents an individual's unique and personal experience of being unwell. People often rationalise their illness experience through a complex web of personal encounters, experiences and belief systems shaped by their cultural and social world. As expressed by Kleinman (1980), individuals would usually develop a personal (or adopt an existing) "explanatory model" that represents their personal conceptualisation of the cause, course and consequences of their illness. For each of the NTDs being discussed in this volume, there is a classic medical description, researched

and acceptable causes and tried and tested treatment options. The conditions according to medicine are either bacterial infections, worm infestations or vector transmitted (mosquito, a fly, etc.). In some instances, there is no clear-cut cause. On the other hand, many people in African societies rationalise their experience of ill health through complex personal experiences and belief systems (sociocultural and/or religious) ingrained in their cultural and social world. An explanation of ill health or physical manifestations, be it by the patient or the people in his or her society, would usually be representative of their personal conceptualisation of the cause, course and consequences of their illness (Green et al. 2002). Patients' perceptions about a disease, its effective treatment and the socio-economic dislocation caused by the illness and related symptoms generally have a significant impact on when and where to go for diagnosis and treatment. Beliefs about the cause and transmission of a disease vary considerably from culture to culture; however, there are some general traits that permeate many cultures. They can be dynamic in that the prolonged nature of a condition and the long period and difficulty of a healing process can lead to assumptions of mystical involvement even for people who attributed their ill health to natural causes at the onset of symptoms. As Peeters Grietens et al. (2012) state, the same condition can also have double causality. In other words, a particular disease may be attributed to natural/medically known causes and simultaneously to mystical causes. Therefore, whilst medical science describes a malfunction in the body, lay perceptions of disease causation relate to their experience with their ill health.

According to Peeters Grietens et al (2012) in Benin, plots of land on which crops are grown are protected by charms to prevent theft, so, in that country, Buruli can be attributed to a charm as a result of trespassing on another person's land thereby disrupting a social order. In Ghana, amongst other causes, Buruli is attributed to a curse "if your mouth is strong", in other words if a person uses powerful words to curse or witchcraft because someone hates you (Renzaho et al. 2007; Stienstra et al. 2002).

In sub-Saharan Africa, there is a dearth of information on perceptions of lymphatic filariasis. Even in Ghana where studies on the subject have been conducted in the Northern and Southern part of the country, there are multiple differences in perceptions of aetiology. Whilst in Southern Ghana the belief is that one gets the disease because of an imbalance in the body's constitution and other physical and sometimes spiritual causes, in the Northern part of the country, the perception is that it is due to external forces like witchcraft or a curse (Gyapong et al. 1996a; Ahorlu et al. 1999).

In the Democratic Republic of Congo, the mode of transmission and dramatic sequelae following sleeping sickness are very well known and recognised by community members (Mpanya et al. 2012). In addition, serious prohibitions (complete rest for 6 months) are linked to those with diseases with severe consequences for individuals if they are not seen to be adhered to. Although considered shameful, having the disease signifies a shift in societal position rather than rejection by the family and community. Guinea worm in Ghana is seen as a normal part of the human anatomy. The worm is not seen as an alien presence. It is normally in people's blood and shows up from time to time (Bierlich 1995).

In Table 1 we show that lay perceptions of these conditions differ sometimes significantly from what is medically known.

Table 1 Lay perceptions on disease causation

Condition	Lay description Perceived cause	Reference
Buruli	Unknown, witchcraft, drinking unclean water, unhygienic practices, playing with an infected person and infraction against social order	Renzaho et al. (2007), Stienstra et al. (2002), Peeters-Grietens et al. (2012), and WHO (2013a)
Dracunculiasis (guinea worm)	Poor drinking water	WHO (2013b) and Sisay (2012)
	Drinking water infected by people with the disease	
Human African trypanosomiasis (sleeping sickness)	The fly, eating the amaranth plant and eating pork	WHO (2013c) and Mapanya et al. (2012)
Leishmaniasis (kala-azar)	Sandflies, dirt, washing in a canal, eating and drinking with patients	WHO (2013d)
Leprosy	Hereditary, witchcraft breaking of a taboo	WHO (2012)
		Gender and leprosy case studies 2009
Lymphatic filariasis	Hydrocele "fever scrotum", elephantiasis, "elephant leg", these are as a result of a curse, poor body constitution and/or are hereditary	WHO (2013e), Gyapong et al. (1996a), and Ahorlu et al. (1999)
Onchocerciasis	Bite of the blackfly causing itching, Several worms in the body, eating improperly cooked leaves	WHO (2013f) and Aninakwah-Boahene et al. (2014)
Schistosomiasis	Sign of growth, hereditary	WHO (2013g)
Soil-transmitted helminths (ascaris, whipworm and hookworm)	No information found	WHO (2015)
Trachoma	Normal part of childhood	WHO (2013h) and Desmond et al. (2005)
Yaws	Poor personal hygiene and sanitation	Anecdotal reports from Ghana

NTDs and Stigma: The Impact on Gender Roles and Relations

Many if not all NTDs discussed in this book cause impairment, disfigurement and sometimes permanent disability, leading to stigma and social discrimination. Many studies on stigma refer to leprosy, and this may be due to the fact that rejection as a result of leprosy dates far back to biblical times to depict a mark of disgrace or physical disorder (to such an extent that sufferers of leprosy subjected to their own mock funeral prior to banishment from their families and communities). In some cases, they endured torture and execution (Roueche 1986) and rejection either for physical or social reasons (Weiss 2008; Goffman 1963). The concept of stigma can

be either enacted (when the affected person faces rejection, discrimination or physical abuse by others) or perceived (when the affected person thinks he or she is or can be stigmatised because of their physical condition). In many cases, the perceived stigma can be worse than that enacted and may lead to known attempts of suicide, emotional stress, depression and anxiety (Heynders 2002; Hyland 1993; Scambler 1998; Van Brakel 2003). Stigma as an important mediator of social burden can lead to invisibility and marginalisation of infected people, emotional distress and delayed diagnosis and treatment even to the extent that free treatment at health facilities is not sought to avoid a public appearance because of the disease (Perera et al. 2007; Pépin et al. 2002).

Discrimination and stigma heighten people's vulnerability to ill health. In all countries of the world, the burden of disease is disproportionately borne by vulnerable and marginalised groups, who often suffer from other social inequities as well as discrimination (United Nations Special Rapporteur 2003: para. 59). It can also be an obstacle to prevention and treatment. This form of discrimination against people living in poverty can be reinforced by other forms of discrimination, such as on grounds of sex or race, which further increase vulnerability to neglected diseases. For example, the status of women in many countries, including their lack of ownership of resources, affects their access to prevention and treatment and means they may well be more vulnerable to stigma and the impact of stigma.

In any society, different roles are assigned to men and women as a result of either culture or religion. This disproportionately affects the extent to which men and women and boys and girls are exposed to and infected by any of the NTDs being discussed and shapes whether infected patients experience enacted (a discriminatory experience as a result of being labelled with a disease) or felt stigma (an imagined social reaction that can change a person's identity) (Crinson 2007). It also affects their perception and health care-seeking behaviour in the event the disease.

Allotey and Gyapong (2005) argue that all functioning societies are built on the abilities of individual members to adopt specific roles and responsibilities. The roles that are assigned to males and females by culture and society, how they are played out and how they relate to each other at the individual and broader sociopolitical levels are described by the concept of gender. That there are gender differences is not in dispute; the problem arises with the different values placed on the various roles and responsibilities and the consequences of this in creating and sustaining disadvantage and inequities. Gender roles and relations shape how individuals and societies operate, the effects of the disadvantage created, and permeate all aspects of life, from production, allocation and distribution of resources to exposure to disease and health-promoting services.

But does all this add value to health-related outcomes, and do these need to be addressed in responses to NTDs? At the very least, retaining a gender focus on any agenda provides information on new ways of approaching health issues and identifying points for specific interventions to address specific issues. On the basis of the conventional health indicators provided through quantitative methodologies, current data are not strong enough to support a definitive response. Data quality are poor and often draw largely on biassed samples; sex disaggregated data are often

not available and, when available, are not always used to inform responsive policy. In addition, qualitative data usually focuses on women without reference to the interaction with men within their societies or the dynamics of gender relations. There is little information to proffer explanations of gender differences from male perspectives.

It must be noted that in spite of cultural or religious diversity, the expression or experience of stigma is similar worldwide. It affects mobility, interpersonal relationships, marriage, employment, leisure activities and attendance at social and religious functions, and the depth and detail of how stigma is experienced is linked to gender, roles, relations and expectations (Van Brakel 2003).

In the case of sleeping sickness and leishmaniasis, men generally tend to contract the disease more than women probably as a result of occupational hazards and general exposure to the vector; however, women tend to be more stigmatised from the consequences of contracting the disease and can experience complications such as amenorrhea, infertility and miscarriage (WHO 2010a).

In the DRC, women appeared to be more knowledgeable about the disease than men due to their role as caregivers which means they are more exposed to health education messages when they send sick family members to a health facility (Pépin et al. 2002; Mpanya et al. 2012). Within this context, having sexual relations when one has the condition is a taboo, and gendered norms mean that women have to leave their matrimonial homes to avoid sex whilst their male counterparts seek other women for sexual interactions (Mpanya et al. 2012).

Both men and women are susceptible and probably equally infected by onchocerciasis, schistosomiasis, soil-transmitted helminths and sleeping sickness with women suffering more of the consequences during pregnancy as a result of anaemia and iron deficiency due to heavy infection (WHO 2010a).

Urogenital schistosomiasis also referred to as female or male genital schistosomiasis (FGS and MGS) is common in Africa. Adolescent girls and women with FGS can experience bleeding and unpleasant discharge from the vagina, genital lesions and nodules in the vulva general discomfort and pain during sex. FGS is a cause of subfertility and miscarriage and can affect vulnerability to HIV and the human papillomavirus, all of which arguably have wide-reaching social and economic consequences, although how women experience symptoms indicative of FGS, their treatment-seeking pathways and the impact on their livelihoods and well-being are poorly understood. Symptoms of MGS in adolescent boys and men include bleeding and egg deposition within semen, yellow discoloration in semen and lumpy semen, the implications of which are poorly understood (Mbabazi et al. 2011).

FGS and MGS are sensitive, private and possibly stigmatising conditions. Messaging therefore needs to be geared to the realities of females' and males' gendered experiences. This requires in-depth qualitative research to explore the context and community discourse surrounding FGS and MGS symptoms and the development of appropriate referral and treatment strategies that are accessible to all women and girls and men and boys, regardless of where they live or how much money or resources they can access.

Although the prevalence of lymphoedema and elephantiasis is higher in women than in men when hydrocele is taken into consideration, more adult men than women appear to have severe chronic consequences of lymphatic filariasis. The consequent disfigurement results in the infected person experiencing stigma, social and psychological distress with women having a far less chance of finding a spouse than men and suffering more problems and general discrimination (WHO 2010a, b).

Clemmons et al. (2002) report that with regard to decision making for MDA for onchocerciasis control, men are the key decision makers. Women are not invited to meetings where issues are discussed and are not given feedback on the major decisions taken. They are informed about CDTI activities by word of mouth just before drug distribution. There are also gender differences in community-based providers: in this context relatively few ivermectin distributors (21 %) are women. Although they receive less support than their male counterparts, female distributors are just as willing to continue ivermectin distribution in the community, and they perform as well or better than men in this regard (Stienstra et al. 2002).

The perception in the Ashanti region of Ghana is that more women have Buruli ulcer than men because of prostitution. However, like lymphatic filariasis, both sexes appear to be equally discriminated against since they are avoided in public places due to fear of contracting the disease, have less chance of being appointed into leadership positions and have problematic marriages and less chance of getting a spouse (Stienstra et al. 2002). Breiger et al. (1998), in their study in Nigeria, documented some issues around stigma related to onchocerciasis from individual survey respondents. Examples of responses are as follows:

> "I am embarrassed because my whole body is covered with Onchocerciasis", It is shameful for having tough skin like a frog", "I am embarrassed because it has destroyed my body", "I am ashamed when it itches me in the midst of a crowd", "It embarrasses me" "I use a long wrap whenever I go out", "It causes disrespect when one scratches in public" "People laugh at him", "People won't want to be close to someone with Onchocerciasis", "Onchocerciasis leads to disrespect because it causes blindness and destroys the skin".

All these expressions, the ways in which perceived and enacted stigma are experienced, depict physical, mental and social attributes, self-hate, self-depravation and lack of social acceptance and stress of illness experience as described by Goffman (1963). The complex ways in which stigma is experienced affect health care-seeking behaviour in many ways. Weiss (2008) suggests some key interventions to address stigma. These are (1) support, (2) enactment of laws and (3) awareness creation in order to challenge sociocultural norms and behaviour.

The Quest for Therapy in the Event of NTDs

Over the last 10 years or so, there have been important advances in the development of diagnostics and massive support from pharmaceutical companies to supply drugs for the treatment of the NTDs. Available treatments are either for free or cost less than a dollar a day, and studies have shown that an integrated MDA using a combination of medicines to prevent or treat the seven most prevalent NTDs yields the best return (Hotez et al. 2007a).

With the exception of guinea worm, the NTDs being discussed in this book can be effectively treated with drugs and the majority through mass drug administration (MDA), provision of clean water, vector control and proper sanitation. Through health education and massive campaigns, NTD control programmes in sub-Saharan Africa have succeeded in treating people over many years; however, the response to attempts at treatment and control varies from disease to disease and depends on the approach used. In the DRC, low attendance at screening sessions for human African trypanosomiasis (HAT) was attributed to, amongst other things, mistrust of mobile team nurses (who were perceived to leave the disease in people's blood with the use of injections), unannounced arrival of staff for screening exercises, fear of lumbar punctures, fear of unsolicited HIV/AIDS tests, other economic priorities and the lack of confidentiality during the screening procedure itself (Mpanya et al. 2012). Side effects, the timing of MDA, the type and attitude of the distributor (community distributor or health worker) and experience with adverse events have also affected MDA for lymphatic filariasis and onchocerciasis, although the expelling of worms after drug administration has been found to be a motivating factor (Abanobi et al. 2011; Abd Elaziz et al. 2013; Babu and Babu 2014; Gyapong et al. 2000b).

People with limited resources, particularly those living in rural areas, invariably seek medical help first from the least expensive, closest and most trusted sources. Treatment may also be sought simultaneously or sequentially before going to a hospital. The first time a person experiences a feeling of being unwell, they ask what is wrong, and then often they will deploy the wait and see what happens next approach. As soon as the condition is prolonged for longer than expected, the "why" questions begin to set in. Why is this happening to me or my family or that person at this time and what can be done about it? This leads to a quest for therapy as described by Kleinman (1980) and Helman (1981) where people irrespective of their socio-economic, religious or cultural background seek traditional and cosmopolitan care simultaneously. Kleinman propounds that when a person is sick, there are three interlinked health sectors that are available for use: popular, folk and professional sectors. In all societies these sectors are available and create a pluralistic health care system with a wide range of options for care seekers to choose from in times of ill health. The popular sector is usually the first point of call and is usually at the home level where advice is sought from relatives and friends. Communities and parents' past experience informs practice at this stage: for example, self-medication is practised with leftover drugs from the home and drugs borrowed from friends or purchased from local drug shops. Conditions like hot body, chills, general

discomfort and malaria, which are considered mild, are dealt with easily within this sector. The folk sector has the more traditional type of healing, and treatment is sought from traditional healers, spiritualists, faith healers, herbalists and traditional birth attendants. This sector can be visited as a first option but in most cases are contacted when the first health-seeking attempt within the household or community does not work. However, the popular and folk sectors may be used concurrently. The professional sector is the more formal sector that has people with formal professional training like doctors, nurses and pharmacists. Others however may rush or be rushed directly to a health facility depending on what they perceived to be the cause of their condition. Due to cost and other factors, it may be the last point of call when all other options have failed by which time the condition would have progressed severely (Fig. 1).

In Benin, Buruli ulcer patients can access home treatments (salves, antibiotics and analgesics), traditional medicine (herbs, divination, incantations) and hospital treatments. Over 70 % of patients interviewed at home and in hospital used traditional and hospital medicine interchangeably (Peeters Grietens et al. (2012). The availability of a pluralistic health care system in African settings, the cost of care, fear of stigma and "mutilation" after treatment are some of the reasons for delay in seeking health care. Interestingly the perceived cause of the disease did not contribute to a delay in care seeking for Buruli ulcer patients in Cameroon (Stienstra et al. 2002). Similarly in the Greater Accra and Ashanti Regions of Ghana, Buruli patients had multiple sources of care available to them and acted in the same way as their counterparts in Benin and Cameroon, applying salves to their nodules and "boils" at

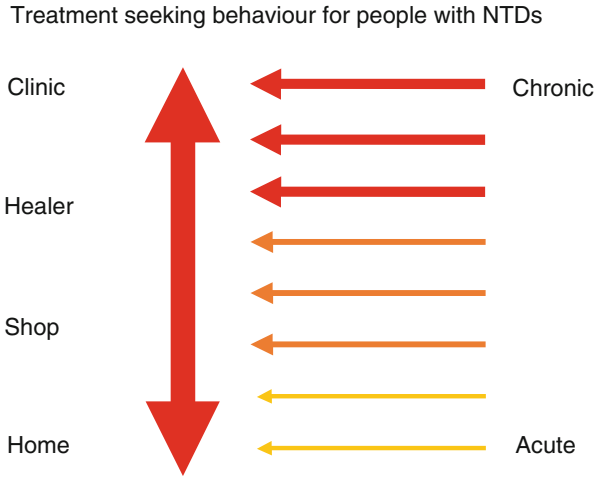


Fig. 1 Treatment-seeking pathway for NTDs (Source: Gyapong and Theobold, unpublished data). A patient suffering from, for example, elephantiasis, has multiple options available for seeking health care which they will use simultaneously depending on what they perceive to be the cause of their problem, what they can afford, what they believe in or advise/pressure from family and friends

home, seeking treatment from a traditional healer and then finally using the hospital as a last resort (Renzaho et al. 2007; Stienstra et al. 2002).

The Economic Impact of Having NTDs

Apart from the physical and psychological suffering caused by NTDs to people in endemic societies, the disease also inflicts an enormous economic burden on the individual, the household, the community and the society at large. For many sufferers, there is a loss of productivity, school absenteeism and high costs from long-term stay in formal and non-formal health care institutions which further exacerbate the entrenched cycle of poverty and ill health for disadvantaged populations (Hunt et al. 2007).

Globally, the burden of disease concept first published by Murray and Lopez (1996) has been used to quantify the burden of premature mortality and disability for major diseases or disease groups. The NTD burden is expressed through disability-adjusted life years (DALYs) that is the years of healthy life lost because of disability or premature death. NTDs constitute the fourth largest disease burden of all communicable diseases and account for 46–57 million DALYs lost (Murray and Lopez 1996; Hotez 2009). NTDs in sub-Saharan Africa (SSA) account for the highest DALY lost affecting about 21.2 million people (Hotez and Kamath 2009).

Hotez and Kamath (2009) estimated DALYs for STH infections and schistosomiasis by adjusting ranges of global estimates according to the percentage of the total number of cases that occur in SSA. Other NTD burdens were quoted directly from WHO estimates. From their analysis, they determined that the total burden of NTDs in SSA is as high as one-half of the disease burden caused by malaria and twice the disease burden caused by tuberculosis in SSA, suggesting that NTDs represent a formidable public health challenge in the region (Hotez and Kamath 2009).

Studies show that the burden of lymphatic filariasis is likely to be underestimated due to stigma, where an affected individual avoids public life and may abandon work (Norris et al. 2012). A study by Gyapong et al. (1996b) in northern Ghana found the mean duration of an ADL episode to be 5.1 days and the mean period of total incapacitation to be about 3 days. This affects family income negatively especially during the rainy season when these subsistent farmers need to be on their farms to till their lands. Marginalised populations are the most affected, and already impoverished, and the impacts of NTDs are likely to be catastrophic. The figures on DALYs – presented above in Table 2 – do not capture or reflect the impact of illness and health care seeking on individuals and households, and this needs to be better understood in order to develop more responsive health services. It is estimated that with chronic conditions, an acute episode of the disease can cause an individual to lose up to 5 days of work per episode (Norris et al. 2012). More than half of Guinea worm patients are unable to leave their beds for about a month, which generally coincides with the peak season of agricultural activities, when labour is in maximum demand. This can lead to malnutrition amongst children in households whose able members are affected. For this reason, in Mali the disease is tellingly called “the disease of the empty granary”. Children miss school

Table 2 Disease burden (DALYs) in sub-Saharan Africa resulting from NTDs

Disease	Estimated global disease Burden in DALYs	Estimated % disease Burden in SSA (%)	Estimated SSA disease Burden in DALYs	Reference
Hookworm	1.5–22.1 million	34	0.5–7.5 million	Hotez et al. (2008) and Bethony et al. (2006)
Schistosomiasis	1.7–4.5 million	93	1.6–4.2 million	WHO (2004) and Hotez et al. (2008)
Ascariasis	1.8–10.5 million	21	0.4–2.2 million	Hotez et al. (2008) and Bethony et al. 2006
Lymphatic filariasis	5.8 million	35	2.0 million	WHO (2004)
Trichuriasis	1.8–6.4 million	27	0.5–1.7 million	Hotez et al. (2008) and Bethony et al. 2006
Human African trypanosomiasis	1.5 million	100	1.5 million	WHO (2004)
Trachoma	2.3 million	52	1.2 million	WHO (2004)
Onchocerciasis	0.5 million	99	0.5 million	WHO (2004)
Leishmaniasis	2.1 million	18	0.4 million	WHO (2004)
Leprosy	0.2 million	14	0.02 million	WHO (2004, 2008)
Dengue	0.6 million	<1	0.005 million	WHO (2004)
Total NTDs	≤56.6 million	15–37	8.6–21.2 million	Hotez et al. (2008)

Source: Hotez and Kamath (2009)

when they have guinea worm and when they substitute for sick members of their households (Ruiz-Tiben and Hopkins 2006: 275–309). A study in Ghana indicates that caregivers and adult patients lost a total of 535 productive days seeking Buruli ulcer care and school-going children lost 365 days to the disease and confirms that its treatment poses significant 45 % economic burden on households (Amoakoh and Aikins 2013).

According to WHO, about 65 % of the global infection of lymphatic filariasis occurs in Southeast Asia (WHO 2013e). India alone spent an average of $1 billion every year on lymphatic filariasis as a result of treatment and productivity lost (WHO 2013; Chu et al. 2010; Norris et al. 2012). The treatment cost within an endemic population is estimated to cost $2 lost per patient per year, and a single dose of treatment per year costs $0.03 per person (Chu et al. 2010; Norris et al. 2012; Ramaiah et al. 2000). In Ghana the average cost of treating Buruli ulcer was estimated to be US$ 780 per patient during 1994–1996, an amount that was greater than the per capita that the government earmarked on health. In 2008 the disease accounted for 25 % of households' yearly earnings on hospitalisation costs in Cameroon, whilst the median total cost of hospital treatment was identified as

€126.70 in the same country (WHO 2013a). An indirect cost valued at US$1,378.67 with a mean of US$21.88 for Buruli ulcer was identified as a cost burden to a household member with the disease in Ghana (Amoakoh and Aikins 2013).

Discussion

NTDs are diseases of poverty and are themselves impoverishing, disproportionally affecting people living in poor or marginalised communities. Hotez (2009) and Person et al. (2009) suggest that women are often particularly isolated and marginalised by stigma-associated NTDs. These diseases play out in multiple ways and across the generations. Children, for example, are withdrawn from school due to financial constraints on older people with disabilities. Vulnerability to different NTDs, ability to access treatment and social and economic impact of NTDS affect different people in multiple ways, and this in turn is dependent on contextual factors. There is a real need for intersectionality (Tolhurst et al. 2012) and approaches that analyse the interplay between gender, poverty, ethnicity, disability, sexuality, religion and age. Additionally adopting an intersectional approach is useful in terms of influencing policy as it provides an inclusiveness, which is often missing when health policies are developed.

There is clear and complex disconnect between biological cause/medical model explanation and social understanding and aetiology of disease. What is important for health promotion is that dialogue needs to be tailored to the understandings and realities of different communities. This is not straightforward, but community-embedded cadres such as community health workers and community-based drug distributors have embedded knowledge that can support interventions. The focus for action needs to go beyond community messaging, to ensure that resilient health systems are developed that are responsive to the needs and realities of socially and economically disenfranchised citizens.

There is also need for qualitative research. The value of qualitative research to better understand the lived realities of affected communities as well as the ability and challenges faced by health systems to appropriately address these is often overlooked when addressing NTDs. However, increasingly those working on NTDs are aware there is a gap in data, which can only be filled by research methods which enable the depth and detail of affected communities and health providers' experiences and challenges to be better understood. For example, through qualitative and participatory approaches, the needs and priorities of frontline providers and volunteers can be documented to ensure these feed into policy and practice to support sustainable and equitable human resource strategies for integrated NTD control.

The social and economic impacts of NTDs go beyond the health sector.

- There is a need for intra- and inter-sectoral action, i.e. links within the health sector itself as well as between the health sector and other sectors like education, agriculture and sanitation. For example, action to address FGS will require new

partnerships within the health sector between NTDs and maternal and sexual and reproductive health as well as strategies at the community level to build links with relevant formal or informal providers (e.g. women who might seek help in the case of infertility).
- New partnerships beyond the health sector, for example, with Ministries of Education, and Gender, Youth and Community Services will be essential in any discussions or action on FGS. Generating and making evidence on interventions that work need to be accessible to stakeholders who should use it in the course of their work, which requires new ways of working together within and across sectors and with stakeholders.
- Poverty alleviation actions are also necessary to address the catastrophic social and economic effects of NTDs on women and men and girls and boys.

Conclusion

In a time when maintaining the integrity of the art of medicine is of critical importance, we are instead witnessing its devaluation due to the current counterposing forces in health care. Disease has become the focus of the technologic and market-driven medical system, whilst illness and the sociocultural aspects of medicine have blurred into the background. Yet, the healing tools and instruments of science are blunt and ineffective when used blindly in ignorance of the complex meaning and context of a patient's illness and the impact of this on their livelihoods and well-being. We need to foster attitudes, values and communication skills that focus on illness, not just disease, to prepare ourselves for the challenges ahead.

Acknowledgement The authors wish to acknowledge Profs. Pascale Allotey of Monash University, Sally Theobold and Russel Stothard of the Liverpool School of Tropical Medicine and Dr. Bertha Garshong of the Research and Development Division of the Ghana Health Service for their comments and inputs into this chapter.

References

Abanobi O, Chukwuocha U, Onwuliri C, Opara K (2011) Primary motives for demand of Ivermectin drug in mass distribution programs to control Onchocerciasis. N Am J Med Sci 3(2):89–94

Abd Elaziz Khaled M, El-Setouhy M, Bradley MH, Ramzy RMR, Weil G (2013) Knowledge and practices related to compliance with Mass Drug Administration during the Egyptian National Filariasis Elimination Program. Am J Trop Med Hyg 89(2):260–264

Ahorlu CK, Dunyo SK, Koram KA, Nkrumah FK, Agaard- Hansen J, Simonsen PE (1999) Lymphatic filariasis perceptions and practices on the coast of Ghana: implications for prevention and control. Acta Trop 73(3):251–261

Ajanga A, Lwambo NJ, Blair L, Nyandindi U, Fenwick A, Brooker S (2006) Schistosoma mansoni in pregnancy and associations with anaemia in northwest Tanzania. Trans R Soc Trop Med Hyg 100(1):59–63

Allotey P, Gyapong M (2005) The gender agenda in the control of tropical diseases: a review of current evidence. TDR/STR/ SEB/ST/05.1

Amoakoh HB, Aikins M (2013) Household cost of out-patient treatment of Buruli ulcer in Ghana: a case study of Obom in Ga South Municipality. BMC Health Serv Res 13(1):507

Aninakwah-Boahene D, Apraku A, Adu-Kumi M (2014) Perception of inhabitants in Bui Township on causes and effects of Onchocerciasis, Ghana. Int J Sci Technol Res 3(4): 328–331

Babu BV, Babu GR (2014) Coverage of and compliance with mass drug administration under the program to eliminate lymphatic filariasis in India: a systematic review. Trans R Soc Trop Med Hyg 108(9):538–549

Babu BV, Mishra S, Nayak AN (2009) Marriage, sex, and hydrocele: an ethnographic study on the effect of filarial hydrocele on conjugal life and marriageability from Orissa, India. PLoS Negl Trop Dis 3(4):e414

Bethony J, Brooker S, Albonico M, Geiger SM, Loukas A, Diemert D, Hotez PJ (2006) Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet 367(9521):1521–1532

Bierlich B (1995) Notions and treatment of guinea worm in northern Ghana. Soc Sci Med 41(4):501–509

Bleakley H (2007) Disease and development: evidence from hookworm eradication in the American South. Q J Econ 122(1):73

Brieger WR, Oshiname FO, Ososanya OO (1998) Stigma associated with onchocercal skin disease among those affected near the Ofiki and Oyan Rivers in western Nigeria. Soc Sci Med 47(7):841–852

Brooker S, Clements AC, Hotez PJ, Hay SI, Tatem AJ, Bundy DA, Snow RW (2006) The co-distribution of Plasmodium falciparum and hookworm among African schoolchildren. Malar J 5(1):99

Carson (2009) Scottish Accessible Information Forum (SAIF). ISBN 9780114973490

Chu BK, Hooper PJ, Bradley MH, McFarland DA, Ottesen EA (2010) The economic benefits resulting from the first 8 years of the Global Programme to Eliminate Lymphatic Filariasis (2000–2007). PLoS Negl Trop Dis 4(6):e708

Clemmons L, Amazigo UV, Bissek AC, Noma M, Oyene U, Ekpo U, Seketeli A (2002) Gender issues in the community-directed treatment with ivermectin (CDTI) of the African Programme for Onchocerciasis Control (APOC). Pathog Glob Health 96(Suppl 1):S59

Crinson I (2007) Concepts of health and illness section 3, labelling and stigma. Health knowledge. Education, CPD and revalidation from public health action support team 2011 Department of Health UK. http://www.healthknowledge.org.uk/. Accessed 16th Jul 2015

Death and DALY estimates for 2002 by cause for WHO Member States. Geneva, World Health Organization, 2004 (http://www.who.int/evidence/ bod).

Desmond N, Solomon AW, Massae PA, Lema N, Anemona A, Foster A, Mabey DC (2005) Acceptability of azithromycin for the control of trachoma in Northern Tanzania. Trans R Soc Trop Med Hyg 99(9):656–663

Eisenberg L (1977) Disease and illness distinctions between professional and popular ideas of sickness. Cult Med Psychiatry 1(1):9–23

Fenwick A (2006) New initiatives against Africa's worms. Trans R Soc Trop Med Hyg 100(3):200–207

Fenwick A, Molyneux D, Nantulya V (2005) Achieving the millennium development goals. Lancet 365(9464):1029–1030

Goffman E (1963) Stigma Englewood Cliffs. Spectrum, NJ

Green AR, Carrillo JE, Betancourt JR (2002) Why the disease-based model of medicine fails our patients. West J Med 176(2):141

Gyapong M, Gyapong JO, Adjei S, Vlassoff C, Weiss M (1996a) Filariasis in Northern Ghana: some cultural beliefs and practices and implications for disease control. Soc Sci Med 43(2):235–242

Gyapong JO, Gyapong M, Evans DB, Aikins MK, Adjei S (1996b) The economic burden of lymphatic filariasis in northern Ghana. Ann Trop Med Parasitol 90:39–48
Gyapong M, Gyapong J, Weiss M, Tanner M (2000a) The burden of hydrocele on men in northern Ghana. Acta Trop 77(3):287–294
Gyapong M, Gyapong J, Owusu Banahene G (2000b) Community directed treatment for filariasis control in Ghana. Ann Trop Med Parasitol 95(1):77–86
Helman CG (1981) Disease versus illness in general practice. Br J Gen Pract 31(230):548–552
Heynders ML (2002) Understanding adherence in leprosy. PhD thesis. South Bank University, London
Hotez PJ (2009) Devastating global impact of neglected tropical diseases. Internet c2009 August cited 2010 May 1. Microbe Magazine
Hotez PJ, Kamath A (2009) Neglected tropical diseases in sub-Saharan Africa: review of their prevalence, distribution, and disease burden. PLoS Negl Trop Dis 3(8):e412
Hotez PJ, Brindley PJ, Bethony JM, King CH, Pearce EJ, Jacobson J (2008) Helminth infections: the great neglected tropical diseases. J Clin Invest 118(4):1311–1321
Hotez PJ, Molyneux DH, Fenwick A, Kumaresan J, Sachs SE, Sachs JD, Savioli L (2007a) Control of neglected tropical diseases. N Engl J Med 357(10):1018–1027
Hotez PJ, Molyneux DH, Fenwick A, Ottesen E, Sachs SE, Sachs JD (2007b) Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria. PLoS Med 3(5):576
Hotez PJ, Fenwick A, Savioli L, Molyneux DH (2009) Rescuing the bottom billion through control of neglected tropical diseases. Lancet 373(9674):1570–1575
Hunt P, Stewart R, Bueno de Mesquita J, Oldring L (2007) Neglected diseases: a human rights analysis. The World Health Organization and TDR (Special topics in social, economic and behavioural research report series; no. 6), "TDR/SDR/SEB/ST/07.2"
Hyland JE (1993). A socio-cultural study of leprosy in Nepal: compliance, patient illness career patterns and health education (Doctoral dissertation, University of Tasmania)
Kleinman A (1980) Patients and healers in the context of culture: an exploration of the borderland between anthropology, medicine, and psychiatry, vol 3. Univ of California Press, Berkeley
Mbabazi PS, Andan O, Fitzgerald DW, Chitsulo L, Engels D, Downs JA (2011) Examining the relationship between urogenital schistosomiasis and HIV infection. Carvalho EM (ed). PLoS Neglected Tropical Diseases. 5(12):e1396. doi:10.1371/journal.pntd.0001396
Molyneux DH, Hotez PJ, Fenwick A (2005) "Rapid-impact interventions": how a policy of integrated control for Africa's neglected tropical diseases could benefit the poor. PLoS Med 2(11):1064
Mpanya A, Hendrickx D, Vuna M, Kanyinda A, Lumbala C, Tshilombo V, Lutumba P (2012) Should I get screened for sleeping sickness? A qualitative study in Kasai province, Democratic Republic of Congo. PLoS Negl Trop Dis 6(1):e1467
Murray CJ, Lopez AD (1996) The Global Burden of Disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020. Cambridge, MA, Harvard School of Public Health. Global Burden of Disease and Injury Series, vol. 1
Norris J, Adelman C, Spantchak Y, Marano K (2012) Social and economic impact review on neglected tropical diseases, Economic Policy/Briefing Paper. Hudson Institute, Washington, DC
Peeters Grietens K, Toomer E, Um Boock A, Hausmann-Muela S, Peeters H, Kanobana K, Muela Ribera J (2012) What role do traditional beliefs play in treatment seeking and delay for Buruli ulcer disease?–insights from a mixed methods study in Cameroon. PLoS One 7(5):e36954
Pépin J, Mpia B, Iloasebe M (2002) Trypanosoma brucei gambiense African trypanosomiasis: differences between men and women in severity of disease and response to treatment. Trans R Soc Trop Med Hyg 96(4):421–426
Perera M, Whitehead M, Molyneux D, Weerasooriya M, Gunatilleke G (2007) Neglected patients with a neglected disease? A qualitative study of lymphatic filariasis. PLoS Negl Trop Dis 1(2):e128

Person B, Bartholomew LK, Gyapong M, Addiss DG, van den Borne B (2009) Health-related stigma among women with lymphatic filariasis from the Dominican Republic and Ghana. Soc Sci Med 68(1):30–38
Ramaiah KD, Das PK, Michael E, Guyatt HL (2000) The economic burden of lymphatic filariasis in India. Parasitol Today 16(6):251–253
Renzaho A, Woods PV, Ackumey MM, Harvey SK, Kotin J (2007) Community based study on knowledge, attitude and practice on the mode of transmission, prevention and treatment of Buruli ulcer in Ga West District, Ghana. Trop Med Int Health 12(3):445–458
Rodrigues LC, Lockwood DN (2011) Leprosy now: epidemiology, progress, challenges, and research gaps. Lancet Infect Dis 11(6):464–470
Roueche B (1986) A lonely road (chapter 5). The medical detectives, volume II. Washington Square Press, Pocket Books, New York
Ruiz-Tiben E, Hopkins DR (2006) Dracunculiasis (Guinea worm disease) eradication. Adv Parasitol 61:275–309
Sachs JD (2008) Commonwealth economics for a crowded planet. The Penguin Press, New York
Scambler G (1998) Stigma and disease: changing paradigms. Lancet 352(9133):1054–1055
Sisay GT (2012) Perceptions and experiences of people in Gambella region of Ethiopia on Guinea worm disease eradication interventions. Thesis submitted in partial fulfillment of Msc in Public health. http://uir.unisa.ac.za/xmlui/bitstream/handle/10500/10002/dissertation_sisay_gt.pdf?sequence=1
Stienstra Y, van der Graaf WT, Asamoa K, van der Werf TS (2002) Beliefs and attitudes toward Buruli ulcer in Ghana. Am J Trop Med Hyg 67(2):207–213
Tolhurst R, Leach B, Price J, Robinson J, Ettore E, Scott-Samuel A, Kilonzo N, Sabuni P, Robertson S, Kapilshrami A, Bristow B, Lang R, Romao F, Theobald S (2012) Intersectionality and gender mainstreaming in international health: using a feminist participatory action research process to analyse voices and debates from the global south and north. Soc Sci Med 74:1825–1832
United Nations Special Rapporteur (2003) para. 59
Van Brakel WH (2003) Measuring leprosy stigma-a preliminary review of the leprosy literature. Int J Lepr Other Mycobact Dis 71(3):190–197
Weiss MG (2008) Stigma and the social burden of neglected tropical diseases. PLoS Negl Trop Dis 2(5):e237
WHO (2010a) Working to overcome the global impact of Neglected Tropical Diseases. First WHO NTD report on Neglected Tropical Diseases
World Health Organization (2010b) Preventive chemotherapy and transmission control databank. World Health Organization, Geneva
World Health Organisation (2012) WHO Fact sheet 101
World Health Organisation (2013a) WHO Fact sheet 199
World Health Organisation (2013b) WHO Fact sheet 359
World Health Organisation (2013c) WHO Fact sheet 259
World Health Organisation (2013d) WHO Fact sheet 375
World Health Organisation (2013e) WHO Fact sheet 102
World Health Organisation (2013f) WHO Fact sheet 374
World Health Organisation (2013g) WHO Fact sheet 115
World Health Organisation (2013h) WHO Fact sheet 366
World Health Organisation (2015) WHO Fact sheet 366
Yokotani K (2001) Promoting inclusive education in Neluwa, a tea plantation area in Sri Lanka, through the community based rehabilitation programme. Unpublished master's thesis). University of Sussex
Zhang Y, MacArthur C, Mubila L, Baker S (2010) Control of neglected tropical diseases needs a long-term commitment. BMC Med 8(1):67

Alternative Interventions Against Neglected Tropical Diseases in SSA: Vector Control

Daniel Boakye, Dziedzom de Souza, and Moses Bockarie

Contents

Abstract Vector control is one of the strategies recommended by World Health Organization for the control and prevention of the neglected tropical diseases (NTDs) apart from preventive chemotherapy, intensified case management, provision of safe water, sanitation and hygiene, and veterinary public health. Although an integrated approach based on a combination of strategies or one strategy

D. Boakye (✉) • D. de Souza
Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Ghana
e-mail: DBoakye@noguchi.ug.edu.gh

M. Bockarie
Liverpool School of Tropical Medicine, University of Liverpool, Liverpool, UK

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_16

targeting a group of diseases is the preferred approach, the current policy for the global elimination of most of the NTDs is based solely on chemotherapy (Molyneux, Adv Parasitol 61:1–45, 2006; Uniting To Combat NTDs, Delivering on promises & driving progress. Available: http://unitingtocombatntds.org/report/delivering-promises-driving-progress-second-report-uniting-combat-ntds [Online]. Accessed 16 May 2014, 2014). Dependance on preventive chemotherapy alone without measures to control vectors and intermediate hosts, vector-borne NTDs like LF and onchocerciasis may not achieve the expected outcome (Bockarie et al., Ann Rev Entomol 54:469–487, 2009) in the set targeted time frame. Vector control has the potential to play a very important role in the control of NTDs and is increasingly becoming a supplementary intervention strategy. However, it requires the commitment of resources, both financial and human, from disease control programs. There is the need for integration at all levels, while adopting the WHO policy guidelines on IVM. Although vector control has been shown to be an effective strategy for the control of vector-borne NTDs (Bockarie et al., Ann Rev Entomol 54:469–487, 2009; Townson et al., Bull World Health Org 83:942–947, 2005), it is faced with some challenges, major among which are insecticide resistance, multiplicity of vector species, changes in vector behavior, and cost. Further research on insecticide resistance and the effect of vector control on one disease, as, for example, malaria vector control on lymphatic filariasis, is still required.

Introduction

Vector control is one of the strategies recommended by World Health Organization for the control and prevention of neglected tropical diseases (NTDs). The others are preventive chemotherapy, intensified case management, provision of safe water, sanitation and hygiene, and veterinary public health. An integrated approach based on a combination of strategies or one strategy targeting a group of diseases is the preferred approach. However, the current policy for the global elimination of most of the NTDs is based solely on chemotherapy especially if there are drugs that can be given to populations at risk [preventive chemotherapy] (Molyneux 2006; Uniting to Combat NTDs 2014). The generous commitments by industry have led to increased availability of drugs for onchocerciasis (Merck & Co., Inc.), lymphatic filariasis (Merck & Co., Inc., GlaxoSmithKline (GSK), and Eisai), and schistosomiasis (Merck KGaA). Dependance on preventive chemotherapy alone for vector-borne NTDs like LF and onchocerciasis may not achieve the expected outcome, looking particularly at the targeted timeframe, if measures to control vectors and intermediate hosts are not considered (Bockarie et al. 2009). Therefore, vector control is increasingly becoming a supplementary intervention strategy. The transmission efficiency of many vector-borne NTDs is poor and the vector-parasite relationship

fragile for Chagas disease, human African trypanosomiasis, onchocerciasis, and lymphatic filariasis.

Vector-Borne Diseases

Vector-borne diseases are those in which the causative pathogens are transmitted between hosts by vector species, mostly arthropods (mosquitoes, sandflies, blackflies, fleas, ticks, flies) but also other organisms such as snails. Vector-borne diseases include some of the most important ailments that have plagued mankind since antiquity. For example, plague (*Yersinia pestis*) transmitted by fleas decimated populations in the Middle Ages, and louse-borne fever had a major impact on armies, for example, the Spanish in 1489, the French in 1528, contributed to Napoleon's retreat from Moscow in 1812, and the death of millions of soldiers and civilians in World War 1 (Pierce 1974; Raoult et al. 2004). Thus, vector-borne diseases represent an important threat to human health, causing severe morbidity and mortality (Varmus et al. 2003; Hill et al. 2006). It has been estimated that vector-borne diseases are responsible for 17 % of the global burden of diseases (WHO 2008) and about 10 % of human deaths (WHO 2011; Rascalou et al. 2012), while contributing significantly to the vicious cycle of poverty by imposing an annual burden of more than 50 million disability-adjusted life years [DALYs] (Gold et al. 2002; WHO 2011; Rascalou et al. 2012). The most important vector-borne disease of all times is malaria (WHO 2011).

The distribution of vector-borne diseases is worldwide. For example, exposure to vector-borne helminths such as *Dirofilaria immitis* is reported to be about 45 % of the total European population (Otranto et al. 2013). Other vector-borne infections like leishmaniasis, onchocerciasis, malaria, and yellow fever, among many, are found mostly in tropical and sub-tropical parts of the world.

Vector-borne diseases particularly those found in tropical and sub-tropical areas promote poverty and impair education and economic development. Some of them such as malaria cause high mortalities, others result in epidemics with high fatality rates, and many cause immense suffering and lifelong disabilities. However, many of the vector-borne diseases together with some other infections apparently do not cause high mortalities such as HIV or TB or malaria and often do not receive the attention they deserve and most often neglected.

The neglected tropical diseases (NTDs) are a group of diseases of different etiology that affects hundreds of millions of people worldwide mostly the poor and developing economies but sometimes also found in the developed world, for example, in the United States (Hotez 2008). Although there are more than 20 diseases that would qualify as neglected in the amount of funds spent on their control, research etc., the World Health Organization officially recognizes 17 of these (Table 1) as the major NTDs.

Table 1 List of officially recognized NTDs by the World Health Organization

Diseases	Vectors	References
Buruli ulcer	Aquatic insects?	Johnson et al. (2007), Marsollier et al. (2002), Portaels et al. (1999)
Schistosomiasis	Snails (*Biomphalaria sp.*, *Bulinus sp.*, *Oncemalania sp.*)	Mandahl-Barth (1965), Morgan et al. (2001), Woodruff et al. (1999)
Dracunculiasis (guinea worm diseases)	Cyclops	Muller (1991), Yelifari et al. (1997)
Onchocerciasis (river blindness)	Blackflies (*Simulium sp.*)	Boakye et al. (1998), Brown (1962)
Lymphatic filariasis	Mosquitoes (*Anopheles sp.*, *Aedes sp.*, *Culex sp.*, *Mansonia sp.*, *Ochlerotatus sp.*)	Zagaria and Savioli (2002), WHO (2013)
Soil-transmitted helminthiasis	–	–
Dengue and severe dengue	*Aedes sp.*	Higa (2011), WHO (2009)
Foodborne trematodiasis	–	–
Rabies	–	–
Trachoma	*Musca sorbens*	Emerson et al. (1999)
Leprosy	–	–
Leishmaniasis	Sandflies (*Phlebotomus sp.*, *Sergentomyia* sp.)	Claborn (2010), Peters and Killick-Kendrick (1987)
Yaws	–	–
Taeniasis/cysticercosis	–	–
Chagas disease	Triatomine bugs	Lent and Wygodzinsky (1979), Ramsey and Schofield (2003)
Echinococcosis	–	–
Human African trypanosomiasis (sleeping sickness)	Tsetse fly (*Glossina sp.*)	Scott (1959), Gouteux (1990)

The Transmission of NTDs

Of the 17 officially WHO recognized NTDs, the transmission of the causative pathogens of eight are directly vector borne (Table 1) and a further two have insect involvement in their transmission. The vector-borne NTDs include some of the most debilitating infections of humans such as onchocerciasis, lymphatic filariasis, and schistosomiasis (Boakye et al. 2007; Traoré et al. 2009; Yirenya-Tawiah et al. 2011) and others like dengue which can lead to high fatalities (Carneiro da Silva et al. 2013).

The vectors are either insects or other arthropods or snails (Table 1) with diverse life histories. For example, the main blackfly species vectors of human onchocerciasis in Africa, members of the *Simulium damnosum* complex, breed in fast-flowing

stretches of rivers (Le Berre 1974; Walsh 1985), while *S. albivirgulatum*, a vector in the Democratic Republic of Congo, breeds in much slower-flowing streams (Fain et al. 1980), and yet still *S. neavei* group are phoretic on crabs (McMahon 1952; Van Someren and Mcmahon 1950). Another example is the different genera of mosquitoes that transmit the causative agents of lymphatic filariasis (de Souza et al. 2012).

Control of Vector-Borne NTDs

The components of a vector-borne disease are the vector, pathogen, and the host. This triad of interlinking components is all influenced by the environment. The understanding of this natural history of vector-borne diseases is critical for implementing any successful control program irrespective of whether it is an NTD or not. Thus, the control should integrate a combination of strategies targeting the pathogen and vector as well as promoting human behavior that leads to prevention or propagation of pathogen or vector.

Historical Approaches

Before the transmission of most of these infections was understood, the control of vector-borne NTDs had generally depended on treating those showing overt symptoms of the disease and/or diagnosed as having infection with a particular pathogen (Brown and Neu 1990; Ligon 2005; Haldar et al. 2011). The observation and understanding that insects, other arthropods, and snails could serve as intermediate hosts for the causative agents of diseases and parasites, bacteria, and viruses between the late 1890s to the mid-1930s (Service 1976) opened the gates for a flurry of measures to then tackle the vectors as a disease control method. These early vector control measures revolved around the view that it should be easy to eliminate the vector and therefore break the transmission of diseases once any factor in the vector life cycle is modified (Kershaw 1963). Thus, other important components of medical entomology such as studies of insect physiology were ignored or progressed slowly (Kershaw 1963). During this early phase of vector control, emphasis was therefore based on ecological science and thinking, particularly physical modification of the environment. The belief that vector-borne diseases could be eliminated easily was even more accentuated with the discovery and use of DDT and other insecticides in vector control (Soper et al. 1947; Chinery 1968; Duchon et al. 2009). Ecological science and thinking, the basis for earlier efforts to control pests and disease vectors, lost its prominence, and vector control became anonymous with insecticide use.

Current Approaches to the Control of Vector-Borne NTDs

The euphoria that followed the discovery and use of potent insecticides such as DDT soon led to the reality of the complexity of the situation. The drive for commercial agriculture led to its heavy use in the 1950s and 1960s (Chapin and Wasserstrom 1981). Insecticide resistance became widespread, and the negative impacts of insecticides on the environment were highlighted as eloquently expressed in the book "Silent Spring" by Rachel Carson in 1962. Subsequently, DDT was banned as an agricultural insecticide, following the Stockholm Convention in 2001. However, its use for disease vector control was never banned, but international pressure restricted its implementation in malarious countries (Stockholm Convention on Persistent Organic Pollutants 2001; Sadasivaiah et al. 2007). Vector control against NTDs was only then acceptable when there was no safe chemotherapeutic agent against a particular disease such as the control of onchocerciasis in the 1970s to early 1990s by the WHO Onchocerciasis Control Programme in West Africa (Amazigo et al. 2006).

This status quo has been maintained starting with the donation of Mectizan® (ivermectin) by Merck and Co. Inc. for as long as needed to control onchocerciasis, followed by that of albendazole by GSK against lymphatic filariasis and recent pledges during the London declaration by other pharmaceutical companies producing drugs against vector-borne/involved NTDs such as schistosomiasis and trichiasis (Uniting to Combat NTDs 2012). This is thus the current backbone of the drive to control or eliminate NTDs such as onchocerciasis, lymphatic filariasis, trichiasis, schistosomiasis, and soil-transmitted helminthiasis (preventive chemotherapy) and the call for more research to develop drugs for the other NTDs.

Importance of Vector Control in NTDs

A factor that has mitigated against the use of vector control interventions among many others is the wrong notion and interpretation that vector control as the name implies is only against the vectors and not one of the strategies for disease control and elimination. Hence, in disease control circles, the use of bed nets is spoken of as preventing morbidity and mortality without taking into consideration the vector components. Notwithstanding this, vector control has a strategic role in the control/elimination of NTDs due to various factors. Chief among these are the fact that some diseases such as African trypanosomiasis, Chagas disease, dengue, and leishmaniasis either have imperfect drugs, vaccines are not available, and therefore, vector control remains the main strategy to prevent transmission (Townson et al. 2005). Furthermore, it is becoming clearer that other chemotherapeutic campaigns (e.g., against lymphatic filariasis) will benefit from a combination with vector control (Bockarie et al. 2009).

An efficient vector control strategy depends on a critical understanding of the biology of the vector in question. This involves being able to specifically identify

the species involved in disease transmission, their distribution, their life cycle, the feeding behavior, resting behavior, and migratory behavior (Lambrechts et al. 2009; Pates and Curtis 2005; Radcliffe and Ragsdale 2002). Another factor in vector control is vector ecology which involves the comprehensive study of an organism and its relation to its environment (breeding sites and resting sites) and environmental factors that influence density and behavior (Ellis and Wilcox 2009).

Vector control measures can be classified into personal protection (repellents, protective clothing, insecticide vaporizers, mosquito nets, and insecticide-treated materials), environmental manipulation (closing of breeding sites, planting of trees that grow rapidly, and use lots of water and biological control), house design (ceiling and trapdoors with screens), and insecticide applications (adulticiding and larviciding). Historically, it has been shown that vector control can effectively reduce disease transmission, when done properly (Townson et al. 2005).

Methods of Vector Control for NTDs

The major vector control methods of insecticide use, personal protection, and environmental modification have remained the same over the years, but the strategy of application has evolved and also depends on the vector being targeted.

Insecticide Use

As indicated above the main vector control strategy revolves around the use of insecticides. These are applied in various forms against different developmental stages of the vectors.

Larviciding/Mollusiciding

The vectors of many of the NTDs (e.g., mosquitoes, blackflies, and snails) have developmental stages that are found in aquatic habitats. The control of these stages therefore is best achieved by the use of insecticides to kill the developmental stages. There are reported successes such as those of the Onchocerciasis Control Programme (OCP) in West Africa (Traore et al. 2009), *Culex* breeding sites (Mulla 1967), and control of snail vectors (McCullough et al. 1980) by using this strategy. However, this is not easily achieved either due to the difficulties in detecting breeding sites, the dispersed nature of breeding sites (*An. gambiae* s.s breeding sites), or the sheer expanse of it (lakes for snail vectors). These apparent challenges have led to a lack of interest in the use of this strategy. Recent improvements in spatial data and analysis are now being employed to accurately determine the presence of breeding sites (Shao and Li 1985; Zhang et al. 2003; Hassan

and Onsi 2004) which will resolve one of the major challenges and lead to targeted control. Furthermore, the use of bio-larvicides which are more specific to particular vectors without affecting nontarget organisms coupled with observations that this method provides a significant level of contribution toward reducing disease transmission is generating a renewed interest (Mittal 2003; Priyadarshini et al. 2012).

Adulticiding

The use of insecticides to kill the adults of most vectors is the commonest form application of insecticides. The adults of most vectors are easily observed and hence can be easily targeted. However, this is effective when the behavioral characteristics (resting, feeding, oviposition habits) of the adult stage of the vector are known and understood. Therefore, while it is useful to target most mosquito vectors of NTDs, it is not effective to target *Simulium* vectors of onchocerciasis. Methods of insecticide application against the adult stages are varied and include indoor spraying of walls and crevices where the adult are found (Pluess et al. 2010), space spraying to kill flying adults as well as outdoor resting vectors (WHO 2003), protective barriers such as insecticide-treated bed nets (Hill et al. 2006), and incorporation into traps [lethal ovitraps] (Perich et al. 2003; Ritchie et al. 2009).

Indoor residual spraying (IRS) has been used extensively against mosquito vectors of lymphatic filariasis (Kelly-Hope et al. 2013), vectors of Chagas disease (Hashimoto and Schofield 2013), and sandfly vectors of leishmaniasis (Davies et al. 2000). Space spraying is used against a variety of insects including those transmitting disease pathogens of man. The commonest form of space spraying is the use of aerosol cans for household insect control. Recently such use of aerosols is found in the airline industry where planes are sprayed with pyrethroid insecticide formulations. Control of *Aedes* mosquitoes is also amenable to the use of space spraying (Esu et al. 2010).

Prevention of Man-Vector Contact

This strategy has been used as a vector control measure since antiquity. This is done either as protective barriers; the most famous and successful is that of bed nets. The incorporation of insecticides into bed nets revolutionized the use of this personal protection method as the most advocated strategy against indoor biting mosquitoes even though in some cases, such as in Ada, Ghana, it is also used outdoors along the beach. The use of insecticide-treated bed nets is the main vector control strategy in malaria control (Hill et al. 2006). However, since the *Anopheles* mosquitoes that transmit malaria in most areas in Africa and the Pacific region are also the vectors of LF, this method is also effective against LF. Another strategy

against mosquitoes to prevent man-vector contact has been improved housing and screening since the early twentieth century in Italy (Celli 1901), Greece (Ross 1913), Panama (Le Prince et al. 1916) and the USA (Boyd 1926). There is ample evidence that house screening contributed to the elimination of malaria from many parts of the world (Lindsay et al. 2002). Although screening has been shown to provide protection against indoor-biting mosquitoes similar to insecticide-treated bed nets in recent times too (Lindsay et al. 2002; Ogoma et al. 2009), this strategy has found little support in control strategies targeting mosquito-borne diseases (Smith 2004).

Challenges to Vector Control

Although vector control has been shown to be an effective strategy for the control of vector-borne NTDs (Bockarie et al. 2009; Townson et al. 2005), it is faced with some challenges, major among which are insecticide resistance, multiplicity of vector species, changes in vector behavior, and cost.

Insecticide Resistance

Insecticide usage continues to be the backbone of most vector control strategies; hence, a major challenge is the development of insecticide resistance in target vectors. This has been responsible for the failure of many campaigns against insect vectors. Currently insecticide resistance has been found in almost all genera of vectors implicated in the transmission of vector-borne diseases (Padonou et al. 2011; Flores et al. 2013; Thomas et al. 2013; Hassan et al. 2012). Although resistance to snails has not been much documented, there is still the possibility of this happening in the only chemical niclosamide (Bayluscide, Bayer, Leverkusen, Germany) recommended by WHO against snail vectors of schistosomiasis (Rapado et al. 2013). This situation poses a threat to vector control of NTDs.

Multiplicity of Vector Species

Many of the vector-borne NTDs are transmitted by a multiplicity of vectors species of the same genus (onchocerciasis, dengue, and trypanosomiasis) or by several species of one genus or of different genera (LF). LF is vectored by species of *Aedes*, *Anopheles*, *Culex*, and *Mansonia* (Bockarie et al. 2009), and although in most geographical locations, different species of one genus are vectors, in other locations, species belonging to different genera are involved in the transmission such as species of *Anopheles* and *Mansonia* in Ghana (Ughasi et al. 2012). This multiplicity of

vector species poses a challenge for vector control since these various vectors may have different breeding habitats and adult behaviors such as exophilly (Service 1982). Furthermore, a less important vector could take on more active role in transmission particularly when the major vector is controlled or after the introduction of MDA or the importation of different strains of the pathogen. An example was the mediation of *Ae. albopictus* as the vector for an imported variant of chikungunya fever virus in Singapore instead of the main vector *Ae. aegypti* (Yoshikawa 2010). Another challenge is that in most endemic areas, all the vectors involved in the transmission of a particular disease are not known. For example, in an endemic area of cutaneous leishmaniasis in Ghana, the vectors are still not known (Boakye et al. 2005; Kweku et al. 2011), and this makes it difficult to plan any vector control strategy.

Lack of Integrated Vector Management

Vector control options are powerful tools in the fight against vector-borne diseases. However, these should not be treated as stand-alone solutions, but rather as part of well-integrated vector control programs in disease-endemic regions. For example, the use of ITNs and/or IRS has been shown to reduce malaria parasite transmission by 90 % or more (Nyarango et al. 2006; Protopopoff et al. 2008). Nonetheless, an important question is how best to eliminate the remaining level of transmission, the answers to which are dependent on existing challenges to integrated management. WHO listed five reasons for the slow uptake of integrated vector control: (1) overestimation of the requirements of integrated control: "*most programme managers are unaware of this possibility that an integrated approach can*, *in principle*, *be introduced without additional resources*"; (2) oversophistication of integrated control: "*in short*, *for many mosquito species enough is already known ....to base the introduction of integrated control*"; (3) insufficient conviction of the advantages of integrated control; (4) misconceptions about the use of pesticides in integrated control: "*project managers need to be assured that integrated control does not*, *nor cannot*, *mean exclusion of pesticides*, *but their more rational and correct use*."; and (5) insufficient consciousness of comparative costs, effectiveness, benefits, and risks: "*application of pesticides*, *especially* via *indoor residual spraying* (*IRS*), *frequently becomes a routine practice*, *regardless of the need or the results obtained*" (Rafatjah 1982; Beier et al. 2008). Other reasons for the slow uptake of IVM include a lack of capacity building, poorly defined roles for advocacy and legislative activities, and a general lack of intersectoral linkage within the health sector (Beier et al. 2008). The authors also discussed reasons why vector control strategies fail in many countries, and these include but are not limited to the following: the lack of intersectoral collaborations, improper use of insecticides, inability of entomologists to convince decision-makers and the failure to link disease burden with societal burden, and the lack of financial resources and logistics.

Research to Support Program Implementation

Experience with vector control methods points to the need for further research and planning. Vector control poses different challenges in different disease transmission environments or settings. In malaria vector control, for example, five research challenges, has been identified:

(i) The development of improved vector control for malaria elimination
(ii) Development of new vector control interventions, including new insecticides and formulations
(iii) An understanding of vector biology for the development of new control interventions
(iv) Development of new approaches such as the genetic modification of mosquitoes in order to reduce the high vectorial capacity in some malaria-endemic regions
(v) Development of innovative cross-disciplinary technologies that are required to control outdoor biting and resting mosquito vectors, measure transmission, and educate communities about vector control (The malERA Consultative Group on Vector Control 2011). These challenges address the need for broader range of insecticides with novel modes of action that can avoid the development of resistance to existing insecticides, particularly the pyrethroids, and the creation of strategies for the use of new insecticides that minimize the emergence of resistance. Furthermore, different species of Anopheles mosquitoes play different vectorial roles in disease transmission. Interventions such as IRS and LLINs only target indoor feeding and/or resting vectors (Terenius et al. 2008), and as such, there is the need to define vector species for which new tools are needed as well as creating tools that will be effective for multiple important vector species. In addition, there is the need to develop new tools that will permanently reduce the vectorial capacities of dominant disease vectors.

The research needs outlined above can be generalized for most vector-borne diseases in addition to the needs of understanding vector behavior and transmission dynamics in different areas. Environmental factors exert much influence on disease vectors, and as such the role of different vectors in different areas must further be investigated to aid vector control efforts. Knowledge of vector dispersal under the greatly changed ecologies (e.g., deforestation, irrigation) is essential for protecting rural and urban areas selected for long-term vector control operations (Zahar 1984).

Development of Personnel and Infrastructure

To most disease control programs in Africa, vector control is synonymous to bed net distribution and usage and the spraying of insecticides to kill disease vectors. Surveillance for control programs for vector-borne diseases is expensive, and the

lack of the financial capabilities leads to an erosion of vector-borne diseases control infrastructure, which in turn leads to an attrition in human resource capacity (Institute of Medicine (US) Forum on Microbial Threats 2008). Thus, most vector-borne disease control programs lack properly trained personnel and infrastructure. For an effective program, the type of training required and the necessity for providing adequate career structures for vector control personnel and adequate funding for the control programs must all be taken into consideration. Shawarby identified some of the key areas for the training of vector control personnel (Shawarby 1963). These include the effective application of the basic principles of vector control according to local environmental conditions, the evaluation of the results of vector control programs, the avoidance of hazards associated with the use of pesticides, the economy of materials through proper planning and organization, proper handling of transport and equipment, and health education in the local community. While it is noted that many organizations including the WHO provide workshops aimed at specific issues related to vectors and vector-borne diseases in disease-endemic areas, such programs, however, fail to address the in-depth training needs in molecular, biological, epidemiological, and information technology techniques, nor do they empower trainees to exploit these techniques effectively in real-world situations (Institute of Medicine (US) Forum on Microbial Threats 2008). Efficient training strategies are necessary to address the human resource needs in all areas of vector-borne diseases, from identification and processing of vectors to gene identification and characterization and to development of GIS and other information technology-based approaches for the control of vectors and vector-borne diseases (Institute of Medicine (US) Forum on Microbial Threats 2008). Building capacity and infrastructure for vector-borne diseases can only be achieved through establishing vector control programs supervised by well-trained professional staff provided with adequate budgetary support.

Sustainability and Financing

The main challenge to the implementation and sustainability of vector control activities, however, has a lot to do with the limited financial resources (Jobin 1979; Yukich et al. 2008). Another challenge is the collaboration on the part of community members and individuals. Vector control activities are usually carried out by programs without much consideration of the roles communities could play in the process. Involving communities in monitoring and environmental modification could significantly help reduce the cost associated with vector control activities in disease-endemic areas.

Conclusion

In conclusion, many infectious diseases around the world are vector borne and neglected. However, despite the availability of effective chemotherapy against these diseases, the cost of treatment remains a significant barrier in disease control. Thus,

other intervention measures like vector control must supplement chemotherapy. Vector control has the potential to play a very important role in the control of NTDs. However, it requires the commitment of resources, both financial and human, from disease control programs. There is the need for integration at all levels, while adopting the WHO policy guidelines on IVM. Finally, research must play an important part in vector control programs. For example, the effect of malaria vector control on other diseases such as lymphatic filariasis must be investigated. The success in controlling onchocerciasis from the Island of Bioko (Traore et al. 2009) as a result of larviciding by the WHO African Programme for Onchocerciasis Control as well as elimination of LF using indoor residual spraying with DDT to control malaria in the Solomon Islands (Pichon 2002; Duerr et al. 2005) underscore an important historical lesson. The campaigns for the control of vector-borne diseases have the best chance of success when multiple interventions that target different points in the disease cycle are implemented concomitantly.

References

Amazigo U, Noma M, Bump J, Benton B, Liese B, Yameogo L, Zouré H, Seketeli A (2006) Onchocerciasis. In: Jamison DT, Feachem RG, Makgoba MW, Bos ER, Baingana FK, Hofman KJ, Rogo KO (eds) Disease and mortality in Sub-Saharan Africa, 2nd edn. World Bank, Washington, DC

Beier JC, Keating J, Githure JI, Macdonald MB, Impoinvil DE, Novak RJ (2008) Integrated vector management for malaria control. Malar J 7(Suppl 1):S4

Boakye DA, Back C, Fiasorgbor GK, Sib APP, Coulibaly Y (1998) Sibling species distribution of the Simulium damnosum complex in the west African onchocerciasis control programme area during the decade 1984–1993, following intensive larviciding since 1974. Med Vet Entomol 12:345–358

Boakye DA, Wilson MD, Kweku M (2005) A review of leishmaniasis in West Africa. Ghana Med J 39:94–97

Boakye D, Baidoo H, Glah E, Brown C, Appawu M, Wilson M (2007) Monitoring lymphatic filariasis interventions: adult mosquito sampling, and improved PCR – based pool screening method for *Wuchereria bancrofti* infection in anopheles mosquitoes. Filaria J 6:13

Bockarie M, Pedersen E, White G, Michael E (2009) Role of vector control in the global program to eliminate lymphatic filariasis. Annu Rev Entomol 54:469–487

Boyd MF (1926) The influence of obstacles unconsciously erected against anophelines (housing and screening) upon the incidence of malaria. Am J Trop Med Hyg 6:157–160

Brown AWA (1962) A survey of simulium control in Africa. Bull World Health Organ 27:511–527

Brown KR, Neu DC (1990) Ivermectin – clinical trials and treatment schedules on onchocerciasis. Acta Leiden 59:169–175

Carneiro Da Silva MM, Gil LHVG, Marques ET-A Jr, Calzavara-Silva CE (2013) Potential biomarkers for the clinical prognosis of severe dengue. Mem Inst Oswaldo Cruz 108:755–762

Celli A (1901) The new preventative treatment of malaria in Latium. Collection of Papers on Malaria. Angelo Celli, 1899–1912. London School of Hygiene and Tropical Medicine, London pp. 1–12

Chapin G, Wasserstrom R (1981) Agricultural production and malaria resurgence in Central America and India. Nature 293:181–185

Chinery WA (1968) Mosquito control in an urban environment with reference to the anti-mosquito operations in Accra and Tema. Ghana Med J 7:205–209

Claborn DM (2010) The biology and control of leishmaniasis vectors. J Global Infect Dis 2:127–134
Davies CR, Llanos-Cuentas EA, Campos P, Monge J, Leon E, Canales J (2000) Spraying houses in the Peruvian Andes with lambdacyhalothrin protects residents against cutaneous leishmaniasis. Trans R Soc Trop Med Hyg 94:631–636
de Souza DK, Koudou B, Kelly-Hope L, Wilson MD, Bockarie MJ, Boakye DA (2012) Lymphatic filariasis vectors and the implications for accelerated elimination of anopheles-transmitted filariasis in West Africa. Parasites Vectors 5:259
Duchon S, Bonnet J, Marcombe S, Zaim M, Corbel V (2009) Pyrethrum: a mixture of natural pyrethrins has potential for malaria vector control. J Med Entomol 46:516–522
Duerr HP, Dietz K, Eichner M (2005) Determinants of the eradicability of filarial infections: a conceptual approach. Trends Parasitol 21:88–96
Ellis BR, Wilcox BA (2009) The ecological dimensions of vector-borne disease research and control. Cad Saude Publ 25(Suppl 1):S155–S167
Emerson PM, Lindsay S, Walraven G, Faal H, Bogh C, Lowe K, Bailey RL (1999) Effect of fly control on trachoma and diarrhoea. Lancet 353:1401–1403
Esu E, Lenhart A, Smith L, Horstick O (2010) Effectiveness of peridomestic space spraying with insecticide on dengue transmission; systematic review. Trop Med Int Health 15:619–631
Fain A, Wery M, Tilkin J (1980) Simulium albivirgulatum Wanson et Henrard, 1944, vector of Onchocerca volvulus, in the central Basin region of Zaire. Preliminary note. Ann Soc Belg Med Trop 60:285–289
Flores AE, Ponce G, Silva BG, Gutierrez SM, Bobadilla C, Lopez B, Mercado R, Black WC (2013) Wide spread cross resistance to pyrethroids in Aedes aegypti (Diptera: Culicidae) from Veracruz state Mexico. J Econ Entomol 106:959–969
Gold MR, Stevenson D, Fryback DG (2002) HALYS and QALYS and DALYS, Oh My: similarities and differences in summary measures of population Health. Annu Rev Public Health 23:115–134
Gouteux JP (1990) Current considerations on the distribution of Glossina in west and central Africa. Acta Trop 47:185–187
Haldar AK, Sen P, Roy S (2011) Use of antimony in the treatment of leishmaniasis: current status and future directions. Mol Biol Int 2011:23
Hashimoto K, Schofield CJ (2013) Elimination of Rhodnius prolixus in Central America. Parasites Vectors 22:45
Hassan AN, Onsi HM (2004) Remote sensing as a tool for mapping mosquito breeding habitats and associated health risk to assist control efforts and development plans: a case study in Wadi El Natroun, Egypt. J Egypt Soc Parasitol 34:367–382
Hassan MM, Widaa SO, Osman OM, Numiary MSM, Ibrahim MA, Abushama HM (2012) Insecticide resistance in the sand fly, Phlebotomus papatasi from Khartoum State, Sudan. Parasites Vectors 7:46
Higa Y (2011) Dengue vectors and their spatial distribution. Trop Med Health 39(Suppl 4): 17–27
Hill J, Lines J, Rowland M (2006) Insecticide-treated nets. Adv Parasitol 61:77–128
Hotez PJ (2008) Neglected infections of poverty in the United States of America. PLoS Negl Trop Dis 2:e256
Institute Of Medicine (Us) Forum on Microbial Threats (2008) Integrating strategies to address vector-borne disease. In: Vector-borne diseases: understanding the environmental, human health, and ecological connections, workshop summary [Online]. Washington, DC. Available from: http://www.ncbi.nlm.nih.gov/books/NBK52950/: National Academies Press (US). Accessed 10 Jul 2014
Jobin WR (1979) Cost of snail control. Am J Trop Med Hyg 28:142–154
Johnson PD, Azuolas J, Lavender CJ, Wishart E, Stinear TP, Hayman JA, Brown L, Jenkin GA, Fyfe JA (2007) Mycobacterium ulcerans in mosquitoes captured during outbreak of Buruli ulcer, southeastern Australia. Emerg Infect Dis 13:1653–1660

Kelly-Hope LA, Molyneux DH, Bockarie MJ (2013) Can malaria vector control accelerate the interruption of lymphatic filariasis transmission in Africa; capturing a window of opportunity? Parasites Vectors 6:39

Kershaw W (1963) Vector-borne diseases in man: a general review. Bull World Health Org 29(Suppl):13–17

Kweku MA, Odoom S, Puplampu N, Desewu K, Nuako GK, Gyan B, Raczniak G, Kronmann KC, Koram K, Botero S, Boakye D, Akuffo H (2011) An outbreak of suspected cutaneous leishmaniasis in Ghana: lessons learnt and preparation for future outbreaks. Glob Health Action 4:5527

Lambrechts L, Knox TB, Wong J, Liebman KA, Albright RG, Stoddard ST (2009) Shifting priorities in vector biology to improve control of vector-borne disease. Trop Med Int Health 14:1–10

Le Berre R (1974) Simulium damnosum. In: Pal R, Wharton RH (eds) Control of arthropods of medical and veterinary importance. Springer, New York

Le Prince JA, Orenstein AJ, Howard LO (1916) Mosquito control in Panama. G.P. Putnam's Sons, New York

Lent H, Wygodzinsky PW (1979) Revision of the Triatominae (Hemiptera, Reduviidae), and their significance as vectors of Chagas' disease. Bull Am Mus Nat Hist 163:3

Ligon BL (2005) Dengue fever and dengue hemorrhagic fever: a review of the history, transmission, treatment, and prevention. Semin Pediatr Infect Dis 16:60–65

Lindsay SW, Emerson PM, Charlwood JD (2002) Reducing malaria by mosquito-proofing houses. Trends Parasitol 18:510–514

Mandahl-Barth G (1965) The species of the genus Bulinus, intermediate hosts of Schistosoma. Bull World Health Org 33:33–44

Marsollier L, Robert R, Aubry J, Saint Andre JP, Kouakou H, Legras P, Manceau A-L, Mahaza C, Carbonnelle B (2002) Aquatic insects as a vector for Mycobacterium ulcerans. Appl Environ Microbiol 68:4623–4628

Mccullough FS, Gayral P, Duncan J, Christie JD (1980) Molluscicides in schistosomiasis control. Bull World Health Organ 58:681–689

Mcmahon J (1952) Phoretic association between Simuliidae and crabs. Nature 169:1018

Mittal PK (2003) Biolarvicides in vector control: challenges and prospects. J Vector Borne Dis 40:20–32

Molyneux DH (2006) Control of human parasitic diseases: context and overview. Adv Parasitol 61:1–45

Morgan JA, Dejong RJ, Snyder SD, Mkoji GM, Loker ES (2001) Schistosoma mansoni and Biomphalaria: past history and future trends. Parasitology 123(Suppl):S211–S228

Mulla MS (1967) Larvicides and larvicidal formulations for the control of Culex pipiens fatigans. Bull World Health Organ 37:311–315

Muller R (1991) Dracunculus in Africa. In: Macpherson C, Craig PS (eds) Parasitic helminths and zoonoses in Africa. Unwin Hyman, London

Nyarango PM, Gebremeskel T, Mebrahtu G, Mufunda J, Abdulmumini U, Ogbamariam A, Kosia A, Gebremichael A, Gunawardena D, Ghebrat Y, Okbaldet Y (2006) A steep decline of malaria morbidity and mortality trends in Eritrea between 2000 and 2004: the effect of combination of control methods. Malar J 5:33

Ogoma SB, Kannady K, Sikulu M, Chaki PP, Govella NJ, Mukabana WR, Gerry F, Killeen GF (2009) Window screening, ceilings and closed eaves as sustainable ways to control malaria in Dar es Salaam, Tanzania. Malar J 8:221

Otranto D, Dantas-Torres F, Brianti E, Traversa D, Petri D, Genchi C, Capelli G (2013) Vector-borne helminths of dogs and humans in Europe. Parasites Vectors 6:16

Padonou GG, Sezonlin M, Gbedjissi GL, Ayi I, Azondekon R, Djenontin A, Bio-Bangana S, Oussou O, Yadouleton A, Boakye D, Akogbeto M (2011) Biology of *Anopheles gambiae* and insecticide resistance: entomological study for a large scale of indoor residual spraying in South East Benin. J Parasitol Vector Biol 3:59–68

Pates H, Curtis C (2005) Mosquito behavior and vector control. Annu Rev Entomol 50:53–70
Perich MJ, Kardec A, Braga IA, Portal IF, Burge R, Zeichner BC, Brogdon WA, Wirtz RA (2003) Field evaluation of a lethal ovitrap against dengue vectors in Brazil. Med Vet Entomol 17:205–210
Stockholm Convention on Persistent Organic Pollutants (2001) Convention text [Online]. Geneva. Available at: http://www.pops.int/documents/convtext/convtext_en.pdf. United Nations Environment Programme
Peters W, Killick-Kendrick R (1987) The leishmaniases in biology and medicine; volume I: biology and epidemiology. Academic, London
Pichon G (2002) Limitation and facilitation in the vectors and other aspects of the dynamics of filarial transmission: the need for vector control against Anopheles transmitted filariasis. Ann Trop Med Parasitol 96:S143–S152
Pierce WD (1974) The deadly triangle: a brief history of medical and sanitary entomology. Natural History Museum of Los Angeles County, Los Angeles
Pluess B, Tanser FC, Lengeler C, Sharp BL (2010) Indoor residual spraying for preventing malaria. Cochrane Database Syst Rev 14, CD006657
Portaels F, Elsen P, Guimaraes-Peres A, Fonteyne PA, Meyers WM (1999) Insects in the transmission of Mycobacterium ulcerans infection. Lancet 353:986
Priyadarshini KA, Murugan K, Panneerselvam C, Ponarulselvam S, Hwang JS, Nicoletti M (2012) Biolarvicidal and pupicidal potential of silver nanoparticles synthesized using Euphorbia hirta against Anopheles stephensi Liston (Diptera: Culicidae). Parasitol Res 111:997–1006
Protopopoff N, Van Bortel W, Marcotty T, Van Herp M, Maes P, Baza D, D'alessandro U, Coosemans M (2008) Spatial targeted vector control is able to reduce malaria prevalence in the highlands of Burundi. Am J Trop Med Hyg 79:12–18
Radcliffe EB, Ragsdale DW (2002) Aphid-transmitted potato viruses: the importance of understanding vector biology. Am J Potato Res 79:353–386
Rafatjah HA (1982) Prospects and progress on IPM in world-wide malaria control. Mosq News 42:491–498
Ramsey JM, Schofield CJ (2003) Control of Chagas disease vectors. Salud Publica Mex 45:123–128
Raoult D, Woodward T, Dumler J (2004) The history of epidemic typhus. Infect Dis Clin N Am 18:127–140
Rapado LN, Pinheiro AD, Lopes PODV, Fokoue HH, Scotti MT, Marques JV, Ohlweiler FP, Borrely SI, Pereira CA, Kato MJ, Nakano E, Yamaguchi LF (2013) Schistosomiasis control using piplartine against Biomphalaria glabrata at different developmental stages. PLoS Negl Trop Dis 7:e2251
Rascalou G, Pontier D, Menu F, Gourbière S (2012) Emergence and prevalence of human vector-borne diseases in sink vector populations. PLoS One 7:e36858
Ritchie SA, Rapley LP, Williams C, Johnson PH, Larkman M, Silcock RM, Long SA, Russell RC (2009) A lethal ovitrap-based mass trapping scheme for dengue control in Australia: I. Public acceptability and performance of lethal ovitraps. Med Vet Entomol 23:295–302
Ross R (1913) Malaria prevention in Greece. Br Med J 1:1186
Sadasivaiah S, Tozan Y, Breman J (2007) Dichlorodiphenyltrichloroethane (DDT) for indoor residual spraying in Africa: how can it be used for malaria control? Am J Trop Med Hyg 77:249–263
Scott D (1959) Human trypanosomiasis in Northern Ghana, 1950–56: an epidemiological review. West African Med J 8:165–184
Service, MW (1976) Mosquito ecology – field sampling methods. Wiley, New York
Service, MW (1982) Importance of vector ecology in vector disease control in Africa. Bull Soc Vector Ecol 7:1–13
Shao JJ, Li SK (1985) A preliminary study of applying Landsat TM images to identify snail habitats in Dongting Lake regions. Hunan Med 2:15–16
Shawarby AA (1963) Training of vector control personnel. Bull World Health Organ 29:177–182
Smith SM (2004) High- and low-tech malaria control. Science 304:1744

Soper FL, Knipe FW, Casini G, Riehl LA, Rubino A (1947) Reduction of anopheles density effected by the pre-season spraying of building interiors with DDT in kerosene, at Castel Volturno, Italy, in 1944–1945, and in the Tiber Delta in 1945. Am J Trop Med Hyg 27:177–200

Terenius O, Marinotti O, Sieglaff D, James AA (2008) Molecular genetic manipulation of vector mosquitoes. Cell Host Microbe 13:417–423

The MalEra Consultative Group On Vector Control (2011) A research agenda for malaria eradication: vector control. PLoS Med 8:e1000401

Thomas TG, Prakash V, Singh S, Mandal AK, Chauhan LS (2013) Insecticide susceptibility status of *Culex quinquefasciatus* Say, the vector of bancroftian filariasis against temephos in Delhi and National Capital Region. Jpn J Infect Dis 66:238–240

Townson H, Nathan MB, Zaim M, Guillet P, Manga L, Bos R, Kindhauser M (2005) Exploiting the potential of vector control for disease prevention. Bull World Health Organ 83:942–947

Traoré S, Wilson MD, Sima A, Barro T, Diallo A, Aké A, Coulibaly S, Cheke RA, Meyer RRF, Mas J, Mccall PJ, Post RJ, Zouré H, Noma M, Yaméogo L, Sékétéli AV, Amazigo UV (2009) The elimination of the onchocerciasis vector from the island of Bioko as a result of larviciding by the WHO African programme for onchocerciasis control. Acta Trop 111:211–218

Ughasi J, Bekhard H, Coulibaly M, Adabie-Gomez D, Gyapong J, Appawu M, Wilson M, Boakye D (2012) *Mansonia africana* and *Mansonia uniformis* are vectors in the transmission of *Wuchereria bancrofti* lymphatic filariasis in Ghana. Parasites Vectors 5:89

Uniting To Combat NTDs (2012) The London declaration on neglected tropical diseases 2012. Available: http://unitingtocombatntds.org/downloads/press/ntd_event_london_declaration_on_ntds.pdf. [Online]. Accessed 28 Dec 2013

Uniting To Combat NTDs (2014) Delivering on promises & driving progress. Available: http://unitingtocombatntds.org/report/delivering-promises-driving-progress-second-report-uniting-combat-ntds [Online]. Accessed 16 May 2014

Van Someren VD, Mcmahon J (1950) Phoretic association between Afronurus and Simulium species, and the discovery of the early stages of Simulium neavei on freshwater crabs. Nature 166:350–351

Varmus H, Klausner R, Zerhouni E, Acharya T, Daar AS, Singer PA (2003) Public health. Grand Challenges Global Health Sci 302:398–399

Walsh JF (1985) The feeding behaviour of Simulium larvae, and the development, testing and monitoring of the use of larvicides, with special reference to the control of Simulium damnosum Theobald s.l. (Diptera: Simuliidae): a review. Bull Entomol Res 75:549–594

WHO (2003) In: WHO (ed) Space spray application of insecticides for vector and public health pest control: a practitioner's guide. WHO, Geneva

WHO (2013) Lymphatic filariasis: a handbook for national elimination programmes. World Health Organization, Geneva

Woodruff DS, Carpenter MP, Upatham ES, Viyanant V (1999) Molecular Phylogeography of Oncomelania lindoensis (Gastropoda: Pomatiopsidae), the intermediate host of Schistosoma Japonicum in Sulawesi. J Molluscan Stud 65:21–31

World Health Organization (2008) WHO position statement on integrated vector management. Wkly Epidemiol Rec 83:177–181

World Health Organization (2009) Dengue guidelines for diagnosis, treatment, prevention and control. WHO, Geneva

World Health Organization (2011) World malaria report. World Health Organization, Geneva

Yelifari L, Frempong E, Olsen A (1997) The intermediate hosts of Dracunculus medinensis in Northern Region, Ghana. Ann Trop Med Parasitol 91:403–409

Yirenya-Tawiah DR, Rashid AA, Futagbi G, Aboagye I, Dade M (2011) Prevalence of snail vectors of schistosomiasis in the Kpong Head Pond, Ghana. West Afr J Appl Ecol 18:39–45

Yoshikawa MJ (2010) Dengue and Chikungunya virus infection in Southeast Asia: active governmental intervention in Republic of Singapore. In: Tanaka K, Niki Y, Akatsuki Y (eds) Current topics of infectious diseases in Japan and Asia. Springer, Tokyo

Yukich J, Lengeler C, Tediosi F, Brown N, Mulligan J-A, Chavasse D, Stevens W, Justino J, Conteh L, Maharaj R, Erskine M, Mueller D, Wiseman V, Ghebremeskel T, Zerom M, Goodman C, Mcguire D, Urrutia J, Sakho F, Hanson K, Sharp B (2008) Costs and consequences of large-scale vector control for malaria. Malar J 7:258

Zagaria N, Savioli L (2002) Elimination of lymphatic filariasis: a public health challenge. Ann Trop Med Parasitol 96(Suppl 2):S3–S13

Zahar AR (1984) Vector control operations in the African context. Bull World Health Organ 62:89–100

Zhang ZY, Xu DZ, Sun ZD, Zhang B, Zhou XN, Zhou Y, Gong ZL, Liu ZJ (2003) Application of satellite image for surveillance of vegetation landscapes of Oncomelenia-snail habitats in marshland using unsupervised classification. Chin J Epidemiol 24:261–264

The Role of Health Systems in the Control of Neglected Tropical Diseases in Sub-Saharan Africa

Justice Nonvignon, Ernest Mensah, Frances B. da-Costa Vroom, Sam Adjei, and John O. Gyapong

Contents

Abstract Neglected tropical diseases (NTDs) mostly affect populations with low socioeconomic status and limited access to health care. The opportunity to combat NTDs is now available, facilitated by increasing partnerships and availability of effective drugs. However, weak health systems (HSs) in NTD endemic areas pose a challenge to delivery of interventions at adequate levels to at-risk populations. To effectively reach target populations with NTD treatment, weak HS challenges must be addressed by fixing specific weaknesses in the HS building blocks – service

J. Nonvignon (✉) • E. Mensah
Health Policy, Planning and Management, School of Public Health, College of Health Sciences, University of Ghana, Legon, Ghana
e-mail: jnonvignon@ug.edu.gh

F.B.d.-C. Vroom
Department of Biostatistics, School of Public Health, College of Health Sciences, University of Ghana, Legon, Ghana

S. Adjei
Centre for Health and Social Service, Accra, Ghana

J.O. Gyapong
Department of Epidemiology and Disease Control, School of Public Health, College of Health Sciences, University of Ghana, Legon, Ghana

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5_17

delivery, health workforce, information, medical products and technologies, financing, and leadership and governance. The building blocks, however, should be tackled with a systems thinking approach to have the best impact. The role of volunteers – community drug distributors (CDDs) – in achieving adequate treatment coverage during mass drug administration (MDA) for NTDs cannot be overemphasised. They serve to extend health service beyond the reach of the formal HS and also contribute to the low cost of drug delivery to target populations; hence demotivating factors that reduce their commitment must be addressed to sustain the gains made so far. CDDs have acceptability challenges in urban areas; however the proposed use of low-cadre community health workers in urban settings must be explored. Commitment by pharmaceuticals and donors to support for NTDs must be accompanied by increased HS investment by governments in SSA to improve weak HS. Current medicines for preventive chemotherapy in NTD control are effective microfilaricides. The development of effective macrofilaricides will not only shorten the number of MDAs required to eliminate lymphatic filariasis and onchocerciasis but also significantly reduce cost. Quality and timeliness of data in NTD control programmes are affected by the literacy levels of CDDs and the largely paper-based system used to collect the data. While the CDD literacy levels will be difficult to alter in the short term, the use of electronic data collection tools and systems can be explored to address the shortfalls listed. Control of NTDs requires also inputs such as potable water and basic sanitation facilities that often do not fall directly under the ministries of health. To effectively control NTDs means building good intersectorial coordination mechanisms that work beyond ad hoc meetings of interministerial agencies whose outcome has no policy implications.

Keywords Neglected tropical diseases • Health systems • Health systems strengthening • Sub-Saharan Africa

Introduction

The neglected tropical diseases (NTDs) comprise a group of 17 diseases that affect mostly impoverished populations living in underdeveloped areas, which experience a lack of the most basic social amenities (Manderson et al. 2009; World Health Organization 2010). Little attention has been paid to these diseases over the years, however, since 2012 there has been significant progress in efforts at eliminating many NTDs with increases in treatment coverage (WHO 2013). Like other diseases that affect millions of people, the NTDs have seen an increase in effective and affordable interventions and technologies devoted to their control, yet health outcomes from these interventions continue to be off target. The reality is that the health systems that are supposed to support delivery of interventions for these diseases in many of the countries with NTDs are themselves often weak. As a consequence the impact from the interventions and technologies that are introduced to those in greatest need is not optimum, neither are they comprehensive nor provided

on an adequate scale. More therefore still needs to be done. There are two reasons why it is critical not to ignore the state of health systems in the delivery of interventions that are aimed at controlling NTDs: first, interventions that target specific diseases or a cluster of diseases – however successful they are in achieving the desired outcome – often leave unexpected and unintended consequences (negative and positive) on the broader health system (Shakarishvili et al. 2010). Evidence abounds to this effect in countries such as Malawi, Ethiopia, and Benin (Stillman and Bennett 2005). Secondly, much as it is important for specific diseases to have developed their own – often vertical – structures to support the delivery of interventions, such structures need to strengthen health systems and make it easy to be adapted for the control of other existing and future diseases. For these reasons, the importance of "health systems thinking" in the development and implementation of interventions targeting NTDs cannot be underestimated (Gyapong et al. 2010).

As health systems are highly context specific, there is no single set of best practices that can be put forwards as a model for improved performance. But health systems that function well have certain shared characteristics. They (a) have procurement and distribution systems that actually deliver interventions to those in need, (b) are staffed with sufficient health workers who have the right skills and motivation, and (c) operate with financing systems that are sustainable, inclusive, and fair. The costs of health care should not force impoverished households even deeper into poverty. It will be impossible to achieve national and international goals – including the Millennium Development Goals (MDGs) and the London Declaration on NTDs – without greater and more effective investments in health systems and services. While more resources are needed, government ministers are also looking for ways of doing more with existing resources. They are seeking innovative ways of harnessing and focusing the energies of communities, non-governmental organisations (NGOs), and the private sector. They recognise that there is no guarantee the poor will benefit from reforms unless they are carefully designed with them in mind. Furthermore, they acknowledge that only a limited success will be realised unless the efforts of other sectors are brought to bear on achieving better health outcomes. All these are health systems issues.

The objective of this chapter is to discuss the role of health systems in the control of NTDs in SSA. It is set out as a presentation and discussion of (i) the building blocks of health systems and the health systems priorities as they relate to the NTDs and (ii) "health systems thinking" as an approach to strengthening the health systems for effectiveness of NTD interventions.

Health Systems Framework

The World Health Organisation (WHO) describes a health system as one that "consists of all organizations, people and actions whose primary intent is to promote, restore or maintain health" (de Savigny and Adam 2009). The final goals of a health system are "improving health and health equity in ways that are responsive, financially fair, and make the best, or most efficient, use of available resources"

(de Savigny and Adam 2009). But intermediate goals are to improve access, coverage, safety, and quality of essential health services and products. Health systems, especially in developing countries, are generally weak, thereby compromising efforts at improving interventions to the people in the greatest need. This weakness poses a challenge to efforts towards the attainment of the health-related Millennium Development Goals targets of reducing child mortality, improving maternal health, and combating HIV/AIDS, tuberculosis, and malaria. So does the system also pose a challenge to the control of NTDs?

In order for health systems to deliver the services to those in the greatest need, the WHO has developed a framework which has six health systems building blocks: service delivery, governance and leadership, financing, human resources, information, and medical products, vaccines, technologies (de Savigny and Adam 2009). The interactions and relationships among the building blocks serve to strengthen the system to better provide essential services. Therefore, any intervention that seeks to strengthen the health systems leads to an interaction between two or more building blocks. While the building blocks provide a useful way of clarifying essential functions, the challenges facing countries rarely manifest themselves in this way. Rather, they require a more integrated response that recognises the interdependence of each part of the health system. Indicators of health status in SSA are among the worst globally. While the region has not been successful in controlling infectious diseases that have been known to the region for decades, it continues to record high incidence of pandemics like HIV/AIDS while non-communicable diseases are on a rapid rise. The poor health indices have been attributed to less than adequate health infrastructure and inadequate numbers of skilled health staff who are often not up to date with modern health-care delivery knowledge and who are poorly motivated. Net outmigration of scarce skilled health workforce aggravates the situation. Access to health care is further constrained by the inequitable financial arrangements which do not provide security from catastrophic health-care costs to the poor. The multiple reasons for the poor health outcomes in SSA are a pointer to the weak health systems. Though health-care outcomes are generally low in SSA, the situation varies greatly from urban to rural areas as health resources are skewed in favour of the urban communities with the distribution of health facilities and skilled health workforce favouring the urban areas.

Service Delivery

Governments remain the largest provider of health care in SSA. However, publicly owned health facilities are supported by quasi-government facilities which are mostly owned by faith-based organisations that receive public support with respect to human resources/staff, equipment, drugs, and payment of remuneration of core clinical health staff among other things. The role of private orthodox health facilities varies across the region. Private orthodox health facilities are often small. Private hospitals, pharmacies, and maternity homes including privately owned small retail drug sellers and dispensaries are mostly located in urban centres.

A three-tier health-care delivery system is identified in most of SSA – the local government (i.e. district/county) level, regional/provincial/state level, and the national/federal level. The public health-care delivery system is made up of a network of health facilities located at the various levels of the decentralised system. At the bottom are the community/village health posts. Health centres are found at the sub-district/sub-county levels and are basically extensions of district hospitals that are located at the district/county levels as the primary tier. The second-tier facilities are relatively large secondary hospitals that operate at regional/provincial level. Teaching/specialised hospitals at the national level constitute the third tier (Macha et al. 2012; Mills et al. 2012). For each of these levels, health facilities at the next higher level act as referral point for those below.

The above health system structure forms the context and state of the health-care infrastructure used to deliver health interventions to populations in most developing countries. It is clear that the largely rural populations are constrained in access to health care, and though efforts have been made in many countries to develop and implement close-to-client approaches to the delivery of health-care services, these have been mainly on pilot basis. Thus, the age-long problem of geographical in access to health-care services by most of the population, especially in rural communities, still exists. It is in this context that NTD control programmes operate.

Current management of NTDs includes four main strategies – preventive chemotherapy (PCT), particularly mass drug administration (MDA), intensified disease management (IDM), vector control, and safe water and improved sanitation and personal hygiene (WHO 2010). Intensified disease management following diagnosis and PCT are the two main interventions. In the first case, an NTD is diagnosed following routine clinical methods followed by use of appropriate drugs or surgical intervention. This is seen as, for example, in leprosy, yaws, leishmaniasis, and guinea worm. Some NTDs such as lymphatic filariasis, schistosomiasis, onchocerciasis, STH, and trachoma are controlled through PCT by MDA. Preventive chemotherapy is a secondary prevention strategy where anthelmintic drugs are used as a public health tool to prevent morbidity and transmission in infected populations who may be asymptomatic (WHO 2006). Populations with high prevalence of the infection are treated as a unit to reduce the prevalence of the infective agent in the population. The strategies require strong and wide coverage of health systems – to make interventions available to wide sections of the population. Weak health systems in SSA mean that the formal health system structures are inadequate to reach large sections of the population with the needed interventions (WHO 2007a).

To address the problem of access to the health system, PCT is delivered in packages that do not require skilled staff at the point of delivery. Community drug distributors (CDDs) have been used to extend MDA to remote communities far removed from the formal health-care infrastructure. Use of volunteers in MDAs has been documented to significantly reduce the cost of delivering anthelmintics to at-risk populations (Conteh et al. 2010; Goldman et al. 2007). The CDDs are community-based volunteers who, with minimal orientation, distribute drugs under the supervision of peripheral health workers. While this strategy seems to have worked to some extent, its effect is less than optimum in terms of achieving and sustaining the high treatment coverage needed to achieve control objectives especially in urban popula-

tions. Factors affecting low treatment coverage are not limited to health system challenges (Dabo et al. 2013). Volunteer fatigue has been cited as a threat to achieving the goals of MDAs. Volunteers consider the opportunity cost of participation in MDAs uncompensated for by the low token rewards. As a result volunteers do a partial job leaving some eligible persons untreated or opt out of MDA leaving some communities unreached with MDA drugs (Parker and Allen 2011). Community volunteers, however, have been found to have specific motivators, key among them being cash rewards, community respect and recognition, and future hope of employment among others (Takasugi and Lee 2012; Yasemin Dil et al. 2012).

These challenges notwithstanding the use of community-based health volunteers in delivering needed health-care services to populations in remote communities have proven to be both effective and cost-effective in many developing countries (Lubell et al. 2010; Chanda et al. 2011; Nonvignon et al. 2012). Thus, the input of volunteers in NTD control will continue to be relevant, but health systems must be strengthened to provide effective supervision and motivation of volunteers while keeping communities continuously interested in contributing to their own health through active participation (Reich et al. 2008).

Health Financing

In the quest to ensure that populations are not impoverished by financial constraints to health care, universal health coverage (UHC) has gained prominence in recent years. The goal of UHC is to ensure that all people have access to essential health-care services without suffering any form of hardship in their attempt to access these services. The concept of UHC hinges on the ability of developing countries to provide adequate funding of health-care services to ensure that both those who can and those who cannot pay for these services have access when they need to use these services. The Executive Board of the WHO, reporting to the 66th World Health Assembly held in May 2013 in Geneva, noted that UHC is "…increasingly seen as being critical to delivering better health…" and proposed that member nations "…modify their health financing systems in the search for universal health coverage…".

In 2001 – a year after the declaration of the MDGs – leaders of SSA country meeting in Abuja, Nigeria, committed to set aside at least 15 % of their annual national budgets for the health sector. During the same meeting, the leaders called on donor partners to ensure that steps are taken to fulfil their pledge of committing 0.7 % of their gross national products (GNP) to developing countries. However, in the 12 years since the pledge, seven African countries – Botswana, Burkina Faso, Malawi, Niger, Rwanda, South Africa, and Zambia – had been reported to have achieved the 15 % target of the Abuja Declaration (World Health Organization 2011). On a per capita basis, SSA countries spend an average of $25–27 on health (purchasing power parity). Furthermore, in real terms, official development assistance to developing countries reduced between 2001 and 2009 (WHO 2011).

Funding of NTD control activities has been shared by international health partners and donors on the one hand and governments in SSA countries endemic for the

NTDs on the other hand. However, partners and donors have received most credit. Partners and donors include large pharmaceutical companies such as Merck & Co. (donors of ivermectin for the control of onchocerciasis and lymphatic filariasis), GlaxoSmithKline (donating albendazole for the control of LF and STH), and Novartis (donors of rifampicin, dapsone, and clofazimine for the treatment of leprosy). Drug donation schemes often include transportation of the drugs to user countries. Other partners like the USAID, the DFID, the Bill and Melinda Gates Foundation, and the WHO provide resources for planning, training, logistics management in-country, data collection, monitoring and evaluation, and operational research. Governments' contribution to NTD control in SSA often involves infrastructure which includes the provision of office space, equipment, vehicles, human resources, and salaries for health staff. The large pool of drug distribution volunteers can be considered as local in-kind contribution to NTD control (Bockarie et al. 2013; Olds 2013).

Government financing of NTDs as described above is not expected to change significantly in the absence of deliberate change of policy direction, since they emanate from general health system units rather than new expenditures. Continued drug donations appear to have the firm assurances of the pharmaceutical companies involved until 2020 and beyond (Anderson et al. 2013). However, funding for operational activities of MDA, monitoring, surveillance, and operational research is subject to donor economic challenges. It is not uncommon to see a disruption in drug distribution when the expiration of one funding agent's commitment and the next donor funding contract is not synchronised properly leaving a financing gap which governments cannot absorb because this was not anticipated or budgeted for. In 2012, only about a third of targeted STH and schistosomiasis populations were treated due to reduced funding resulting from the economic recession in the west (Hooper et al. 2013; Olds 2013).

Nevertheless, with a change in the income status of some SSA countries – i.e. from low-income country (LIC) to lower-middle-income country (LMIC) – these countries are expected to create and tap into additional fiscal space for financing of general health services as well for NTD activities. In recent years, SSA countries such as Ghana and Kenya among others moved to LMICs. Much as such developments are welcome, indicating that the economies of these countries are expanding, there are implications for the funding of general services, including the provision of health services. The attainment of a higher income status means that such countries become ineligible to receive funding support from key international health partners (Moss and Majerowicz 2012). This reduced funding directly affects the delivery of services for the control of NTDs which typically depend on donor support at the moment. It is therefore important for such countries to mobilise resources from local sources to support health-care delivery. Given the strain on public sources of financing social services – such as tax and through social health insurance– it is important for developing countries to explore new and alternative ways to fund the control of NTD, such as through public-private partnerships. One way of doing this could be for the public sector to invest in research that estimates the economic gains – reduced employee absenteeism due to ill health but specifically due to such NTDs – that private entities would derive from investing in such activities.

Medical Product Challenges

The PCT strategy is perhaps the biggest arsenal in the fight to combat NTDs. Not only does it prevent suffering from the disease but also protects sufferers from the debility and disability associated with NTDs which is the cause of the cycle of poverty. PCT hinges on the availability of potent, effective, safe, affordable, and accessible drugs. There are major challenges to ensuring that the right drugs are available in the right quantities to those who need them most. First is the affordability question considering the cost of research and development of drugs which in the case of NTDs cannot be competitively priced to recoup the investment (Oprea et al. 2009; Pollastri 2014; Stefanakis et al. 2012). This makes research and development of NTD drugs unattractive to the global pharmaceutical giants with the expertise and technology to produce the drugs. Secondly even where the drugs are available, a complex and expensive supply chain network needs to be put in place to get the drugs to often remote communities at most risk of GNTD (2015). The cost is often out of the reach of developing countries that have weak health systems and invest very little in health infrastructure. While current drugs for PCT including ivermectin have proven effective against microfilaria of both *Onchocerca* and *Wuchereria*, it has less effect on the adult worm which in the case of *Onchocerca* can live and reproduce for up to 15 years in infected persons. Treatment for onchocerciasis for at least 15 years is therefore required in endemic populations to ensure effective control. The long-term treatment presents real challenges of compliance, data management, and cost. Effective and easy to use macrofilaricidal drugs will not only shorten the duration of PCT but will also contribute to a reduced cost of the control effort. The potential for killing the adult worm that causes LF exists. The bacteria *Wolbachia* is known to be in a symbiotic existence with the adult *Wuchereria* necessary for growth and survival of the worm. Various doses of the antibiotic doxycycline have been found to either sterilise the adult worm through inhibiting further production of microfilaria or kill it (Hoerauf et al. 2008; Makepeace et al. 2006). However, the challenge has been that at least 4 weeks of daily treatment with doxycycline is required to be effective (Bockarie et al. 2009).

Finding workable solutions to the challenges outlined above will be crucial to the drive to control, elimination, or eradication NTDs within the global targets set. Encouraging efforts are ongoing to address these challenges to availability of effective and affordable drugs for the control of NTDs. The Drugs for Neglected Tropical Diseases Initiative which now has about ten pharmaceutical companies have promised to make existing NTD drugs available to endemic countries at no cost through their collaboration with the WHO and international non-profit development partners GNTD (2015). In fact global NTD drug donations have been increased significantly following pledges by the group as part of the London Declaration. In some cases drug donation has increased by more than 80 % in the past 3 years GNTD (2015). These increases have occurred for both PCT and IDM diseases. To address the challenge of making these donated drugs available to the affected populations, the NTD Supply Chain Forum constituted by the donating pharmaceutical companies, other

global donor foundations, and logistics companies such as DHL are ensuring that the cost along the supply chain of donated NTD drugs is not the burden of affected countries.

The collaboration outlined above working around donation and distribution of currently available NTD drugs appears to be well taken care of at least to 2020 and perhaps up to 2030. However, it is no news that new more effective drugs especially microfilariae's are needed to ensure that the war against NTDs can be won in good time if at all (Slingsby and Kurokawa 2013; Stefanakis et al. 2012). Developing new drugs takes up to a decade to have a promising molecule and perhaps another decade to bring it to public use through the various phases of trial coupled with the stringent licencing regimes (Olliaro et al. 2012). For drugs which are not likely to pay for the cost invested in their research and development, there is very little motivation for giant global pharmaceutical companies to invest resources in these drugs. Investment in this area is therefore left to non-profit organisations and academic institutions who may not have the technology and personnel to succeed in good time (Pollastri 2014). There have been some proposals and actual activities that have tried to surmount the challenge to motivate the pharmaceutical companies to develop the needed new breakthrough drugs to move the fight against NTDs to the next level. One of such attempts was the US Food and Drugs Administration's (FDA) priority review voucher (PRV) system which started in 2007 (Stefanakis et al. 2012). The PRV system issues a voucher to a company that develops a drug for NTDs, malaria, or TB. The reward is that that company can receive priority review from the FDA for other drugs that it may subsequently develop which may have commercial value but will otherwise not qualify for priority review. The effect is that a pharma company could gain up to a year on the review process to bring the next drug into the market. The voucher which is estimated to be worth up to 500 million dollars could be traded in the open market to another company. However, this system did not see much patronage for the first 5 years after its introduction (Stefanakis et al. 2012). Contributing to solutions to addressing lack of motivation for pharmaceutical companies to invest in important drugs with little market value, Oprea L et al. (2009) looked at the situation as a market failure and proposed the setting up of a "global fund" for pharmaceuticals based on the morbidity or mortality averted. Funding to the scheme must be by global NGDO, governments, and international organisations. Essentially the global community pays for morbidity or mortality averted based on an assumption that the health of the world is interrelated; disease anywhere is disease everywhere. While this proposal has not been fully implemented, the Japan-based Global Health Innovative Technology (GHIT) fund is yet the most promising initiative with real promise to provide the motivation to global pharmaceutical giants to bring their expertise and technology to bear on developing novel drugs for public good including NTD drugs (Slingsby and Kurokawa 2013). Set up in 2013, the GHIT aims to accelerate the development of novel drugs to address infectious diseases through funding collaborative research and development practice in the pharmaceutical industry. It has funding from the Japanese government, the UN Development Programme agency, the Bill and Melinda Gates Foundation, and pharmaceutical companies. It facilitates sharing of, hither to, highly guarded

trade secrets of pharmaceutical companies such as data, pharmaceutical compounds in various stages of development, and new technologies. The challenges present in the NTD drugs arena are formidable but the current efforts appear equal to the task if they are sustained with increasing investment for the next decade or two.

The success of NTD control efforts depends on making effective, safe drugs widely available to at-risk populations and infected persons at affordable costs. The donation and long-term pledge of Merck & Co. and GlaxoSmithKline to provide ivermectin and albendazole, respectively, for the treatment of onchocerciasis, LF, and STH answers the question of drug availability. Merck is working in partnership with the WHO to donate praziquantel for control of schistosomiasis. However this has not been adequate to meet the needs of endemic countries. Merck in 2012 proposed to expand its commitment by increasing production levels and also making the drug available until elimination. Meanwhile some NTD partners are supporting schistosomiasis endemic countries to purchase generic praziquantel to address the short fall (Bockarie et al. 2013; WHO 2010, 2012).

Given the need for long-term treatment with ivermectin and the challenges thereof, effective and easy to use macrofilaricidal drugs will not only shorten the duration of PCT but will also contribute to a reduced cost of the control effort. The potential for killing the adult worm that causes LF exists. The bacteria *Wolbachia* is known to be in a symbiotic existence with the adult *Wuchereria* necessary for growth and survival of the worm. Various doses of the antibiotic doxycycline have been found to either sterilise the adult worm through inhibiting further production of microfilaria or kill it (Hoerauf et al. 2008; Makepeace et al. 2006). However, the challenge has been that at least 4 weeks of daily treatment with doxycycline is required to be effective (Bockarie et al. 2009). This dosage does not lend itself readily to use in MDA.

Health Workforce

The WHO's first report on NTDS stated that "health workforce should be able to perform responsively, fairly and efficiently to achieve the best health outcomes possible, given the available resources and circumstances (e.g. there should be enough trained and competent staff evenly distributed to meet needs)" (World Health Organisation 2010). This suggests that health workers engaged to implement NTD activities in their locales should be adequately trained to handle the responsibility. The workforce for NTD programmes involve health workers such as nurses, disease control officers, health information officers, and community health nurses at the various health administration levels in various countries. These are salaried workers who have their core duties outlined. The other arm of the NTD workforce consists of school teachers for school-based MDAs and community drug distributors (CDDs) who volunteer to help their communities. Formal health sector workers act as focal persons and supervise programme activities within their locality (Amazigo et al. 2012).

Programmes in SSA have relied heavily on the volunteer CDDs to administer the drugs needed for elimination of NTDs. Their efforts have ensured the availability of treatment for communities in remote places and, therefore, such efforts cannot be discounted. A large number of these CDDs have been with the programmes from the onset of the drug distribution in their communities. They are usually chosen or nominated by elders and other community members. The main criteria used are their level of literacy – which is sometimes translated as their ability to spell their own names – and trustworthiness. Apart from drug distribution, CDDs are also tasked to educate and conduct social mobilisation activities to generate interest and a desire for community members to receive the drugs.

Incentives for CDDs are an important component of NTD programmes. These can be categorised as monetary and non-monetary incentives. Like other community health volunteers, CDDs are paid some minimal allowances only when they are involved in mass campaigns; these volunteers are often not remunerated for other services rendered. While CDDs understand they are volunteers, their expectation of remuneration for the services they render is quite high. The low remuneration has affected CDD enthusiasm for the programme over the years. This has led to some volunteers abandoning the programme when opportunities of earning money from other activities occur. There have been few instances of volunteers receiving drugs and registers with the intention of distributing but not making the effort to. Other incentives CDDs ask for include free medical care, first-in-line treatment at health centres, bicycles, raincoats, wellington boots, and bags to carry their medicines and registers. Compared to other public health programmes using community-directed approaches, NTD MDAs are considered the most tedious and least rewarding. Expansion of communities, increase in population, and difficult terrain all account for the apathy. There have been suggestions of paying CDDs wages but this has been considered unsustainable and difficult to manage by donors and Ministries of Health for endemic countries (Bhattacharyya et al. 2001; Miller et al. 2014). While monetary incentives may be difficult to sustain, non-monetary incentives may help increase CDD enthusiasm. Various countries may have to assess their local conditions and determine appropriate incentives for their volunteers. Retention of CDDs is important for programme sustainability.

The issues discussed previously contribute to high attrition rate among volunteers. Bhattacharyya et al. (2001) indicated in their paper that attrition among volunteer community health workers is higher than that of paid community health volunteers. Emukah et al. (2008) also reported a 10.9 % attrition rate among volunteers in an onchocerciasis programme in two states in Nigeria. In this study, 66 % of the volunteers attributed their decision to quit to the lack of incentives by the programme. Some other reasons for attrition could also be that the substantive volunteer had travelled, others could not be reached by phone, and other CDDs had chosen other persons in their communities to replace them. These replacements were usually their children or other younger people they had worked with over the years. Others may be dropped due to poor performance (Miller et al. 2014).

There appears to be fewer younger persons volunteering for MDAs. This could be due to the inadequate or lack of incentives. A number of current of CDDs are

aging and they are holding on because they cannot find replacements in their communities. This issue will have to be addressed seriously by the health systems of SSA to ensure continued progress. Formal sector health workers play supervisory roles in ensuring the smooth implementation of the NTD programmes. A cascading structure of supervision and reporting is used in most countries from national, regional, and provincial to district and finally to community level (Hodges et al. 2011). The health workers at community health posts then train and supervise the CDDs (Dembélé et al. 2012). A number of these workers stay in their communities for years and this is beneficial to the programme. They gain experience in NTD programme management and develop stronger bonds with the CDDS and community members. However, transfer of the health workers drains the programme of valuable experience. New supervisors may not have adequate knowledge and good grasp of the epidemiology of the diseases and the management of adverse reactions. They may also appear disconnected from the programme because most are managed as a vertical programmes within the health service. It becomes an additional task "outside" of their core duties as public health nurses or disease control officers. There is also a lack of enthusiasm on the part of supervisors, who are meant to motivate the volunteers to give of their best. Since the community health officers interact with the CDDs directly, they bear the brunt of their frustration with the programme. There should be a level of integration with the health systems so NTD MDAs or activities are considered part of their core duties. Due to the vertical nature of the programme, district health management teams do not commit any of their resources to the management of the programme. Supervisory visits are sometimes made based on how much fuel allocation has been made by the programme. However, most often provision is just enough to collect registers from volunteers when the drug distribution is completed. Although volunteers have effectively delivered interventions in rural areas in developing countries, use of volunteers in urban areas faces challenges like willingness of people to serve as such in these areas and acceptance of volunteers by residents in urban setting (Hodges et al. 2010).

Governance

The governance structure of NTD control programmes in many developing countries follows a similar trend as follows: at the top – central level – of the structure is a dedicated programme with a director/manager and staff. At the regional and decentralised levels, the established health system structures are used to deliver interventions. However, like general health service delivery, NTD control programmes fall within the health system, whose governance is affected by the actions of outside forces. As the Lancet Commission on Global Health Governance points out, inequities in health service delivery sometimes fall on non-state actors, and until the issue of health governance is given a regional perspective, it will be almost impossible to depend on internal and state actors alone to fix the numerous governance challenges facing health-care delivery in developing countries. Global

politics and power plays a key role in determining the governance structures in many countries (Ottersen et al. 2014). Furthermore, the complexities of the health systems in many developing countries create challenges for the delivery of health-care services. Fortunately NTD control has not been left to country health system actors. The control of NTDs is a global endeavour with critical participation at the highest level of the global health governance – the WHO (Hotez and Pecoul 2010). The WHO has shown its leadership through the setting up of the Department of Control of Neglected Tropical Diseases which "coordinates and supports policies and strategies to enhance global access to interventions for the prevention, control, elimination and eradication of neglected tropical diseases, including some zoonotic diseases" (World Health Organization 2015) and produces several policy documents to guide member countries in their effort to control NTDs while setting up implementation goals and monitoring same (WHO 2007b, 2010, 2011, 2012). At the international level, NTD control efforts also enjoy considerable partnership with international NGDO, state development support agencies, and international collaborations including the Uniting to Combat NTDs, the Bill and Melinda Gates Foundation, the USAID, and the DFID.

While the international community feels responsible to support the control of NTDs, it must be stated that the greatest responsibility for the control of NTDs may rest with affected country governments who must demonstrate political commitment to the control of NTDs to make the support of global partners towards NTD control have the greatest impact (Narain et al. 2010). This is important for several reasons. First, is the human right dimension of health which is a fundamental responsibility of national governments (WHO 1978). While nearly all governments have signed the UN convention on the right to health, few have taken steps to put in place laws to guarantee this right to their citizens (Heymann et al. 2013). Secondly, NTDs have gained prominence due to their impact on the socioeconomic fortunes of affected populations particularly so when its greatest burden is on the poorest countries. The return on investment case for NTDs is considered very high making it imperative for governments of developing countries to pay attention to their control as a complement to poverty reduction strategies (Allen and Parker 2012; Chu et al. 2010). The benefit of NTD control is a healthy population who can contribute meaningfully to the economic development of their countries.

At the country level, NTD control must leverage the advantage of the health system to multiply the impact of interventions and also for sustainability. There is the need to integrate NTDs with similar delivery strategies on the same platform to make efficient use of resources (Gyapong et al. 2010). The PCT NTDs could be managed as an integrated NTD programme. Some aspects of the IDM NTDs such as lymphoedema management in LF and management of ulcers in leprosy and buruli ulcer can be integrated. In sub-Saharan Africa, NTDs coexist with other conditions such as malaria, TB, and HIV/AIDS. Clear points of convergence exist either in the area of common vectors such as the anopheles mosquito transmitting malaria and LF and genital schistosomiasis increasing the risk of HIV in affected women (Molyneux et al. 2009). There must be some collaboration between these programmes in the same country working in co-endemic communities to enhance

their impact. Yet another collaboration that holds great potential for NTD control is that with the water, sanitation, and hygiene (WASH) programmes and ministries. Schistosomiasis, soil-transmitted helminths, trachoma, and guinea worm are sustained through insanitary conditions and inadequate access to potable water. Sectors such as water and sanitation, though outside the health sector, play a key role in control of NTDs. Inter-sectoral approach involving these sectors to control NTDs is necessary to achieve desired results. The challenge has been how to successfully and effectively bring the health and other sectors to work together for the common good. The NTD benefits of NTD control can mainstream into WASH programming to accelerate achievement of NTD targets. Currently most WASH activities use only the human rights argument for improvement of WASH indicators (Freeman et al. 2013). Similarly governments can align policies of ministries in the area of water and sanitation to NTD programming in endemic communities to accelerate achievement of NTD control.

Health Information

Successful health programmes depend on good quality information for decision making and planning. Health information from NTD programmes are generated at the community level by field staff who could be community health volunteers or salaried health workers and researchers. They usually generate and report disease surveillance data, treatment coverages, and morbidity and mortality data. Treatment coverage data is generated when CDDs register and record drug dosages for communities eligible for MDAs. Active case identification data, such as the recent drive to certify Ghana as being Guinea worm-free, is also carried out especially in places where specific diseases are suspected or earmarked for elimination or eradication (World Health Organization 2015). Once data collection is completed, staff at the community or district are expected to summarise the data collected for onward submission to the programme. Data is reported in the same way cascading training is conducted. Each administrative level of the health system is expected to provide checks on the data they receive to ensure good quality data is being submitted. The information generated should be timely, accurate, and complete.

One of the biggest challenges with the NTD health information is untimely reporting. The source of information for NTD programmes makes it prone to inaccuracies and often untimely submission. This tends to affect the quality of data generated. Dembélé et al. (2012) have attested to the fact that data collection for NTD programmes can be difficult. More often than not, data is not reported in a timely manner, therefore affecting planning for the next years' annual programme. Untimely submission of data was also identified in a study by da-Costa Vroom et al. (2015) in two districts in Ghana. Some reasons identified for this challenge were poor numeracy skills of CDDs, poor road networks to some communities, and inadequate resources for transportation to some communities. This study also suggested

that the slow reporting process starts at the sub-district level since CDDs usually kept to their deadlines for drug distribution.

CDDs generate a bulk of ongoing data collection in NTD programmes. Their literacy levels also have an effect on the quality of data being reported by the programmes. A basic requirement for CDDs is their ability to read and write (da-Costa Vroom et al. 2015; Njomo et al. 2012). Observation of MDA registers has shown discrepancies and incomplete recording of data. A few surveys conducted to assess drug coverages of NTD data found some variance between reported treatment coverage and actual treatment coverage (Parker and Allen 2013; Worrell and Mathieu 2012). Such overestimation or underestimation can have an adverse effect on planning for logistics and drugs for the next years' MDA campaign.

Attempts have been made to introduce electronic data capture and management tools for NTD programmes. One such study by Stanton et al. (2015) tested SMS reporting tool for assessing LF morbidity burden in selected communities in Malawi and Ghana. This allowed health surveillance assistants (Malawi) and community health volunteers (Ghana) report cases of lymphoedemas and hydrocele for physician follow-up. This was a simple cost-effective tool that can easily help with disease surveillance efforts in any country. LINKS is another tool for electronic data capture for Global Health programmes (Pavluck et al. 2014). It has been used by the Global Trachoma Mapping Project (GTMP) to map the prevalence of trachoma in suspected endemic countries. SSA countries can employ such tools to help in disease surveillance efforts. When data from field sites reach programmes rapidly, it ensures decisions and relevant implementation plans can be executed. More of such electronic tools can be deployed by programmes to ensure data is captured correctly and delivered in a timely fashion. Mobile phone technology has become ubiquitous and can therefore enhance community engagement through simplifying the exchange of information between staff at the community level and health programmes (Stanton et al. 2015).

National health information systems (HIS) is said to be the best way of managing health information for countries. Data collection for health facilities and programmes should be integrated into the national HIS, for the purpose of producing timely quality information for evidence-based decisions and interventions (Bergquist and Whittaker 2012). NTD programmes are managed as vertical programmes in most health systems so data generated is donor driven rather than country needs driven. While a number of countries are aiming to create and use national health information systems, NTD data are left out of the HIS database. This does not allow a complete picture of the state of health in any country to be seen. Countries such as Ghana, Burkina Faso, Sierra Leone, Uganda, and Kenya have implemented the open-source District Health Information System version 2 (DHIS2) to collect, collate, and manage national health data (HISP). Other countries like Burundi and the Democratic Republic of Congo (DRC) have rolled it out for programme-specific purposes such as malaria and maternal health. However, none of these countries seem to be integrating NTD data with the national health information systems. If this integration occurs, NTDs could receive more attention and potentially benefit from national funding not just donor funding.

Integration of Neglected Tropical Diseases into Routine Health Services

In the past decade, there has been some effort in providing health care to the most disadvantaged communities through close-to-client services in an attempt to strengthen the concept of primary health care. Examples of such services include home-based care for malaria and fevers in children under 5 years in 18 sub-Saharan African countries (Nonvignon et al. 2012). Studies have shown that using community health volunteers to deliver needed services to communities is effective (Kidane and Morrow 2000; Sirima et al. 2003; Chinbuah et al. 2012) and cost-effective (Lubell et al. 2010; Chanda et al. 2011; Nonvignon et al. 2012). Scaling-up coverage of these services will be crucial for integrating NTDs into the general health service. Integration of health-care services could occur vertically, horizontally, or diagonally.

The control of many diseases in developing countries has been implemented through vertical integration. Vertical integration involves the planning, direction, supervision, and implementation of health services, wholly or to a great extent, by a specialised service units through workforce dedicated for that specific programme. Vertical programmes have the advantage of ensuring that people focus on the specific health programme being worked on, therefore, channelling all energies and resources to that programme. However, a major challenge of this type of programme implementation is that parallel structures are created for different diseases or health programmes, each tackling a specific disease or programme. In the process, there is no coordination among programmes and this undermines the health systems, making it weak and unresponsive to any major threat that may affect the entire population. Furthermore, vertical programmes lead to inefficiency in the use of scarce health resources, providing incentives for waste of such needed resources.

Horizontal integration, on the other hand, refers to the use of existing structures or permanently created structures that tend to serve all health programmes (Gyapong et al. 2010). The use of horizontal integration minimises (if not eliminates) the problems of lack of coordination through parallel structures and inefficiency in the use of health resources. However, the extent of achieving desired goals in specific health programmes may be sacrificed as the workforce and existing structures are faced with a broad range of issues to tackle at any given time. Vertical programmes are regarded as attractive to many donors and the international community as they tend to show quick results and are easier to manage than horizontal programmes. However, for national governments and policymakers, vertical programmes are seen as diverting the critical and often limited human and financial resources, thereby being detrimental to overall health systems strengthening and responsiveness to emergencies (Schreuder and Kostermans 2001).

Thus, effective combination and coordination of both vertical and horizontal programmes (sometimes referred to as the diagonal approach) could ensure better outcomes for NTD control in developing countries. Diagonal integration means that programmes keep their specific focus but at the same time implement activities that

strengthen the whole system, thus carrying the system along with it. This ensures that the entire health system would benefit from such effort as it will lead to strengthened health systems capable of meeting emergencies. According to Gyapong et al. (2010), important elements need to be worked together to effectively integrate NTD control into the health system. These elements include logistics and infrastructural development, human resource development, strategies for delivery of the interventions, information systems including ICT, governance issues, and financing. For the general population, integration is essential as it enhances the accessibility and equity of services (Namadi et al. 2002). Studies have shown that successful integration requires strong leadership, good preparation and planning, and the need to address many context-specific health system hurdles (Namadi et al. 2002; Visschedijk et al. 2003).

Opportunities and Future Research for Policy

In spite of the challenges, there are opportunities for the control of NTDs in developing countries. The recent London Declaration in 2012 saw commitment to sustain NTD control up to 2020. However, governments are expected to incorporate NTD control in national health plans, budgets, and development strategies including poverty reduction and to gradually take up significant financing of NTD control in SSA (Bockarie et al. 2013). Integration of NTD programmes has been found to increase funding for NTD control activities in some countries compared to the vertical programmes. Integration provides the platform for effective use of resources (Hooper et al. 2013; Olds 2013). Allowances for volunteers could be provided in such a way that they are not tied to specific programmes activities but rather individual programmes should pool resources and pay uniform amounts to volunteers.

Furthermore, global health partnerships, which are currently growing as evident in the MDGs and also on the post-2015 development agenda, may be required to address the shortfall in NTD drug production as well as cost and affordability to affected populations. In relation to health workforce, due to the difficulty in identifying volunteers who are willing to work in urban areas, and the challenge with urban dwellers accepting these volunteers, an ideal approach will be to use health workers (e.g. community health nurses) for NTD control interventions. Furthermore, with the increasing application of ICT in health service delivery, the opportunity for the development of IT-based approaches for data collection and management could be explored.

The current state of MDA and available drugs for control of the major NTDs are not adequate to achieve elimination targets. New more effective drugs especially macrofilaricidal medicines will give a big boost to the elimination effort. The use of doxycycline as an anti-*Wolbachia* drug with consequent macrofilaricidal effect on adult worms of *Wuchereria bancrofti* and *Onchocerca volvulus* holds some promise. Further research is needed to either refine the regime/dosage or identify subsections of endemic populations where the anti-*Wolbachia* therapy will be most appropriate

and effective. As country NTD programmes approach elimination stage, there is the need to refine the tools to accurately determine end points for stopping MDA and verify elimination while minimising the risk of recrudescence. This requires further research to inform policy to guide country programmes as well as research in the areas of post-elimination surveillance to serve as early warning system to recrudescence.

References

Allen T, Parker M (2012) Will increased funding for neglected tropical diseases really make poverty history? Lancet 379:1097–1098. doi:10.1016/S0140-6736(12)60159-7, Correspondence

Amazigo UV, Leak SGA, Zoure HGM, Njepuome N, Lusamba-Dikassa P-S (2012) Community-driven interventions can revolutionise control of neglected tropical diseases. Trends Parasitol 28(6):231–238, doi:http://dx.doi.org/10.1016/j.pt.2012.03.002

Anderson RM, Truscott JE, Pullan RL, Brooker SJ, Hollingsworth TD (2013) How effective is school-based deworming for the community-wide control of soil-transmitted helminths? PLoS Negl Trop Dis 7(2):e2027. doi:10.1371/journal.pntd.0002027

Bergquist R, Whittaker M (2012) Control of neglected tropical diseases in Asia Pacific: implications for health information priorities. Infect Dis Poverty 1(1):3. doi:10.1186/2049-9957-1-3

Bhattacharyya K, Winch PJ, LeBan K, Tien M (2001) Community health worker incentives and disincentives: how they affect motivation, retention, and sustainability. Published by the Basic Support for Institutionalising Child Survival Project (BASICS II) for the United States Agency for International Development, Arlington

Bockarie MJ, Taylor MJ, Gyapong JO (2009) Current practices in management of lymphatic filariasis. Expect Rev Anti Infect Ther 7(5):595

Bockarie MJ, Kelly-Hope LA, Rebollo M, Molyneux DH (2013) Preventive chemotherapy as a strategy for elimination of neglected tropical parasitic diseases: endgame challenges. Philos Trans R Soc Lond B Biol Sci 368(1623):20120144

Chanda P, Hamainza B, Moonga H et al (2011) Relative costs and effectiveness of treating uncomplicated malaria in two rural districts in Zambia: implications for nationwide scale-up of home-based management. Malar J 10:159, Available at: http://www.malariajournal.com/content/10/1/159

Chinbuah MA, Kager PA, Abbey M, Gyapong M, Awini E, Nonvignon J, Aduik M, Aikins M, Pagnoni F, Gyapong JO (2012) Impact of community management of fever (using antimalarials with or without antibiotics) on childhood mortality: a cluster-randomized controlled trial in Ghana. Am J Trop Med Hyg 87(suppl 5):11–20

Chu BK, Hooper PJ, Bradley MH, McFarland DA, Ottesen EA (2010) The economic benefits resulting from the first 8 years of the global programme to eliminate lymphatic filariasis (2000–2007). PLoS Negl Trop Dis 4(6):e708. doi:10.1371/journal.pntd.0000708

Conteh L, Engels T, Molyneux DH (2010) Neglected tropical diseases 4: socioeconomic aspects of neglected tropical diseases. Lancet 375:239–247

Dabo A, Bary B, Kouriba B, Sankaré O, Doumbo O (2013) Factors associated with coverage of praziquantel for schistosomiasis control in the community direct intervention (CDI) approach in Mali (West Africa). Infect Dis Poverty 2:11

da-Costa Vroom FB et al (2015) Data reporting constraints for the lymphatic filariasis mass drug administration activities in two districts in Ghana: a qualitative study. SAGE Open Med 3 doi:10.1177/2050312115594083

de Savigny D, Adam T (eds) (2009) Systems thinking for health systems strengthening. Alliance for Health Policy and Systems Research, WHO, Geneva

Dembélé M, Bamani S, Dembélé R, Traoré MO, Goita S, Traoré MN, . . . Zhang Y (2012) Implementing preventive chemotherapy through an integrated national neglected tropical disease control program in Mali. PLoS Negl Trop Dis 6(3):e1574

Emukah EC et al (2008) Factors affecting the attrition of community-directed distributors of ivermectin, in an onchocerciasis-control programme in the Imo and Abia states of south-eastern Nigeria. Ann Trop Med Parasitol 102(1):45–51. doi:10.1179/136485908x252241

Freeman MC et al (2013) Integration of water, sanitation, and hygiene for the prevention and control of neglected tropical diseases: a rationale for inter-sectoral collaboration. PLoS Negl Trop Dis 7(9):e2439. doi:10.1371/journal.pntd.0002439.t001

Global Network for NTDs (GNTD) 2015 Country leadership and collaboration on neglected tropical diseases: third report of London declaration

Goldman AS et al (2007) National mass drug administration costs for lymphatic filariasis elimination. PLoS Negl Trop Dis 1(1):e67. doi:10.1371/journal.pntd.0000067

Gyapong JO, Gyapong M, Yellu N, Anakwah K, Amofah G, Bockarie M, Adjei S (2010) Integration of control of neglected tropical diseases into health-care systems: challenges and opportunities. Lancet 375:160–165

Heymann J, Cassola A, Raub A, Mishra L (2013) Constitutional rights to health, public health and medical care: the status of health protections in 191 countries. Global Pub Health 8(6):639–653. doi:10.1080/17441692.2013.810765

HISP (2015) DHIS 2 in action. Retrieved 04/08/2015, from https://www.dhis2.org/inaction

Hodges MH et al (2010) High coverage of mass drug administration for lymphatic filariasis in rural and non-rural settings in the Western Area, Sierra Leone. Parasite Vector 3:120. doi:10.1186/1756-3305-3-120

Hodges ME, Koroma JB, Sonnie M, Kennedy N, Cotter E, MacArthur C (2011) Neglected tropical disease control in post-war Sierra Leone using the onchocerciasis control programme as a platform. Int Health 3(2):69–74. doi:10.1016/j.inhe.2011.03.003

Hoerauf A et al (2008) Wolbachia endobacteria depletion by doxycycline as antifilarial therapy has macrofilaricidal activity in onchocerciasis: a randomized placebo-controlled study. Med Microbiol Immunol 197(3):295–311. doi:10.1007/s00430-007-0062-1

Hooper PJ et al (2013) The effects of integration on financing and coverage of neglected tropical disease programs. Am J Trop Med Hyg 89(3):407–410. doi:10.4269/ajtmh.13-0018

Hotez PJ, Pecoul B (2010) "Manifesto" for advancing the control and elimination of neglected tropical diseases. Hotez PJ, Pecoul B (2010) PLoS Negl Trop Dis 4(5):e718 4(5):e718 doi:10.1371/journal.pntd.0000718.t001

Kidane G, Morrow RH (2000) Teaching mothers to provide home treatment of malaria in Tigray, Ethiopia: a randomised trial. Lancet 356:550–555

Lubell Y, Mills AJ, Whitty CJM, Staedke SG (2010) An economic evaluation of home management of malaria in Uganda: an interactive markov model. PLoS ONE 5:e12439, Available

Macha J et al (2012) Factors influencing the burden of health care financing and the distribution of health care benefits in Ghana, Tanzania and South Africa. Health Policy Plan 27(Suppl 1):i46–i54. doi:10.1093/heapol/czs024

Makepeace BL, Rodgers L, Trees AJ (2006) Rate of elimination of Wolbachia pipientis by doxycycline in vitro increases following drug withdrawal. Antimicrob Agents Chemother 50(3):922–927. doi:10.1128/AAC.50.3.922-927.2006

Manderson L, Aagaard-Hansen J, Allotey P, Gyapong M, Sommerfeld J (2009) Social research on neglected diseases of poverty: continuing and emerging themes. PLoS Negl Trop Dis 3(2):332. doi:10.1371/journal

Miller JS, Musominali S, Baganizi M, Paccione GA (2014) A process evaluation of performance-based incentives for village health workers in Kisoro district, Uganda. Hum Resour Health 12:19. doi:10.1186/1478-4491-12-19

Mills A, Ally M, Goudge J, Gyapong J, Mtei G (2012) Progress towards universal coverage: the health systems of Ghana, South Africa and Tanzania. Health Policy Plan 27:i4–i12. doi:10.1093/heapol/czs002

Molyneux DH, Hotez PJ, Fenwick A, Newman RD, Greenwood B, Sachs J (2009) Neglected tropical diseases and the global fund. Lancet 373:296–297

Moss T, Majerowicz S (2012) No longer poor: Ghana's new income status and implications of graduation from IDA. Center for Global Development Working Paper 300. Accessed from www.cgdev.org

Namadi A, Visschedijk J, Samson K (2002) The leprosy elimination campaign in Jigawa, Nigeria: an opportunity for integration. Lepr Rev 73(2):138–146

Narain JP et al (2010) Elimination of neglected tropical diseases in the South-East Asia Region of the World Health Organization. Bull World Health Organ 88(3):206–210. doi:10.2471/BLT.09.072322

Njomo DW, Amuyunzu-Nyamongo M, Magambo JK, Njenga SM (2012) The role of personal opinions and experiences in compliance with mass drug administration for lymphatic filariasis elimination in Kenya. PLoS One 7(11):e48395. doi:10.1371/journal.pone.0048395

Nonvignon J, Chinbuah MA, Gyapong M, Abbey M, Awini E, Gyapong JO, Aikins M (2012) Is home management of fevers a cost-effective way of reducing under-five mortality in Africa? The case of a rural Ghanaian District. Tropical Med Int Health. doi:10.1111/j.1365-3156.2012.03018.x

Olds GR (2013) Deworming the world. Trans Am Clin Climatol Assoc 124:265–274

Olliaro P, Vaillant MT, Sundar S, Balasegaram M (2012) More efficient ways of assessing treatments for neglected tropical diseases are required: innovative study designs, new endpoints, and markers of effects. PLoS Negl Trop Dis 6(5):e1545. doi:10.1371/journal.pntd.0001545.g001

Oprea L, Braunack-Mayer A, Gericke CA (2009) Ethical issues in funding research and development of drugs for neglected tropical diseases. J Med Ethics 35(5):310–314

Ottersen OP, Dasgupta J, Blouin C, Buss P, Chongsuvivatwong V, Frenk J et al (2014) The political origins of health inequity: prospects for change, report of the Lancet-University of Oslo Commission on Global Health Governance. Accessed from http://dx.doi.org/10.1016/S0140-6736(13)62712-9, http://dx.doi.org/10.1016/S0140-6736(14)60050-7

Parker M, Allen T (2011) Does mass drug administration for the integrated treatment of neglected tropical diseases really work? Assessing evidence for the control of schistosomiasis and soil-transmitted helminths in Uganda. Health Res Policy Syst/BioMed Cent 9:3. doi:10.1186/1478-4505-9-3

Parker M, Allen TIM (2013) Will mass drug administration eliminate lymphatic filariasis? Evidence from northern coastal Tanzania. J Biosoc Sci 45(4):517–545. doi:10.1017/S0021932012000466

Pavluck A, Chu B, Mann Flueckiger R, Ottesen E (2014) Electronic data capture tools for global health programs: evolution of LINKS, an android- web-based system. PLoS Negl Trop Dis 8(4):e2654. doi:10.1371/journal.pntd.0002654

Pollastri MP (2014) Finding new collaboration models for enabling neglected tropical disease drug discovery. PLoS Negl Trop Dis 8(7):e2866. doi:10.1371/journal.pntd.0002866

Reich MR, Takemi K, Roberts MJ, Hsiao WC (2008) Global action on health systems: a proposal for the Toyako G8 summit. Lancet 371(9615):865–869. doi:10.1016/s0140-6736(08)60384-0

Schreuder B, Kostermans C (2001) Global health strategies versus local primary health care priorities – a case study of national immunisation days in Southern Africa. S Afr Med J 91(3):249–254

Shakarishvili G, Atun R, Berman P, Hsiao W, Burgess C, Lansang MA (2010) Converging health systems frameworks: towards a concepts-to-actions roadmap for health systems strengthening in low and middle income countries. Glob Health Gov III(2):1–6

Sirima SB, Konate' A, Tiono AB et al (2003) Early treatment of childhood fevers with pre-packaged antimalarial drugs in the home reduces severe malaria morbidity in Burkina Faso. Tropical Med Int Health 8:133–139

Slingsby BT, Kurokawa K (2013) The Global Health Innovative Technology (GHIT) fund: financing medical innovations for neglected populations. Lancet Glob Health 1(4):e184–e185. doi:10.1016/s2214-109x(13)70055-x

Stanton MC, Mkwanda SZ, Debrah AY, Batsa L, Biritwum NK, Hoerauf A, . . . Kelly-Hope LA (2015) Developing a community-led SMS reporting tool for the rapid assessment of lymphatic filariasis morbidity burden: case studies from Malawi and Ghana. BMC Infect Dis 15:214. doi:10.1186/s12879-015-0946-4

Stefanakis R, Robertson AS, Ponder EL, Moree M (2012) Analysis of neglected tropical disease drug and vaccine development pipelines to predict issuance of FDA priority review vouchers over the next decade. PLoS Negl Trop Dis 6(10):e1803. doi:10.1371/journal.pntd.0001803.g001

Stillman K, Bennett S (2005) System-wide effects of the global fund: interim findings from three country studies. The Partners for Health Reformplus, Abt Associates Inc., Bethesda

Takasugi T, Lee ACK (2012) Why do community health workers volunteer? A qualitative study in Kenya. Pub Health 126(10):839–845

Visschedijk J, Engelhard A, Lever P et al (2003) Leprosy control strategies and the integration of health services: an international perspective. Cad Saude Publica, Rio de Janeiro 19(6):1567–1581

WHO/Department of Control of Neglected Tropical Diseases (2013) Sustaining the drive to overcome the global impact of neglected tropical diseases. World Health Organization, Geneva

World Health Organization (1978) Declaration of Alma Ata. Paper presented at the International Conference on Primary Health Care, Alma Ata, Russia

World Health Organization (2006) Preventive chemotherapy in human helminthiasis: coordinated use of anthelminthic drugs in control interventions: a manual for professionals and programme managers. World Health Organization, Geneva

World Health Organization (2007a) Everybody business: strengthening health systems to improve health outcomes: WHO's framework for action. World Health Organization, Geneva

World Health Organization (2007b) Global plan to combat neglected tropical diseases, 2008–2015. World Health Organization, Geneva

World Health Organization (2010) First WHO report on neglected tropical diseases: working to overcome the global impact of neglected tropical diseases. World Health Organization, Geneva

World Health Organization (2011) The Abuja declaration ten years on. Accessed from http://www.who.int/healthsystems/publications/Abuja10.pdf

World Health Organization (2012) Accelerating work to overcome the global impact of neglected tropical diseases – a roadmap for implementation. World Health Organization, Geneva

World Health Organization (2015) WHO certifies Ghana free of dracunculiasis. In: http://www.who.int/dracunculiasis/Ghana_free_of_dracunculiasis/en/. Accessed 06/08/2015

Worrell C, Mathieu E (2012) Drug coverage surveys for neglected tropical diseases: 10 years of field experience. Am J Trop Med Hyg 87(2):216–222. doi:10.4269/ajtmh.2012.12-0167

Yasemin Dil Y, Strachan D, Cairncross S, Seidu Korkor A, Hill Z (2012) Motivations and challenges of community-based surveillance volunteers in the northern region of Ghana. J Community Health 37:1192–1198. doi:10.1007/s10900-012-9569-5

Index

J. Gyapong, B. Boatin (eds.), *Neglected Tropical Diseases - Sub-Saharan Africa*, Neglected Tropical Diseases, DOI 10.1007/978-3-319-25471-5