# MAPPING THE SPATIAL DISTRIBUTION AND EPIDEMIOLOGY OF PODOCONIOSIS IN ETHIOPIA: IMPLICATIONS FOR DISEASE CONTROL

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## Abstract

In the last ten years, there has been significant progress towards the prevention, control and elimination of podoconiosis as a health problem. There are however gaps in our understanding of the epidemiology and geography of podoconiosis that hinder the planning and scale-up of intervention activities. Therefore, this PhD project aimed to define the current geographical distribution and disease burden of podoconiosis in Ethiopia and investigate underlying risk factors.

This thesis adopted two main approaches to understanding distribution: first, historical data were compiled and analysed; second, a nationwide mapping survey was conducted. These data were contextualised through a systematic review of the literature on neglected tropical diseases (NTDs) in Ethiopia. The data were also used to develop elimination targets and endemicity classifications in a Delphi exercise involving a range of international NTD experts.

A systematic review of podoconiosis prevalence data was used to generate a spatially-referenced national database. The results indicated widespread occurrence of podoconiosis in Ethiopia but exhibited marked geographical variation associated, in part, with key environmental factors. The review also highlighted the lack of contemporary data.

To address this information gap, integrated mapping of podoconiosis and lymphatic filariasis was conducted in Ethiopia, June- October 2013. Two-stage cluster convenience sampling was used. Two villages were selected from each *woreda* (district) based on reported history of lymphoedema cases collected through interviewing the *woreda* health

officials, health providers and village leaders one day prior to the survey. The secondary sampling unit was individuals selected within each village using systematic sampling from a random start point. Data were collected from 129,959 individuals in 1,315 communities in 659 *woreda*. Data and cluster-level GPS coordinates were collected using smartphones by trained local health workers. We estimated the prevalence of podoconiosis in surveyed communities to be 4.0% (95% confidence interval [CI]; 3.9 - 4.1%) among individuals ≥15 years old. Detailed analyses of individual and cluster-level risk factors underlying the distribution of podoconiosis identified a number of key socio-demographic and environmental correlates. The geo-statistical models also indicated that podoconiosis risk is moderately variable over relatively short geographical distances. These findings emphasise the importance of local epidemiology and the need for robust and well-designed survey methodologies to identify areas of high risk.

Subsequently, a range of environmental and climatic data and boosted regression tree (BRT) modelling was used to predict the spatial occurrence of podoconiosis. The results indicated that the probability of podoconiosis occurrence varies with certain environmental factors. Based on the BRT model, we estimated that in 2010, 37.9 (95% CI: 22.6-56.0) million people (i.e. 47.8%; 95% CI: 28.4-70.1% of Ethiopia's national population) lived in areas environmentally suitable for the occurrence of podoconiosis. Podoconiosis is more widespread in Ethiopia than previously estimated, but occurs in distinct geographical regions that are tied to identifiable environmental factors.

For the first time using the Delphi technique case definition, endemicity classification and elimination targets of podoconiosis were developed. The resultant work lead to potential

indicators for monitoring elimination, clinical outcomes and endemicity classifications for this disabling disease.

This thesis provides the first systematic investigation into the spatial distribution of podoconiosis in Ethiopia; identified individual and environmental risk factors with potential programmatic implications. In particular, the resultant maps can be used to guide programme planning and implementation and estimate disease burden in Ethiopia. This work provides a framework with which the geographical limits of podoconiosis could be delineated at a continental and global scale.

**Keywords:** Elephantiasis, Elimination, Geographical distribution, Mapping, Non-filarial elephantiasis, Podoconiosis, Spatial epidemiology.

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## List of acronyms

| | |
|---|---|
| AAU | Addis Ababa University |
| ADLA | Acute dermatolymphangioadenitis |
| AfSIS | The African Soil Information System |
| AHRI | Armauer Hansen Research Institute |
| APOC | African Programme for Onchocerciasis Control |
| AUC | Area under the receiver operator characteristics curve |
| BRT | Boosted Regression Tree |
| BSMS | Brighton and Sussex Medical School |
| CDC | Centres for Disease Control and Prevention |
| CDD | Community based Drug Distributors |
| CDTI | Community-directed treatment with ivermectin |
| CGIARCSI | Global-Aridity datasets |
| CL | Cutaneous leishmaniasis |
| CNTD | Center for Neglected Tropical Diseases |
| DALY | Disability-adjusted life year |
| DCL | Diffuse cutaneous leishmaniasis |
| DIC | Deviance Information Criteria |
| DRC | Democratic Republic of Congo |
| EHNRI | Ethiopian Health and Nutrition Research Institute |
| ENVISAT | UN land cover classification system using the environmental satellite |
| EOS | Enhanced Outreach Strategy |
| EPHI | Ethiopian Public Health Institute |

| | |
|---|---|
| ESRI | Environmental Systems Research Institute Inc. |
| EVI | Enhanced vegetation index |
| FAO | Food and Agricultural Organization |
| FGD | Focus group discussions |
| FMOH | The Federal Ministry of Health of Ethiopia |
| GAHI | The Global Atlas of Helminth Infections |
| GBD | Global Burden of Disease |
| GIS | Geographic information system |
| GPS | Global Positioning System |
| GRUMP | Global Rural-Urban Mapping project |
| HAT | Human African Trypanosomiasis |
| HEW | Health extension workers |
| HMIS | Health Management Information System |
| ICT | Immunochromatographic card tests |
| IOCC | International Orthodox Christian Charites |
| LF | Lymphatic filariasis |
| LSHTM | London School of Hygiene & Tropical Medicine |
| LST | Land Surface Temperature |
| LSTM | Liverpool School of Tropical Medicine |
| MCMC | Markov chain Monte Carlo |
| MDA | Mass Drug Administration |
| MERIS | Medium Resolution Imaging Spectrometer |
| MeSHs | Medical Subject Headings |

| | |
|---|---|
| NaPAN | National Podoconiosis Action Network |
| NDVI | Normalized Difference Vegetation Index |
| NOTF | National Onchocerciasis Task Force |
| NTDs | Neglected Tropical Diseases |
| PCA | Principal Components Analysis |
| PET | Potential Evapo-transpiration |
| RAGFIL | The Rapid Geographical Assessment of Bancroftian Filariasis |
| RAPLOA | Rapid Assessment Procedure for loiasis |
| RCT | Randomized Controlled Trial |
| REMO | Rapid Epidemiological Mapping of Onchocerciasis |
| SAFE | Surgery, antibiotic therapy, facial cleanliness and environmental improvement strategy |
| SNNP | Southern Nation and Nationalities and People |
| SRTM | Shuttle Radar Topography Mission |
| SSA | Sub-Saharan Africa |
| STH | Soil-transmitted helminths |
| TDR | Tropical Disease Research |
| UK | United Kingdom |
| UNICEF | United Nations Children's Fund |
| USD | United States Dollar |
| VL | Visceral Leishmaniasis |
| WASH | Water, Sanitation and Hygiene |
| WHO | World Health Organization |

| | |
|---|---|
| YLD | Years of life lived with a disability |
| YLL | Years of life lost to premature death |

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**Author's declaration**

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to these or any other university for a degree, and does not incorporate any material already submitted for a degree.

**Signed:** ___________________________________ **Dated:** 18 September, 2015

Kebede Deribe

# Chapter 1: Introduction

## 1.1. Background and context

Podoconiosis is a non-filarial, non-infectious lymphedema of the lower limb. The disease is geochemical and caused by exposure to red clay soil [1]. The disease is a complex interaction between gene and environment occurring over many years. Mineral particles from the soil penetrate the skin and are taken up by macrophages in the lymphatic system which causes inflammation and fibrosis of the vessel lumen leading to blockage of the lymphatic drainage. This results in oedematous feet and legs and subsequently progresses to elephantiasis and nodular skin changes [2]. The disease causes progressive bilateral swelling of the legs (**Figure 1.1**).

**Figure 1.1** Podoconiosis at different stages in four approximately 50 year old women, from western Ethiopia, (Picture by Jessica Shortall).

In 2011, the World Health Organization (WHO) included podoconiosis in its list of neglected tropical diseases (NTDs) [3]. Although this was an important first step, there is still no global elimination strategy. The lack of any strategy acts as a constraint for the control of the disease[4]. To achieve rapid and community wide impact, the scale-up of podoconiosis interventions is very important. One of the critical impediments for the scaling up of interventions is that the distribution of podoconiosis in space and time is poorly understood[4]. The absence of a global strategy may partly be attributed to the lack of clear understanding of the geographical distribution and burden of the disease. Most countries are considered endemic based on historical and anecdotal reports[5]. Lack of clinical suspicion and diagnostic tests has probably underestimated podoconiosis prevalence in the past. The disease is not well-known to health workers or within the health system and is often confused with lymphatic filariasis (LF), another major cause of lymphoedema in the tropics[6]. There were a few mapping attempts documented in some endemic countries, but these data are as old as 40 years[7,8]. Recent localized studies have also been conducted, but these are limited to a few endemic areas[9-15]. Risk maps based on climate and environmental measures linked with data from past surveys can broadly predict where occurrence is possible, but not enough reliable historical data exists[16,17]. In addition, our understanding of the environmental factors determining the distribution of podoconiosis is limited to very few observations[18-20].

A first step to understanding the distribution of the disease is to clearly describe its epidemiology in person, space and time. In addition, it is important to understand risk differences between individuals, households and communities. Earlier studies identified variation in genetic susceptibility at individual and household levels, which resulted in clustering of the disease among susceptible families [21-23]. Risk differences among individuals, households and communities might not be confined only to genetic susceptibility and may relate to individual protective and preventive behaviours, while the large scale differences may associated with differences in the environment. Only a few studies have identified risk factors at individual and community levels [18,24]. No previous studies have systematically investigated the large scale variation in the risk of podoconiosis disease or identified factors which affect the distribution of the disease.

To accelerate the global momentum towards the control of podoconiosis, it is critical to map the geographical distribution of the disease in all endemic countries. This thesis describes the epidemiology and geographical distribution of podoconiosis in Ethiopia using contemporary and historical data, describes the survey methods used in Ethiopia, estimates the population at risk and the environmental limits of the disease in Ethiopia, identifies individual and environmental risk factors and defines endemicity classifications and elimination targets. This first thesis chapter provides an introduction, describes podoconiosis pathology and clinical features, reviews what is known of the epidemiology of the disease, and outlines the rationale and objectives of the thesis.

## 1.2. Overview of podoconiosis

### 1.2.1 General overview

Podoconiosis affects low-socioeconomic, genetically susceptible individuals who often go barefoot (**Figure 1.2**) [1,2]. It causes gross bilateral, often below-the-knee lymphoedema of the lower limb. The term podoconiosis was coined from two Greek words *podos* and *konos,* which mean foot and dust, respectively, and implies that the disease is caused by exposure of feet to irritant clay soil [2,25]. The Federal Ministry of Health of Ethiopia identified podoconiosis as one of the eight priority NTDs in the country and included it in the three year national master plan (2013-2015) for integrated control of NTDs [26].

**Figure 1.2** Women walking barefoot to the market in podoconiosis endemic area in Ethiopia (Picture by Kora Images)

Implementation of podoconiosis control programmes requires prevalence estimates to decide where to initiate morbidity management services. In the context of integrated foot care, identifying the areas of overlap among diseases (LF, leprosy and Buruli ulcer) which require morbidity management will create synergetic effects. Prevention interventions such as provision of footwear and hygiene education are cross-cutting interventions across multiple NTDs [27]. Therefore, one crucial consideration for the effective integration of prevention and morbidity management for neglected tropical diseases is whether podoconiosis overlaps with filariasis or other NTDs.

## 1.3. Basic biology

Podoconiosis is a multifactorial disease with evidence of genetic susceptibility and environmental exposure (**Figure 1.3**). Based on existing evidence, the cause is that mineral particles induce inflammation among individuals who are genetically susceptible to the disease. This interaction of genetic factors and the environment induces an inflammatory reaction which leads to fibrosis of the lymphatic vessel lumen. Although the mechanism is yet to be studied, it is hypothesised that the mineral particles are engulfed by macrophages and induce an inflammatory response in the vessels which leads to fibrosis, oedema and gross elephantiasis [2].

The disease only affects some barefoot individuals - not all exposed individuals develop podoconiosis. In his clinic during the 1970s in Addis Ababa, Ethiopia, Price noticed that affected individuals would often bring their affected relatives or report that they had affected relatives. Subsequently, he studied 90 families and concluded that the existence of autosomal recessive traits was a factor in the disease. The gene frequency was calculated to be 30% (range 15-40%) in the general population [22].

A 2005 pedigree study among 59 multi-generational families with multiple affected members in southern Ethiopia presented evidence for a genetic basis to podoconiosis. The study illustrated that both genetic and environmental factors contribute to the pathophysiology of podoconiosis [21]. 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. Each of the known susceptibility alleles confers an increased podoconiosis risk, with odds ratios of between 1·79 and 2.0. The location of the risk alleles within the HLA locus suggests that podoconiosis is a T-cell mediated inflammatory condition [23].

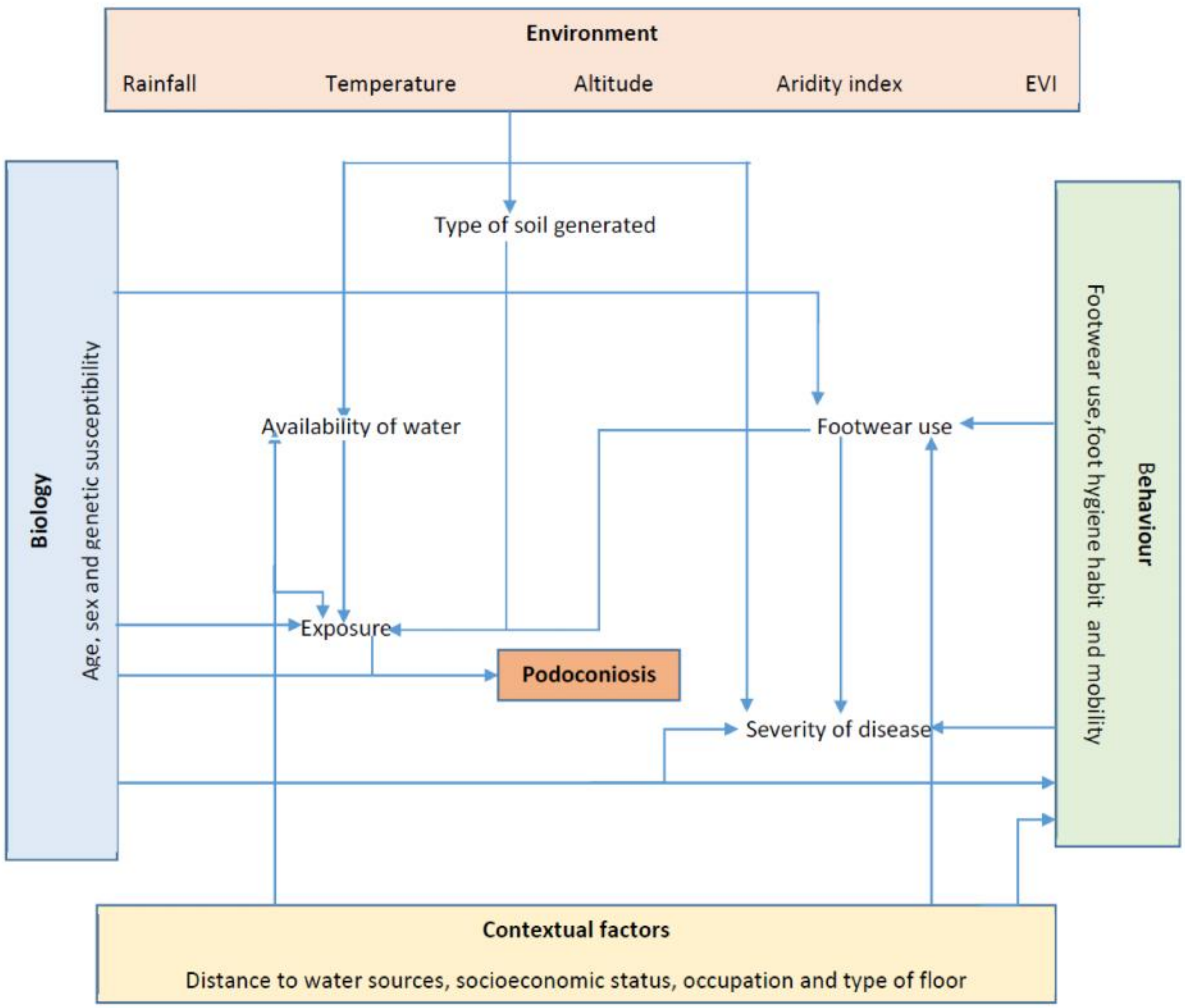


**Figure 1.3** Conceptual framework for the interaction between biology, environment, behaviour and contextual factors. Environment plays an important role in the causation of podoconiosis; the type of soil and soil characteristics being dictated by climate and environmental factors which generate the mineral content and physical properties for the putative triggers. Biological factors such as genetic susceptibility, age and sex determine an individual's risk of acquiring the disease. Behavioural factors such as footwear use, foot hygiene and mobility determine the exposure of individuals to irritant soil particles. Contextual factors such as household economy and access to water determine how individuals practice protective behaviours such as footwear us be and foot hygiene.

### 1.4. Environment

Epidemiological and observational studies have indicated some environmental factors to be associated with podoconiosis. Price noted an association of red clay soil with podoconiosis. In his study[19], he noted a rapid fall of podoconiosis prevalence outside red soil areas. The prevalence of podoconiosis decreased from 6.92% to 2.96% at the edge of the red soil, and further decreased to 0.79% and 0.98%, 25 kilometres away from the edge in two different directions [19]. Climatic factors which may affect the type of soil generated were found to be associated with the high prevalence of podoconiosis. In earlier studies, it was postulated that areas with high prevalence of podoconiosis are characterized by red clay soil, altitude> 1500 metres above sea level(masl), and annual rain fall of 1000mm [19]. The exact cause of podoconiosis in red clay soil is yet to be determined. Previous studies indicated a range of mineral particles. Price suggested that silicate particles cause subendothelial oedema, endolymphangitis, collagenisation and obliteration of the lymphatic lumen [28]. Overlaying the prevalence of podoconiosis on geological maps indicated that there was some correlation between alkali basalt rocks and podoconiosis [20]. The weathering of such rocks produces fine reddish soil which is capable of penetrating intact skin. Soils in the highland endemic areas are more likely to be characterized by particle size $<5\mu m$ size than those found in non-endemic lowland areas [29]. Fyfe and Price [30] injected silica into the lymphatics of the lower extremities of rabbits and found similar changes to that of podoconiosis. Frommel and colleagues [31] also suggested that beryllium and zirconium might be the cause of podoconiosis. A recent study involving geological, spatial, and soil chemical analyses showed that smectite, mica and quartz within the soil were associated with podoconiosis [18]. Some of these particles have been documented to induce an inflammatory response and fibrosis.

Podoconiosis is common among barefoot subsistence farmers, who are exposed to red clay soil due to their work. The disease commonly begins between the age of 10 and 19 [2]. The onset of the disease is more common in the second and third decades of life with the disease occurring up to the sixth decade [21]. The prevalence in the first decade is almost zero. A study from Uganda reported no cases among <10 years old [32], and in southern Ethiopia only 6.8% of the patients were ≤15 years old [11,32]. There are inconsistent findings about the sex ratio in podoconiosis distribution. Most studies indicated that females are disproportionately more affected than males [9,14,15,33], while one study indicated that males are more affected than females[12]. A few studies found no sex difference in the distribution of the disease[11,32] ( **Table 1.1**).

**Table 1.0-1** Sex distribution of podoconiosis

| Study | Number of patients | Male to female ratio |
|---|---|---|
| Price, 1975[34] | 189 | 1:1.4 |
| Mengistu et al, 1987[35] | 146 | 1:4.2 |
| Onapa et al, 2001[32] | 26 | 1:1 |
| Desta et al, 2003[11] | 1890 | 1:0.98 |
| Wanji et al, 2008[33] | 66 | 1:2 |
| Alemu et al, 2011[9] | 1935 | 1:1.94 |
| Molla et al, 2012[14] | 1704 | 1:1.01 |
| Geshere et al, 2012[12] | 123 | 1:0.84 |
| Tekola-Ayele et al, 2013[15] | 379 | 1:1.41 |

### 1.5. Disease presentation

The clinical presentation of the disease starts with a burning sensation and itching on the foot. The disease is bilateral but asymmetrical and almost always limited to below the knees **(Figure 1.4)** [1,9,12,14,15].

**Figure 1.4** Podoconiosis with gross lymphoedema of 45 year old man, from northern Ethiopia, (Picture by Kebede Deribe).

A system for grading the clinical stages of podoconiosis has been developed and validated **(Figure 1.5).** 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 programs in Ethiopia and treatment outcomes have been monitored [36].

| | Stage & Clinical signs | | Stage & Clinical signs |
|---|---|---|---|
|  | **Stage 1.** Swelling reversible overnight. The swelling is not present when the patient first gets up in the morning. |  | **Stage 4.** Above-knee swelling that is not completely reversible overnight; knobs / bumps present at any location. |
|  | **Stage 2.** Below-knee swelling that is not completely reversible overnight; if present, knobs / bumps are below the ankle only. |  | **Stage 5.** Joint fixation; swelling at any place in the foot or leg. The ankle or toe joints become fixed and difficult to flex or dorsiflex. This may be accompanied by apparent shortening of the toes. |
|  | **Stage 3.** Below-knee swelling that is not completely reversible overnight; knobs / bumps present above the ankle. | | |

**Figure 1.5** Clinical staging of podoconiosis, showing the five stages of podoconiosis. Adapted from Tekola et al. (2008) [36].

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 dorsum of the foot, and rough, warty and papillomatous growths that look like moss on the anterior one-third and heel of the foot (**Table 1.2**) [2,37,38]. The stratum corneum of the lower leg and foot of patients with podoconiosis is significantly less hydrated than that of unaffected controls [39]. With time, the swelling becomes soft and pitting ('water-bag type') or nodular and fibrotic ('leathery type'). Late stage disease is characterized by fusion of the inter-digital spaces and ankylosis of the inter-phalangeal and ankle joints [2,37,38,40].

Little is known of the molecular pathogenesis of podoconiosis, but early evidence suggests

**Table 1.0-2** Frequency of signs among podoconiosis patients adapted from Oomen, 1969[7]

| Sign | Number | Percent |
|---|---|---|
| Lymphoedema only | 14 | 15.9 |
| Lymphoedema and skin atrophy | 19 | 21.6 |
| Lymphoedema, skin atrophy and moss | 32 | 36.4 |
| Lymphoedema and moss | 12 | 13.6 |
| Skin atrophy only | 7 | 8.0 |
| Skin atrophy and moss | 3 | 3.4 |
| Moss only | 1 | 1.1 |

that transforming growth factor β-1 (TGF β-1) may play a role [41] .

### 1.6. Diagnosis

Accurate diagnosis of podoconiosis is important for case management, surveillance, and research. Podoconiosis is a clinical diagnosis. There is no gold standard point-of-care diagnostic tool. Although lymphoedema of the lower leg in endemic areas is highly suggestive, no clinical signs of disease are pathognomonic 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 [9,12-15]. Therefore, enquiring about family history may also assist as a pointer towards the diagnosis of podoconiosis although shared risks of LF might also result in clustering of LF cases within a household.

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 establishing 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 [2], 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 [1]. 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 immunochromatographic card tests (ICT) (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 this 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 [1]. Onchocerciasis also 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.

**1.7. Control strategies.**

The key strategies for podoconiosis control are prevention of contact with irritant soil (primary prevention) and lymphoedema morbidity management (secondary and tertiary prevention) [42]. The primary prevention of podoconiosis includes using footwear, regular foot hygiene and covering the house floor. These measures will prevent contact between foot and the minerals, triggering the inflammatory process. Secondary and tertiary prevention of the disease are based on lymphoedema management which consists of foot hygiene, foot care, wound care, compression, exercises and elevation, treatment of acute attack and use of shoes and socks to reduce further exposure to the irritant soil (**Figure 1.6**). In some cases with nodules, surgical excision of the nodules is a routine practice. Price described the objectives of secondary and tertiary prevention, which are [43]

- To arrest progress of early disease
- To reduce the frequency of acute attack
- To reduce the swelling of the limbs
- Surgical reduction of the swelling and
- To maintain reduction of the swelling


**Figure 1.6** Components of podoconiosis lymphoedema management.

The first proof-of-concept study of podoconiosis lymphoedema morbidity management indicated modest clinical improvement and significant improvements in quality of life [44]. Currently, there is an ongoing Randomized Controlled Trial (RCT) which is aimed at measuring the effectiveness and cost-effectiveness of morbidity management[45].

## 1.8. Public health impact

Podoconiosis results in a high economic burden on both endemic country governments and individuals [46]. 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 United States Dollar (USD) per year, which when extrapolated to the whole country, suggests a 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 in the same occupations. Podoconiosis patients lose 45% of their economically productive time because of morbidity associated with the disease [46]. Total direct costs of podoconiosis amounted to the equivalent of US$ 143 per patient per year.  The total cost of successfully treated tuberculosis cases in Ethiopia was found to be $158.9[47], while the direct outpatient and inpatient cost for hospitalized cervical cancer patients were found to be $334.2 and $329, respectively[48]. In another study in Ethiopia the direct cost of malaria was estimated at $1.6 per episode [49]. Another study estimated the total direct cost of HIV at $266 (pretreatment costs) and $73 (annual antiretroviral treatment costs)[50].

Studies have documented that 77.4% to 97% of patients have experienced acute dermatolymphangioadenitis (ADLA) at least once per year [9,14,15]. 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 characterized 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[9,14,15].

The social impact of podoconiosis is also significant. Qualitative studies in Southern Ethiopia have shown that podoconiosis is considered the most stigmatizing health problem in endemic areas [51,52]. 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 [14,15,51-53]. In a study conducted in northern Ethiopia, 13% of patients mentioned that they had experienced one or more forms of social stigmatization at school, church, or in the market place [14]. In southern Ethiopia, 55.8% of community members showed stigmatising attitudes towards social interactions with podoconiosis patients [53]. 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 [54]. In addition, there is a widespread belief that podoconiosis cannot be prevented nor treated [6]. 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 NTDs such as soil-transmitted helminths (STH) [55]. Using a validated stigma scale [56], a quantitative study in northern Ethiopia showed that the mean felt stigma was 21.7 (range 0 to 45) and mean enacted (experienced) stigma, 9 (range 0 to 51) [57].

### 1.9. Distribution and burden of podoconiosis

The contemporary global distribution of podoconiosis is not well understood. Using anecdotal and empirical evidence, current estimates of populations at risk have been derived only crudely. Globally, it is estimated that there are 4 million people with podoconiosis[23]; mainly in tropical Africa, central and South America and Southeast Asia. Nonetheless, there is no clear information how the figure is estimated. In Africa, the disease has been reported from Burundi [34], Cameroon [33,58,59], Cape Verde [60], Equatorial Guinea [61], Ethiopia [40], Kenya [40], Rwanda [34], Sao Tome & Principe [62], Sudan [60], Tanzania [63] and Uganda [32]. Podoconiosis was reported in the Central American highlands in Mexico and Guatemala south to Ecuador, Brazil [2,5,64], Suriname and French Guiana in the coast of South America [65,66]. In Asia, although filarial elephantiasis predominates in India, podoconiosis has been reported from north-west

India, Sri Lanka and Indonesia,[2,5] (**Figure 1.7**). Except in a few countries, most of the reports are as old as 40 years and need to be updated (**Table 1.3**).

**Table 1.0-3** Summary and sources of geographical distribution of podoconiosis

| Study, study or publication year | Year of study | Country | Location | Sampling method | Case ascertainment | Case (sample size) | Prevalence, % (95%CI) |
|---|---|---|---|---|---|---|---|
| Africa | | | | | | | |
| Price, 1976[34] | 1976 | Burundi & Rwanda | Nationwide | Market survey | Observation of frank lymphoedema | Burundi 61 (6156)<br>Rwanda 128 (20446) | 0.99 (0.77-1.27)<br>0.63 (0.53-0.75) |
| Price & Henderson, 1980 [58] | 1979 | Cameroon | North-west | Community based survey | Clinical, parasitological, pathology and mineralogy | 130 cases | |
| Wanji et al 2008[33] | 2006 | Cameroon | North West province, Ndop and Tubah | Community based | Clinical, parasitological and entomological | 66 (834) | 7.91 (6.27-9.94) |
| Cho-Ngwa et al., 2009[67] | 2003 | Cameroon | Bambui Health District of NW Cameroon | Community based | Clinical and parasitological | 16 (301) | 5.32 (3.30-8.46) |
| Corachan et al 1988[61] | 1988 | Equatorial Guinea | Bioko Island | Case report | Biopsies of the lymph nodes. | 2 cases | |
| Price 1990[2] | 1988 | Equatorial Guinea | Bioko Island<br>Equatorial Guinea | Community based | Clinical | 26 (3577) | 0.73 (0.50-1.07) |
| Tekola Ayele et al, 2013[15] | 2011 | Ethiopia | Bedele Zuria district | Community based | Clinical | 379 (6710) | 5.65 (5.12–6.23) |
| Molla et al, 2012[14] | 2011 | Ethiopia | Debre Eliyas and Dembecha | Community based | Clinical | 1,704 (51,017) | 3.34 (3.19-3.50) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | districts | | | | |
| Geshere Oli et al, 2012[12] | 2012 | Ethiopia | Midakegn district, | Community based | Clinical, parasitological | 123 (1,656) | 7.43 (6.26-8.79) |
| Alemu et al, 2011[9] | 2011 | Ethiopia | Gulliso woreda | Community based | Clinical | 1,935 (69,465) | 2.79 (2.67–2.92) |
| Morrone et al 2011[68] | 2010 | Ethiopia | Tigray | Hospital based | Clinical parasitological | 18 cases | |
| Desta et al, 2007[11] | 2001 | Ethiopia | Wolaitta Zone | Community based | Clinical | 1890 (33,678) | 5.46 (5.21-5.71)* |
| Birrie et al., 1997[10] | 1997 | Ethiopia | Pawe settlement area | Community based | Clinical, parasitological | 68 (1900) | 3.58 (2.83-4.51) |
| Formell et al, 1993[31] | 1993 | Ethiopia | Ocholo | Community based | Clinical | 153 (3022) | 5.06 (4.33-5.90) |
| Kloos et al., 1992[13] | 1992 | Ethiopia | Gera & Didessa,<br>Western Ethiopia | Community based | Clinical | 31 (416) | 7.45 (5.30-10.52) |
| Mengistu et al., 1987[35] | 1987 | Ethiopia | Ocholo Gamo Gofa | Community based | Clinical | 146 (2,689) | 5.43 (4.64-6.35) |
| Price,1974[19] | 1974 | Ethiopia | Wolaitta Zone, Wajifo, Shenoe and Alaba | Market survey | Observation of frank lymphoedema | 1781 (43573) | 4.09 (3.91-4.28) |
| Oomen, 1969[7] | 1969 | Ethiopia | Nationwide | Market survey | Observation of frank lymphoedema | 6770 (247,908) | 2.73 (2.67-2.79) |
| Cohen, 1960 [40] | 1954 (Ethiopia)<br>1958 (Kenya) | Ethiopia and Kenya | Fort Hall and Nairobi (Kenya)<br>Addis Ababa (Ethiopia) | Facility based | Clinical and parasitological | 32 (13 Kenya and 19 Ethiopia) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Clark, 1948[69] | 1948 | Kenya | Fort Hall | Facility based | Clinical and parasitological | 200cases | |
| Crivelli, 1986[70] | 1986 | Kenya | Nyambene Range | Community based | Clinical and parasitological | 105 (2711) | 3.87 (3.21-4.66) |
| Ruiz 1994 [62] | 1988 | Sao Tome & Principe | Districts of Cantagalo and Lemba | Community based | Clinical and pathological | 11 (1200) | 0.92 (0.52-1.64) |
| Jordan et al 1956 [71] | 1956 | Tanzania | Tanganyika | Community based | Clinical and pathological | 74 cases | |
| de Lalla et al 1988 [63] | 1988 | Tanzania | Iringa district | Hospital based | Clinical and parasitological | 30 cases | |
| Lowenthal, 1934[66] | 1934 | Uganda | Kampala | Facility based | Clinical and histological | 11 cases | |
| Onapa et al 2001[32] | 1998 | Uganda | Kapchorwa District | Community based | Clinical, parasitological and entomological | 26 (575) | 4.52 (3.10-6.54) |
| Price, 1984[2] | 1984 | Sudan | Jebel Marra | Observation | Observation of frank lymphoedema | 28 cases | |
| De Meira et al, 1947[72] | | Cape Verde | | Community based survey | Observation of frank lymphoedema | 21 (7000) | 0.30 (0.20-0.46) |
| Pfaltzgraff, 1975[2] | | Nigeria | | Report | Not indicated | | |
| Asia | | | | | | | |
| Russel et al., 1983[73] | 1974-1982 | India | Imphal, Aizawal & Bikaner | Community based survey | Clinical and parasitological | 9 (4214) | 0.21 (0.11-0.40) |
| Price, 1990 [2] | | Sri Lanka | | Report | Not indicated | | |

| | | | | |
|---|---|---|---|---|
| Partono, 1982 [2] | Indonesia | Report | Not indicated | |
| Americas | | | | |
| Price, 1990 [2] | Mexico | Report | Not indicated | |
| Price, 1990 [2] | Guatemala | Report | Not indicated | |
| Price, 1990 [2] | Ecuador | Report | Not indicated | |
| Tada & Marsden, 1993[64] | Brazil | Case report | Not indicated | 1 case |
| Price, 1990 [2] | Colombia | Report | Not indicated | |
| Price, 1975 [2] | El Salvador | Report | Not indicated | |
| Price, 1990[2] | Costa Rica | Report | Not indicated | |
| Lowenthal, 1934[66] | Honduras | Report | Not indicated | |
| Lowenthal, 1934[66] | Peru | Report | Not indicated | |

Based on market counts, the 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% [34]. Podoconiosis commonly begins between the ages of 10 and 19[2]. 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 [32]. In a study conducted in the Northwest province of Cameroon, a prevalence of 8.1% was documented among individuals ≥15 years old [33].

Ethiopia is where most studies on podoconiosis have been conducted. Studies conducted in 1960 and 1970 reported widespread occurrence of podoconiosis in Ethiopia [8]. Localized studies over the past ten years have documented that the prevalence of podoconiosis ranges from 2.8% to 7.4% in endemic areas [9,12-15,74].

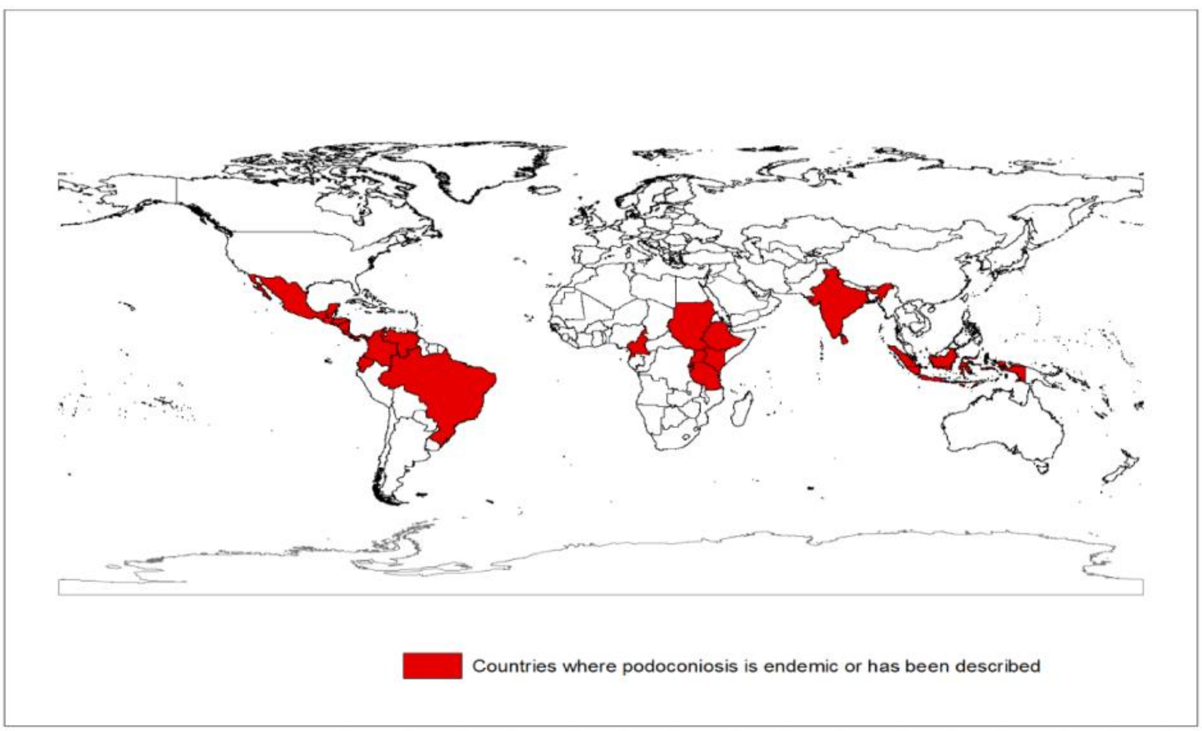

**Figure 1.7** Countries where podoconiosis is endemic or has been described (Adapted from WHO website)[3].

## 1.10 Mapping the distribution of podoconiosis

Mapping serves as a geographic decision-making tool for identifying areas of particular risk as well as for the design, implementation and monitoring of control programmes. In the last decade, mapping of several diseases have been used as a powerful tool to scale up large scale programs. Mapping of STH infection [75,76], schistosomiasis [77,78], LF [79], trachoma [80], malaria [81], *Loa loa* [82,83], onchocerciasis [84] and human trypanosomiasis [85] and leishmaniasis [86] has been conducted at a variety of spatial scales.

A first step in mapping is the collation of survey data available from both published and unpublished sources. Collation of global surveys on STH through Global Atlas of Helminth Infection (GAHI) and geostatistical modelling led to the mapping of STH at a global level and to estimate transmission limits, infection prevalence and population at risk [76,87]. In addition, the mapping platform provides country level maps of schistosomiasis, LF and water sanitation and hygiene (WASH) services [75,79]. The Rapid Geographical Assessment of Bancroftian Filariasis (RAGFIL) was developed by WHO/Tropical Disease Research (TDR) [88]. The RAGFIL uses a grid sampling with 25 kilometres or 50 kilometres between sampled communities. The prevalence of LF is estimated using ICT for the detection of circulating antigen from adult *W. bancrofti* filarial antigenaemia [89,90]. Rapid Epidemiological Mapping of Onchocerciasis (REMO) developed by WHO/TDR has been an important mapping approach to define the geographical distribution of onchocerciasis which led to its effective control [84]. REMO uses a rapid mapping technique to identify high risk communities for onchocerciasis based on proximity to fast flowing rivers. The approach uses sampling of individuals and assessing them for onchocercal nodules and classify areas into risk categories [91]. Rapid Assessment Procedure for loiasis (RAPLOA), was also developed by WHO/TDR and is a rapid assessment procedure for loiasis that relates the prevalence of key clinical manifestation of loiasis i.e. history of eye worm to the level of endemicity of the infection, is a very useful tool to identify areas at potential risk of *Loa loa* post ivermectin treatment encephalopathy [92]. Based on a subsample of the communities selected, the prevalence of history of eye worm will be determined, which will inform the treatment strategies. The outcome of the mapping have been extensively used by African Programme for Onchocerciasis Control (APOC) [82]. The global mapping of trachoma [80] and malaria are also important initiatives which inform geographical decisions of interventions [81].

A second major aspect of mapping is predictive risk mapping using environmental variables [77] which can help predict distributions in areas without suitable empirical data. The Bayesian framework is one of the approaches widely used, which is more flexible and a more robust modelling approach than the frequentist approach. The Bayesian framework offers a number of advantages over the frequentist approach[93]. First, unlike the frequentist approach the Bayesian framework uses prior probability distribution of parameters based on information from previous studies in interpreting data from a current study. Although there are continued debates about the importance of the use of priors with the fear of subjectivity[93]. Nonetheless there are objective selection of priors based on previous data and sensitivity analyses to evaluate the robustness of the prior choice. In addition for investigators who wish to avoid incorporating prior information certainly can choose a non-informative prior (i.e., one that assigns equal or close to equal probability to a wide range of plausible values) for the regression coefficients of interest, which yield results that are quite similar to maximum likelihood-based inferences[94]. Second, Bayesian methods use Markov chain Monte Carlo (MCMC) algorithms, which repeatedly generate random samples from a target distribution, conditional on the data. After convergence, these samples represent serially correlated draws from the joint posterior distribution of the model parameters. Based on a large number of iteratively generated samples, one can easily obtain estimates of the posterior distribution of any parameter or function of parameters in a model. The advantage of the Bayesian MCMC approach is it is flexibility, and ability to fit realistic models to complex data sets with measurement error, censored or missing observations and multilevel structures and multiple endpoints[93]. Third, Bayesian approaches have the advantage of allowing access to the posterior distribution for useful summary statistics. One can also estimate the posterior probability that a parameter is greater than certain values and can incorporate prior information with the empirical data for a flexible decision framework. This is particularly useful for disease mapping[95].

The Bayesian framework can readily take into account the spatial variability in the epidemiological and environmental data and can account for model uncertainty. Predictive risk mapping has been employed to determine target areas for mass treatment for STH in Kenya [16]. Survey data collected between 1974 and 2009 were assembled and high resolution satellite data were extracted to the survey locations. Using Bayesian space-time geostatistical modelling, the probability that infection prevalence exceeded the 20% threshold across Kenya for both 1989 and 2009 was estimated. Models were validated in subset of data randomly allocated. It was possible to identify districts requiring treatment which exceed the 20% threshold. The model estimated the number of school-age children who live in districts which require treatment. In addition, the estimation of uncertainty in the spatial predictions help identify the area where further data collection is required.

Another analytical framework used for predictive mapping is Boosted Regression Tree (BRT) modelling [96,97]. This approach has been effectively used in global mapping of dengue, LF, leishmaniasis and malaria vector mosquitos [79,86,98,99] and has superior predictive accuracy compared to other distribution models [100]. In brief, BRT modelling combines regression or decision trees and boosting in a number of sequential steps [96,97]. First, the threshold of each input variable that results in either the presence or the absence of a disease is identified, allowing for both continuous and categorical variables and different scales of measurement amongst predictors [96]. Second, boosting is a machine-learning method that increases a model's accuracy iteratively, based on the idea that it is easier to find and average many rough 'rules of thumb', than to find a single, highly accurate prediction rule. Recently, the BRT model was used to develop the global risk map of LF [79]. Data from a systematic search and combined with a set of gridded environmental covariates known, or proposed, to affect LF transmission status built BRT model. The finding helped in delineating the transmission limits of LF globally and provided insight into post-mass drug administration surveillance and targeted control.

A third important application of mapping is the estimating the burden of disease burden. In this work there is a need to provide comparable indicators across diseases and injuries, based on standardized summary measures [101]. The disability-adjusted life year (DALY) is a commonly used metric used by the Global Burden of Disease (GBD) study [101]. The

DALY is calculated as a weighted measure of morbidity and mortality. It is a sum of the years of life lost (YLL) to premature death and years of life lived with a disability (YLD). YLLs are calculated by multiplying number of death at each age by the standard life expectancy. YLDs are calculated by multiplying prevalence of a given disease and sequelae by disability weights. Such approaches were used extensively by the Global Burden of Disease Study and several NTDs. A seminal work by Pullan and colleagues [87] used prevalence data for 6,091 locations in 118 countries for STH. The data were used to estimate age-stratified mean prevalence of disease using a combination of geo-statistical models and empirical approaches. The results of the estimation were incorporated into the Global Burden of Disease Study 2010 analytic framework [101] to estimate the public health burden of STH. The findings helped in estimating the global number of infected and YLL due to STH, the relative burden of STH and a benchmark for evaluating future interventions of STH. No equivalent work has been conducted to date to estimate the global disease burden of podoconiosis.

The first attempt of mapping podoconiosis was conducted in 1970s in Ethiopia [8]. Oomen conducted markets surveys in 56 markets in several provinces of Ethiopia with the help of US Peace Corps [7]. Two enumerators were located at an entrance road to the market and they counted all individuals estimated to be 15 years old. Individuals with frank lymphoedema were recorded segregated by sex. Oomen acknowledged several limitations of the approach. First, advanced forms of elephantiasis limits walking and people with such forms of elephantiasis are less likely to attend markets. Second, early cases will be less visible and might be missed by the enumerators. Third, all oedemas of the lower leg due to other causes might be mistaken for elephantiasis. Fourth, individuals tend to attend more than one market per day and this might result in double counting. Finally, the survey excluded much of the eastern part of the country. Subsequently, Price combined anecdotal evidence among rural health clinics and schools, data from elephantiasis clinic attendants, and Oomen's (1969) market based survey[7] and produced a map of podoconiosis in Ethiopia [8]. Although the map is an important piece of work and has served as an important source of information, it has several limitations. First, the 1,226 patients seen in his clinic might give biased information rather than a true distribution of the disease. Most patients seen in the clinic were from close provinces. This might be simply a result of proximity than the true underlying distribution of the disease. Second, the school enquiry technique included asking older students whether they have seen elephantiasis cases in their communities. Although the approach provides some indication of the presence or absence of elephantiasis cases in the communities, the quality of the information depends on the availability of schools and understanding of the students. In addition, differentiating different causes of elephantiasis would be impossible. In recent years, surveys limited to endemic areas have been conducted. Most of the surveys used a complete census of the community [9,11,14,15] and conducted parasitological or ICT test in sub-sample of the cases to exclude causes such as LF. Recent studies have 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 [12,102]. Although communitywide census was ideal for counting the exact number of podoconiosis cases in a community, it was found to be resource-intensive and logistically challenging at a large scale. Therefore, a more practical and less costly mapping approach is required to map the distribution of podoconiosis at country, continental and global level.

As reviewed above, mapping approaches and spatial modelling techniques have been applied extensively in other diseases including NTDs, but their application to podoconiosis has been minimal to date. Only one study [18] used spatial modelling to explore potential mineral causes of podoconiosis. The application of these techniques will have paramount importance in identifying environmental drivers of podoconiosis, estimating population at risk of podoconiosis and characterising environments suitable for the occurrence of podoconiosis and delineating the environmental limits of podoconiosis. Delineation of the limits and identification of ecological correlates will help to develop risk maps in other potentially endemic counties. Where there is scarcity of data, a geostatistical framework can be used to predict the prevalence of podoconiosis in un-sampled areas.

### 1.11 Elimination of podoconiosis targets, definitions and metrics

The possibility of eradicating and eliminating diseases has been discussed over serval decades [103,104]. Historically, several diseases have been targeted for elimination or eradication including yellow fever, yaws, malaria and leprosy [105]. Smallpox was eradicated, polio and Guinea worm are in the last stage [106]. Inspired by the World Health Organization's 2020 Roadmap on NTDs[107], the London declaration is one of the most important milestones for the control and elimination of ten NTDs. The declaration aims to sustain and expand interventions to eradicate Guinea worm disease, and to eliminate lymphatic filariasis, leprosy, sleeping sickness (human African trypanosomiasis) and blinding trachoma by 2020. The declaration also has the objective to help control schistosomiasis, soil-transmitted helminthes, Chagas disease, visceral leishmaniasis and river blindness (onchocerciasis) by 2020[108]. The declaration aims to ensure drug supply, advance research and development, enhance collaboration, ensure adequate funding, provide technical support and provide regular updates on progress. These elimination declarations are highly motivating as described by Whitty [104].

> "Eradication is highly attractive as a concept. The idea that one generation can, for all time, get rid of a disease for all successive generations is very motivating, including to people not usually involved in public health. Under some circumstances, eradication can be highly cost effective, because a time-limited surge in spend can save for all time, and this certainly was the case for smallpox [104]"

Some argue that unrealistic elimination targets may have negative consequences [109,110]. After leprosy was declared to be eliminated in terms of public health important in some countries, there was a significant reduction in funding, experts and research outputs [104,110]. This highlights the need to carefully consider appropriate target-setting and communication surrounding the meaning of elimination [111].

The concept of disease reduction should be clearly defined, in 1998, Dowdle proposed a definition of 'control' as a reduction in the incidence, prevalence, morbidity or mortality of an infectious disease to a locally acceptable level; 'elimination' as a reduction to zero incidence of disease or infection in a defined geographical area; and 'eradication' as the permanent reduction to zero of worldwide incidence of infection [106]. Elimination is also defined in terms of a public health problem as a reduction of prevalence to such a low level that it is no longer considered a public health problem, based on arbitrary criteria or definitions [110]. As can be seen from Dowdle [106] definition of eradication, there is no need for continuation of intervention after eradication of a disease worldwide, while there is a need for continued intervention after control and elimination to prevent re-emergence and re-establishment of diseases or infections. It is the need for continuation of interventions after elimination that leads to confusion among policy makers [103].

Elimination and eradication efforts have often been focused on infectious diseases [103]. Nonetheless, the Centres for Disease Control and Prevention (CDC) [105] identified non-infectious disease conditions potential for elimination including vitamin A deficiency, iron deficiency and folic-acid-dependent neural tube defects (FADNTDs) and iodine deficiency [105]. As a non-infectious disease, podoconiosis appears to be a target for elimination, given the simple and effective interventions. Podoconiosis elimination, however, needs clear targets and metrics to implement focused, sustained and measurable interventions. Given the non-infectious nature of podoconiosis, concepts such as reproduction number required for mathematical modelling do not hold true [104]. Hence, the elimination targets could follow pragmatic approaches such as a Delphi technique to define targets based on access to services. The metrics should also extend to endemicity classifications which are important in priority setting.

## 1.12 Rationale, objectives and thesis outline

### 1.12.1 Rationale of the study

The last five years have been remarkable and historic in podoconiosis control and research. In 2011, podoconiosis was identified as one of the NTDs by the WHO. While this is an important milestone in this dynamic and complex global health arena, the distribution of the disease is not clearly known. The elimination of podoconiosis needs detailed, up-to-date understanding of the distribution of the disease to identify priority areas, estimate individuals requiring interventions and to monitor future progress. International donors, development partners and endemic country governments are allocating resources for the prevention, treatment and elimination of NTDs. Endemic countries and implementing partners are required to make evidence-based plans and to track progress and show the effectiveness of program implementation to cope with resources constraints and changing demands [112].

Mapping the geographical distribution of podoconiosis will generate important evidence for estimating disease burden and guiding control programs. Spatially referenced data will help us to understand the distribution at large and small scales. In turn, this will enable us to first, estimate the population at risk, second, estimate disease burden, and third, stratify priority areas which could guide control and prevention interventions leading to cost-effective interventions. In addition, these data may help to identify areas of overlap with other neglected tropical diseases (NTDs), which will help in integrated control. Overall, the mapping of podoconiosis disease burden will help target resources, monitor control progress, and advocate for investment in podoconiosis prevention, control, and ultimately elimination.

Yet the recognition of the importance of mapping is not being accompanied by an adequate understanding of the geographical distribution of the disease. Practically there are no contemporary mapping activities for podoconiosis. Today, there are only a few localized studies conducted in some parts of Ethiopia and other endemic counties [9,11,12,14]. Partly this is due to the absence of a mapping strategy for podoconiosis. Identifying risk factors at individual and cluster levels, understanding the spatial distribution, determining the environmental limit and population at risk would require a well-designed and robust study. Unfortunately, to date, there have been no such studies to respond to these questions in Ethiopia and elsewhere.

My starting point is to conduct a review of the historical and contemporary literature and develop a repository of podoconiosis mapping data. I sought to geo-locate the data points to understand the historical distribution of the disease [113]. Such data could inform the distribution of the disease and, if appropriately modelled for various changes which have occurred, predict the current status of the disease. I proposed also to conduct a nationwide mapping of podoconiosis in Ethiopia to be used as a valuable tool for policy makers and program planners. In addition, the mapping approach could also be used in other endemic countries. This research, therefore, directly contributes to the necessary evidence for the implementation of podoconiosis interventions and provides evidence of a mapping approach which can be used in other potentially endemic countries.

### 1.12.2 Thesis objectives

#### 1.12.2.1 General objective

The aim of this thesis is to investigate the spatial distribution of podoconiosis using rapid epidemiological mapping techniques, to generate a map on which to base podoconiosis control in Ethiopia and develop a methodology that can be used in other endemic countries.

#### 1.12.2.2 Specific objectives

1. To describe the spatial distribution of podoconiosis in Ethiopia using historical data and identify information gaps;

2. To describe podoconiosis mapping techniques used in Ethiopia and to document lessons applicable to other endemic countries;
3. To identify individual and cluster-level factors underlying spatial patterns of podoconiosis risk in Ethiopia;
4. To identify the environmental determinants, spatial limits and to estimate the number of people at risk of podoconiosis in Ethiopia;
5. To define the endemicity classification and elimination targets of podoconiosis.

### 1.12.3 Thesis outline

The thesis is organized into eight chapters, according to the aims and objectives mentioned above. As outlined in **Table 1.4**, each chapter focuses on describing one part of the study, from the historical distribution, risk factors, contemporary distribution of disease, the applicability of the mapping approach and discussion of implications for future mappings and disease control.

| **Table 1.0-4** Outline of the thesis |
|---|
| **Chapter 1:**The background and context<br><br>**Chapter 2:** The burden of neglected tropical diseases in Ethiopia<br><br>**Chapter 3:** Historical distribution of podoconiosis in Ethiopia<br><br>**Chapter 4**: Mapping of lymphatic filariasis and podoconiosis, the approach and lessons learnt<br><br>**Chapter 5:** Multilevel and geostatistical modelling of podoconiosis risk: results from the first nationwide mapping<br><br>**Chapter 6:** Mapping and modelling the geographical distribution and environmental |

limits of podoconiosis in Ethiopia

**Chapter 7:** Measuring elimination of podoconiosis, endemicity classifications and targets: an international Delphi exercise

**Chapter 8:** Discussion

In order to provide a broader context of the work, Chapter 2 describes the burden, distribution of disease, challenges and implementation status of control and elimination for a range of NTDs in Ethiopia. Chapter 3 describes the assembly of historical data in Ethiopia and their use to assess the historical distribution of the disease and identify environmental variables potentially associated with podoconiosis prevalence. Chapter 4 details the integrated mapping approach for podoconiosis and LF and discusses the potential approach for other endemic countries. Chapter 5 uses a multilevel modelling approach to explore the respective roles of individual, socio-demographic, household and environmental factors on podoconiosis risk and the relative importance of variation in risk at different levels. Chapter 6 uses a boosted regression tree (BRT) to predict the spatial occurrence of podoconiosis. These results helped to identify environmental factors associated with the occurrence and prevalence of podoconiosis, define the spatial limits of disease occurrence, and estimate the population living in areas at risk from the disease (**Figure 1.8**). Chapter 7 describes the definition of endemicity classification and elimination targets for podoconiosis using the Delphi technique among experts. The results here were used in Chapter 6 to classify districts according to endemicity classes. Chapter 8 discusses the main findings and highlights the important issues that have arisen from this work.

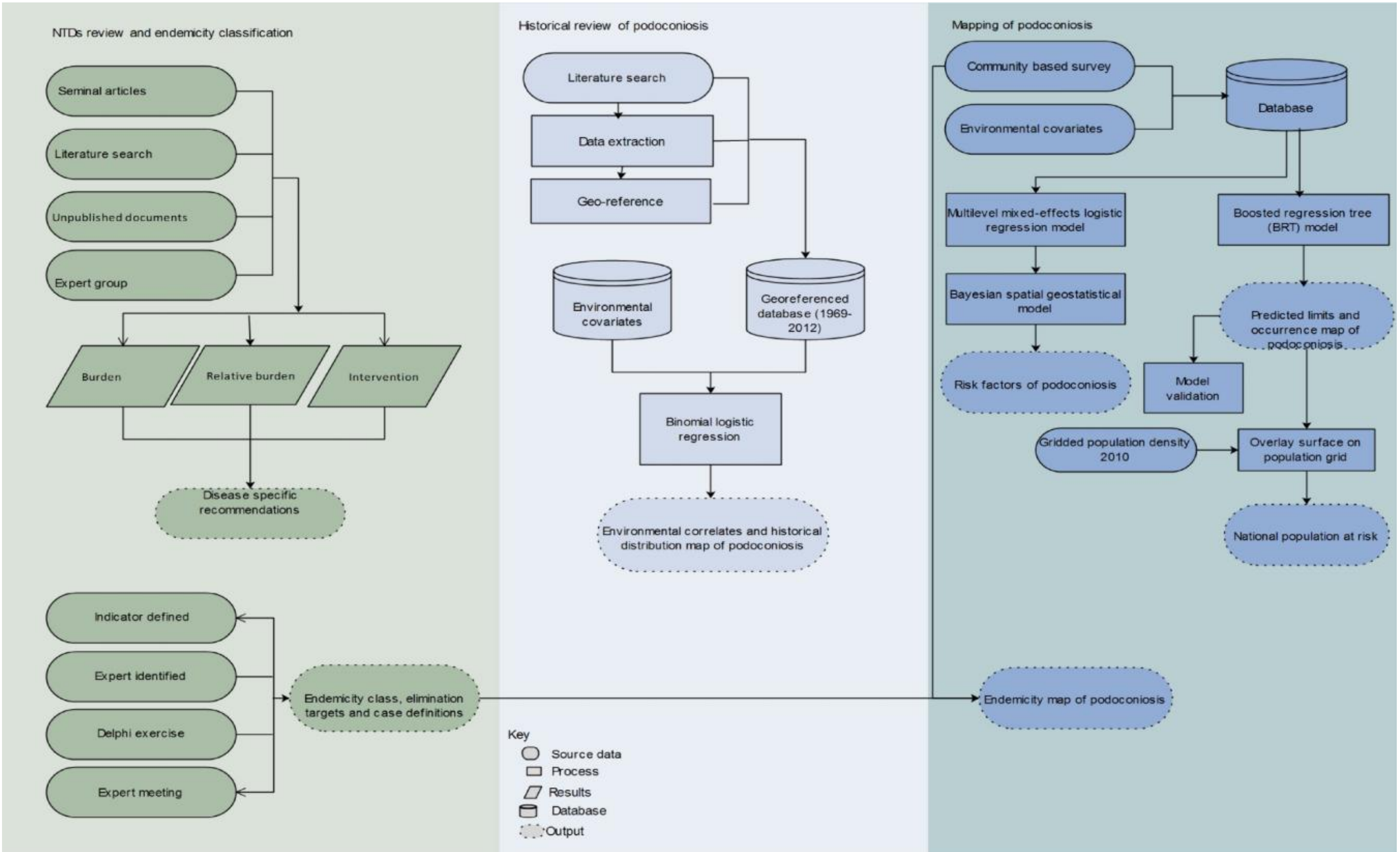


**Figure 1.8** Thesis chapters and their relationship and outputs. The first shade indicates review of literature for the burden of NTDs in Ethiopia and elimination targets, the second shade indicates database from the historical data, the last shade indicates the contemporary mapping activity.

# Chapter 2: The burden of Neglected Tropical Diseases in Ethiopia

## 2.1 Overview

The current chapter describes the burden of neglected tropical diseases (NTDs) in Ethiopia. It provides a background to the thesis and acted as a comprehensive review as Ethiopia was preparing to launch an integrated neglected tropical disease (NTD) master plan. There had not been a comprehensive work to back the master plan and serve as a background document. Although there were studies on many of the NTDs, there was no single document in which readers could find a concise review of the evidence about disease burden and the status of control measures in the country. This review also allowed us to understand the relative contribution of podoconiosis in Ethiopia, a disease classified as a NTD by the WHO in 2011[1], in the context of all NTD burden in Ethiopia.

This chapter describes the distribution of NTDs, their burden and the status of control interventions in Ethiopia. Important disease specific recommendations and approaches towards integrated prevention and control of NTDs are discussed. The work presented here was published [114].

## 2.2 Introduction

NTDs are a group of chronic parasitic diseases and related conditions that represent the most common illnesses of the world's poorest people or the 2.7 billion people who live on less than US$2 per day [115,116]. More than 1 billion people – a seventh of the world's population – suffer from one or more NTDs [117]. Despite the substantial disease burden they impose, NTDs have largely been ignored in the global health architecture until recently. Social stigma, prejudice, marginalization and the extreme poverty of afflicted populations are among the factors contributing to the neglect of these diseases. Lack of funding for the prevention and treatment of these diseases is also a contributing factor [118]. Although NTDs contribute to severe morbidity and disability, they contribute fewer years lost due to disability in terms of Disability Adjusted Life Years (DALYs) compared to the five big diseases (pneumonia, HIV/AIDS, diarrheal diseases, tuberculosis and malaria)[119]. According to the Global Burden of Disease (GBD) and risk factors study 2013, pneumonia contributed 411 million, HIV/AIDS 361.9 million, diarrheal diseases 330.6 million, tuberculosis 316 million, malaria 103.6 million and all NTDs 101.5million DALYs in Ethiopia[120].

Of more than seventeen NTDs, seven attract the most attention because of their high prevalence and amenability to control worldwide [121]. These are the soil-transmitted helminth infections (hookworm, ascariasis, and trichuriasis); lymphatic filariasis; schistosomiasis; trachoma and onchocerciasis [121]. Globally, an estimated 438.9, 819.0 and 464.6 million people were infected with hookworm ascariasis, and trichuriasis in 2010 respectively[87]. Worldwide 200 million people are infected with schistosomiasis, and 120 million with lymphatic filariasis in 83 countries [121,122]. Onchocerciasis affects nearly 37 million people in 34 countries, and is most abundant in Africa, with small foci in southern and Central America [123]. Trachoma affects 84 million people globally [118].

NTDs have tremendous health and development impacts. These diseases hinder economic development, cause chronic life-long disability, and impair childhood development in the poor and disenfranchised communities in which they are most prevalent. They reduce child survival, educational attainment and agricultural productivity, and result in significant treatment costs [118,121,124,125].

In Ethiopia, most of the NTDs included in the WHO list are present, except for probably Chagas disease and yaws. Although comprehensive, systematic and integrated responses are lacking, control programs for individual NTDs such as onchocerciasis and trachoma exist on a national scale. Despite the huge burden of NTDs in Ethiopia, no comprehensive reviews have quantified the burden or distribution of these NTDs. This review was conducted to document the prevalence and burden of NTDs in Ethiopia.

We identified seminal articles published in peer-reviewed journals and reports that were pertinent to the control of NTDs. We consulted with experts on this subject, and searched key databases, including PubMed, Medline, Embase, Cochrane, Web of Science, CINAHL Plus, and Popline databases, contacted experts, and hand-searched reference lists for eligible studies, archives of Ethiopian national journals and the WHO's Weekly Epidemiological Record, using search terms including the specific diseases listed as NTDs by the WHO. The websites of central and regional governments and of international agencies were accessed for relevant reviews, guidelines, and databases. The exclusion and inclusion criteria for the papers were deliberately kept flexible. The scope of the review was increased on the basis of findings from the review of key papers and reports. Relevant published and unpublished technical documents were accessed for review. Senior experts in several NTDs were included to mediate between the information found in the literature and practical knowledge on the ground.

## 2.3 Review of Disease Burden

### 2.3.1 Soil Transmitted Helminths

In Ethiopia, hookworm is estimated to infect 11 million people (Table 2.1,). Ethiopia bears 5.6% of the hookworm burden in sub-Saharan Africa (SSA) and is the country with the third highest burden of disease in SSA [126]. Most parts of Ethiopia are suitable for the transmission of STHs, except parts of Somali and Afar regions where the annual mean temperature is too high for transmission [76]. The national prevalence of hookworm is estimated at 16% [127]. The prevalence of hookworm among school age children in Ethiopia was reported to be 38% in Jimma(2007 &2009) [128,129], 26.8% in Boloso Sore(2000) [130], 53% in central Ethiopia (1987)[131], 20.6% in Southwest Ethiopia (2008) [132], and 19% in northwest Ethiopia(2009)[133]. There was no significant gender difference [132]. According to a study conducted in southwest Ethiopia, 92% of the hookworm infections were due to *N. americanus* and 8% were due to *A. duodenale*. None of the cultures showed mixed infection (i.e. infection by two or more species) [128].

Ethiopia has the second highest burden of ascariasis in SSA: 26 million people are infected, which is 15% of the overall burden in SSA [126]. The prevalence among school age children was recorded at 28.9% in northern Ethiopia [134], 83.4% in southern Ethiopia [135], 22% in northwest Ethiopia [133], and the national average is estimated at 37% [127]. Similarly, Ethiopia has the 4th highest burden of Trichuriasis, with 21 million people infected, which is 13% of the disease burden in SSA [126]. The national prevalence is estimated at 30% [127]. The global atlas of helminth infection (http://www.thiswormyworld.org/maps/ethiopia/archive) provides a map of STH in Ethiopia[75].

**Table 2.0-1** Summary of burden of Neglected Tropical Disease in Ethiopia, 2012

| **Disease** | **Geographical Distribution** | **Burden of disease in Ethiopia** | **Proportion of SSA prevalence[126]** |
|---|---|---|---|
| Hookworm infection | Most of Ethiopia is suitable for transmission | 11 million[126] | 29% |
| Ascariasis | Most of Ethiopia is suitable for transmission | 26 million [126] | 25% |
| Trichuriasis | Most of Ethiopia is suitable for transmission | 21 million [126] | 24% |

| | | | |
|---|---|---|---|
| Schistosomiasis | Most of Ethiopia is suitable for transmission | 5.01 million [136], 37.5 million at risk | 25% |
| Lymphatic filariasis | Gambella (7), Beneshangul-Gumuz (13), SNNPR (9), Amhara(2) and Oromia (3) endemic districts.[137] | 30 million at risk[126] | 6%–9% |
| Leishmaniasis | VL is found in Tigray, Amhara, Oromia, Somali, Afar and SNNPR, whereas CL is prevalent in Tigray, Amhara, Addis Ababa, SNNPR, and Oromia. | 3,700-7400 new cases of VL per annum [138] 20-50,000 cases of CL per annum[138] | 13% VL 54% CL |
| Trachoma | Trachoma is found in all regions of Ethiopia. Six regions - Amhara, Oromia, SNNPR, Tigray, Somali and Gambella - bear high burden. | Ethiopia 10.3 million active trachoma, 1.3 million TT cases,[139], >65 million at risk | 3% |
| Onchocerciasis | Amhara Region (North Gondar), Benishangul-Gumuz (Metekel Zone), Oromia (Jimma, Illubabor, Wellega, West Shoa), SNNPR (Kaffa, Sheka and Bench Maji Zone) and Gambella. | 5 million cases and 12 million at risk [127] | 5% |
| Leprosy | Leprosy has been reported from most part of the country except part of Afar and Somali region. | 4,611 new cases per annum[140] | <0.01% |
| Rabies | Most part of the country | 996-14694(12.6/million-18.6/100,000) per annum[141,142] | Unknown |
| Dracunculiasis | Gambella Region and historically South Omo (SNNPR) | 8 cases in 2011 [143] | <0.01% |
| Human African trypanosomiasis | Historically Gambella and South Omo (SNNPR) | No cases of HAT since 1984 [144] | <0.01% |
| Buruli ulcer | Two case reported from Arbaminch Zuria district (SNNPR) and Tigray regions | 2 cases reported [145,146] | <0.01% |
| Echinococcosis | Unknown | 1817( 2.3/100,000) per annum [147] | Unknown |
| Fascioliasis | Unknown | Unknown | Unknown |
| Podoconiosis | One fifth of the surface of Ethiopia | 1 million cases, 19.2 million at risk[148,149] | |

### 2.3.2 Schistosomiasis

In Ethiopia, 5.01 million are thought to be infected with schistosomiasis and 37.5 million to be at risk [136]. The national schistosomiasis survey of 1988-89 reported an overall prevalence of 25% [150,151]. Among 365 communities surveyed for *S. mansoni* between 1961 and 1986, prevalence ranged from 10 to 92% [152]. Transmission occurs mainly through streams, irrigation schemes, and lakes. The intensity of infection correlates with severity of infection, and varies from locality to locality in Ethiopia.

In some studies the prevalence of *S. mansoni* infection was higher in children and adolescents [151], because children had higher environmental contamination potential. Prevalence in males and in females was 42.4 % and 26.5% respectively [150].

### 2.3.3 Leishmaniasis

Ethiopia is one of the six countries (i.e. Bangladesh, Brazil, Ethiopia, India, Nepal and Sudan) in which more than 90% of global Visceral Leishmaniasis (VL) cases occur and one of the ten countries with the highest estimated case counts, which together account for 70 to 75% of global estimated VL incidence [115]. Both Cutaneous Leishmaniasis (CL) and VL are growing health problems in Ethiopia, with endemic areas that are continually spreading. Geographically, VL is found in Tigray, Amhara, Oromia, Afar, Somali and SNNPR, whereas CL is prevalent in Tigray, Amhara, SNNPR, Addis Ababa and Oromia regions.

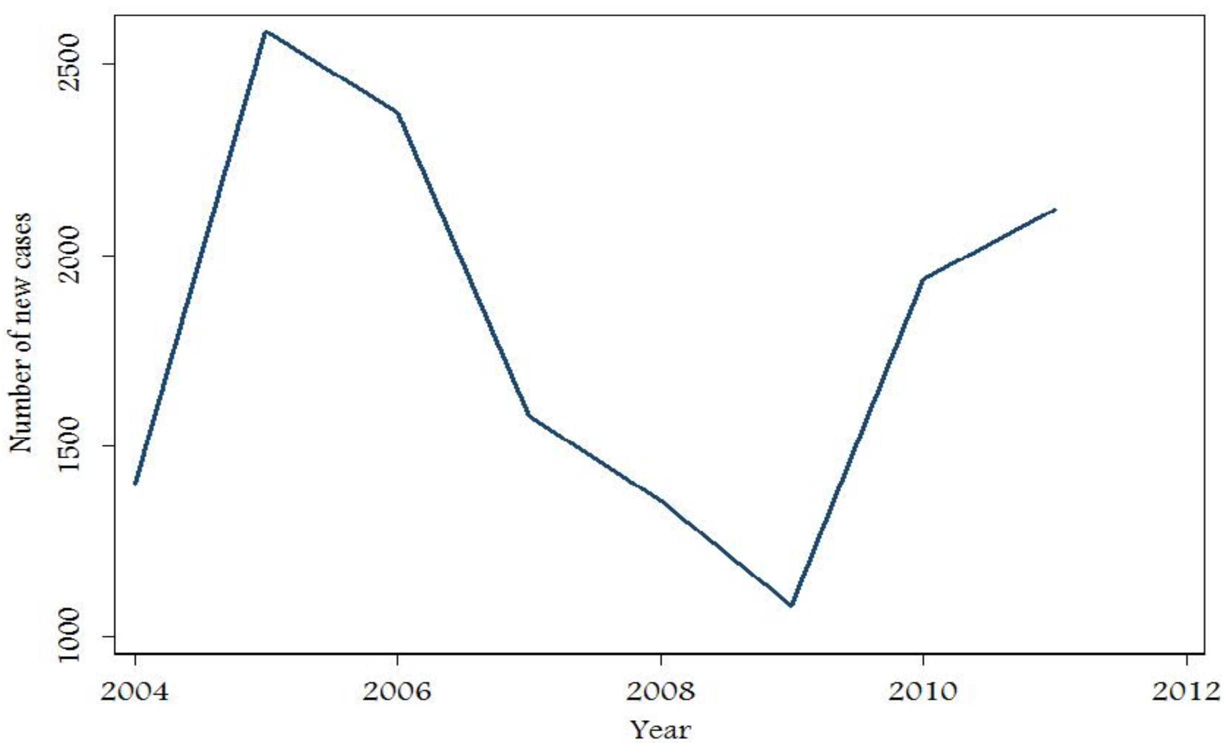


**Figure 2.1** Cases of Visceral Leishmaniasis, Ethiopia, 2004-2011[138]

Historically the first case of VL in Ethiopia was identified in 1942 in southern Ethiopia. Every year, an estimated 3700-7400 cases occur in Ethiopia(Figure 2.1) [153]. The disease occurs in the lowlands of the northwest, central, south and southwestern parts of the country. In the north, the vector is associated with Acacia-Balanites forest, in the south with termite hills. In Ethiopia, VL affects mainly children and young adults (the mean age of affected in northern Ethiopia is 23) in endemic areas the mean age is much lower [138,153]. In northwest Ethiopia, where migrant laborers are at risk of exposure to VL, annual incidence ranges from 5 to 8 cases per 1000 population. The annual incidence among at risk populations in southern and south eastern Ethiopia ranges from 1 to 5 cases per 1000 population with huge geographical variation (Personal communication, Asrat Hailu).

CL has been well known since 1913, and is endemic in most regions, mainly in the highlands of Ethiopia in the altitude ranges of 1400 – 2900m. It is a highly neglected disease with a zoonotic cycle involving rock hyraxes. There are estimated 20-50,000 cases yearly in Ethiopia, but only 450 cases were reported in 2008 [138]. There are three clinical forms of CL in Ethiopia: localized CL, mucosal leishmaniasis and diffuse cutaneous leishmaniasis (DCL), all mainly caused by *L. aethiopica*. CL is most common in children [154,155]. In highly endemic areas, children aged less than 10 years are most often affected. For example, 8.5% of all children aged less than 10 years in Ochollo, south-western Ethiopia [156]. The prevalence of CL in the vast majority of the endemic areas varies from 0.1% to 1.0% (AH unpublished observations); higher prevalence rates have been reported in hyperendemic areas, such as 3.6-4.0% in Ochollo[156], and 4.8% in Silti Woreda [157].

Outbreaks of leishmaniasis have occurred in Ethiopia. Between 2005-2008, a documented outbreak of VL occurred in Amhara Region (Libo Kemkem district), with 2,500 cases and with a very high mortality [158,159]. An outbreak of CL also occurred in Silti district 2003-2005[157]. In 2010, cases of VL were identified in Tigray (Tahtay Adiabo district) and East Imey, a district in Somali region [153].The incidence of HIV-Leishmania co-infection is very high (23% in 2008) in north Ethiopia[160,161].

### 2.3.4 Lymphatic filariasis

Lymphatic filariasis (LF) is a parasitic disease caused by three species of filarial parasites: *Wuchereria bancrofti*, *Brugia malayi* and *B. timori*, which are transmitted by anopheline and culicine mosquitoes [122,162,163]. LF is one of the most debilitating and disfiguring diseases in Ethiopia and is caused by *W. bancrofti*. The adult worms inhabit the lymphatics, and may lead to lymphoedema and elephantiasis. The disease is poverty-related and predominantly affects the poor and marginalized people [163]. In Ethiopia, 30 million people have been estimated to be at risk of LF, which would make Ethiopia the 4$^{th}$ highest burden country in SSA, bearing 7.8% of the burden of LF in SSA (Table 2.2). However, some experts question the validity of this estimate, considering it to be an overestimation compared to recent surveys (Personal communication, Asrat Hailu). The on-going mapping activities are intended to provide a realistic figure about the numbers of people at risk.

**Table 2.0-2** Burden of Neglected Tropical Disease in Ethiopia and relative contribution and rank within Sub-Saharan Africa, 2012

| Disease | Ethiopia | SSA[126] | Percentage contribution of Ethiopia to SSA | Disease burden rank from SSA |
|---|---|---|---|---|
| Hookworm infection | 11 million[126] | 198 million | 5.6% | 3 |
| Ascariasis | 26 million[126] | 173 million | 15.0% | 2 |
| Trichuriasis | 21 million[126] | 162 million | 13.0% | 4 |
| Schistosomiasis | 5.01 million[136] | 192 million | 2.6% | 14 |
| Leishmaniasis | Ethiopia 4,000 new Cases annual[138] | 19,000–24,000 | 16.7%-21.1% | 2 |
| Lymphatic filariasis | Ethiopia 30 million at risk[126] | 382–394 million at risk | 7.6%-7.8% | 4 |
| Trachoma | Ethiopia 10.3 million[126,139] | 30 million | 34.3% | 1 |
| Onchocerciasis | 5milion , 12 million at risk [127] | 37 million | 8.1% | Using annual treatment figures provided by APOC in 2010 as proxy indicators, Ethiopia stands 4th following Nigeria, DRC and Cameroon. |
| Leprosy | Ethiopia 4,611 annual [140] | 30,055 | 15.3% | 2 |
| Rabies | 996-14694 annual [141,142] | Unknown | Unknown | Unknown |
| Dracunculiasis | 8 cases in 2011[143] | 1058 | 0.75% | 4 |
| Human African trypanosomiasis | 0 since 1984[144] | 50,000-70,000 | 0 | |
| Buruli ulcer | 2 cases [145,146] | >4,000 | Unknown | Unknown |
| Echinococcosis | 1,817annual[147] | Unknown | Unknown | Unknown |
| Fascioliasis | Few cases reported | Unknown | Unknown | Unknown |
| Podoconiosis | 1 million cases, 19.2 million at risk[148,149] | 4 million | 25% | 1 |

*Using annual treatment figures provided by APOC in 2010 as proxy indicators, Ethiopia stands 4th following Nigeria, DRC and Cameroon.

According to recent mapping based on 11,685 individuals living in 125 villages (112 districts) of western Ethiopia, the prevalence of lymphatic filariasis was 3.7%, but there was high geographical clustering and variation in prevalence (ranging from 0% to more than 50%). The prevalence of hydrocele (in males) and limb lymphoedema was 0.8% and 3.6%, respectively.  Endemic districts were identified in the following regions: Gambella Region (seven districts), Beneshangul-Gumuz Region (thirteen districts), and Southern

Nations, Nationalities and Peoples' Region (SNNPR) (nine districts). The other five districts were from Amhara (two districts) and Oromia (three districts) regions[137].

### 2.3.5 Trachoma

Trachoma, caused by *Chlamydia trachomatis* (an obligate intracellular bacterium), is the leading infectious cause of blindness worldwide [164].

The national blindness, low vision and trachoma survey conducted in Ethiopia in 2005-2006 suggests that Ethiopia is the most trachoma-affected country in the world. The entire rural population of approximately 65 million people in Ethiopia is at risk for blinding trachoma. It was estimated that in 2008, there were 9.84 million children with clinical signs of active disease and 1.36 million adults with trachomatous trichiasis. In the same study, projections suggested that in 2008 a total of 1,143,151 people were blind from avoidable causes, of which trachoma accounted for 11.5%. Provided appropriate interventions are in place, about 90% of all blindness in the country is avoidable [165]. The prevalence of blindness in Ethiopia is thought to be the highest in the world. After cataract, the preventable bacterial infection trachoma was the second-leading cause of blindness in Ethiopia. There are 10 million individuals with active trachoma in the country placing the vast majority of the population at risk. The prevalence of active trachoma was 40.1% among children 1-9 years old [165,166]. Ethiopia ranks first in the list of high burden SSA countries and bears 34.5% of the trachoma burden in the region. Ethiopia is one of the five countries including Guinea, India, Nigeria and Sudan bearing half of the global burden of active trachoma [115].

Trachoma is widely distributed in Ethiopia, with six regions bearing high burdens namely Amhara, Oromia, SNNPR, Tigray, Somali and Gambella regions [166].

### 2.3.6 Onchocerciasis

Onchocerciasis, also known as river blindness, is caused by a nematode filarial worm, *Onchocerca volvulus* that causes blindness and debilitating skin lesions [167].

The existence of onchocerciasis in Ethiopia has been known since 1939 as a result of investigation by Italians in south-western Ethiopia[168]. In Ethiopia, 5 million are estimated to be infected, with a further 12 million at risk from this disease [127,169,170]. The recent REMO mapping activity estimated that 5.2 million people are living in hyper- or meso-endemic areas [171]. Prevalence of onchocerciasis varies from place to place, from 84% in western endemic areas [172], to 19.5% in the north-western endemic areas [136].

Onchocerciasis in Ethiopia is confined to the western part of the country, despite the presence of the vector in the other parts of the country. APOC-sponsored, nation-wide Rapid Epidemiological Mapping of Onchocerciasis (REMO) was first conducted in 1998. As a result, onchocerciasis was found to be prevalent in the North Gondar zone (Amhara Region), in Metekel and Assosa zones (Benishangul Region), Agnua and Mezhenger zones (Gambella region), in Illubabor, Jimma, East and West Welega zones (Oromia region), and in north Omo, South Omo, Kaffa Sheka and Bench-Maji zones (SNNPR) [171]. In 1999 the National Onchocerciasis Control Program was established. The National Onchocerciasis Task Force (NOTF) was established in 2000 and the first CDTI project was launched in Kaffa-Sheka Zone that same year. REMO refinement surveys were conducted in 2001, 2004 and 2011[173].

### 2.3.7 Leprosy

In 2010, Ethiopia was one of the 17 countries reporting 1000 or more new cases per annum of leprosy. Between 2004 and 2010, 4000-4500 new cases were diagnosed at health facilities annually. Ethiopia is the second highest burden country in SSA, after the Democratic Republic of Congo [174]. However, according to WHO, Ethiopia reached the leprosy elimination target of 1 case/10,000 population in 1999, and since then, the incidence has not changed appreciably [175]. As in other endemic countries, about 5,000 new cases are detected yearly and over 30,000 people are living with permanent leprosy-related disability. In 2002, clusters of endemicity with prevalence rates higher than the elimination target were recorded in four of the 14 administrative regions in the country [175]. In 2010, the total number of leprosy patients registered in the country was 5,303, and of these, 4,430 were new cases. Of the registered new cases, 1,308 were female and 331 children. In the same year, 357 relapse cases were registered [174].

Ethiopia ranked 7th among the 18 countries that report 93% of all new cases detected globally in 2009, although the number of cases dropped from 5081 to 4516, the average number of new cases remained constant at around a mean of 4524 (range 4153-4940) between 2001-2011 (Figure 2.2). This translated to a drop in national case notification rate of 0.8/10,000 to 0.6/10,000. A 7.8% proportion of children under 15 and prevalence of 9.8% grade II disability among those newly diagnosed suggests an unknown magnitude of hidden cases. Regional variation in case notification rate varied between 0.16/10,000 in SNNPR (which nevertheless, 45% had grade II disability) to 0.76/10,000 in Oromia [176].

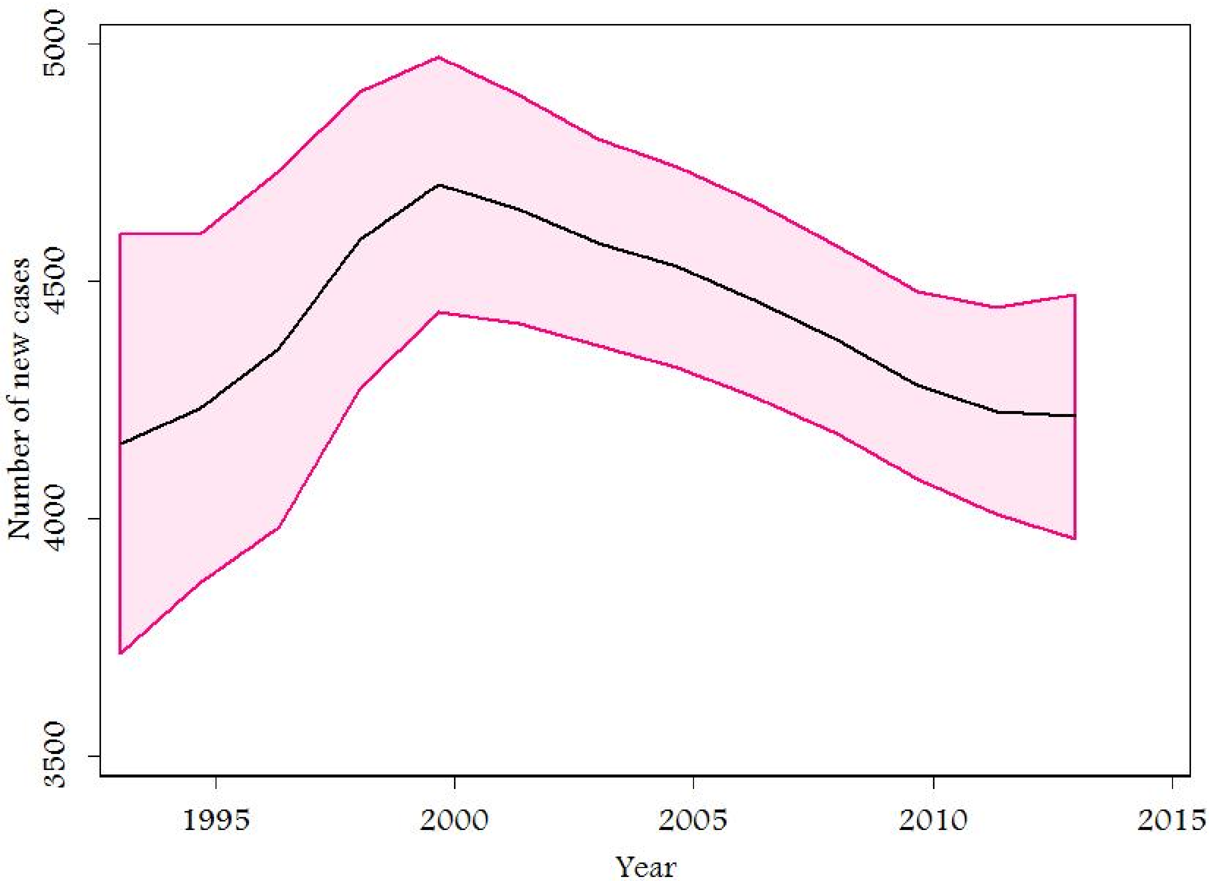


**Figure 2.2** Local polynomial smooth line fitted to the number of new cases of leprosy in Ethiopia 1993-2013. Lines represent the mean estimate, while shaded areas depict associated 95% confidence interval.

### 2.3.8 Rabies

Rabies is an important neglected zoonotic disease. Annually 996-14,694 cases of human rabies are estimated to occur in Ethiopia [141,142], mostly acquired through dog bites [177-179]. According to a study in and around Addis Ababa, 92% of humans who received post-exposure anti-rabies treatment had been bitten by dogs. In Africa, the highest recorded number of human deaths due to rabies for the year 1998 was 43, reported from Ethiopia [180]. Most cases of fatal rabies occur among children in Ethiopia [180]. Almost all of these deaths are preventable through prompt medical attention comprising wound cleaning and post-exposure prophylaxis with rabies vaccine. Often all had attempted some form of herbal remedies by traditional healers before presenting to health facilities [180]. There has been no apparent decline in the number of recorded human rabies cases over 20 years [180,181].

### 2.3.9 Dracunculiasis (Guinea worm)

Dracunculiasis is caused by the parasitic filarial worm *Dracunculus medinensis*, the largest of all the filarial worms (nematodes) affecting human [182],[183]. Dracunculiasis used to be a formidable public health problem, mainly in terms of morbidity, incapacity and suffering of those affected. About 50% of cases suffer from secondary infections and become severely incapacitated [184].

In Ethiopia a case of dracunculiasis was reported first in 1969 [185]. Geographically, the disease was prevalent in Gambella region and South Omo (SNNPR). The eradication program in Ethiopia stated in 1990, and has reduced the number of cases from 1,252 in 1994 to only 8 in 2011(Figure 2.3)[186,187]. Ethiopia was one of only four countries that still reported dracunculiasis in 2011. The key challenge to achieving complete interruption of transmission is the very frequent migration and interaction of the people along the Ethio-Sudan border and very high likelihood of cross-border cases from South Sudan.

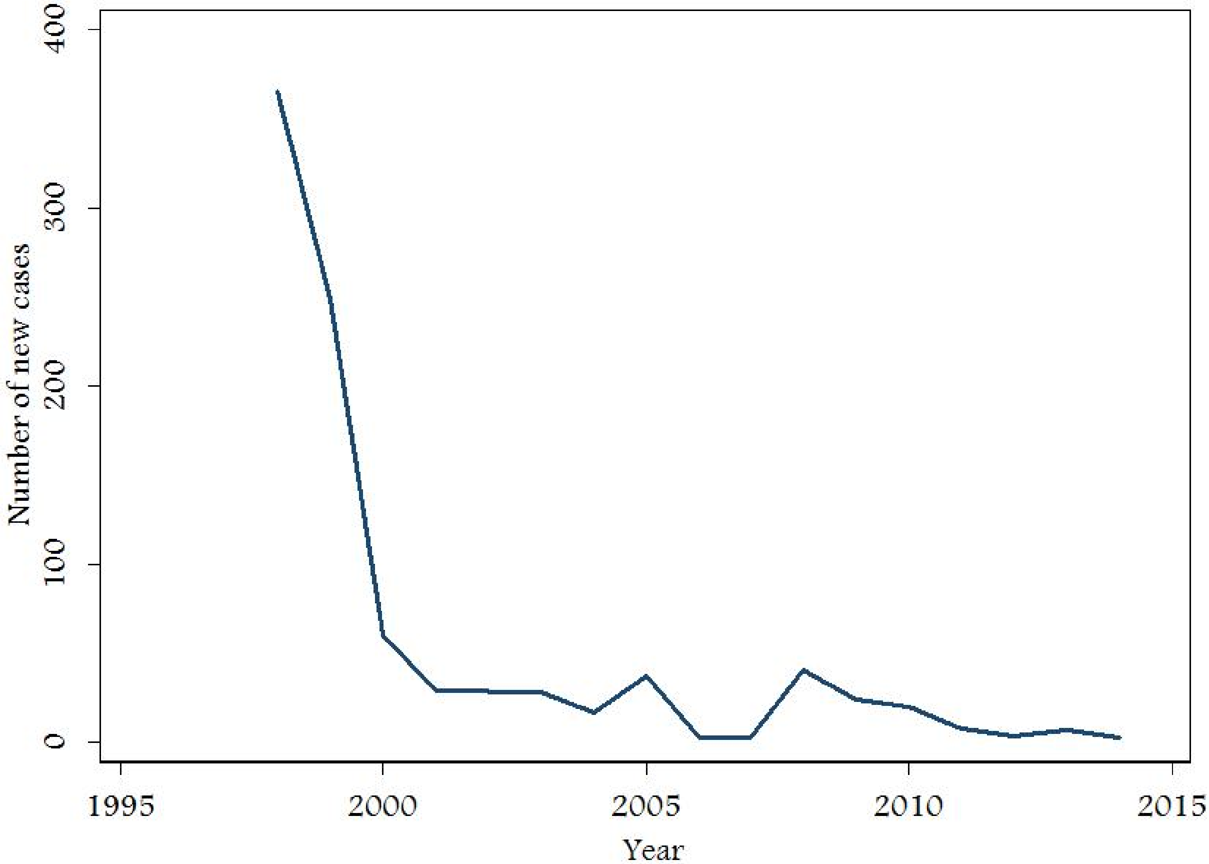


**Figure 2.3** New cases of Dracunculiasis in Ethiopia, 1998-2014.

### 2.3.10 Other NTDs in Ethiopia

Human African Trypanosomiasis (HAT) was previously reported in Ethiopia. The geographical distribution was in Gambella, with sporadic cases reported from Gamo Gofa, Keffa and Wellega. Since 1984 there have been no cases reported to WHO [186,188].

Echinococcosis is a zoonotic disease caused by four species of *Echinococcus: E. granulosus* (causing cystic or unilocular echinococcosis); *E. multilocularis, E. vogeli* and *E. oligarthrus* (species causing polycystic or alveolar echinococcosis). In Ethiopia, humans have become infected accidentally with *E. granulosus* through contact with dog's feces [186]. In a review of 36,402 patients admitted for an ultrasound examination, an incidence of 2.3 cases per 100,000 per year was estimated [147].

Buruli ulcer is caused by infection with *Mycobacterium ulcerans*. In Ethiopia, only 2 cases were reported [145,146] from Arbaminch Zuria district. Ethiopia is not on the list of thirteen countries listed as endemic for Buruli ulcer in the African region.

#### 2.3.11 Podoconiosis

Based on the review, the burden of podoconiosis in Ethiopia is significant with more than 15 million people at risk and 1 million people affected by the disease[23,189]. In comparison with other NTDs, the burden of podoconiosis is less than STHs, trachoma, onchocerciasis, schistosomiasis and LF which affect millions of people in the country although the podoconiosis burden is higher than all other NTDs in endemic areas. Comparisons based on the numbers affected and population at risk may seem appealing, but such measures only tell part of the story without quantifying the additional burden due to associated functional limitations. Therefore, standardized summary measures that combine information on resultant morbidity, mortality and economic losses is important to understand the relative burden of podoconiosis compared to other diseases or sequelae in the country, such as disability-adjusted life year (DALY) and years lost due to premature mortality (YLLs)[101].

## 2.4 Current Status of Control and elimination of Neglected Tropical Diseases in Ethiopia

### 2.4.1 Soil Transmitted Helminths

Ethiopia launched the Enhanced Outreach Strategy (EOS) in 2004; one of the objectives of the initiative was to deworm 2-5 year old children every six months. The strategy was implemented in every district in the country except Addis Ababa and by 2009, the program had reached more than 11 million children in 624 districts. Every six months, with UNICEF support, Regional Health Bureaus organize the EOS. Each district has one EOS team per sub-district, composed of one health worker and one HEW who mobilize the community to come to the nearest health post on a specific day, the EOS day, when the EOS team deworms all children under five years and distributes vitamin A supplements. In many instances, the Regional Health Bureaus use this opportunity to deliver other essential services, such as measles vaccination, tetanus vaccination, mosquito net distribution, HIV/AIDS prevention, or iodine capsule distribution [190].

### 2.4.2 Schistosomiasis

Although Ethiopia is highly endemic for schistosomiasis, control of this disease is still in its infancy, and no recent mapping of schistosomiasis has taken place[191]. At a stakeholders meeting convened in July 2012 by the Schistosomiasis Control Initiative and the Ministry of Health, nationwide mapping of schistosomiasis integrated with mapping of other NTDs was planned for 2013, and strategies to expand MDA on the basis of the mapping outlined.

### 2.4.3 Leishmaniasis

In 2006, a leishmaniasis control program that included mandatory notification was established. Although patients are not required to pay for VL drugs and rK39 tests, other tests are not free of charge. It is estimated that treatment of VL patients usually requires a high cost to complete a full course of antimony-based treatments [138], and many are too poor to pay for these services. There are no vector control programs in place specifically for leishmaniasis, and bed net distribution and insecticide spraying take place in the context of malaria control [138,153,154]. A national Leishmaniasis control guideline has been developed. A geographic information system (GIS)-based risk mapping of leishmaniasis is being completed for the country and treatment guidelines for cutaneous leishmaniasis have been developed through an international consultation process organized by the FMoH in collaboration with the Armauer Hansen Research Institute (AHRI) and the World Health Organization (Proceedings available at AHRI).

### 2.4.4 Lymphatic filariasis

In 2009, with the support from The Carter Center, the Ethiopian Ministry of Health launched a LF elimination program in five districts of Gambella Region. The program reached 84% of its target by providing annual MDA of a single dose of ivermectin and albendazole to a target of almost 100,000 people. Recent LF mapping has identified new endemic districts in other regions indicating the need for expansion of the program to these places [137,173]. Integration must take into account both treatment goals and target group [192]. Currently there are other initiatives to establish sentinel sites and expand the treatment program.

### 2.4.5 Trachoma

Ethiopia has a two-phase national five year Strategic Plan for eye care. Since 2000, Ethiopia has been implementing the WHO-approved SAFE strategy for trachoma control — surgeries, antibiotics, face and hand washing and environmental hygiene. Through The Carter Center alone, using what is known as the MalTra-Week Strategy (combining malaria case detection and treatment with mass azithromycin distribution) more than 14.7 million people received azithromycin in 2010 [173]. In 2011, a total of 17.7 million people were treated with azithromycin in 195 districts. Over the past few years, 60 – 90,000 cases of trichiasis have received TT surgery annually (FMOH, unpublished annual reports). Hygiene education and latrine promotion have been implemented nationwide through the national health extension program. As a result, it was confirmed by DHS 2011 that individual latrine coverage (ownership and utilization) reached 45% for rural households [193].

A number of clinical trials and pieces of operational research have been conducted to guide effective implementation of interventions for the eventual control and elimination of trachoma in Ethiopia. A PubMed search indicated that a total of 86 trachoma research papers from Ethiopia have been published on this topic in local and international journals since 2001.

### 2.4.6 Onchocerciasis

**Table 2.0-3** Onchocerciasis treatment in CDTI zones in 2010 in Ethiopia[173]

Although onchocerciasis was reported as early as 1939, regions in Ethiopia were not recognized as endemic until the 1970s [168]. The first national plan to fight onchocerciasis was developed in 1999. In 2000, the National Onchocerciasis Task Force was established by Ethiopia's Ministry of Health with a mission to: mobilize and educate onchocerciasis-endemic communities; coordinate Mectizan® tablet procurement (donated by Merck) and distribution; and coordinate all partners in the program [168,173]. The Carter Center, Light for the World and the African Program for Onchocerciasis Control (APOC) play a critical role in supporting the Mectizan distribution program in these areas. The program went on to expand into other areas, doubling treatments each year until reaching scale in 2004. Treating more than 4 million annually, the program's geographic coverage reached 99.2% and sustained therapeutic coverage of 77.4 %( Table 2.3) [171].

| CDTI Zone | Ultimate treatment goal | Total population | Population treated 2010 | % Ultimate treatment goal | % total population treated |
|---|---|---|---|---|---|
| Kaffa | 840,886 | 1001,055 | 784,716 | 93 | 78 |
| Sheka | 180,053 | 214,349 | 177,540 | 99 | 83 |
| Bench Maji | 579,848 | 690,295 | 543,038 | 94 | 79 |
| North Gondar | 238,369 | 283,773 | 215,632 | 90 | 76 |
| Illubabor | 648,750 | 772,321 | 639,544 | 99 | 83 |
| Jimma | 765,511 | 911,323 | 743,218 | 97 | 82 |
| Metekel | 127,079 | 151,284 | 121,072 | 95 | 80 |
| Gambella | 84,611 | 101,013 | 73,435 | 87 | 73 |
| Total | 3,465,107 | 4,125,413 | 3,298,195 | 95 | 80 |

### 2.4.7 Leprosy

An organized leprosy control program was established within the Ministry of Health in 1956 with a detailed policy issued in 1969 operating as a vertical program. Multiple Drug Therapy (MDT) was implemented in 1983 leading to relatively rapid reduction in prevalence of leprosy. In 1994, leprosy was combined with tuberculosis under a joint control programme. By 2001, the leprosy component had been fully integrated into the general health services [176].

The FMoH is pursuing an Enhanced Global Strategy of integration with the general health service, reaching undeserved communities and effective partnership to reduce the rate of new cases with Grade II disabilities by at least 35% by the end of 2015, compared to the baseline at the end of 2010 in line with the HSDP target of reducing Grade II disability to 1% by 2015 [176].

Ethiopia achieved the leprosy elimination target of 1 case/10,000 population in 1999. The leprosy control program has been integrated with the tuberculosis control program within the national health system. Diagnosis and treatment services are provided free of charge for patients in every health center. In addition, rehabilitation services are provided for patients [174,175]. Early case detection remains a critical challenge. Specialized Leprosy expertise at the central level has been depleted over the last few years because of the shift of funding to tuberculosis and other diseases.

### 2.4.8 Dracunculiasis

The Ethiopian Ministry of Health established the National Dracunculiasis Eradication Program in 1993, and launched a village-by-village nationwide search during which 1,120 cases were found in 99 villages in the southwest part of the country [168,186]. Transmission of Guinea worm disease in the Southern Nations, Nationalities and Peoples Region (SNNPR) was interrupted in 2001 [186]. In 2007, Ethiopia reached a milestone by reporting zero indigenous cases for more than 12 consecutive months. Unfortunately, transmission of the disease resumed in 2008 when the country reported 41 indigenous cases [186]. The unexpected resurgence of Guinea worm disease in Gambella Region during 2008 demonstrates the constant need for vigilance in eradication efforts. Ethiopia reported eight cases of dracunculiasis in 2011, including two cases imported from South Sudan [143]. In addition to the active case finding program, it is vital to enhance behavioural change and mobilize communities to prevent contamination of sources of drinking water. A cash reward system for case detection and reporting was found to be very helpful in facilitating effective surveillance and case containment activities.

### 2.4.9 Other Neglected Tropical Diseases

In Ethiopia there have been no reported cases of HAT since 1984 [144]. No national program for control of rabies exists, although a national rabies survey is underway and there are sporadic initiatives to vaccinate dogs and provide post exposure vaccination free of charge. There is currently no detailed information about the extent of Buruli ulcer, echinococcosis and fascioliasis.

### 2.4.10 Podoconiosis

Community-based lymphoedema management for podoconiosis was started in 1998 in Ethiopia by a non-government organization in Wolaita. The treatment appears to be effective, and patients have showed improvement after an average of three months of treatment [44], though rigorous controlled assessment of this treatment is still necessary. The treatment includes foot hygiene, bandaging and elevation. Currently it is being run in regions of Ethiopia by independent non-government organizations [42,44]. Although the implementation is still at small scale, it is attracting the attention of health care providers and health authorities for future possible integration into the national health system.

Podoconiosis interventions, similar to other NTDs, use a community-based approach. Patient-led groups are central to the treatment of podoconiosis. These groups are involved in patient identification, supervision of self-care and follow-up of cases. The geographical coverage of podoconiosis interventions in the country is limited, with less than 25 districts having access to such interventions. Although these interventions began in the country more than a decade ago, at the end of 2014 only 60,000 (6%) patient have been treated. Similarly, interventions for STH, trachoma, onchocerciasis, schistosomiasis and LF interventions have also had limited geographic coverage. Most NTD interventions in Ethiopia are led by the government and are integrated within the national health system.

MDA for STH, trachoma, onchocerciasis, schistosomiasis and LF and case management for Dracunculiasis and leishmaniasis are integrated within the health system and are led by the Federal Ministry of Health. Contrary to the interventions for most of the NTDs, podoconiosis interventions are exclusively run by non-governmental organizations. This makes scaling up podoconiosis interventions a continuous challenge in addition to integration with the national health system.

## 2.5 Discussion

This review indicates that NTDs are significant public health problems in Ethiopia. Compared to other countries in sub-Saharan Africa, Ethiopia bears a significant burden of many of these diseases. However, disease burden estimations are based on limited and often old data. From the analysis reported here, Ethiopia stands out as having the third largest total number of NTD cases following Nigeria and DRC. Ethiopia is estimated to have the highest burden of trachoma, podoconiosis and cutaneous leishmaniasis in SSA, the second highest burden of ascariasis, leprosy and visceral leishmaniasis, and the third highest burden of hookworm. Infections such as schistosomiasis, trichuriasis, LF and rabies are also common, yet, despite the high disease burden of these infections, the control of most NTDs in Ethiopia is limited.

Understanding which geographical areas require intervention is fundamental for cost-effective disease control [75,192,194]. Mapping of diseases should be preceded by review of existing data and followed by collection of data for those areas lacking this information. The most recent Rapid Epidemiological Mapping of Onchocerciasis identified new foci of transmission (meso and hyper endemic communities) that require mass treatment with ivermectin [173], as well as areas to be refined before final decisions over inclusion or exclusion from treatment. Similarly, the western part of Ethiopia was mapped for LF [137] and identified new transmission foci of LF beyond the previous altitude limits of transmission. Further mapping is therefore necessary to build a complete picture of the geographical distribution of LF in Ethiopia. Collection of data for mapping of podoconiosis will improve understanding of the spatial distribution of podoconiosis and ecological factors determining this distribution. Experiences from Uganda [192,195], Togo [196] and South Sudan [197] indicate the possibility of integrated disease mapping [112]. Togo and South Sudan conducted integrated mapping of STH, LF, trachoma, schistosomiasis, and onchocerciasis. These surveys were found to be cost-effective [197], with commendable epidemiological rigor. Such integrated disease mapping will have implications both in efficient resource utilization and integrated disease control. For example, integrated mapping of LF and podoconiosis is possible: the large scale autocorrelation of podoconiosis [74] suggests that sample sizes designed for LF will be more than adequate to capture the spatial distribution of podoconiosis. Second, diagnosis of LF needs exclusion of podoconiosis and vice versa, hence integrating the mapping of these two diseases will bring benefits in terms of reduced costs.

In Ethiopia, the nationwide blindness and trachoma prevalence survey conducted in 2006 [165] was followed by implementation of a five year strategic plan. To monitor the progress of this plan and identify areas that require further intervention, it will be necessary to update the trachoma map. Experience from Ethiopia has shown the feasibility of integrating trachoma surveys with malaria surveys, resulting in reduced costs, although some logistical challenges may arise [198]. It is not always mandatory to conduct surveys for mapping. Historical data modelled for environmental and demographic changes may be used for mapping the spatial distribution of disease and identifying populations at risk. For example in Kenya [16], historical and contemporary survey data were used to guide disease control. In Ethiopia many surveys have been conducted on soil-transmitted helminth (STH) infections and schistosomiasis [76,152], and these might be used to identify high risk areas for prioritization and generate maps for initiating interventions, as appropriate.

Traditional efforts to treat and prevent NTDs through vertical programs are often costly, and the integration of program components has the potential to cut the costs of NTD programs [199-203]. Because NTDs tend to overlap in geographic areas(Figure2.4), it is logical to attempt an integrated approach to NTD control [199]. Since 2004, there has been greater advocacy for the integrated control of NTDs [200]. In Ethiopia there are geographical overlaps among NTDs, for example, according to the recent mapping of LF in Ethiopia [137], overlap between LF and onchocerciasis occurs in considerable geographical areas in the southwest of the country. Out of 34 LF endemic districts, 20 were also endemic for onchocerciasis. The existence of a well-established onchocerciasis control program in Ethiopia suggests that integration of other NTDs into this program might successfully build on the existing networks of community based drug distributors (CDDs). In addition, a successful trachoma prevention and treatment program exists, into which MDA and deworming campaigns might be integrated. One practical example is the integration of trachoma services into the existing onchocerciasis control program through CDDs in North Gondar. In most of the Community Directed Treatment with Ivermectin (CDTI) areas, the malaria program is integrated into the daily activities of CDDs. Malaria prevention activities are now included in the integrated CDD training course. CDDs are trained to record the number and condition of long lasting insecticidal nets (LLIN) [173]. Prevention efforts such as shoe wearing for podoconiosis may also help in prevention of chronic larva migrans and snakebite, so health promotion emphasizing the multiple benefits of shoe wearing may be valuable.

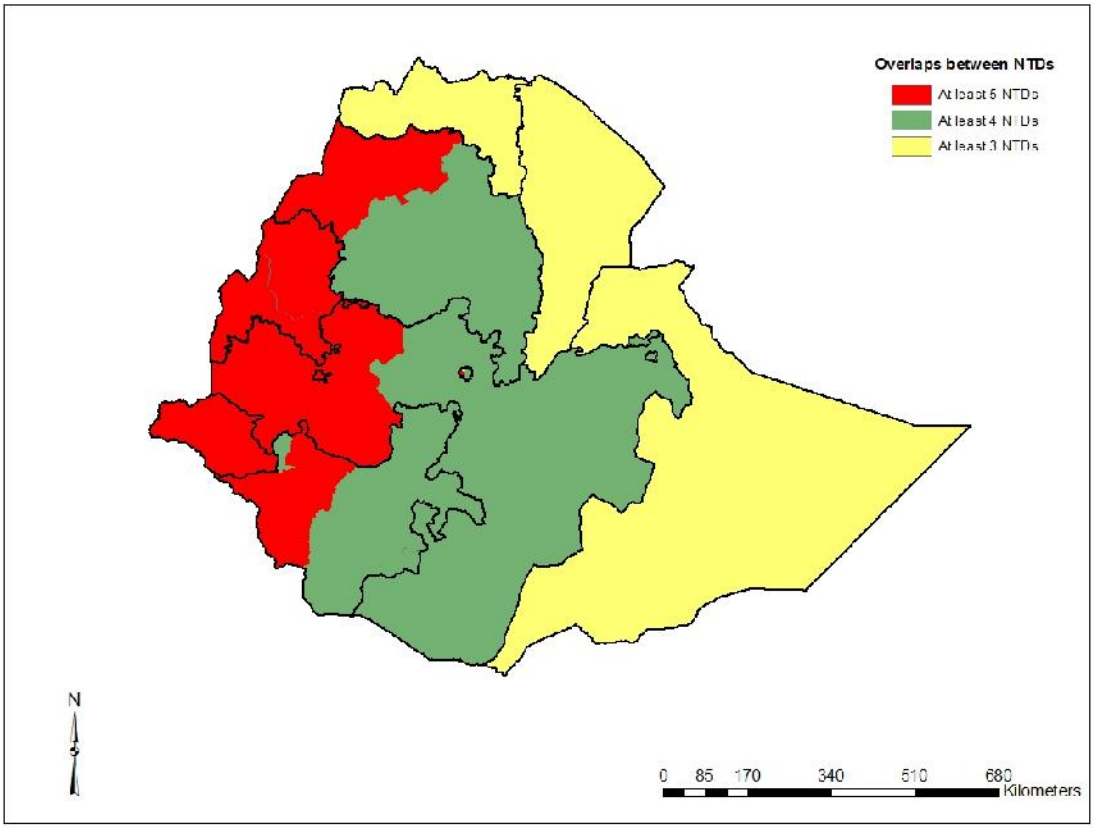


**Figure 2.4** Overlap between five common NTDs (soil-transmitted helminth infections; lymphatic filariasis; schistosomiasis; trachoma and onchocerciasis) in Ethiopia as reported by health providers and maps.

Integration of NTD control into the existing health system is also another important issue. The integration of NTD control into the health system will help ensure the sustainability of programs by sharing resources with better resourced control programs such as HIV/AIDS, tuberculosis and malaria [204]. In Ethiopia the control of NTDs is coordinated by a focal person in the Federal Ministry of Health, and the existence of more than 38,000 trained Health Extension Workers (female salaried health workers) offers great opportunities for integrated NTD control. Two health extension workers are located in each *kebele* (the lowest administrative unit, consisting of approximately 1000 households). Possible areas of integration might include MDA, health education and hygiene promotion.

The other important area for integration is monitoring and evaluation of control and elimination activities. The current Health Management Information System (HMIS) in Ethiopia captures only a few of the NTDs, and unless this is rectified so that routine data on NTDs are collected via the health system, costly and inefficient surveys will be necessary to monitor NTD programs. Data collected via the HMIS could in the future benefit district offices as they monitor their own activities and make decisions at local level. It is anticipated that the National Master Plan for Integrated Control of NTDs 2012-2015 will outline a more precise road map for the implementation of integrated mapping and control of NTDs (Table 2.4).

**Table 2.0-4** Summary of WHO recommended control strategies and their status in Ethiopia, 2012

| **Disease** | **National Target** | **WHO recommended control strategy** | **Status in Ethiopia** |
|---|---|---|---|
| Soil Transmitted Helminthes (STH) (Hookworm, Ascariasis and Trichuriasis) | To reduce morbidity due to STH to a level where it is no longer of public health significance. | Annual mass treatment of schoolchildren and whole communities in high-prevalence areas | Deworming 2-5 year old children every six months nationwide |
| Schistosomiasis | To reduce morbidity due to schistosomiasis to a level where it is no longer of public health significance. | Annual mass treatment of schoolchildren and whole communities in high-prevalence areas | No active control program case management and MDA in few places |
| Leishmaniasis | To control leishmaniasis in Ethiopia | Case detection and treatment and personal protection through use of mosquito nets | Case management in endemic areas |
| Lymphatic filariasis | To eliminate LF as a public health problem by 2020 | Annual MDA to treat the entire population for a (currently undefined) period, to interrupt transmission | Annual MDA in identified endemic areas since 2009 |
| Trachoma | To eliminate blinding trachoma through SAFE strategy by 2020 | Surgery, antibiotic therapy, facial cleanliness and environmental improvement (SAFE) strategy | Surgery, antibiotic therapy, facial cleanliness and environmental improvement (SAFE) strategy |

| | | | |
|---|---|---|---|
| Onchocerciasis | To eliminate onchocerciasis as a public health problem by 2015 | Vector control through spraying of larvicides and annual CDTI | CDTI since 2000 |
| Leprosy | Eliminated from Ethiopia | Multidrug therapy | Multidrug therapy, reduce disability, early case detection |
| Rabies | No target | Controlling rabies in both wild and domestic animals; providing pre-exposure immunization to humans at occupational risk of contracting the disease; and on delivering post-exposure prophylaxis to potentially exposed patients | Post-exposure prophylaxis to potentially exposed patients. |
| Dracunculiasis | Eradication of Guinea worm in Ethiopia with certification by the international commission by 2015 | Active case detection and containment, provision of water supply, abate application and use of cloth and pipe filters | Active case detection and containment, provision of safe water supply, abate application and use of cloth and pipe filters |
| Human African trypanosomiasis | Cases were not reported since 1984 | Case detection and treatment. Vector control through spraying, traps and targets | None |
| Buruli ulcer | No target | Case detection, treatment and surgery | Case management |
| Echinococcosis | No target | Case detection and treatment, regular deworming of dogs, providing health information and inspecting meat. | Case management |
| Fascioliasis | No target | Preventive chemotherapy and case detection and treatment | Case management |
| Podoconiosis | To control podoconiosis in Ethiopia | Under development; includes community-based treatment of cases consisting of foot hygiene, use of shoes, wound care, etc | Community-based treatment of cases consisting of foot hygiene, use of shoes, wound care in few endemic places |

## 2.6 Conclusion

Most NTDs are highly prevalent in Ethiopia, resulting in an enormous disease burden compared to other Sub-Saharan African countries. However, despite this burden of diseases, the control of most NTDs in Ethiopia is in its infancy and mostly underfinanced. The key to control of NTDs lies in understanding the geographical distribution of disease in a given country. At the time of this review, only a few NTDs were adequately mapped in Ethiopia. This indicates the need for integrated mapping to better understand the distribution of particular diseases and areas of overlap for treatment and control. Resource mobilization for conducting integrated surveys should be prioritized. Once mapping is completed and disease distribution is known, cost estimates for the control of common NTDs within Ethiopia will enable resource mobilization and guide donors and partners.

This review and analysis highlights the important next steps for defining the burden of podoconiosis to inform programmatic action. The burden of podoconiosis and the population at risk is very high. However, the geographical distribution of the disease is not clearly understood. The first step to understand the geographical distribution of podoconiosis is to collate historical podoconiosis data and map the distribution of the disease. Therefore, the following chapter will assemble the historical data of podoconiosis and map the distribution of podoconiosis in Ethiopia to inform the mapping needs in Ethiopia.

# Chapter 3: Historical distribution of podoconiosis in Ethiopia

## 3.1 Overview

The previous chapter described the burden of NTDs in Ethiopia. The chapter highlighted a very high burden of NTDs in the country including podoconiosis. Nonetheless, the interventions for most NTDs in Ethiopia are still small-scale (for example, podoconiosis interventions have been limited to 25 districts in three regions). This current chapter will focus on the geographical distribution of podoconiosis using historical data.

Mapping the geographical distribution of a disease is a pre-requisite for targeted and cost-effective control. In order to provide effective and targeted control interventions for podoconiosis, understanding its geographical distribution is very important. As an initial first step in defining this distribution, existing surveys may be collated and mapped to describe geographical trends in endemicity and identify gaps where data are lacking, and thus guide future data collection. This approach has been used to map the distribution of several NTDs. This section describes the identification, assembly and mapping of historical data of podoconiosis surveys conducted between 1969 and 2012. Prevalence data were extracted from published and unpublished works and geo-referenced using online gazetteers. The final repository was used to identify the historical distribution and environmental factors associated with podoconiosis distribution. The results presented here were published in 2013[74].

## 3.2 Introduction

The first step in disease mapping is the collection of historical data and geo-locating them to understand the historical distribution of the disease. Such data will inform the distribution of the disease and, if appropriately modelled for different changes which have occurred, can predict the current status of the disease[77,113]. In areas where there is no information, further data collection is recommended. For podoconiosis there were some historical data and small scale surveys in Ethiopia. In fact, there was a historical map which was produced from market and school based surveys [8,9,11,12,14,15]. In addition to these surveys, there were various relevant environmental observations. In 1984, Price noted that non-filarial elephantiasis occurred in areas where soil originated from volcanic rocks (including basalt) at altitudes greater than 1000 masl [60], and that the prevalence of podoconiosis decreased significantly at the limit of the red soil, declining to almost zero 25 km from the edge of these soils [205]. Meanwhile, Frommel *et al*. described high concentrations of the trace elements zirconium and beryllium in high prevalence areas of southwest Ethiopia [206].

In recent years, robust and practical approaches to mapping have been developed for a range of diseases [78,89-91,207]. Mapping the distribution of NTDs such as onchocerciasis, lymphatic filariasis, schistosomiasis and soil transmitted helminths has led to successful targeting of control measures to areas of greatest need [77,78,89-91,207]. With the recent availability of new technologies such as remote sensing and geographic information systems along with advances in spatial and temporal statistics, the theories of landscape ecology can be used analytically [208,209]. In relation to podoconiosis, the presence of certain environmental factors conducive to the production of irritant soil may be mapped and used to predict the extent of podoconiosis. If interventions for the treatment and prevention of podoconiosis are to be scaled up, information on the distribution and extent of the disease must be available to decision makers. The objective of this study was therefore to investigate the spatial distribution and ecological correlates of podoconiosis using historical survey data.

## 3.3 Methods

### 3.3.1 Data source and abstraction

The bibliographic databases of MEDLINE (http://medline. cos.com/), EMBASE (http://www.embase.com/) and PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) were searched for relevant English language studies. For identification of publications on podoconiosis, the following Medical Subject Headings (MeSHs) were used to identify relevant studies published between 1960 and 2012: podoconiosis, non-filarial elephantiasis and Ethiopia. Abstracts of studies presenting prevalence were reviewed and full texts retrieved if they contained relevant information. References from articles and key reviews were screened for additional studies. Finally, leading researchers in the area and authors of key papers were contacted to ask about unpublished or un-indexed data, and this yielded a number of additional datasets. Archives of Ethiopian national journals were hand searched and articles related to the subject were included.

Cross-sectional studies were included, but health facility based surveys were excluded. If in a given area, multiple surveys had been conducted at different times, each was included in the analysis. From each study, the design, study population, method of diagnosis, date and location of survey, age range of sampled individuals, and number of individuals examined and diagnosed with podoconiosis were abstracted. Longitude and latitude of the survey locations were identified through a range of methods, including online search with GeoNames (www.geonames.org) or Wikipedia (www.wikipedia.org). For recent data from lymphatic filariasis mapping [210], the geographical positioning system (GPS) information relating to each location was obtained from the investigators.

### 3.3.2 Environmental and climatic data

Previous studies suggest the importance of temperature, altitude and annual rainfall in the formation of irritant clay soil [60]. The Normalized Difference Vegetation Index (NDVI) is also considered to be associated with soil erosion [211]. Among other environmental characteristics, two were used: texture of the soil (classified as coarse, medium or fine), and the topography of the land. The topography of the land was obtained from University of Bern Centre for Development and Environment through the Ethiopian GIS society (http://www.cde.unibe.ch/Pages/Publication/1431/Default.aspx). The altitude, mean air temperature at 30-arcsecond (1 km) resolution were downloaded from the WorldClim website for the period 1950–2000 at 1 km spatial resolution [212]. These climate variables were produced from global weather station temperature records gathered from a variety of sources for the period 1950–2000 and interpolated using a thin-plate smoothing spline algorithm [213]. The digital soil map of the world (Land and Water Development Division, FAO, Rome) at a nominal scale of 1:5,000,000 was downloaded from the GeoNetwork website [214]. As detailed in this document, the original data sources for our environmental variables came in a variety of formats, with varying spatial resolutions. To overcome these incompatibilities and generate a fully standardised suite of input grids, we derived a standard template around which all grids were processed. Where input grids were defined at spatial resolutions other than 1km x 1km bilinear interpolation was applied to resample numeric (continuous) raster data sets, whereas nearest neighbor interpolation was used with ordinal raster layers. Input grids were either extended or clipped to match the geographic extent of a land mask template of Ethiopia, and eventually aligned to it. Survey and covariate data were linked in ArcGIS 10. (Environmental Systems Research Institute Inc. [ESRI] Inc., Redlands CA, USA) based on the WGS-1984 Web Mercator projection at 1 $km^2$ resolution.

### 3.3.3 Data analysis

The prevalence and GPS data were entered using a Microsoft Excel 2007 spreadsheet and exported into STATA 11.0 (Stata Corporation, College Station, TX, USA). Point prevalence maps were developed in ArcGIS 10. Data for each location were extracted from the raster maps of each of the environmental variables.

Associations between prevalence of podoconiosis and individual environmental variables were investigated using the non-parametric Spearman's rank correlation. The association between environmental variables and prevalence was further assessed using binomial logistic regression. Variables contributing to the model based on the log likelihood ratio test were retained in the final model. P-values <0.05 were considered significant. Statistical analyses were performed using STATA. All variables except topography (slope) and NDVI were treated as categorical variables. We have explored for linearity of the variables and in most cases non-linearity was observed which lead to categorizing them. The categories were based on expert opinion and previous observations in east Africa, where some cut-off points were indicated.

A multivariate regression model allowing for clustering was fitted using STATA 11 to assess the potential predictors of podoconiosis prevalence. The associations between podoconiosis prevalence, slope of the land (as surrogate for topography), altitude, mean annual LST, standard deviation of NDVI, and soil texture were examined. For each predictor, the Odds Ratio (OR), 95% confidence interval (CI), and p-values were recorded. Collinearity was checked between all possible pairs of potential environmental variables; altitude and mean LST had a correlation coefficient >0.9, and since the mean LST has more to do with weathering of soil, altitude was excluded from the final model. All other variables were entered into the model adjusted for each other.

## 3.4 Results

### 3.4.1 Characteristics of the survey data

Ten studies conducted between 1969 and 2012 included data for 401,674 individuals older than 15 years of age from 229 locations (data points) in 9 of the 11 regional states of Ethiopia. Eight community based surveys, one market survey and one school based survey were included (Table 3.1).

Five of the studies were conducted after the year 2000. Most of the studies used physical

**Table 3.0-1** Studies included in producing a podoconiosis map of Ethiopia

| **Publication year** | **Place of study** | **Number of individuals sampled (prevalence)** | **Data points** | **Type of survey** |
|---|---|---|---|---|
| 1969[215] | Multiple sites | 247,908 (2.72%) | 56 | Market survey (visible leg swelling) |
| 1973[216] | Multiple sites | 13,138 (2.77%) | 25 | School enquiry |
| 1987[35] | Ocholo, Southwest Ethiopia | 2689 (5.4%) | 1 | Community based (physical examination) |
| 1992[217] | Gera & Didessa, Western Ethiopia | 416 (7.5%) | 2 | Community based (physical examination) |
| 1997[10] | Pawe Northwest Ethiopia | 1900 (7%) | 1 | Community based (physical examination and microscopic examination of midnight sample) |
| 2003[218] | Wolaita zone, Southern Ethiopia | 33,678 (5.46%) | 7 | Community based (physical examination) |
| 2011[219] | Gulisso west Ethiopia | 38,420 (5.0%) | 1 | Community based (physical examination) |
| 2012[220] | Midakegni | 1,656 (7.4%) | 1 | Community based (physical examination, microscopic examination of midnight sample and ICT) |
| 2012[14] | Debre Elias and Dembecha Northern Ethiopia | 50,620 (3.3%) | 2 | Community based (physical examination) |
| 2012[210] | Western Ethiopia in 112 Woredas | 11,249 (4.6%) | 133 | Community based (ICT card) |
| Total | | 401,674 (3.4%) | 229 | |

examination to diagnose podoconiosis. Two of the market and school-based studies used visible lymphoedema. Only three studies used laboratory testing to exclude other causes of lymphoedema.

Most (n=101, 44.1%) of the data points were from Oromia, the largest regional state in the country in terms of geographical area and population, 50 (21.8%) were from Southern

Nations Nationalities and Peoples Region (SNNPR), and 24 (10.5%) from Amhara. There was no information for Addis Ababa or Somali (Figure 3.1).

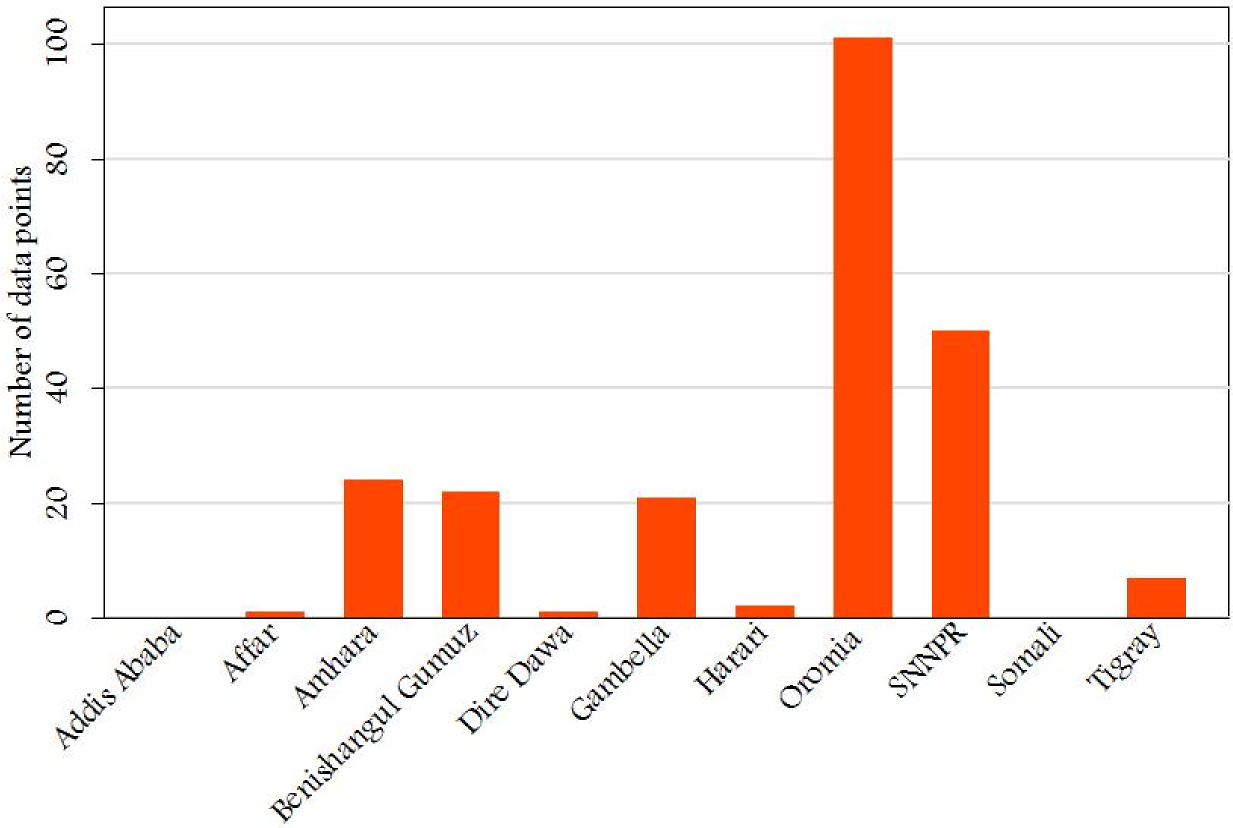


**Figure 3.1** Distribution of surveys included in the analysis, by region. The bar indicates the number of data points surveyed between 1969 and 2012. The surveys excluded clinic based surveys.

The 229 data points were from 190 *woredas* (districts), of which 80 (43.1%) were within Oromia and 47 (24.7%) within SNNPR. Based on these results, the average prevalence of podoconiosis in Ethiopia was estimated to be 3.4% (95% CI: 3.3 to 3.4). The prevalence of podoconiosis varied by region: 4.8% in SNNP, 4.4% in Harari, 3.0% in Amhara, 2.5% in Oromia, 1.6% in Tigray, 0.6% in Gambella, 0.4% in Benishangul Gumuz and 0.4% in Dire Dawa.

### 3.4.2 Geographical distribution of podoconiosis

Figure 3.1 shows the geographical distribution of podoconiosis. There was wide geographical variation of prevalence from 0.0% to 48.0%. High prevalence of podoconiosis occurred in the southwest and southern parts of the country. The highest prevalence was recorded in Kelem Welega and Illubabor zones of Oromia. The prevalence of podoconiosis was generally lower in the far western part of the country, such as Gambella. Except for one location (with zero prevalence), no information was available about the occurrence of the disease in Affar and Somali (Figure 3.2).

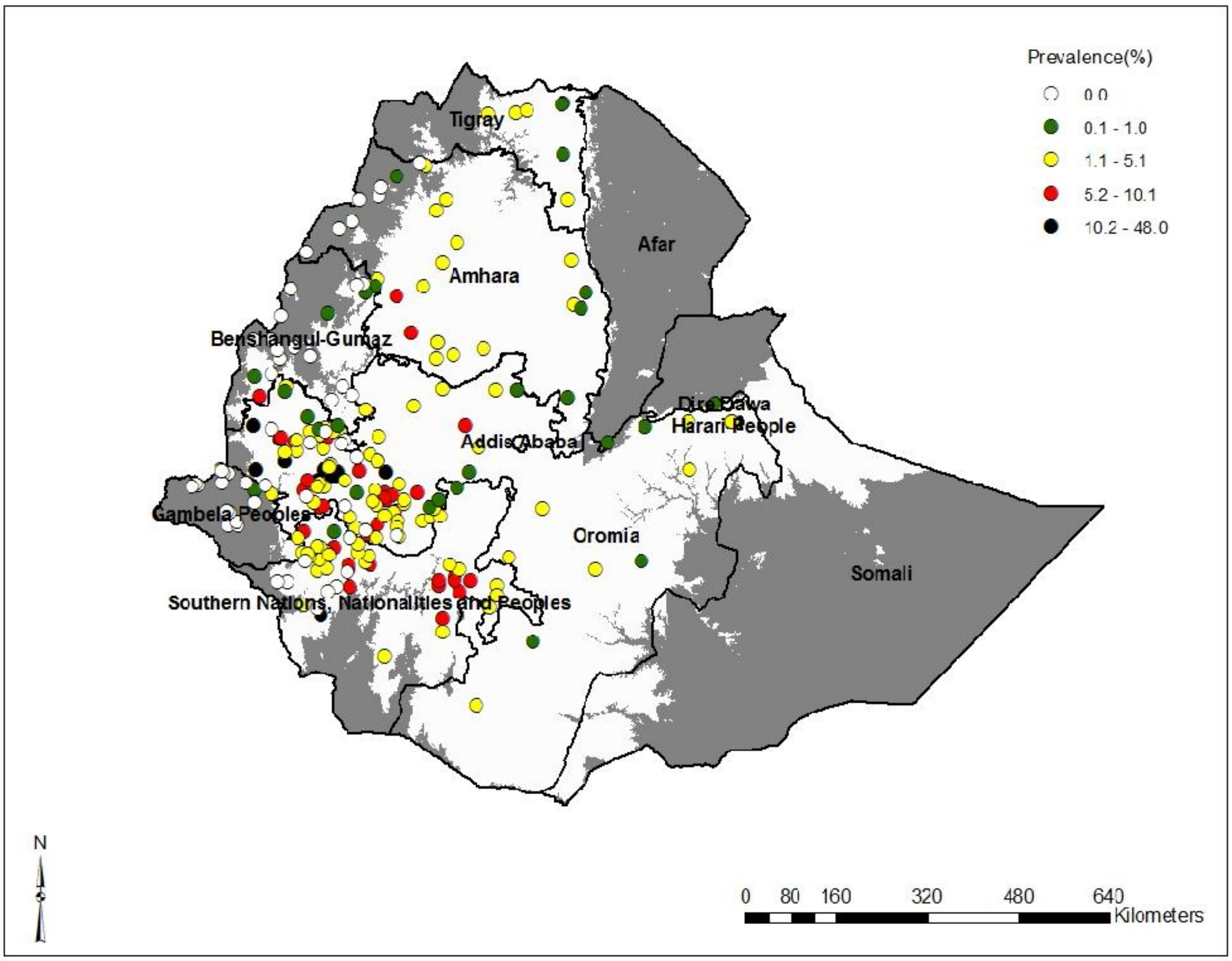


**Figure 3.2** Geographical distribution of podoconiosis in Ethiopia, results from historical maps and recent surveys conducted on podoconiosis. In total 229 locations were identified

with podoconiosis prevalence figures, and were geo-referenced. Circles indicate prevalence in villages and markets surveyed. Grey areas indicate areas where either altitude is below 1225 meters above sea level or mean annual rainfall is <900 mm or annual mean air temperature >24°C.

Based on the analysis of 190 *woredas* included in the 9 regional states, 39 *woredas* had zero prevalence, 104 a prevalence of 0.01- 5.0%, 32 a prevalence of 5.1-10.0%, and 15 a prevalence of ≥10.0%. Of those *woredas* with a prevalence >5.0%, 27 (57.4%) were in Oromia and 16 (34.0%) in SNNPR; almost all (13 out of 15) *woredas* with a prevalence >10.0% were in Oromia (Table 3.2).

**Table 3.0-2** Prevalence distribution of podoconiosis by *woreda* and region.

| | **Number of *woredas* by prevalence of podoconiosis** | | | | | |
|---|---|---|---|---|---|---|
| **Region** | **0.0%** | **0.01% to 1.0%** | **1.1% to 5.0%** | **5.1% to 10.0%** | **>10.0%** | **Total** |
| Afar | 1 | 0 | 0 | 0 | 0 | 1 |
| Amhara | 3 | 3 | 14 | 2 | 0 | 22 |
| Benishangul Gumuz | 13 | 3 | 3 | 1 | 0 | 20 |
| Gambella | 8 | 1 | 3 | 0 | 0 | 12 |
| Harari | 0 | 0 | 1 | 1 | 0 | 2 |
| Dire Dawa | 0 | 1 | 0 | 0 | 0 | 1 |
| Oromia | 7 | 6 | 40 | 14 | 13 | 80 |
| SNNPR | 7 | 1 | 23 | 14 | 2 | 47 |
| Tigray | 0 | 2 | 3 | 0 | 0 | 5 |
| **Total** | **39** | **17** | **87** | **32** | **15** | **190** |

### 3.4.3 Environmental variables associated with podoconiosis

Areas with zero prevalence were characterized by a mean altitude of 1055 masl, mean annual rainfall of 1293mm, topography of 2.1 degrees and temperature of 24°C. High prevalence areas (>5%) were characterized by mean altitude >1600masl, mean air temperature <20.5°C and mean annual rainfall >1500mm (Table 3.3).

**Table 3.0-3** Environmental characteristics of different categories of prevalence of podoconiosis

| **Environmental variable** | **Prevalence classification** | | | |
|---|---|---|---|---|
| | 0% | 0.1%-5.0% | 5.1%-10% | >10.0% |
| Mean altitude (masl) | 1055.2 | 1820.6 | 1804.8 | 1685.3 |
| Mean annual rainfall (mm) | 1292.9 | 1407.7 | 1592.6 | 1638.5 |
| Mean slope of the land (º) | 2.1 | 2.1 | 2.9 | 1.8 |
| Mean annual air temperature (°C) | 23.8 | 19.3 | 19.4 | 20.2 |

Correlation of the observed geographical distribution of podoconiosis with selected large-scale environmental variables was investigated. Absence or very low prevalence of podoconiosis was observed in areas with annual total rainfall <900mm (p=0.36, *p<0.001)*, and in areas with annual mean air temperature >24°C (p= -0.35, *p<0.001).*

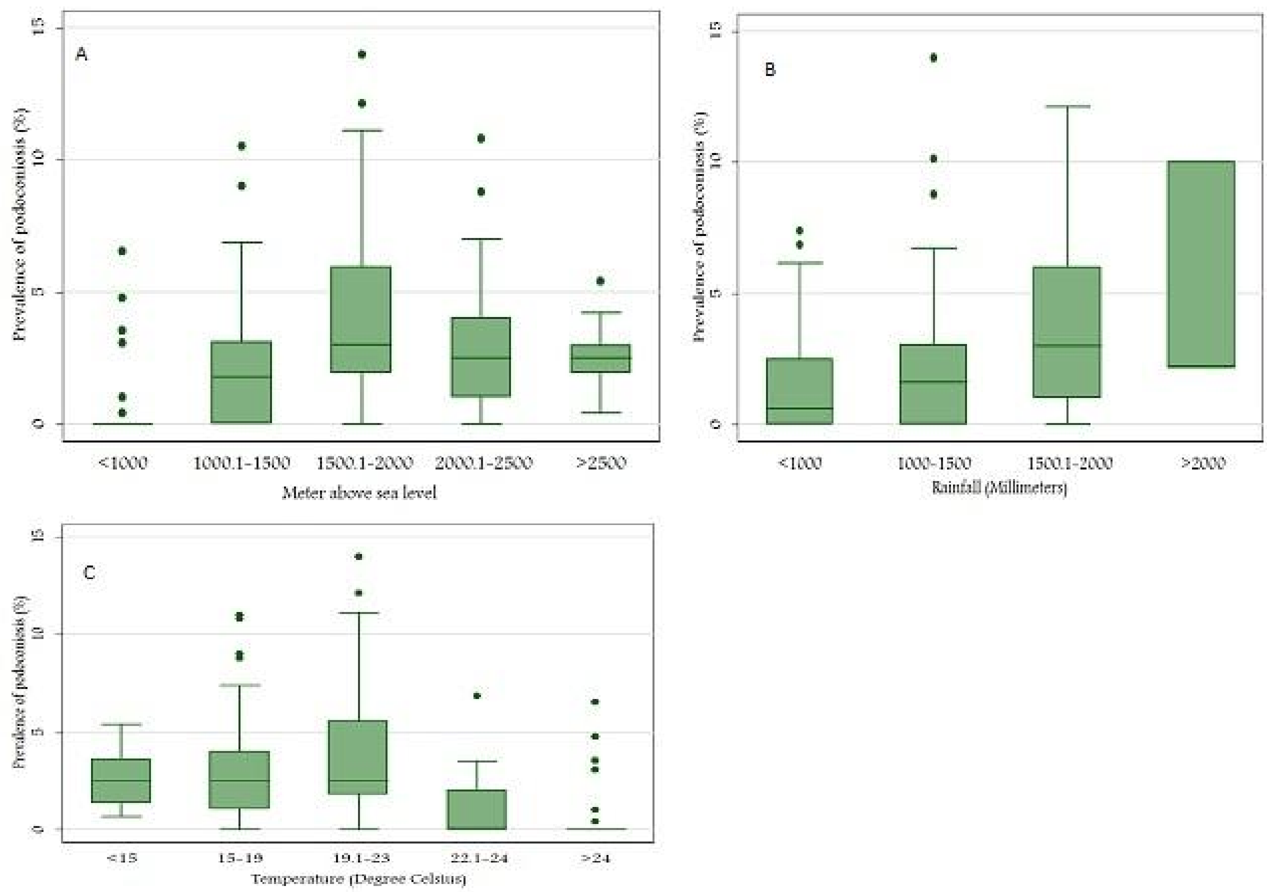


**Figure 3.3** Box plots of environmental variables and prevalence of podoconiosis a) altitude in meters versus prevalence of podoconiosis b) annual rainfall in mm versus prevalence of podoconiosis c) Mean annual air temperature and prevalence of podoconiosis and

Possible associations of environmental variables previously documented to be associated with podoconiosis were identified and associations were checked using box plots (Figure 3.3). There was a clear trend of increasing prevalence as altitude and rainfall increased. The possible association of environmental variables and prevalence of podoconiosis was modelled. The final model showed that a one-unit increase in slope was associated with an increase of approximately 16% increase in the podoconiosis prevalence (OR = 1.16; 95% CI = 1.15 to 1.17; $p < 0.001$). Compared to areas with annual mean annual air temperature ≤24ºC, those areas with mean annual air temperature >24ºC had lower odds of high prevalence of podoconiosis (OR = 0.48, 95% CI = 0.41 to 0.57). Compared to medium size soil texture, areas with fine texture had higher odds of high prevalence podoconiosis (OR=1.09, 95% CI = 1.03 to 1.16) (Table 3.4).

**Table 3.0-4** Output of binomial logistic regression of environmental variables and prevalence of podoconiosis, 229 locations in Ethiopia.

| Variable | Category | Unadjusted Odds Ratio | AOR 95% Conf. Interval | P>\|z\| |
|---|---|---|---|---|
| | | | | |
| Mean annual air temperature (ºC) | ≤24 | 1.00 | | |
| | >24 | 0.40 (0.34 to 0.47) | 0.48 (0.41 to 0.57) | <0.001 |
| | | | | |
| Mean annual rainfall (mm) | ≤1000 | 1.00 | 1.00 | |
| | >1000 | 1.21 (1.14 to 1.27) | 0.97 (0.92 to 1.03) | 0.436 |
| | | | | |
| Altitude (masl) € | ≤1225 | 1.00 | | |
| | >1225 | 3.06 (2.60 to 3.59) | | |
| | | | | |
| Soil texture | Fine | 1.08 (1.02 to 1.15) | 1.09 (1.03 to 1.16) | 0.002 |
| | Medium | 1.00 | 1.00 | |
| Topography of the land(º) | | 1.17 (1.15 to 1.18) | 1.16 (1.15 to 1.17) | <0.001 |
| SD of NDVI§ | | 1.00 (0.99 to 1.00) | 0.99 (0.99 to 1.03) | 0.192 |

§ SD= standard deviation, NDVI= Normalized Difference Vegetation Index, masl=Meters above sea level, mm= millimetre, € Collinearity was checked between all possible pairs of potential environmental variables: altitude and mean annual air temperature had a correlation coefficient >0.9, and since the mean annual air temperature has more to do with weathering of soil, altitude was excluded from the final model.

### 3.5 Discussion

Podoconiosis is gradually attracting global attention [221,222], and as the profile of the disease increases, understanding the geographical distribution and environmental factors affecting this distribution will become important. Identifying the environmental correlates of disease distribution is the first step to producing risk and distribution maps to guide decision making for interventions. Although podoconiosis has been described in Ethiopia for four decades [216,223], the current disease burden and geographical distribution is not known. Here, we summarize its distribution based on historical and contemporary data and identify environmental variables associated with the distribution of the disease.

The average prevalence of podoconiosis in Ethiopia was found to be 3.4%, which is higher than the 2.7% reported by Ooman in 1969 [215] in his market-based survey of 56 sites or the 2.8% reported by Price from school-based surveys conducted in 1974 [216]. It is also higher than the prevalence documented in Burundi (1.0%) and in Rwanda (0.6%) in the 1970s [34]. More recent studies included in the current analysis have indicated prevalence estimates of 5.5% in Wolaita, southern Ethiopia [218], 5.4% in Ocholo [35], southwestern Ethiopia, 7.0% in Pawe [10], 7.5% in Gera and Didessa [217] and 5.2% in Gulisso [224], western Ethiopia, and 7.4% in central Ethiopia [220]. Absence of information from Addis Ababa, Affar and Somali regions and the diagnostic methods used reduces the precision of this estimate. In addition, one of the largest surveys included in this review was based on purposive sampling, covering areas that were thought to be endemic for podoconiosis, which might result in over estimation of the prevalence.

There was significant geographical variation within Ethiopia; high regional prevalence estimates were recorded in SNNPR, Oromia and Amhara. These are consistent with findings from individual studies and environmental characteristics studied. All of the areas with prevalence >10% were found to be non-endemic for LF (ICT positivity of 0%) [210]. These districts are located in Illubabor and Kelem Welega zones of Oromia, and these areas were already identified by civil society organizations as endemic for podoconiosis.

In this analysis, we found associations between prevalence and temperature, altitude, rainfall, topography of the land and soil texture. Previous studies have documented association of temperature, altitude and rainfall with occurrence of podoconiosis in East

Africa [60]. High prevalence of podoconiosis was documented in areas with altitude of >1500masl, mean annual rainfall of >1500mm and mean annual mean annual air temperature of 19-21°C. Altitude affects temperature and rainfall, and these lead to weathering. Hot and humid environments increase weathering and type of soil produced. In arid regions, the lack of precipitation inhibits chemical weathering, leading to coarse textured soil [208,209]. The topography of the land increases water runoff and thus, weathering of rocks [208,209] and in the present study, was also associated with podoconiosis prevalence. Soil texture was also associated with prevalence of podoconiosis, confirming an earlier study which documented an association between particle size and occurrence of podoconiosis [29].

Absence of podoconiosis was associated with mean annual rainfall <900mm, mean altitude of 1225masl and mean annual air temperature of >24°C. Previous studies in east Africa documented the absence of podoconiosis in areas at ≤1000masl and with annual rainfall ≤1000 mm. These findings might justify exclusion of areas below these environmental limits in future mapping activities [60]. Based on these findings, Affar and the majority of Somali regional state should be classified into the 'no podoconiosis' category. This is in agreement with the expert opinion of two Ministry of Health Regional Health Bureaus, who state that podoconiosis is absent in their regional states (Nebiyu Negussu, Somali Regional Health Bureau and Aregawi Gebremedhin, Affar Regional Health Bureau, personal communications). Of note, lymphatic filariasis was recently documented in areas up to 1698 masl [210], indicating that there are potential areas between 1225 and 1698 masl where filariasis and podoconiosis co-occur – clearly, this must be taken into account when mapping either disease. In areas of possible overlap between the two diseases, anti-filarial antibody examinations may be required [225,226] as well as entomological studies of the vector population [33]. The best strategy in countries where both LF and podoconiosis exist is coordinated mapping: both diseases have similar clinical features and differential diagnoses will have to be made, and both have the same population group for mapping (i.e. individuals >15 years old).

There is no systematic, large scale podoconiosis control program in Ethiopia. For over 20 years, podoconiosis treatment and prevention has been offered on a small scale by a range of community based organizations and international non-governmental organizations. Recently, podoconiosis was recognized by the Ministry of Health as one of the eight national priority NTDs, and was included in the National Master Plan for NTDs (2013-2015). With this inclusion, and growing interest from the regional health bureaus, it is likely that the treatment and prevention of podoconiosis will be scaled up in Ethiopia. By describing the geographical variations of podoconiosis within Ethiopia, we hope to characterize areas in which prevention and treatment should be targeted. The rainfall, altitude and temperature limits of podoconiosis will help to exclude areas in which the disease is unlikely to be a significant public health problem, and so will enable limited resources to be focused on priority areas. We are planning to conduct nationwide mapping of podoconiosis in Ethiopia and the results presented here have implications for this exercise. For example, the majority of districts in Affar, Gambella, Somali and part of Benishangul Gumuz are characterized by the environmental features associated with zero prevalence.

There are limitations to the current work; the surveys included used different methods, and the case definition of podoconiosis across the studies was inconsistent. The two largest surveys included in this analysis used market count and school enquiry techniques, both of which may underestimate prevalence. However, the investigators validated the surveys by comparing with community based censuses, and demonstrated good agreement [223]. In the older map developed by Price [216] some of the locations do not have precise estimates of prevalence, so the average of the lower and upper boundaries was taken. The studies included in the analysis are over two generations; there may be changes in shoe wearing practices over time affecting the prevalence of podoconiosis. Nonetheless, repeated surveys[14,218] in some areas suggest that there have been no significant changes in prevalence of podoconiosis over the last 40 years. The other limitation of the analysis is that most of the surveys did not use a diagnostic test, relying on observations or physical diagnosis. Only three used any biomedical test to enable differential diagnoses of conditions with a similar symptomatology to podoconiosis (e.g. lymphatic filariasis). Nonetheless, most of the studies were conducted in areas potentially endemic for podoconiosis based on geographical parameters. In addition, we have used data from recent LF mapping to exclude areas endemic for LF from the analysis. Rapid diagnostic tests for lymphatic filariasis are now available, and will decrease misclassification in areas where these two diseases overlap. The lack of information from three regional states of Ethiopia is also another limitation, although only 12% of the population lives in these three regional states. In addition, Addis Ababa is the capital city, and shoe-wearing is almost universal. The upcoming mapping projects will address the above mentioned limitations and will generate more reliable estimates.

## 3.6 Conclusion

Our analysis provides an initial insight to the ecology of podoconiosis in Ethiopia, and shows that podoconiosis only represents a public health problem of major concern under certain environmental conditions, presumably those conditions favourable for the weathering of rock to produce specific types of soil. The disease is highly prevalent in the highlands of Ethiopia, particularly in the southern and south central areas. Climatic conditions, primarily altitude, rainfall and temperature, influence the weathering of rocks and determine the type of soil generated, which in turn probably influences the distribution of podoconiosis. High prevalence areas are characterized by mean altitude >1500masl, temperature between 19-21°C and mean annual rainfall >1500mm. Identifying other variables influencing prevalence might be achieved through inclusion of high resolution geological and soil maps in future analyses. Deciding on a threshold for classification of districts as 'endemic' or 'non-endemic' for podoconiosis will be a priority in targeting interventions to where the disease is prevalent.

As discussed in this chapter, the geographical distribution of podoconiosis in Ethiopia is widespread and influenced by various environmental factors. Most of the high prevalence districts are found in Amhara, Oromia and SNNP regional states and mapping efforts should target gaps in these regions. The findings here helped the mapping of podoconiosis in Ethiopia by indicating areas which should be prioritised for disease mapping as compared to areas that could be potentially excluded from mapping activities. The findings here will also help in the selection of environmental variables for further analysis. The next chapter will discuss the methods used in the integrated mapping of podoconiosis and LF in Ethiopia. The subsequent chapters will use multilevel modelling to investigate variation in the risk of podoconiosis at a national scale and use environmental and climatic covariates to predict the risk of podoconiosis.

# Chapter 4. Mapping of lymphatic filariasis and podoconiosis, the approach

## 4.1 Overview

In the previous chapter, we discussed the historical distribution of podoconiosis. The findings indicated that podoconiosis is widespread in Ethiopia, the distribution tied to certain environmental characteristics. Although the historical data were important for illustrating the distribution of podoconiosis in the country, the review also identified areas lacking data in some parts of the country. There were also methodological limitations identified in most of the historical data. While a useful step in defining the historical distribution of podoconiosis, the findings highlighted the need for up-to-date data to estimate the disease burden and the population at risk of podoconiosis in Ethiopia.

Mapping of podoconiosis has been lacking in many potential endemic countries, which may be partly due to the absence of a documented mapping approach for podoconiosis. In recent years, experts have advocated for integrated mapping of NTDs[112]. Integrated mapping, when applicable, is found to be cost-effective compared to mapping of individual diseases[227]. Therefore, we conducted integrated mapping of podoconiosis and LF in Ethiopia. Here, we present the details of the methods used for the integrated mapping of these two diseases. The approach used here could be potentially adopted by other endemic counties. The results presented here were published in 2014[228]. Chapter 5 will present the findings of the survey.

## 4.2 Introduction

International donors, development partners and endemic country governments are allocating resources for the prevention, treatment and elimination of NTDs. To benefit from these resources, endemic countries and implementing partners are required to develop evidence-based plans, which would allow them to track progress and show the effectiveness of programme implementation [112,229,230].

Disease mapping is the systematic collection of georeferenced data to visualise the distribution and prevalence of a disease in space and time [231]. It provides clear information on the geographical distribution of diseases and the population at risk, both of which are important pre-requisites for determining the areas and populations to be targeted for treatment and control of NTDs [230,231]. WHO, international donors and partners have emphasized the importance of integrated --rather than vertical-- control of NTDs [107,232]. Integrated mapping has several advantages over standalone surveys: costs can be reduced by coordinated use of personnel and transport, and co-endemic areas can be more precisely identified as compared to disease-specific mapping [112,196,197,233,234]. It is the first step for integrated planning of programmes, efficient resource allocation and monitoring progress and impact of control [112,196,197,235,236]. Previous integrated mapping efforts have focused on a range of diseases, including trachoma, onchocerciasis, schistosomiasis, soil-transmitted helminthiases and lymphatic filariasis (LF) [195-197,236-238]. However, integrated mapping may also be logistically intensive and methodologically difficult, because of differences in the target groups to be mapped and sites to be selected according to the ecology of each disease.

There are two principal causes of elephantiasis, or lymphoedema, in the tropics [239]. The most common cause is LF due to the parasitic nematode *Wuchereria bancrofti* (and, in Asia, *Brugia malayi* and *B. timori*), which is transmitted by blood-feeding mosquitoes [122,240]. The second principal cause is podoconiosis, a form of elephantiasis arising in barefoot subsistence farmers who are in long term contact with irritant red clay soil of volcanic origins [148]. It has been estimated that 1 million cases of podoconiosis exist in Ethiopia, but the nationwide distribution has not been clearly defined. The overall distribution of LF in Ethiopia is also not well established. According to a recent review, approximately 30 million people are thought to be at risk of LF, and Ethiopia bears 6-9% of the LF burden in sub-Saharan Africa [114].

Despite these huge burden estimates for both LF and podoconiosis in Ethiopia, no nationwide podoconiosis mapping data existed, and only 125 of the country's 817 districts had been mapped for LF [210]. Ethiopia launched its integrated National NTD Master Plan in May 2013 [26], and LF and podoconiosis were identified as priority diseases along with six other NTDs (i.e. soil-transmitted helminthiases, schistosomiasis, leishmaniasis, onchocerciasis, trachoma and dracunculiasis) [26]. Mapping was identified as a critical first step before implementing any operational programming for the control and elimination of these NTDs.

In recent years, advances in technology, such as the availability of remote sensed data, application of geographic information systems and mobile technology, have enabled rapid mapping of NTDs [112,113,241,242]. We conducted the first integrated mapping of podoconiosis and LF in Ethiopia using mobile-based technology. This chapter aims to describe the methodology used for integrated mapping of podoconiosis and LF, document the lessons learnt, and to provide recommendations for future, similar mapping efforts.

The study was conducted between June and October 2013, in seven regional states (Tigray, Affar, Amhara, Oromiya, Somali, Southern Nations Nationalities and Peoples [SNNP], and Harari) and two city administrations (Addis Ababa and Dire Dawa Administration Councils).

Although integrated mapping is intuitively appealing, there may be practical challenges. To further explore potential challenges we conducted two focus group discussions (FDGs) with survey team members. Each FGD consisted of six individuals, and four in-depth interviews with enumerators, team leaders, and supervisors once the mapping was complete. I conducted the in-depth interviews and FGDs. Flexible interview guides were used to conduct FGDs and in-depth interviews. Interviews were conducted in Amharic, audiotapes were transcribed anonymously and translated into English. Data were analysed manually. Interpretation of data was informed by experience during implementation of the survey as well as from the analysis of the qualitative data.

## 4.3 The approach used

### 4.3.1 Integration of LF and podoconiosis mapping protocols

The mapping was conducted by a consortium of universities and institutions, including the Ethiopian Public Health Institute (EPHI, previously EHNRI), Brighton and Sussex Medical School (BSMS), the Centre for Neglected Tropical Diseases (CNTD) at LSTM and the Global Atlas of Helminth Infections (GAHI) at the London School of Hygiene & Tropical Medicine (LSHTM). Initially, the mapping of these two diseases was planned separately. BSMS and GAHI-LSHTM were working on mapping podoconiosis and the EPHI and CNTD/LSTM were working on mapping LF. However, through discussion with the Federal Ministry of Health of Ethiopia, the possibility of integrated mapping was raised. Experts from both mapping groups held a meeting and identified the advantages and disadvantages of integrated versus disease-specific mapping. Reasons in favour of integrated mapping included i) both LF and podoconiosis had been identified as priority NTDs in the National NTD Master Plan of Ethiopia (2013-2015) [26]; ii) the two conditions have similar clinical manifestations and the same target age group; iii) diagnosis of podoconiosis requires exclusion of LF; iv) analysis of the data from the 112 districts already mapped for LF indicated potential distribution overlaps in areas between 1225 and 1698 meters above sea level [74]; v) information from other countries indicated that integrated mapping would lead to cost savings compared to multiple disease-specific mapping exercises [112]; vi) the recently-launched WHO morbidity management guideline recommends the integrated management of these two diseases [243]; and vii) both conditions are known to exist in other countries including Cameroon, Kenya, Uganda and Tanzania, so the development of a protocol for integrated mapping might have application beyond Ethiopia.

The challenges identified were i) that experts preferred targeted rather than nationwide mapping for LF, mainly due to resource constraints, ii) the lack of existing guidelines for integrated mapping of LF and podoconiosis; iii) the lack of clear diagnostic criteria for podoconiosis; iv) the logistical challenges of large field teams; and v) that the institutions had no history of working together.

Through further discussion, two of these challenges were ameliorated by deciding to use the WHO guideline for LF mapping [235] as the basis for integrated mapping, and through the development of an algorithm for the diagnosis of podoconiosis (**Figure 4.1**), which was accepted by both mapping groups. Preparation for mapping then proceeded on an integrated basis.

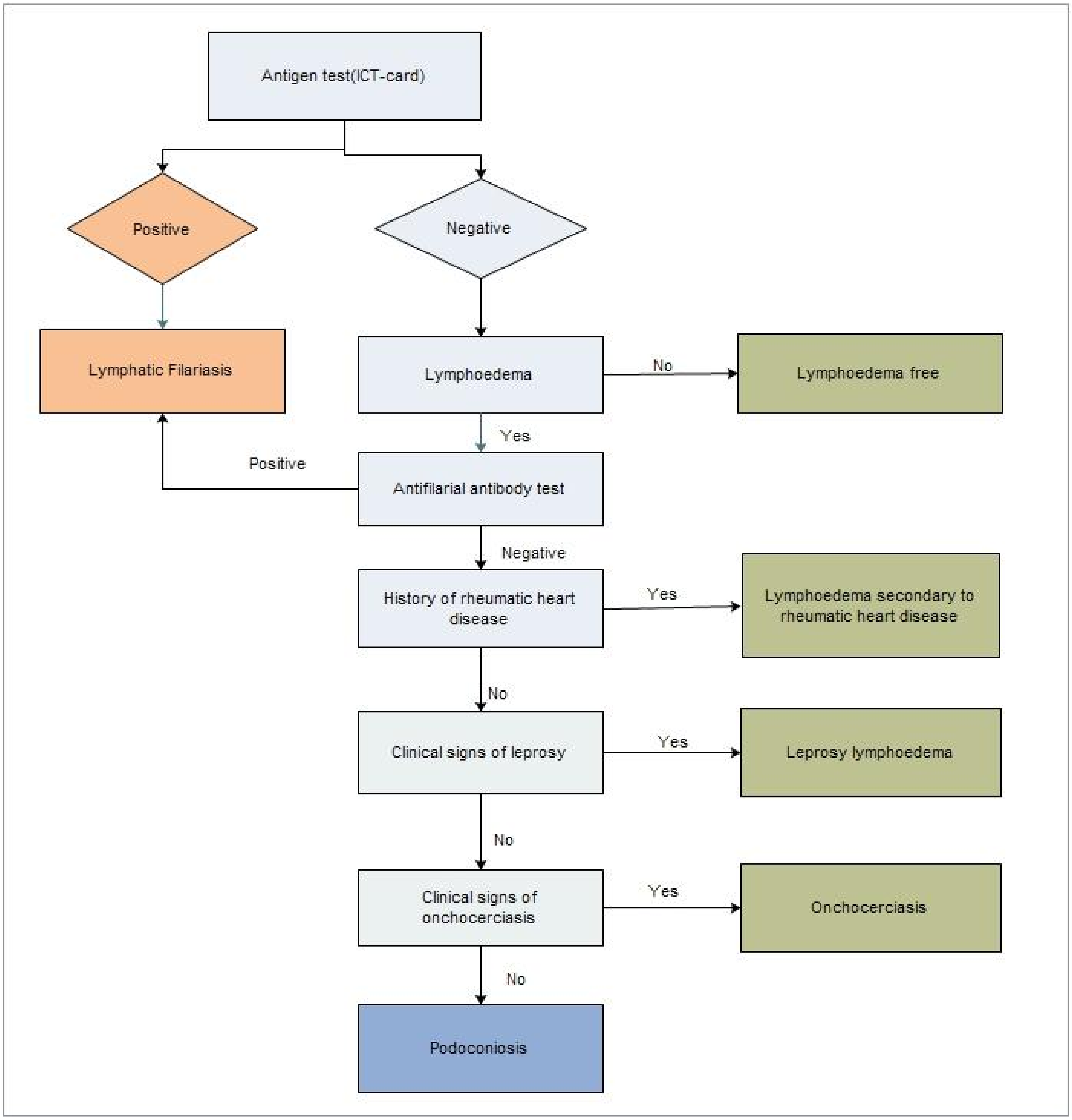


**Figure 4.1** Clinical algorithm for podoconiosis diagnosis. There is no point-of-care diagnostic tool for podoconiosis. Currently, podoconiosis is a diagnosis of clinical exclusion based on history, physical examination and certain disease-specific tests to exclude common differential diagnoses. All individuals included in the survey were tested for circulating *W. bancrofti* antigen using an ICT. Those found to be positive, regardless of the

presence or absence of lymphoedema, were excluded from further clinical examination for podoconiosis. The common differential diagnoses of podoconiosis are lymphoedema due to LF, systemic disease and leprosy.

### 4.3.2 Preparatory phase

#### *4.3.2.1 Ethics Approval and Consent*

Ethics approval was obtained from the Institutional Review Board of the Faculty of Medicine, Addis Ababa University (090/11/SPH) and the Research Governance & Ethics Committee of Brighton & Sussex Medical School (11/116/DAV) for podoconiosis mapping, and from the Ethiopian Public Health Institute (EPHI, previously EHNRI) and Liverpool School of Tropical Medicine (LSTM) (12.22) for LF mapping. Once the decision to do integrated mapping was made, amendments were requested and approved by each of these ethical approval committees. Approval to conduct the surveys was obtained from the Ministry of Health Regional Health Bureaus, followed by the Zonal Health Offices. The study was explained to each village leader and written consent was obtained to conduct the study in each village. The purpose of the study was explained to all individuals gathered, and the inclusion criteria were explained. The study was then explained to each individual that met the inclusion criteria, and each was asked for consent. Those who provided consent were registered and requested to sign or fingerprint the consent form. Individual written informed consent was obtained from each participant (≥18 years of age). For those less than 18 years old, consent was obtained from their parents/guardians and the participant themselves provided informed assent. Confirmed *W. bancrofti* infection was treated by co-administration of one tablet of albendazole and ivermectin, as indicated by a dose-pole according to WHO recommendations [244]. For those with lymphoedema, education was given about morbidity management.

#### *4.3.2.2 Development of contracts*

Contracts were developed between EHNRI/EPHI and both disease-specific partners (BSMS and CNTD). These set out roles and responsibilities, timelines and budgets. In addition, a Data Sharing Agreement was developed between BSMS and CNTD to delineate the ownership, analysis and publication of data arising from the mapping.

#### *4.3.2.3 Development of mapping protocol*

Initially, disease-specific mapping protocols were developed. Experts in mapping and epidemiology were involved in harmonizing the two protocols and helped to resolve differences between the two approaches. The planning drew on experience from previous large scale studies in the country such as the Malaria Indicators Survey [245,246], previous LF mapping [210] and the national tuberculosis survey [246]. After the final protocol was developed, disease-specific training manuals and standard operating procedures (**supplementary material 4.1**) for conducting the mapping were developed.

#### *4.3.2.4 Procurement and storage of supplies*

Supplies and consumables required for the mapping were procured from local markets, while smartphones and immunochromatographic card tests (ICT) were procured internationally. The ICTs (BinaxNOW® Filariasis, Alere, Massachusetts, U.S.) were stored at a central warehouse in EPHI according to the manufacturer's guidelines, and then transported to the field following the appropriate cold chain procedures. Each team was provided with a cold box and ice packs. On arrival at each district, the team was able to exchange the ice packs with deep-frozen ones at the respective health facility. Subsequent batches of ICTs were distributed to each team during supervisory visits. Due to limited availability of ICT cards at manufacturer level and the uncertainty that the project could be accomplished on time, shipment of the ICTs occurred in four batches; this required repeated clearance through customs resulted in additional costs and supply chain breakdown.

> *"The customs clearance took a lot of time. The ICTs were sent in four batches and had to pass through the clearance process four times, each taking 3-4 weeks. If all the ICT had been shipped together, the cost of transport and storage would have been reduced. We were paying for customs on a daily basis. Because of the ICT shortage, there was a one week interruption of the mapping which incurred cost. I think sending the ICTs in one batch would have avoided all these problems."* [Coordinator]

*4.3.2.5 Transport*

One local supplier was identified following a competitive bid process. In total, 34 vehicles were hired and 4 additional vehicles for supervision for the entire project period. Each team was provided with one vehicle and travelled together during the data collection period. The supplier was responsible for covering vehicle maintenance and drivers' allowances. One focal person from the supplier was identified, and one person responsible for coordination of the transport was identified on the mapping team. Any communications regarding vehicle and transport issues were dealt with by the focal persons. As far as possible, the same vehicles were used throughout the mapping process, enabling each team to develop a relationship with the driver. Some of the drivers were not willing to drive in challenging areas nor to include individuals selected from the community among their passengers, thinking that it was not their duty.

*"Transportation is key for the success of large scale surveys such as this and the driver is a key person. To reduce disharmony, it is important to clearly indicate what is expected from the drivers and include this in the agreement with the suppliers."* [Team leader]

*"Clear agreement should be signed with car suppliers because some of the drivers were not willing to go to difficult places. In my view, incentivizing drivers could be helpful to get their maximum support."* [Enumerator]

*"The payment for the vehicle rental was a flat rate; all were paid the same price. The payment should be context specific and should consider the distance from the capital and the topography."* [Team leader]

#### *4.3.2.6 Smartphone data collection*

Motorola Atrix HD smartphones with an android application were used for data collection, each costing $136 (unit price) [247]. Four forms - 'Community', 'ICT result', 'Podoconiosis questionnaire' and 'LF questionnaire' - were linked using a unique identifier. The questionnaire interface was developed by experts from the Taskforce for Global Health (Supplementary material 4.1). The smartphones had touch screen displays and exchangeable batteries, which served for 4-5 hours. They used local Wifi and mobile internet services and were linked to a server in Atlanta[247]. After the application and questionnaires were installed, pilot testing was conducted and changes were made before the start of the actual work. An internal GPS allowed the direct capture of geographic coordinates.

Data for this study were collected using the LINKS system [247], a mobile application (app) which allows data to be entered on mobile devices running Android and sent through a 256-bit encrypted connection to a centralized cloud-based database server. Eighty Motorola Atrix HD mobile phones were used for this project; two per team and 12 spare for any emergency replacements. Hierarchical data were collected using separate surveys for community level information and for individual level information. These surveys were later linked together to produce a full analytic dataset. The community survey focused on collecting information on the site (region, zone, w*oreda* (district), and *kebele* (sub-district)), but also included population counts and information about community-wide treatment of LF and other deworming activities in the past year (Supplementary material 4.1). The individual and examination survey included information regarding general demographics as well as an assessment of LF morbidity. The observation of the data collectors on smartphone-based data collection are presented in Table 4.1. A major concern was data ownership, as well as the lack of technical expertise at a local level to deal with technical and operational challenges of the android smartphones and the LINKS system.

> *"Currently, we have an agreement with the server owner about data use. But I would prefer if the server was under our control….In the future, if we get capacity building training and if we administer the server in-country, it would be more secure and preferable. In the current situation, you feel that you can't control your data."* [Coordinator]

*4.3.2.7 Data collector training*

Recruitment of the data collectors was conducted through a formal procurement procedure including national newspaper specific job advertisements; job requirements included hands-on experience of data collection and previous use of ICT or other rapid test. A training of trainers (TOT) workshop was organized by the BSMS and EPHI team for six trainers. A participatory approach was used to train the trainers on the smartphones, training manuals and testing procedures. Subsequently, a total of 136 health providers were given two days' classroom-based training (e.g. on the mapping protocol, how to operate the smartphones and how to collect data using the android application) and one day field practice in a nearby community. On the first day, all data collectors attended a common plenary session and then a breakout session according to their specialty. These individuals were formed into 34 teams, each including a health officer, two nurses and a laboratory technician. The TOT training was instrumental in bringing all the trainers to the same level.

> *"The TOT training was important: we had thorough discussion among ourselves [trainers], and this helped us to clear some ambiguities. During the training, every trainer was talking the same language."* [Coordinator]

**Table 4.0-1** Data collectors' perceptions of data collection using smartphones

| Aspect | Perception |
|---|---|
| Time | Saves time during data collection through automated skip patterns.<br>Saves time during entry: Electronic data collection avoided double data entry with paper-based data collection requires.<br>Writing on a smartphone is easier than writing on |

| | |
|---|---|
| | paper. |
| Data quality | Some restrictive rules reduced error. For example, it was impossible to enter age less than 15 years.<br><br>The skip pattern reduced error in entering irrelevant data. |
| Transport and logistics | Smartphone was easy to carry compared with thousands of questionnaires.<br><br>Reduces duplication, stamping and transportation. Smartphones are handy and easily portable. |
| Data storage | Smartphones sends data instantly. However, in case of lack of network access, data must be stored and could be lost.<br><br>Electronic-based data are easier to keep clean as compared to paper-based. |
| Communication | Unless you explain to the respondents that they may think that you are playing a game or not fully attending when you are entering data onto a smartphone.<br><br>People are more familiar with paper and would be more comfortable to respond to questions as compared to electronic-based methods. |
| Feedback mechanism | Feedback is received on a regular basis, since the data managers at the central level have access to the completed data instantly. In paper-based data collection, you have to wait until a supervisor comes and collects the questionnaire. |
| Other concerns | Charging in areas where there is no electricity is difficult.<br><br>Smartphones are costly and may attract robbery.<br><br>Once data are sent there is no room to correct, unless you contact people in the central level. |

### 4.3.3 The mapping process

Each team was provided with supplies and assigned a vehicle for the entire mapping period. Four days were allowed for mapping two sub-districts. On the first day, the district health offices were contacted, the mapping explained, permission obtained and suspected high-risk communities were identified based on review of the health records. An additional four community health workers were recruited in each district to serve as community mobilizers and translators. On the second and third days, data collection was carried out in each sub-district, and the fourth day was used to travel to the next district. In practice, three days per district was usually found to be sufficient, despite the mapping exercise being carried out during the rainy season, which often severely restricted travel.

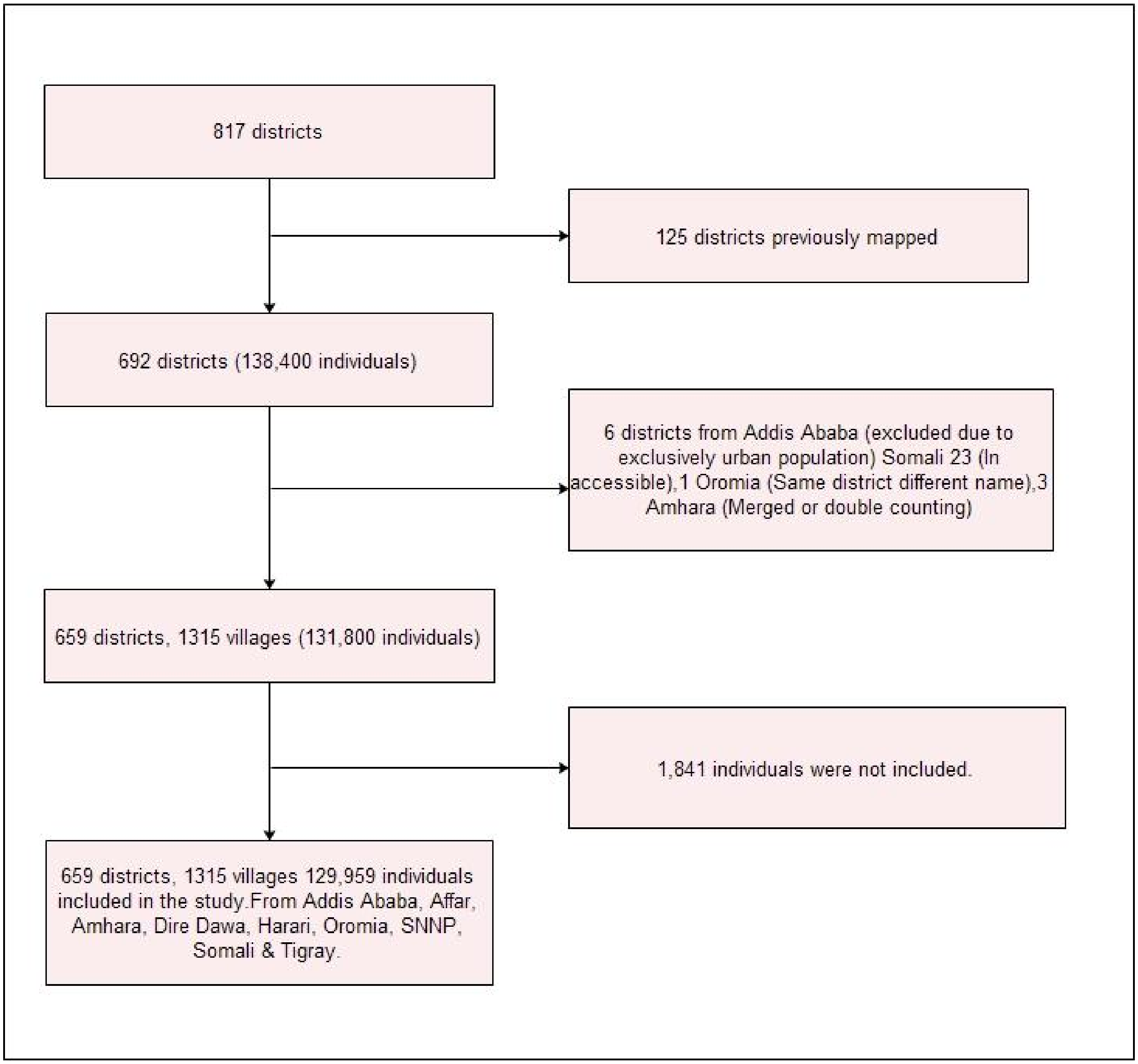


**Figure 4.2** Sampling framework for LF and podoconiosis mapping in Ethiopia, 2013

*4.3.3.1 Sampling*

Two-stage cluster convenience sampling was used. The primary sampling unit for the survey was the *kebele* (lowest level administrative structure, population approximately 5000) (**Figure 4.2**). Two *kebele* were selected from each *woreda* (district) based on reported history of lymphoedema cases collected through interviewing the *woreda* health officials, health providers and village leaders one day prior to the survey. Villages within each *kebele* were also purposively sampled. The secondary sampling unit was individuals selected within each village using systematic sampling from a random start point. Mobilization was conducted one day prior to the survey using Health Extension Workers (HEW: community health workers with an average of two attached to each *kebele*). Every adult in the community was informed through house-to-house visits that a survey was to be conducted, and they were invited to participate. On the day of the survey, all persons aged 15 years and above living in the selected communities were invited to gather at a convenient point. The study objectives were then explained in the local language, and those willing to participate were asked to form two lines, one of men and the other of women. Fifty individuals were selected from each line using systematic sampling from a random start point, resulting in an overall sample of 50 males and 50 females. Two hundred individuals were therefore tested in each *woreda*. In most villages, it was possible to mobilize all adults in the community and obtain appropriate samples. Individuals were excluded from the study if they had not lived in the *woreda* for at least 10 years, had left the *woreda* for more than 6 months in the year prior to the survey, or did not provide informed consent.

#### *4.3.3.2 Data collection*

Participants were requested to provide a finger-prick blood sample to be tested for circulating *W. bancrofti* antigen using ICTs. All the participants were tested for ICT, and results were recorded with the individual's ID number both on the card, and on the smartphone proforma after 10 minutes. In villages where there was at least one ICT-positive individual, all ICT-negative people with lymphoedema were asked to provide 5 ml blood for antifilarial antibody (Wb123 assay) testing at the central laboratory in Addis

Ababa. The clinical algorithm used in the mapping process was found to be easily understandable by the data collectors. For individuals with lymphoedema, an algorithm was used to identify possible differential diagnoses of podoconiosis (**Figure 4.1**). In this study, a confirmed podoconiosis case was defined as a person residing in the study *woreda* for at least 10 years, with lymphoedema of the lower limb present for more than 3 months for which other causes (i.e. LF, onchocerciasis, leprosy, Milroy syndrome, heart or liver failure) had been excluded. The differentiation of podoconiosis from LF used a panel approach, including clinical history, physical examination, antigen and antibody tests. The swelling of podoconiosis starts in the foot and progresses upwards [2], whereas the swelling in LF starts elsewhere in the leg. Podoconiosis lymphoedema is asymmetric, usually confined to below the knees, and unlikely to involve the groin [1]. In contrast, lymphoedema due to LF 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 was used to distinguish between the two causes of lymphoedema, although the majority of LF patients are also negative for the antigen-based test. The antibody-based Wb123 test was used to further establish exposure to LF in areas in which at least one ICT positive individual was found. To distinguish between podoconiosis and leprosy, clinical history and physical examination was used. 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. Patients were asked if they had been diagnosed with leprosy and physical examination was conducted to exclude signs of leprosy including sensory loss. Onchocerciasis has clear clinical features which can easily be distinguished from podoconiosis. All lymphoedema cases were examined for signs of onchocerciasis. Systemic causes of lymphoedema were ruled out by examination of other organ systems. Hereditary causes of lymphoedema were excluded since they occur at birth or immediately after birth, whereas podoconiosis requires extended exposure to red clay soil.

A diagram showing the order of stations used during data collection is shown as Figure 4.3. In those individuals clinically confirmed to have podoconiosis, duration of illness, family history of similar illness among blood relatives, and disease stage according to the validated podoconiosis staging system [36] were recorded.

> *"The algorithm was very clear and there was nothing difficult about it. We were given intensive training before we departed to the field. Because of these reasons, it was not difficult to use the algorithm. In case there were some uncertainties, the team had a discussion to arrive at a diagnosis."* [Team leader]
>
> *"The algorithm was supplemented by pictorial presentation of different stages of podoconiosis. Any health workers who had never heard of podoconiosis could easily use the algorithm after the training."* [Enumerator]

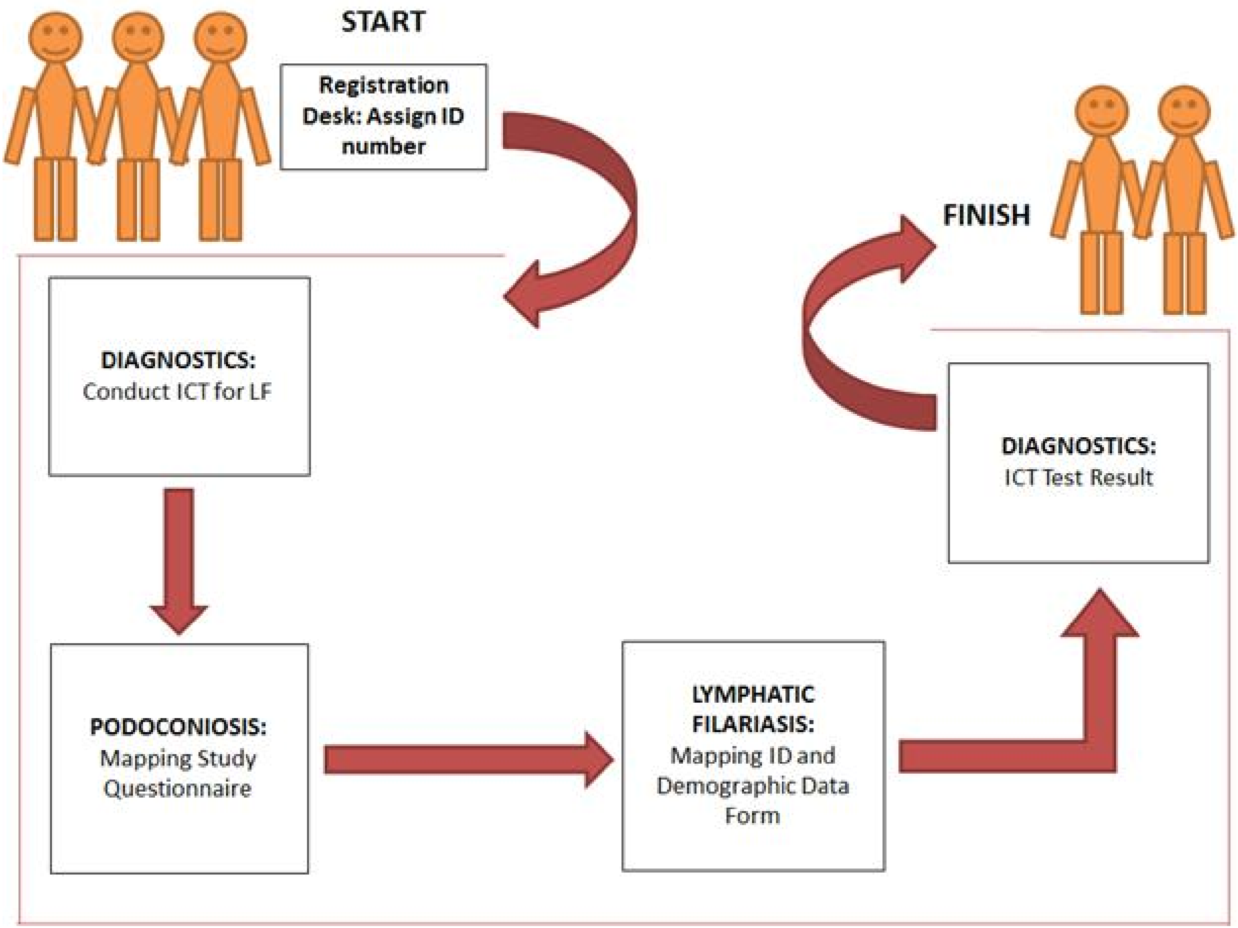


**Figure 4.3** Mapping survey setup. Each individual participating in the survey was registered and gave informed written consent. Then they were assigned an in individual ID and were given a card. The participants retained the card throughout the survey. Then, ICT tests were conducted, followed by podoconiosis and LF questionnaires. Finally, ICT test results were provided to each individual.

#### *4.3.3.3* *Field supervision*

A team from EPHI, BSMS, CNTD and other partners supervised the data collection. The supervision was intensive during the first two weeks of the start of the project. Experts experienced in both diseases and who had participated in TOT training participated in supervision. During supervision, adherence to the protocol and standard operating procedures were checked. Given the extended experience of the data collectors, adherence to the protocol was found to be very high.

> *"The supervision was very important. First, the data was collected by smartphones; although we have demonstrated the use of smartphones to everyone, there were some practical challenges in the field which needed immediate solutions. There were also some practical challenges regarding standard operating procedures, which were given solutions at the field level. Particularly, during the first three days, there were some problems, but in subsequent days the mapping continued very smoothly. Personally, I was checking adherence on the standard operating procedures, I was giving them practical solutions in the field. For example, some of the sites were not accessible since the data collection coincided with the rainy season. So we facilitated the use of motorbikes, boats and horses."* [Supervisor]

#### *4.3.3.4 Data flow and monitoring*

Data were uploaded in real time to an Amazon Elastic Compute Cloud (Amazon EC2) hosted central database which is managed by the Taskforce for Global Health using mobile internet services. Data summarized by district and village could be monitored by two experts given authorized access. This enabled rapid consultation and correction of data in consultation with the field teams. Additionally, the national NTD control team leader at the Federal Ministry of Health had access to the interface to observe progress, though this access did not permit data editing. The data collection was conducted between June and October 2013. In total, 129,959 individuals in 1,315 communities in 659 districts were mapped over a period of just three months.

#### *4.3.3.5 Costs of the survey*

According to the planning budgets, the cost of LF-only mapping covering 659 districts was $1,212,209, while the budget for podoconiosis-only mapping covering 659 districts was estimated at $1,211,664. The actual financial cost of the integrated mapping of LF and podoconiosis was $1,291,400 – a significant cost reduction through savings in the areas of team training, ICT and supplies, and travel, as described in Table 4.2. Overall, the individual survey costs 1.9 times as high as the integrated survey approach.

#### *4.3.3.6 Summary of the results*

Individual level data were available for 129,959 individuals from 1,315 communities in 659 districts (Figure 4.4.). A total 8,110 individuals with lymphoedema of the lower limb were identified. A total of 139 individuals were found to be positive for *W. banchrofti* antigen with ICT. At least one ICT positive case was found in a total of 89 sub-districts in 75 districts. The mapping results are presented in detail in chapter 5 and chapter 6.

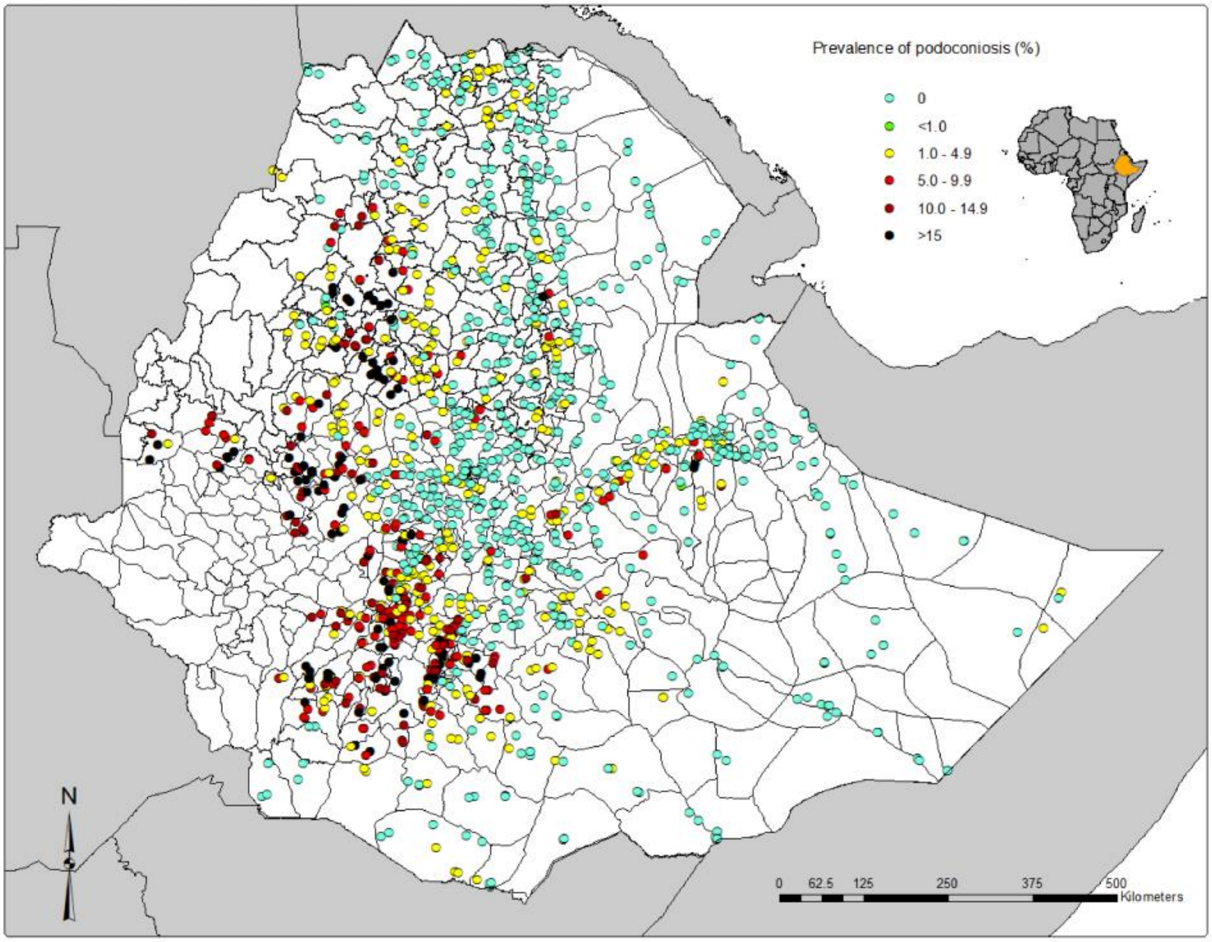


**Figure 4.4.** Locations where the samples were collected. Data were collected from 1315 villages in 659 districts all over Ethiopia.

**Table 4.0-2** Budgets and actual costs of LF and podoconiosis mapping in Ethiopia

| **Item** | **LF only mapping (originally budgeted)** | | **Podoconiosis only mapping (originally budgeted)** | | **Integrated mapping (actual expenditures)** | |
|---|---|---|---|---|---|---|
| | Description | Amount (US$) | Description | Amount (US$) | Description | Amount (US$) |
| Training | For 102 data collectors (without 34 podoconiosis nurses) | 12,958 | For 102 data collectors | 12,958 | For 102 data collectors+34 Nurses | 17,278 |
| Personnel | For 102 data collectors (central), supervisors, drivers, and local data collectors (without 34 podoconiosis nurses) | 350,376 | For 102 data collectors (central), supervisors and drivers, and local data collectors (without 34 nurses for LF) | 350,376 | For 102 data collectors (central), supervisors and drivers, and local data collectors | 419,793 |
| Vehicle rent | For each team (34 teams) | 269,100 | For each team (34 teams) | 269,100 | For each team (34 teams) | 269,100 |
| Fuel | | 27,961 | | 27,961 | | 27,961 |
| ICT cards | | 399,800 | | 399,800 | | 399,800 |
| Mobile phones | 44 mobile phones (without 40 mobile phone for podoconiosis data collection) | 6,000 | 40 mobile phones | 5,454 | 84 mobile phone | 11,454 |
| Other mapping supplies | | 81,045 | | 810,45 | | 81,045 |
| Data management | | 1,667 | | 1,667 | | 1,667 |
| Result dissemination and project execution | | 18,302 | | 18,302 | | 18,302 |
| Bench Fee | | 45,000 | | 45,000 | | 45,000 |
| **Total cost** | | **1,212,209** | | **1,211,664** | | **1,291,400** |

## 4.4 Discussion

This study present the methodology used for integrated mapping of LF and podoconiosis in Ethiopia. By presenting the approach, it is hoped to provide important guidance for future integrated mapping of these and other NTDs. Notably, it was able to implement the first integrated mapping of LF and podoconiosis as planned without any major challenges. The project received support from the community, district, regional and federal officials. The approach enabled extensive geographical coverage at relatively low cost, which would have been difficult to attain using disease-specific mapping. It is hoped that the approach may be implemented in other countries where both diseases are endemic. In countries where LF mapping has already been conducted, applying the approach is likely to be beneficial in monitoring LF intervention progress. In countries where there is no LF, but podoconiosis is suspected to be endemic, the approach could be applied to identify areas requiring intervention.

The mapping data were formally presented to the Federal Ministry of Health within one year of the start of the project. The results were disseminated at the national level in the presence of stakeholders. The maps generated will be used to inform LF elimination and podoconiosis control programs in the country. The endemic districts identified will be the basis for the scale-up of interventions, while the population-at-risk estimations serves as the basis for expanding preventive interventions.

The integrated mapping approach clearly indicated how integrated mapping, international collaboration and mobile technology together can enable the conduct of large surveys for NTDs control and elimination. There were several factors that contributed to the success of the project: firstly, the mapping was needs-based - both the national program, international donors and partners needed the data urgently; secondly, the Federal Ministry of Health was an integral part of the planning and implementation of the mapping, which greatly facilitated collaboration from district health offices and other stakeholders; and thirdly, other recent national surveys [241,248] meant that officials on the ground were familiar with the importance of large scale surveys.

The integrated mapping proved to be an appropriate, well-received alternative to individual disease surveys. It is probable that resources were saved because the cost for adding podoconiosis to the LF mapping only added one more smartphone per team and one more person for data collection and associated tests, such as collection of serum for the antibody test. Parallel efforts and duplication of training, transport, community mobilization, ICT testing, and a database server of two independent disease-specific surveys were avoided. The resources saved from such duplication allowed more districts to be covered, which enabled mapping of all the districts of Ethiopia. In the initial individual plans, the disease-specific mapping projects targeted smaller areas where the diseases were suspected. There are other advantages of the integrated mapping approach beyond cost-saving. Logistic issues were also addressed together, such as signing agreements, procurement of supplies, vehicle rental and data management. All of these activities would have been duplicated if the individual surveys had been conducted separately. Importantly, the NTD experts were taken away from their daily activities for shorter periods of time.

The application of mobile technology for mapping was a highly effective tool in a resource-constrained setting such as Ethiopia. Previous studies have documented that the time spent and the cost of mobile-based data collection was much lower than paper-based data collection [241]. Our planning budget suggested that the cost of data collection and entry was reduced by half when moving from paper-based to mobile-based data collection. In addition, the data were available in real time allowing experts to give prompt feedback to field teams. To overcome the challenges of power shortages, a car adapter was procured and each team was able to charge their smartphones from the assigned vehicle. In addition, the mobiles were kept on flight mode during data collection to save power. In areas with no mobile network coverage, the smartphones were able to store data for up to 10,000 individuals, making data collection extremely flexible. Throughout the process, only one mobile phone became non-functional, and this was because the enumerators mistakenly uninstalled the program. Each team was provided with 500 paper based questionnaire in case of any problems with the smartphones.

Strong community mobilization was another important component of the mapping. The support obtained from federal, regional and district level officials was instrumental in implementing the project without significant challenge. The involvement of the village level support team, including HEWs and *kebele* leaders, was vital for community mobilization. Given the strong link and trust built between the HEW and the community, mobilization was achieved in a relatively short period of time. Identifying community level personnel such as HEWs is important to build trust between data collectors and the community, and to achieve adequate mobilization and consent for participation. Given the presence and work in the community, Health Extension Workers are uniquely positioned to estimate the number of adults in the community and conduct house to house mobilization [249,250]. Furthermore, written consent was thought to be appropriate by community leaders before the start of the community mobilization. In some communities, community leaders were consulted in the decision to participate or not. Community leaders were found to be catalysts for participation in the study.

Despite initial concerns surrounding the podoconiosis algorithm used in the current study, it was easily understood by the enumerators. Supervisors witnessed a high level of accuracy in the use of the algorithm by the data collectors. In cases where there were doubts, a discussion was held among the teams. Previous studies have indicated that health workers can easily identify podoconiosis from other causes of lymphoedema in endemic districts [102]. However, in the current study, the clinical algorithm was used in areas where podoconiosis is not endemic or potentially co-endemic with LF. The combination of clinical history, physical examination and blood tests were used to reach a diagnosis. Although easily understood by the enumerators, at times, the procedure was found to be lengthy and tedious: further refinement of the algorithm is important. This could be achieved through evaluating the predictive diagnostic performances of individual signs and symptoms of podoconiosis.

The skills acquired through the integrated mapping of these two diseases are highly transferrable to other disease mapping exercises. The smartphones used for the mapping were provided to EPHI, and are currently being used for mapping STH and schistosomiasis. We trained some 136 health workers to use smartphones in mapping and these skilled enumerators are available for future mapping activities. Integrated mapping has led to further integration of control of these two diseases, for example, the development of integrated morbidity management guidelines for LF and podoconiosis, and the inclusion of an indicator (i.e. the number of lymphoedema cases segregated by cause and age) in the routine national health management information system (HMIS).

## 4.5 Challenges

Although the mapping project was successfully completed in a very short period of time, it was not without obstacles. First, bringing two independently planned projects together resulted in several challenges, since the two projects were initially intended to cover different geographical areas, and the planned sample size and methodology were different. This was partly due to the absence of integrated mapping guidelines for these two diseases, and partly because this was the first nationwide mapping conducted for podoconiosis. Challenges also arose related to contracts and agreements - different organizational cultures hold different expectations, so harmonizing these multi-organizational agreements took considerable time (i.e. 3 to 8 months). In addition, funding was not available at the same time for the different partners. Second, although the use of smartphones was a key strength of the mapping, technical support was provided remotely by a team from the Task Force for Global Health. During the pilot phase, some inconsistencies in the flow of the questionnaires were identified which needed immediate solutions. Solving simple technical problems took time due to the limitations of virtual communication. Third, the server for the data was hosted outside the country, initially giving rise to concerns over data ownership (Table 4.3). Fourth, the ICTs were shipped in four batches, which led to unnecessary cost, waste of time and interruption of data collection for a week.

**Table 4.0-3** Challenges and solutions taken during the mapping

| Challenges | Solutions taken |
|---|---|
| Batteries running out of charge | Charge all the chargers after work and prepare them for the next day. Use of car charger in areas where there is no electricity. In a few cases where charging was not possible, paper based data collection was |

| | |
|---|---|
| | conducted for one day, while the other team members charged the smartphones in nearby towns. |
| Inability to edit once data are submitted into the smartphone. | Communicate with the central team to discuss any errors and edit the data promptly. |
| Lack of network | Store the data in the smartphone and transfer when there is access to the internet. |
| Community mobilization | Discuss the best time for the community for mass gathering, such as early in the morning or late in the afternoon. Whenever appropriate, use holidays. |
| Inaccessibility (some districts during rainy season) | Use alternative transport such as motorbikes, boats or horses. In areas where no other possibilities existed, walking was the last resort. |

**4.6 Conclusion**

To achieve the London Declaration of 2020 targets and the WHO road map for NTDs [107], rapid NTD mapping is very important. Integrated mapping of podoconiosis and LF in Ethiopia was conducted at a large scale in a short period of time. The approach is the first of its kind and provides important lessons for co-endemic or podoconiosis-endemic countries. Strong in-country leadership, international collaboration and use of mobile technology contributed to the success of the exercise. The approach reduced costs, expanded geographical coverage and sped up the availability of data for decision makers. Data were formally presented to the Ministry of Health within one year of the start of the project and will be used to inform national control and elimination programs.

In conclusion for the first time globally, we conducted integrated mapping of podoconiosis and LF. The chapter clearly indicated that integrated mapping of podoconiosis and LF is feasible and, if properly planned, can be quickly achieved at nationwide scale. The approach used here can be adapted in other endemic countries. To scale up interventions of podoconiosis clear understanding of the epidemiology and the risk factors of podoconiosis are important to develop risk maps. The next chapter describes the epidemiology of podoconiosis and identifies the individuals and environmental risk factors of podoconiosis which inform risk mapping to refine podoconiosis burden estimate.

# Chapter 5. Multilevel and geostatistical modelling of podoconiosis risk: results from the first nationwide mapping

## 5.1 Overview

As highlighted in chapter 3 and 4, there is scarcity of information about the geographical distribution and the disease burden of podoconiosis. Such scarcity hinders the targeting of intervention programmes and the reliable quantification of the disease burden of podoconiosis. There are also few studies which have examined the individual and household risk factors for podoconiosis. Previous studies have established familial aggregation and clustering, due to genetic susceptibility [21-23]. Reportedly, a third to one-half of patients have other podoconiosis-affected close relatives or family members. A few studies have identified individual correlates of podoconiosis[24]. These include education, income, shoe-wearing practice and age at first wearing shoes. Environmental factors that are associated with podoconiosis risk have been suggested [18,19,28]. These factors facilitate formation of the red clay soils that contain the putative inorganic particles that penetrate barefoot skin and trigger the inflammatory response leading to podoconiosis. Although the above studies have identified individual correlates of podoconiosis and indicated environmental determinants, no study has combined individual data and climatic and environmental variables to understand their relative contributions.

Therefore, in the current analysis, potential environmental variables which contribute to the formation of soil, socioeconomic status, type of floor, access to water at a household level, shoe wearing practice, and foot hygiene behaviour at an individual level were investigated. In this chapter, I aimed to identify individual, household and environmental risk factors of podoconiosis. The results presented here were published in 2015[251].

## 5.2 Introduction

The first comprehensive epidemiological study of elephantiasis in Ethiopia dates from 1969 and included 6770 patients [7]. Subsequently, Price conducted a range of epidemiological studies in east African countries and Cameroon [2]. These studies excluded causes such as LF, leprosy and onchocerciasis as a cause of the non-filarial elephantiasis he observed [7,8,34,40,58]. Subsequent studies documented the clinical features and pathology of the disease, a possible genetic susceptibility, and the role of soil particles and environment [2]. After his extensive multidisciplinary work, Price named the disease podoconiosis [2]. In recent years, studies have documented the presence of podoconiosis in Ethiopia [9,11,12,14,15], Uganda [32] and Cameroon[33]. A study conducted in Ethiopia identified several individuals correlates such as female sex, lower education, being unmarried and having lower income [24]. Price documented a variety of environmental correlates of podoconiosis [2,28], some of which have been confirmed through recent study of the environmental factors associated with podoconiosis, including the soil type, precipitation and altitude[18]. A recent study indicated that particles such as smectite, mica and quartz within the soil were associated with podoconiosis prevalence[18].

Although of great interest, each of these studies had limitations. Some studies relied on clinical diagnosis of podoconiosis without a clear case definition. Important information about how possible differential diagnoses were excluded is missing in most of the studies. In earlier studies, the use of a purely descriptive approach without measuring statistical significant associations and confounding is another limitation. Although some studies identified individual or environment correlates, no single study has simultaneously evaluated individual, household, climatic and environmental variables to understand their relative contributions, or accounted for underlying spatial pattern in disease occurrence. In the present chapter, I use data from the national survey described in chapter 4 to investigate the epidemiology of podoconiosis in Ethiopia and determine individual, household and environmental risk factors of the disease. Analysis is based on Bayesian hierarchical models (BHM) which provide a robust and well established methodology to identify risk factors at different levels[252].

## 5.3 Methods and materials

### 5.3.1 Study setting

Ethiopia is located in the Horn of Africa and has a surface area of some 1.1 million square kilometers [253]. According to the 2007 national population census, the total population was estimated at 73.8 million in 2007 and projected to be 86.6 million in 2013 [253,254]. Ethiopia has great geographical diversity; its topographic features range from the highest peak at 4,550 metres above sea level, down to the Danakil depression, 110 metres below sea level [254]. Ethiopia has a federal system of administration with nine regional states and two city administration councils [248]. The regional states/city administrations are sub divided into Zones, *woreda*, *kebele* (sub-districts) and *gotte* (villages). In 2013, there were 817 *woreda* in Ethiopia. A *woreda* is the country's basic decentralized administrative unit and has an administrative council composed of elected members. The 817 *woreda* are further divided into about 16,253 *kebele*.

### 5.3.2 Sampling strategy and participant selection

This was a cross-sectional community-based study using convenience cluster sampling, conducted in seven regional states (Tigray, Affar, Amhara, Oromiya, Somali, Southern Nations Nationalities and Peoples [SNNP], and Harari) and two city administrations (Addis Ababa and Dire Dawa Administration Councils). Surveys for podoconiosis and LF were implemented simultaneously. The details of the methods used for the data collection were described in detail in chapter 4.

### 5.3.3 Selection of environmental and climatic data

Environment and climate variables were selected based on a conceptual framework according to outcome, individual, household and environmental factors (**Figure 5.1**). First, variables which play an important role in weathering of rock and soil formation were selected, and then characteristics of soil thought to play an important role in the disease process, were selected based on the literature [2,28]. Podoconiosis is caused by long term barefoot exposure to red clay soil of volcanic origin [2], so understanding how soil is formed is an important entry point in linking podoconiosis occurrence, the environment and climate. There are five classic factors for soil formation: climate, topography, parent material, time and organisms (flora and fauna) [255-257]. In addition, soil characteristics which facilitate exposure such as soil type, content and particle size were considered as detailed in Supplementary material 5.1.

Soil varies depending on a range of climatic conditions[258]: temperature and precipitation influence the degree of weathering and leaching[256]. Seasonal and daily variability of temperature affect chemical reactions, moisture, biological activity and vegetation type, through influences on weathering[259]. The aridity of an area plays an important role, and winds in arid zones may redistribute sands and other soil particles.

Topography of the land, both altitude and slope, affects weathering. Altitude governs temperature, rainfall and vegetation of an area. Areas with steep slopes facing the sun are warmer, in addition, soils on slopes may more easily be eroded than soils on level ground. Plants, animals, microorganisms and human beings affect soil weathering[256]. Human activities such as erosion and deforestation have significant impact on soil formation[260]. Few soils weather directly from the underlying rock, and may therefore have completely different chemical and physical properties, making underlying rock a poor predictor of overlying soil type[259]. Fine particles have been linked to podoconiosis occurrence[29,74], and are thought to easily penetrate the skin and enter the body. Other factors such as distance to surface water are likely to be relevant to preventive behaviors such as foot hygiene, and so were included, as was urban-rural variation.

### 5.3.4 Sources of satellite driven data

The elevation data at 90 $m^2$ resolution were extracted from a digital elevation model provided by the shuttle radar topography mission [261] and these data were processed to calculate slope in degrees. The mean, minimum and maximum atmospheric temperature, temperature in coldest and warmest quarters and precipitation at 30-arcsecond (1 km) resolution were downloaded from the WorldClim website for the period 1950–2000 at 1 $km^2$ spatial resolution [262]. In addition, average and variance estimates of long-term land surface temperature (LST) at 1 $km^2$ resolution were extracted from the African Soil Information System project [263].

Euclidean distance to water bodies was calculated using SRTM Water Bodies data files at $250m^2$ resolution [264]. Land cover type was extracted from the qualitative global land cover map, defined within the UN land cover classification system using the environmental satellite (ENVISAT) mission's Medium Resolution Imaging Spectrometer (MERIS) sensor at $300m^2$ resolution. Normalized difference vegetation index (NDVI) and enhanced vegetation index (EVI) at 250 $m^2$ resolution were extracted from the African Soil Information System project [263]. Population density was extracted from the AfriPop project at $90m^2$ [265], and rural-urban classification at 1 $km^2$ from the Global Rural-Urban Mapping project (GRUMP)[266]. Aridity index and potential evapo-transpiration (PET) data were extracted from the Global-PET and Global-Aridity datasets (CGIARCSI), at 1 $km^2$ resolution[267]. Soil data including silt, clay and sand content, dominant soil type and pH of the water at 1 $km^2$ resolution were extracted from ISCRI and the African Soil Information System project [268]. Finally, soil texture was extracted from the harmonized soil map of the world at 1 $km^2$ resolution from FAO Geonetwork [269]. Environmental data were extracted to cluster locations using ArcMap 10.0 (Environmental Systems Research Institute Inc., Redlands CA, USA). Bilinear interpolation was applied to resample numeric (continuous) raster data sets, whereas nearest neighbor interpolation was used with ordinal raster layers. Input grids were either extended or clipped to match the geographic extent of a land mask template of Ethiopia, and eventually aligned to it.

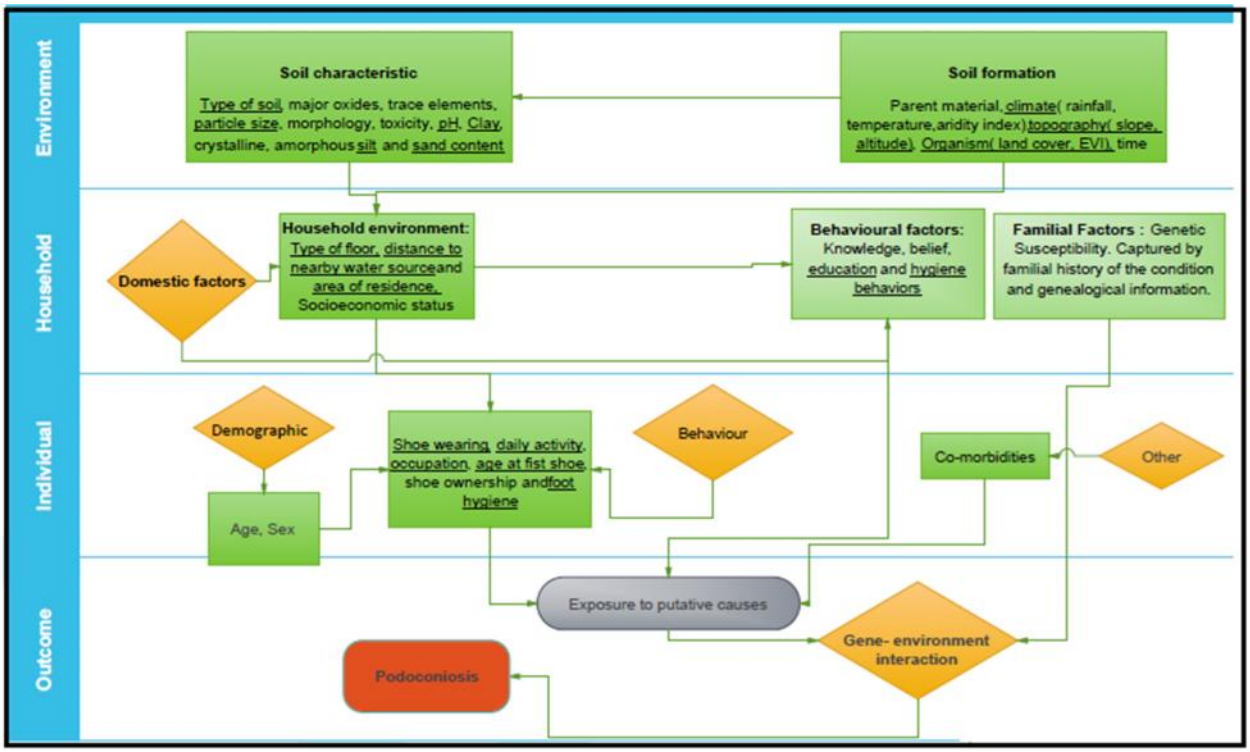


**Figure 5.1** Conceptual framework to represent the relationship between environmental, household and individual level variables. Environmental variables such as climate, topography, flora and fauna of the areas are important factors for generation of soil and determine the characteristics of the soil. Soil physical and chemical properties including type of soil, particle size, morphology, pH etc are important factors which either facilitate the penetration of skin barriers by putative mineral particles or increase exposure to them. Socioeconomic status affects household factors such as floor condition, access to water and individual factors such as shoe ownership and foot hygiene practices which in turn affect the risk of podoconiosis. Genetic susceptibility is an important factor in determining the outcome of the exposure, and is best measured by pedigree study. In the current study, we only measured the familial history of a similar condition. The underlined variables are those measured in the current analysis. The framework guided the analysis; principal component analysis was used to identify important covariates which explained most of the variation among many multicollinear environmental and climate variables. Subsequently, a multilevel mixed-effects logistic regression model was developed using a likelihood-based approach, with random intercepts for village and woreda, for environment and individual variables separately, to identify candidate variables for the geostatistical model. Bayesian hierarchical models were developed to identify and measure the relative contributions of the risk factors for podoconiosis.

### 5.3.5 Data analysis

Data were checked for accuracy daily and feedback was given to the field team the following day. After completion of the data collection, the data were downloaded in Excel format and imported to STATA 13.0 (Stata Corporation, College Station, TX) and further cleaned. Maps of the prevalence of podoconiosis were developed using ArcGIS 10.0 (ESRI, California). Survey and covariate data were linked in ArcGIS 10. (Environmental Systems Research Institute Inc. [ESRI] Inc., Redlands CA, USA) based on the WGS-1984 Web Mercator projection at 1 $km^2$ resolution.

Most of the climate and environmental variables showed multicollinearity. To deal with these challenges, we used exploratory principal components analysis (PCA) which reduces correlated variables to a smaller set of uncorrelated variables which explain most of the variation [270] [271]. The majority (92.7%) of the total variation was explained by the first two principal components, which had eigenvalues >1 and were visually below the elbow of the scree plot. The first principal component explained 78.4% of the variance and two contrasting groups of variables emerged. Most of the variables had similar loading. The first group was related to temperature including LST, annual mean, minimum and maximum temperature, mean temperature in the coldest and warmest quarters and annual PET. Altitude, aridity index and rainfall were the contrasting variables. Mean annual temperature was selected from the first group based on the loading and literature[19]. From the contrasting group, altitude was selected since other studies have repeatedly found it to be associated with podoconiosis[18,19]. Annual precipitation, aridity index and EVI showed the highest loads in the second principal component, which explained 13.6% of the variation. From the second component, EVI and annual precipitation were selected since both of them had equally high loading.

Selection of candidate variables for the geostatistical model was conducted using a multivariate multilevel mixed-effects logistic regression model using a likelihood-based approach, with random intercepts for *kebele* and *woreda*. All identified variables were initially included and non-significant (p>0.1) variables sequentially removed using backwards stepwise elimination to derive a minimally adequate model. Similarly, a model was developed to identify environmental factors associated with podoconiosis. Bayesian spatial geostatistical models were run in WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge and Imperial College London, UK), incorporating a geostatistical random effect. A burn-in of 10,000 iterations was allowed, followed by 20,000 iterations where values for monitored variables were stored and thinned by 10. Diagnostic tests for convergence of the monitored variables were undertaken, including visual examination of history and density plots. The runs were also assessed for evidence of autocorrelation.

Bayesian hierarchical models were selected for several reasons. In regression models, the main objective is to model the main outcome as a function of predictor variables. It is clear that not all results will fit on the regression line, thus an error term is added to capture this variation. Such considerations will lead to formulation of complex models, with multiple levels. Bayesian hierarchical models provide space for developing spatially structured multilevel models and allow incorporation of covariates at different levels. Such models use Markov chain Monte Carlo (MCMC) algorithms to produce robust estimates and can use prior information and produce posterior distribution[93].

Final equivalent Bayesian models were run in WinBUGS version 1.4 (MRC Biostatistics Unit, Cambridge and Imperial College London, UK), incorporating a geostatistical random effect. Models took the form:

$$Y_{ij} \sim Bernoulli(p_{ij})$$

$$logit(p_{ij}) = \alpha + \sum_{i=1}^{p} \beta_i \times x_i + \sum_{j=1}^{p} \beta_j \times x_{i,j} + v_i + u_i$$

Where $Y_{ij}$ is the disease status of individual $i$ in cluster *j*, $p_{ij}$ is the probability of a positive response, α is the intercept, $\sum_{i=1}^{p} \beta_i \times x_i$ is a vector of independent variables at the individual level measured in the field multiplied by their coefficient $\beta_i$, $\sum_{j=1}^{p} \beta_j \times x_{i,j}$ is a vector of independent variables at the cluster level multiplied by their coefficient $\beta_j$, $v_i$ is a non-spatial random effect (NSRE)and $u_i$ is a spatial random effect (SRE). Non-informative priors were specified for the intercept (uniform prior with bounds $-\infty, \infty$ ) and the coefficients (normal prior with mean=0 and precision, the inverse of variance = $1 \times 10^{-6}$). NSREs were incorporated into all models, in order to allow residual variation to have uncorrelated and correlated components. The SRE models any residual correlation that is spatially structured using a stationary exponential decay function. The NSRE had a non-informative priors imposed on its variance (uniform distribution with delimiting values of 0.01 and 100).

A burn-in of 10,000 iterations was allowed, followed by 20,000 iterations where values for monitored variables were stored and thinned by 10. Diagnostic tests for convergence of the monitored variables were undertaken, including visual examination of history and density plots. The runs were also assessed for evidence of autocorrelation. Model performance was assessed by comparing deviance information criteria (DIC) the details are presented in Supplementary material 5.1.

## 5.4 Results

The study was planned to be conducted in 692 (84.7%) of the 817 *woreda* of Ethiopia, and mapping was achieved in 659 (95.2%) of these. Thirty-three (4.8%) *woreda* were excluded or were inaccessible during the survey: 6 in Addis Ababa were excluded due to an exclusively urban population and almost universal shoe wearing practice, 23 in Somali were inaccessible due to conflict, and 1 *woreda* in Oromia and 3 in Amhara had been merged or double counted. Individual-level data were available for 129,959 individuals from 1,315 villages in 659 *woreda* (**Figure 5.2**). The median age of the participants was 34 years (inter quartile range [IQR], 25 to 46). The male to female ratio of the respondents was 1.0:1.0, reflecting the selection process. The mean number of individuals per community was 98.

In total, 8,110 individuals with lymphoedema of the lower limb were identified. The overall prevalence of lower limb lymphoedema was 6.2% (95% CI 6.1-6.4%), and there was a significant difference between prevalence in men (5.3 %, 95% confidence interval [CI]; 5.2-5.5%) and that in women (7.1%, 95% CI; 6.9 - 7.3%). Of these 8,110 cases of lymphoedema of the lower limb, 24 (0.3%) were found to be ICT positive. In 268 (3.3%), the swelling was of the descending type, starting from higher up in the leg. Groin involvement was observed in 782 (9.6%) of the cases. Based on the clinical algorithm for diagnosis of podoconiosis, a total of 2,833 (34.9%) cases of lymphoedema due to other causes were excluded. The total number of people with podoconiosis was determined to be 5,253 out of 129,959 individuals in selected woredas (**Figure 5.2**). Therefore, the overall prevalence of podoconiosis in our study sample was found to be 4.0% (95% CI; 3.9 - 4.1%). The prevalence among men was 3.4% (95% CI; 3.3 - 3.5%) and among women was 4.7% (95% CI; 4.5 - 4.8%). Prevalence steadily increased with age ($p<0.001$) (**Figure 5.3**).

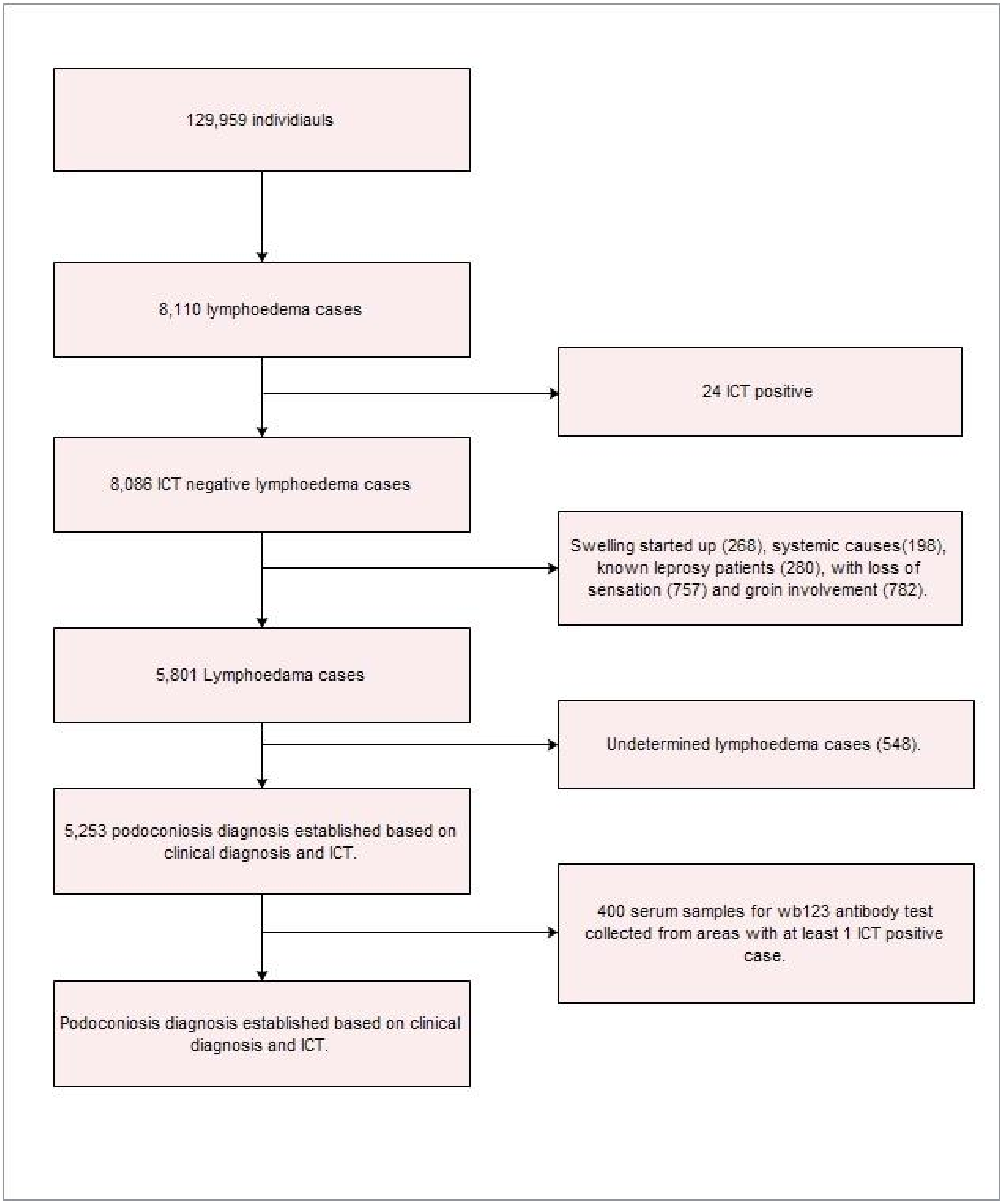


**Figure 5.2** Podoconiosis diagnosis algorithm used in the national survey in Ethiopia 2013

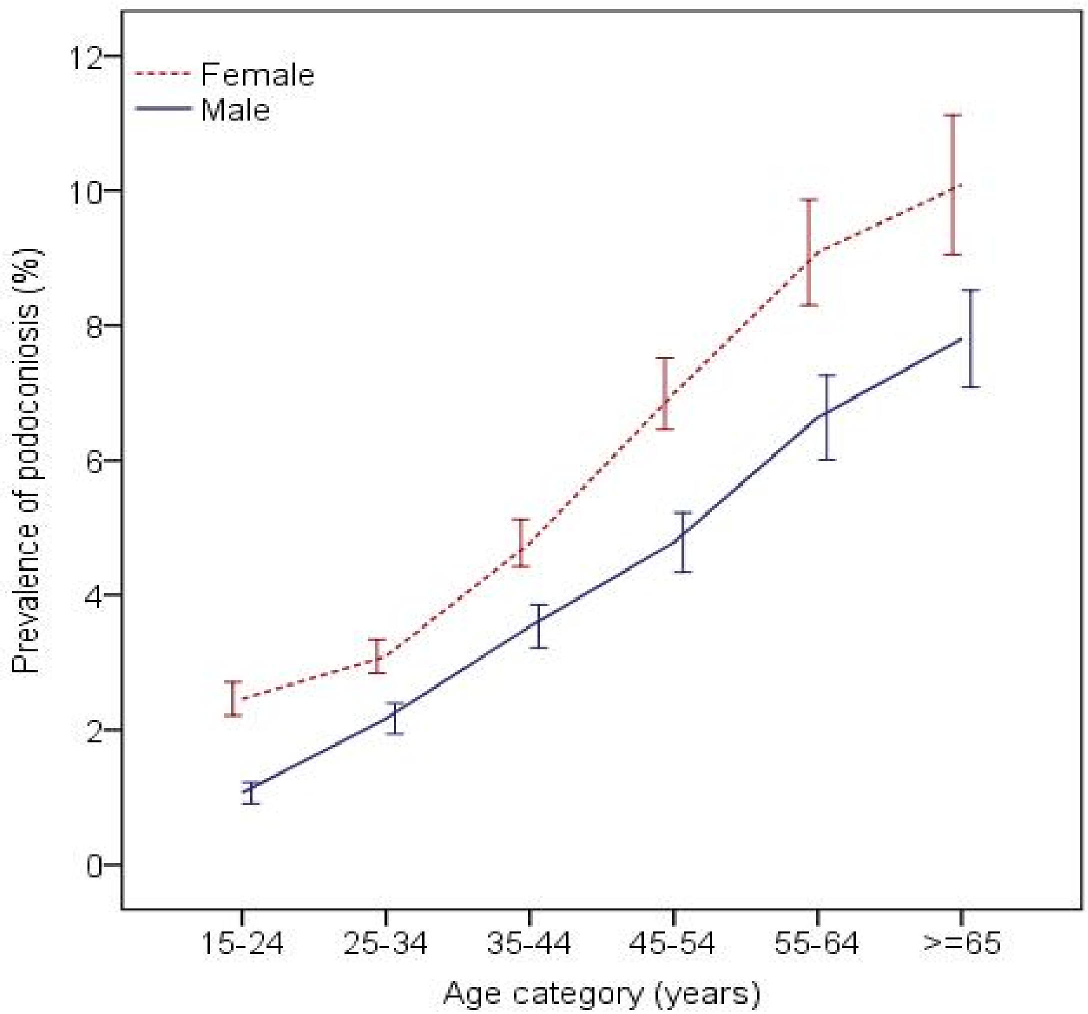


**Figure 5.3** Age and sex disaggregated prevalence of podoconiosis among adults aged ≥ 15 years in Ethiopia. The two graphs show that as age increases, the prevalence of podoconiosis increases. Higher prevalence is recorded among females in all age categories as compared to males. The bar shows 95% Confidence Intervals.

### 5.4.1 Characteristics of people with podoconiosis

Of the 5,253 people with podoconiosis, the male to female ratio was 0.7:1.The majority of affected people were in the age group 35-54 years, while only 10.2% were in the age group 15-24 years. The mean age at first noticing the swelling was 25.0 years (± standard deviation [SD] 14.6), ranging from 5-87 years. There was a slight sex difference in age at first noticing swelling. On average, women noticed swelling earlier (23.9 years, SD ± 13.8) than men (26.6 years, SD ± 15.5, $p<0.001$). Only 12.0% had noticed swelling when younger than 10 years old, while 8.1% first noticed the swelling when older than 50 years of age. More than half (52.0%) noticed leg swelling while they were between the ages of 10 and 30 years (**Table 5.1).** On average, people with podoconiosis had lived with leg swelling for 19.8 years (SD ± 14.2), men for 20.9 years (SD ± 14.62) and women for 19.1 years (SD ± 13.9) ($p<0.001$).

One fifth (22.7%) of people with podoconiosis had or remembered at least one relative with a similar condition. The majority (48.8%) of people with podoconiosis had stage two disease, and 26.6% had stage three disease (**Table5.1**). There was no significant difference in the distribution of disease stage among men and women.

**Table 5.0-1** Descriptive statistics of people with podoconiosis ≥15 years old in Ethiopia (N=5,253 individuals with podoconiosis among 129,559 surveyed individuals).

| **Variable** | | **Number (%)** |
|---|---|---|
| Gender | Female | 3045 (58.0) |
| | Male | 2208 (42.0) |
| Age (years): | 15-24 | 538 (10.24) |
| | 25-34 | 918 (17.48) |
| | 35-44 | 1119 (21.30) |
| | 45-54 | 1064 (20.26) |
| | 55-64 | 868 (16.52) |
| | >=65 | 746 (14.20) |
| Marital status | Unmarried | 557 (10.6) |
| | Married | 3722 (70.9) |
| | Divorced | 272 (5.2) |
| | Widowed | 702 (13.4) |
| Duration of podoconiosis Mean (Standard Deviation [SD]) | | 25.04 (14.58) |
| Shoe wearing duration in years Mean (SD) | | 22.42 (14.76) |
| Disease stage | Stage 1 | 875 (16.7) |
| | Stage 2 | 2562 (48.8) |
| | Stage 3 | 1399 (26.6) |
| | Stage 4 | 308 (5.9) |
| | Stage 5 | 109 (2.1) |
| Occupation | Professional | 68 (1.3) |
| | Semi-Skilled | 3488 (66.2) |
| | Unemployed | 1705 (32.5) |
| Residence | Rural | 4467 (85.0) |
| | Urban | 786 (15.0) |
| Ever attended school | Yes | 1087 (20.7) |
| | No | 4166 (79.3) |
| Literacy | No formal education | 4166 (79.3) |
| | Primary (1-8) | 906 (17.2) |
| | Secondary (9+) | 181 (3.4) |
| Family history of leg swelling | Yes | 1192 (22.7) |
| | No | 4061 (77.3) |
| Age at first noticing the swelling Mean (SD) | <10 | 630 (12.0) |
| | 10-19 | 1395 (26.6) |
| | 20-29 | 1335 (25.4) |
| | 30-39 | 898 (17.1) |
| | 40-49 | 567 (10.8) |
| | ≥50 | 428 (8.1) |
| Years lived with swelling | <10 | 1817 (34.6) |
| | 10-19 | 1478 (28.1) |
| | 20-29 | 918 (17.5) |
| | 30-39 | 555 (10.6) |
| | 40-49 | 318 (6.1) |
| | >=50 | 167 (3.2) |

### 5.4.2 Podoconiosis-preventive behaviours

Among all respondents, most (89.6%) had at some time worn shoes and 85.2% of them were wearing shoes during the interview. Regarding the type of shoe, most (50.7%) were wearing hard plastic shoes, followed by open sandals (32.0%), leather shoes (12.8%) canvas shoes (4.1%) and other types of shoe (0.39%). Only 57.9% of the respondents were wearing protective (enclosed) shoes during the interview. The mean age at first shoe wearing was 11.8 years (SD 9.6) with a slight difference between men (mean ± SD: 12.1 years ± 9.8) and women (mean ± SD: 11.4 years ± 9.4 women, $p<0.001$). On average, the participants had worn shoes for 24.1 years (SD; 13.6). More men (87.0, 95% CI; 86.8 - 87.3%) than women (83.3, 95% CI; 83.0 to 83.5) were wearing shoes at the time of the interview. There was no significant difference in protective shoe-wearing between men (58.3, 95% CI; 57.9 - 58.7) and women (57.6, 95% CI; 57.2 - 57.9). Most respondents wore shoes while going to market (98.2%) or when walking a long way (97.2%), and fewer, though still substantial numbers, during the rainy season (90.6%), at home (89.8%) and when going to the field (80.1%). Most (69.5%) of the participants practiced foot hygiene (washing the feet with soap) on a daily basis, while 25.4% practiced foot hygiene twice per week. Looking at the overlap of these preventive practices, only 4.6% practiced all three, while 54.4% practiced daily foot hygiene and wore shoes (**Figure 5.4**).

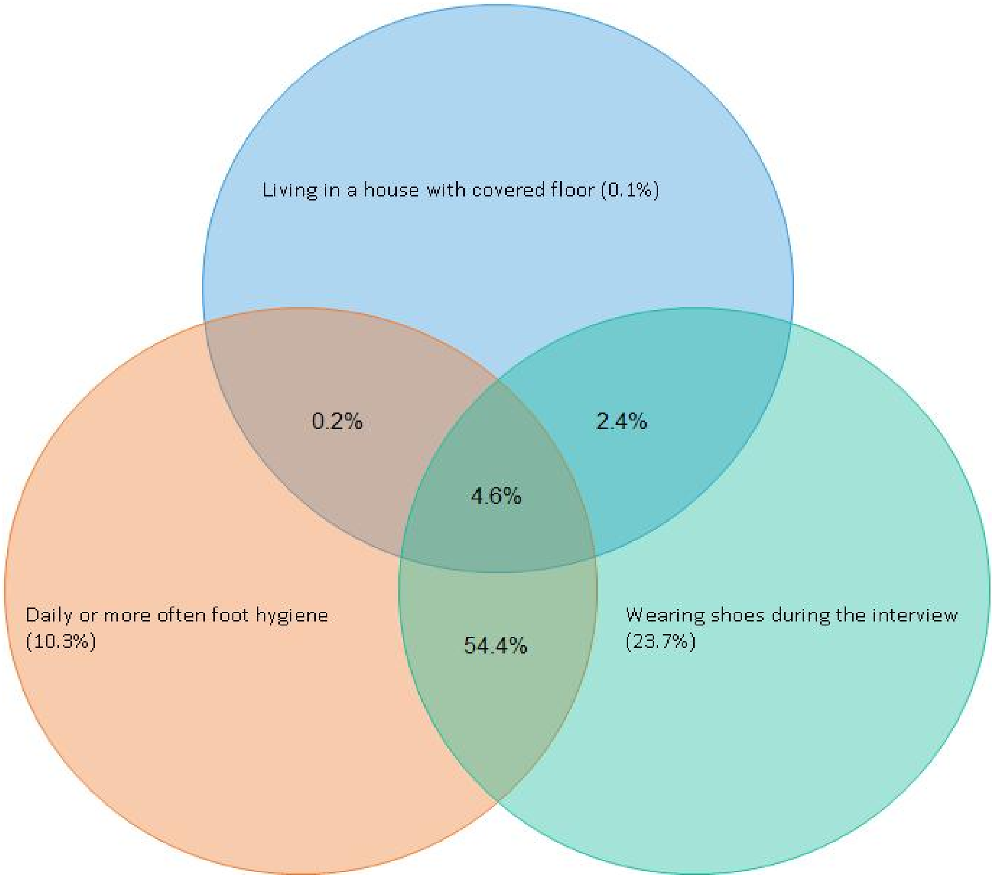


**Figure 5.4** Overlap between the three key prevention practices for podoconiosis. The blue circle shows that 7.3% of patients live in houses with covered floors. The green circle shows that 85.1% of those interviewed wore shoes during the interview. The orange circle shows that 69.5% of patients interviewed wash their feet daily or more often. The overlapping sections indicate the intersections of these three podoconiosis preventive practices.

### 5.4.3 Geographical distribution of podoconiosis

**Figure 5.5** presents the prevalence of podoconiosis by survey cluster and shows marked geographical variation, with prevalence ranging from 0–54.6%. Clusters of high prevalence (>5%, denoted by red colour in **Figure 5.5**) were exclusively found in Amhara, Oromia and SNNP regional states, which represent most of the central highlands of Ethiopia. Most of the eastern and far northern part of the country had zero or near zero prevalence. All of the communities in Addis Ababa, Affar, Dire Dawa and Harari had zero prevalence of podoconiosis. Few cases were identified in Tigray and Somali regional states. The south-western part of the country also had high prevalence communities.

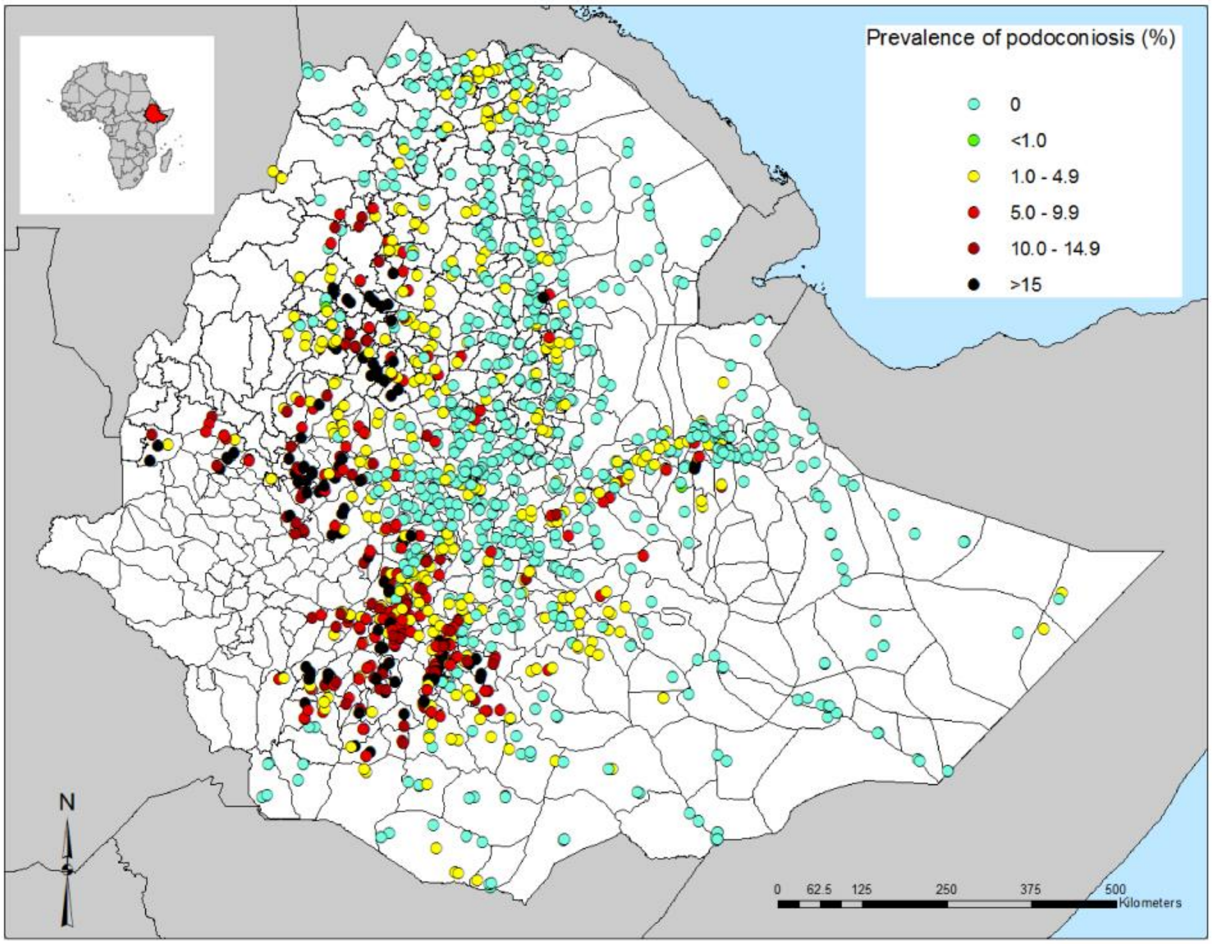


**Figure 5.5** The geographical distribution of the prevalence of podoconiosis among adults aged ≥15 years in Ethiopia, 2013.

**Table 5.0-2** Summary statistics of the reduced set of climatic and environmental covariates included in model building

| **Variable** | **Median (range)** [a] |
|---|---|
| **Climate** | |
| Mean annual temperature (°C) | 19.0 (10.0-31.0) |
| Annual rainfall (mm) | 1042 (139-2090) |
| **Environmental** | |
| Altitude (meters) | 1895 (-105-3238) |
| Savannah or Grasslands [b] (%) | 27.67% |

| | |
|---|---|
| Urban classification (%) | 26.8% |
| Population density ($km^{2}$) | 129.0 (0.82-92863) |
| Enhanced vegetation index (EVI) | 0.27 (0.04-0.56) |
| Distance to nearest surface water (km) | 6.4 (0-144) |
| Fine soil texture (%) | 43.13% |
| pH of the water in the soil | 6.20 (4.60-9.3) |
| Slope of the land (°) | 1.67 (0.01-17.75) |
| Clay content (%) | 35.5 (17-60) |
| Sand content (%) | 30 (10-71) |
| Silt content (%) | 32 (9-50) |
| High activity soil (%) | 76.56% |

[a] Proportion of sites for binary variables (Savannah/Grasslands, urban classification, fine soil texture, clay content, sand content, silt content, heavy activity soil)
[b] Reclassified from global land cover;

### 5.4.4 Risk factors

A summary of the environmental factors is presented in Table 5.2. In the final spatial model, both individual and environmental factors were found to be risk factors for podoconiosis. Thus, individual-level factors associated with an increased risk for podoconiosis included female gender (OR=1.3; 95% BCI; 1.2-1.4), age (OR=1.02; 95% BCI; 1.02-1.03), being unmarried (OR=1.4; 95% BCI; 1.3-1.5), being unemployed (OR=2.2; 95% BCI; 1.7-2.8) and other religions compared to Muslim (OR=3.4; 95%BCI; 3.1-3.6). Factors associated with a decreased risk included secondary or higher education, increased foot hygiene (OR=2.9; 95%BCI; 2.4-3.4), housing with covered floor (OR=0.3; 95% BCI; 0.3-0.4). Among individual factors, there was no significant association between shoe wearing and risk of podoconiosis. Three environmental variables were found to be associated with risk of podoconiosis after accounting for spatial dependence: rainfall, EVI and altitude (**Table 5.3**).

The geo-statistical models also indicated that podoconiosis risk can be moderately variable over relatively short distances, with spatial variances of 0.25 and an estimated spatial range of roughly 31 km.

**Table 5.0-3** Adjusted odds ratios of individual, household and geographical risk factors of podoconiosis using a Bayesian model and data from 1313 villages throughout Ethiopia.

| Variable | Category | **Adjusted 95% Bayesian credible intervals (BCI)** OR (95% BCI) |
|---|---|---|
| Sex | Male | 1.0 |
| | Female | 1.3 (1.2-1.4)* |
| Age in years (Continuous) | | 1.02 (1.02-1.03)* |
| Education | No formal education | 1.0 |
| | Primary 1-8 | 0.6 (0.6-0.7)* |
| | Secondary 9-12 | 0.3 (0.3-0.4)* |
| | Post-secondary >12 | 0.1 (0.1-0.2)* |
| Marital status | Married | 1.0 |
| | Unmarried | 1.4 (1.3-1.5)* |
| Religion | Muslim | 1.0 |
| | Other | 3.4 (3.1-3.6)* |
| How often do you wash your legs? | Daily or more often | 1.0 |
| | Two-Three times a week | 0.9 (0.8-1.0) |
| | Weekly or less often | 2.9 (2.4-3.4)* |
| Occupation: | Professional | 1.0 |
| | Semi-skilled | 2.4 (1.9-3.0)* |
| | Unemployed | 2.2 (1.7-2.8)* |
| Type of floor | Mud/earth | 1.0 |
| | Cement/wood/plastic | 0.3 (0.3-0.4)* |
| Enhanced Vegetation Index (EVI) | <0.2 | 1.0 |
| | 0.2- 0.4 | 0.6 (0.5-0.6)* |
| | >0.4 | 0.4 (0.3-0.4)* |
| Mean annual rainfall | 1000 | 1.0 |
| | >=1000 | 1.1 (1.0-1.1)* |
| Altitude | <1000 | 1.0 |
| | 1000-2800 | 1.3 (1.2-1.4)* |
| | >2800 | 1.8 (1.5-2.1)* |
| Range of the spatial effect [range in km] | | 31.1 (6.1-198.0) |
| Spatial variance | | 0.25 (0.25-0.49) |

*significant

## 5.5 Discussion

Understanding the epidemiology of a disease is the first step in designing control and prevention strategies. For podoconiosis, such data have to date been derived from small scale studies. Here I describe the epidemiology of podoconiosis using nationwide data from Ethiopia, including disease burden and associated risk factors. Podoconiosis cases were identified using a pre-defined clinical algorithm and a panel of diagnostic approaches to exclude other potential causes of lower limb lymphoedema. In addition, a robust modelling approach was used to identify individual and environmental risk factors of podoconiosis among adults 15 years of age and above. Podoconiosis accounted for 64.8% of cases of lymphoedema of the lower limb. The prevalence of podoconiosis in surveyed high risk communities was 4.0%, with higher prevalence among women and older age groups. A number of risk factors were identified in our analysis including sex, age, foot hygiene practice, education and type of floor. In addition, environmental and climate variables (altitude and EVI) determined the large scale risk of podoconiosis across Ethiopia.

At 4.0%, the prevalence of podoconiosis in high-risk communities in our study is higher than previous national level estimates. Our recent review of published work indicated a national prevalence of 3.4% [74] and studies suggested prevalence of 2.7% (by Ooman in 1969[7]) and 2.8% (by Price in 1974[8]). Recent studies have indicated high prevalence of podoconiosis in certain areas [9,11,12,14,15]. Five studies conducted in north, central, southern and western Ethiopia between 2000 and 2012 recorded prevalence ranging from 2.8% to 7.4%[9,11,12,14,15]. In addition, a recent study conducted in Uganda in high risk communities documented 4.5% prevalence [32], while another in Cameroon documented prevalence of 8.1% [33]. The difference between our estimate and previous estimates may be attributed largely to differences in methodology.

Female sex was found to be associated with increased risk of podoconiosis. Other studies have yielded inconsistent findings surrounding the sex ratio in podoconiosis. The only other study which adjusted for covariates showed that women had increased odds of podoconiosis compared to men (OR=3.01; 95% CI: 1.73 to 5.25)[24]. Two studies conducted in western Ethiopia documented male to female ratios of 0.7:1[15], and 0.5:1 [9], and another, in Cameroon, recorded a ratio of 0.5:1 [33]. Most of the other studies found an equal sex ratio (1:1) in southern [11] and northern [14] Ethiopia, and in Uganda [32]. The only contemporary study which found men outnumbering women was conducted in central Ethiopia and indicated a sex ratio of 1.2:1 [12]. Our finding could be due to gender differences in preventive behaviours such as shoe-wearing practices between men and women. Equally, gender imbalances between men and women may influence access to resources including shoes and socks. In addition to these social factors that may mediate the effect of gender on disease risk, differences in genetic susceptibility [23] and biological influences, particularly hormonal, may also be important.

In the study, the prevalence of podoconiosis increased steadily with age, and high prevalence of podoconiosis was found among individuals aged ≥65 years. Previous studies in Ethiopia have also documented prevalence increasing with age [9,11,14,15,24,34], as have studies in Uganda [32] and Cameroon [33]. Given that podoconiosis is a chronic condition and that most patients and health professionals are unaware that treatment is possible, it is to be expected that prevalence increases with age. Other factors that may be important include cumulative exposure to the putative causes over an individual's life, and changes in shoe-wearing practices. This study indicates a linear decrease in the age at first shoe use by age category (**Figure 5.6**) or a secular trend towards earlier shoe-wearing in the younger age groups.

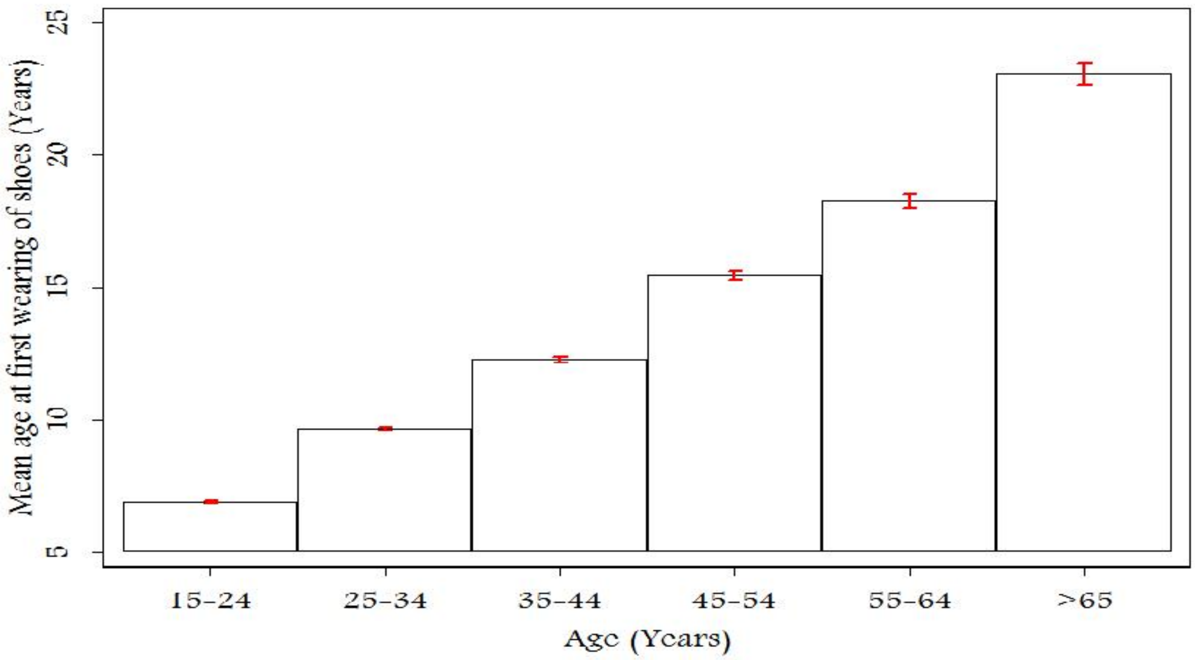


**Figure 5.6** Graph showing age at first shoe use by age among adults aged 15 years and above in Ethiopia. The graph shows a decreasing secular trend of age at first wearing shoes: the younger age groups tend to start wearing shoes at an earlier age than the older age groups.

Foot hygiene practices were associated with podoconiosis disease status. These findings further strengthen the importance of promotion of these behaviours in preventing podoconiosis. The role of water, sanitation and hygiene (WASH) in NTD control has been gaining much attention recently [272]. Studies have indicated the interplay between NTDs and WASH [272], and this study adds to the evidence. Shoe-wearing was not found to be associated with podoconiosis. The explanation for this may be reverse causality, in that people with podoconiosis tend to start wearing shoes after developing the disease either to prevent progression of disease or to conceal the swelling. Living in a house with an uncovered (mud or earth) floor was associated with podoconiosis, which may reflect either the importance of indoor exposure in addition to outdoor exposure or the influence of socioeconomic status of the individual. Occupation was also found to be associated with podoconiosis. Occupation may be related to the underlying socioeconomic status of individuals, which in turn may affect individual access to shoes, water and foot hygiene practices or more broadly access to information which leads to preventive behaviours. In our study, people with podoconiosis were less likely to be married or to have attended formal schooling. The interplay between podoconiosis stigma and mate selection has been described in qualitative studies[52,273]. Due to a widespread misconception that podoconiosis runs within families whatever the environmental exposure, people with podoconiosis experience great difficulty in finding a marriage partner, particularly one without podoconiosis[51,52]. The interaction between podoconiosis and education may be bidirectional. People with podoconiosis may have less access to education due to lack of finances, (itself due to reduced productivity [46]), attendant illness such as acute attacks [9] or dropout from school as a consequence of stigma and discrimination [9,51,52]. Equally, more educated people may be more informed of how to prevent podoconiosis and may have more access to shoes and water. One interesting finding was that other religions had increased risk of podoconiosis compared to Muslims, which could be explained in two ways. First, two regions which are non-endemic for podoconiosis are inhabited mostly by Muslim communities. Second, in endemic areas the low risk might be due to frequent foot washing related to religious practices among Muslims.

There are two prevention strategies for podoconiosis. The first is early and consistent protective shoe-wearing [21,65]. The prevalence of shoe-wearing was 85.2%, which is considerably higher than that reported in northern Ethiopia in 2011 (76.4%) [14] and in southern Ethiopia in 2007 (55.2%) [53]. However, only 60% of respondents were wearing protective shoes, and only 60% had worn shoes before 12 years of age. Although the age at first use of shoes is diminishing, the rate of protective shoe use needs more attention, as only half of shoe-wearers are using such shoes. Since our study was conducted during the rainy season, it is unlikely that the rate of open shoe wearing is related to weather conditions as reported elsewhere [274]. An encouraging result is that age at first shoe wearing is significantly lower in the younger age groups (**Figure 5.6**). The second prevention strategy is washing the feet with soap and water. Although, on average, the respondents have reasonable access to water [15], of those who were barefoot during the interview, one third (29.4%) were not washing their feet on a daily basis. Such behaviours may further expose barefooted individuals to podoconiosis.

After controlling for the above individual factors, rainfall, altitude and EVI were found to be associated with risk of podoconiosis. At this scale, these environmental factors may affect the risk of podoconiosis through influencing soil formation, or by affecting human exposure to the soil. Annual rainfall >1000 mm was associated with an increased risk of podoconiosis [19,74] in previous studies. First, rainfall is one of the climatic factors which governs the generation of soil and moisture is important factor which facilitate weathering and leaching. Second, rainfall can play important role in exposure to the putative mineral particles, by producing sticky mud which increases the contact time with the soil. Previous studies have indicated that soils associated with podoconiosis are slippery and adhesive if allowed to dry. Such occlusive adhesion encourages absorption of the particles by increasing exposure time[19]. The topography of the land affects weathering and soil formation. Altitude governs temperature, rainfall and vegetation of an area, all of which play an important role in weathering and soil formation in an area. Similar to our study, previous studies have indicated the potential association of podoconiosis and altitude, suggesting that podoconiosis was common in areas with altitude >1000 meters above sea level[209]. My findings indicate that greener areas had a lower risk of podoconiosis, which could be due to decreased exposure to putative soil particles in areas with high vegetation cover.

The current study has several strengths. First, it used a predefined clinical algorithm to exclude other causes of lower limb lymphoedema. Second, we used ICT diagnostic tests to exclude lymphoedema due to lymphatic filariasis. Third, we were able to sample almost all previously unmapped *woreda* in Ethiopia, yielding a large sample size and extensive geographical coverage. Despite the robust approach used to analyze and model these data, a number of caveats should be acknowledged. Currently, there is no confirmatory test for podoconiosis, so our diagnosis was based on excluding other etiologies and identifying clinical features specific to podoconiosis. Although this technique has been found to have excellent predictive value in endemic communities [11], it has not been validated in non-endemic communities. Our sampling approach included use of anecdotal reports of lymphatic filariasis and podoconiosis at *kebele* level, which is likely to lead to an overestimate of the number of lymphedema cases. Furthermore, individual selection was done after gathering the village community centrally, potentially leading to self-selection bias, as individuals with lymphoedema may come forward preferentially. However, we achieved high turnout of individuals in these communities through house-to-house mobilization, minimizing selection bias. We note that research on filariasis treatment coverage estimates in Haiti found little difference between coverage estimates obtained through a convenience sample of houses near distribution points compared to a cluster survey [275]. Although our sampling is based on selection of high risk communities, we consider it likely to give representative figures for the districts for the following reasons. First, the distribution of podoconiosis is driven by environmental factors which do not significantly vary within a district. Our semivariogram analysis demonstrates that podoconiosis shows spatial dependency over large distances (Supplementary material 5.1). Second, comparisons between surveys conducted in similar settings yielded comparable results.

The prevention, control and treatment of podoconiosis are important components of the health and development of endemic countries. The importance of NTD prevention and control as a development agenda has been documented [121]. Previous studies have estimated the economic impact of podoconiosis, which reduces individuals' productivity by half [46], and its social consequences, including stigma and discrimination [51-53,57]. Understanding the geographical distribution of podoconiosis is very important in identifying priority areas, targeting control, planning for elimination and monitoring progress. Until now, such data were limited for podoconiosis. Previous studies used inaccurate diagnostic tools and provided older estimates, failing to reflect the current status of the disease. Up-to-date, reliable information at high resolution is urgently required in Ethiopia and in other endemic countries to guide interventions [4]. The next critical step will be to identify the environmental limits of podoconiosis, estimate the population at risk and predict the prevalence using robust models such as Bayesian model-based geostatistical (MBG) approaches [17] to predict continuous distribution of podoconiosis while measuring the uncertainties and accounting for spatial dependency.

## 5.6 Conclusion

In conclusion, I report here the epidemiology of podoconiosis in Ethiopia. The results demonstrate a high burden of podoconiosis in Ethiopia, influenced by both individual and environmental factors. The findings could help in future risk mapping of podoconiosis using environmental variables to provide important information for decision-makers for prioritizing interventions to high-risk individuals. The results additionally serve as a baseline for the Ethiopian Federal Ministry of Health in podoconiosis programming and resource allocation. The next chapter will use boosted regression tree (BRT) modelling to predict the variation in the risk of occurrence of podoconiosis.

# Chapter 6. Mapping and modelling the geographical distribution and environmental limits of podoconiosis in Ethiopia

## 6.1 Overview

The previous chapter identified important individual and environmental factors which determine the risk of podoconiosis. Such understanding not only enhances our epidemiological understanding of the disease but also provides important information for targeted intervention for high risk individuals and communities and informs future mapping surveys. In this chapter, I use data from chapters 4 and 5, a suite of environmental and climatic data and boosted regression tree (BRT) modelling to predict the spatial occurrence of podoconiosis. Such analyses will have several practical implications. First, I will be able to clearly define the population-at-risk of podoconiosis in Ethiopia, which will be an input for geographical decisions in programing. Detailed estimates of the prevalence of podoconiosis and populations living in areas known to be endemic are essential for targeting control activities. Second, I will determine the environmental limits of podoconiosis which will help to develop risk models in other potentially endemic countries. The results presented here were published in 2015[276].

## 6.2 Introduction

Identification of factors which predict the risk of podoconiosis has often been focused on individual factors [15,24]. Nonetheless as discussed in Chapter 1 the risk of podoconiosis is multifaceted. Podoconiosis is caused by exposure to mineral particles in the soil [1] influenced by factors acting at different level; at individual level, biology (e.g. genetics) and individuals' behaviors (e.g. footwear) affects the small scale variations in the disease, while the large scale variation in the disease is attributed to contextual (e.g. access to water), environmental and climatic variables (e.g. altitude, rainfall). Nonetheless, only a few observational studies have investigated the large scale variation of podoconiosis risk [28,60].

The investigation of the large scale risk of podoconiosis plays an important role both in the understanding of the pattern of disease, and in planning of future surveys and interventions. First, with the availability of remotely sensed data, risk mapping has become an important geographical tool [238]. This approach has been utilized for a broad range of tropical and non-tropical infectious diseases [16,17,277]. Combining the remotely sensed data with survey data, one can produce smoothed surface of disease risk, which could help in prioritizing areas for intervention and surveillance. Second, quantification of the population living in areas suitable for the occurrence of the disease is an important input for planning. Preventive interventions such as footwear can be targeted to all at risk communities. Third, risk mapping enables the delineation of the occurrence limits of podoconiosis within Ethiopia which, in turn, can help guide future mapping of podoconiosis in other countries.

Although a well-established and widely used approach for other NTDs [16,17,78,83], risk mapping has never been conducted for podoconiosis. Given the environment-related nature of the disease, the risk of podoconiosis is likely to be explained by environmental and climatic factors which drive the formation of soil. Previous observations in eastern and western African countries indicated that the distribution of the disease is associated with certain climatic and environmental conditions, including soil derived from volcanic rocks, altitude and rainfall [28,60]. My own work in chapters 3 and 5 identified environmental correlates of podoconiosis, indicating the important role risk mapping could play in estimating podoconiosis at risk at a country scale [74,251].

Building on the previous chapters, the aims of this chapter are to (i) describe the geographical distribution of podoconiosis across Ethiopia, (ii) identify environmental factors associated with the occurrence and prevalence of podoconiosis, (iii) define the spatial limits of disease occurrence, and (iv) estimate the population living in areas at risk from the disease.

## 6.3 Methods

### *6.3.1 Data sources*

The data originated from two sources: the nationwide integrated LF and podoconiosis mapping in 2013 and a LF mapping survey in western Ethiopia, 2008-2010. The details of the 2013 survey is provided in Chapters 4 and 5. The 2008-2010 survey included 116 districts located in five regional states in western Ethiopia, conducted by a team from Addis Ababa University. Thirty-seven of the 116 districts were found to be endemic for LF. Cases of podoconiosis were extracted from this data set, based on expert opinion. Presence of lymphoedema cases in districts not endemic for LF, without sign or symptoms of other potential causes were considered podoconiosis cases (**see Supporting Information 6.1**). All 37 districts endemic for LF were excluded from data extraction to avoid misclassification of cases, while podoconiosis data were extracted from the remaining 79 [210]. Combined, the two surveys contributed 1,442 clusters from 775 districts of Ethiopia (**Figure 6.1 A&B**).

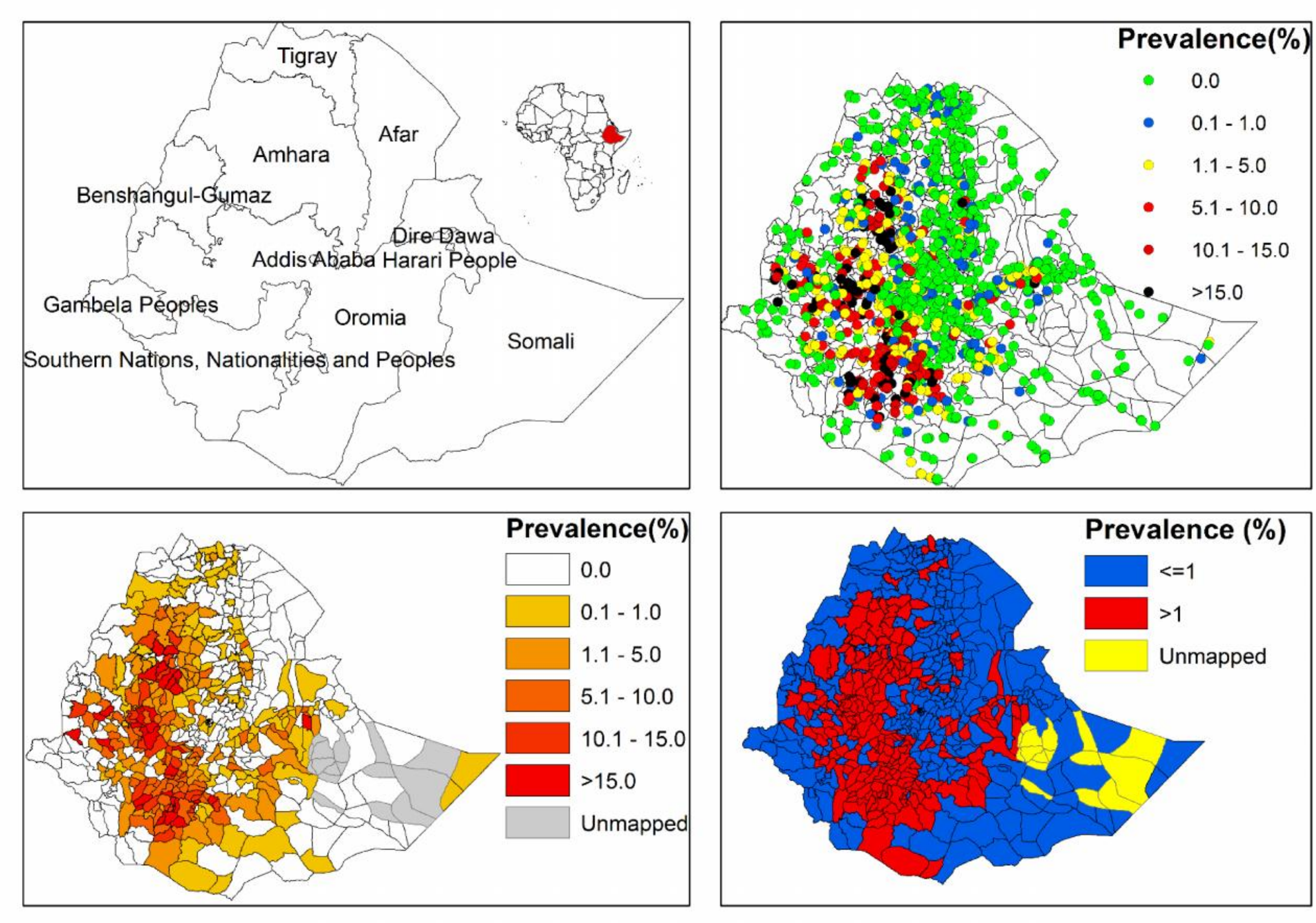


**Figure 6.1** Map of Ethiopia with regional boundary (A); geographical distribution of podoconiosis in 1,442 communities in 775 districts from all regions of Ethiopia (B); district level distribution of podoconiosis in 775 districts of Ethiopia(C, D).

### 6.3.2 *Sources of climatic and environmental data*

The elevation data at 90 m resolution were derived from a gridded digital elevation model produced by the Shuttle Radar Topography Mission (SRTM) [278], and these data were processed to calculate slope in degrees. The mean atmospheric temperature and annual mean precipitation at 30-arcsecond (approx. 1 km) resolution were downloaded from the WorldClim database for the period 1950–2000 [213]. A suite of raster surfaces containing values of Enhanced Vegetation Index (EVI) were obtained from the African Soil Information System (AfSIS) project [263].

Soil data including silt, clay and sand content, dominant soil type and soil-pH at 1 $km^2$ resolution were downloaded from the ISRIC-World Soil Information project [279]. A gridded map of soil texture included in the Harmonized Soil Map of the World at 1 $km^2$ resolution was obtained from the Africa Soil Information Service (AfSIS), which is developing continent-wide digital soil maps for sub-Saharan African [279]. Straight line distance to water bodies was calculated using the data layers of water bodies produced by the SRTM at 250 m resolution [278]. Land cover type, according to the United Nations (UN) land cover classification system, was extracted from the qualitative global land cover map, produced at 300 m resolution from data collected by the environmental satellite (ENVISAT) mission's Medium Resolution Imaging Spectrometer (MERIS) sensor [280]. Gridded maps of both population density and rural-urban classification for 2010 were obtained from the WorldPop project [281,282] and the Global Rural-Urban Mapping project (GRUMP), respectively [283,284]. Finally, Aridity Index data were extracted from the Global-Aridity datasets (CGIARCSI) [285,286]. Survey and covariate data were linked in

ArcGIS 10.1 (Environmental Systems Research Institute Inc. [ESRI] Inc., Redlands CA, USA) based on the WGS-1984 Web Mercator projection at 1 $km^2$ resolution. Bilinear interpolation was applied to resample numeric (continuous) raster data sets, whereas nearest neighbor interpolation was used with ordinal raster layers. Input grids were either extended or clipped to match the geographic extent of a land mask template of Ethiopia, and eventually aligned to it.

### *6.3.3 Data analysis*

The data were entered using a Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA) spreadsheet and exported into STATA 11.0 for analysis (Stata Corporation, College Station, TX, USA). Point prevalence maps were developed in ArcGIS 10 (ESRI, Redlands, CA) and covariate data extracted for each data point. Multicollinearity between the covariates was initially explored using cross-correlations and where correlation coefficients were >0.7 only non-linearly related covariates were included in the analysis (**Supplementary material 6.1**).

Boosted Regression Tree (BRT) modelling [96,97] was used to identify the environmental factors associated with the occurrence of podoconiosis in Ethiopia. This approach has been effectively used in global mapping of dengue, LF, leishmaniasis and malaria vector mosquitos [79,86,98,99] and has superior predictive accuracy compared to other distribution models [100]. In brief, BRT modelling combines regression or decision trees and boosting in a number of sequential steps [96,97]. First, the threshold of each input variable that results in either the presence or the absence of podoconiosis is identified, allowing for both continuous and categorical variables and different scales of measurement amongst predictors [96]. Second, boosting is a machine-learning method that increases a model's accuracy iteratively, based on the idea that it is easier to find and average many rough 'rules of thumb', than to find a single, highly accurate prediction rule.

The Boosted Regression tree was preferred over Bayesian modelling for several reasons. First, as indicated in the objective, the aim of the current analysis was to determine the environmental limits and population at risk for podoconiosis. Second, since we have empirical data from all districts across Ethiopia, predicting the prevalence was not important. Third, the BRT modelling approach was selected so as to make predictions at continental and global scale. The results from Ethiopia were used to predict occurrence in other countries, which will be further validated by collecting ground truthing data from potentially endemic countries.

Boosted Regression Tree utilizes data on both presence and absence of podoconiosis. Presence was defined as an area with at least one case in the two surveys and absence as an area with no cases in either survey. A selection of 16 environmental and climate covariates were included in a single BRT model in order to explore the relative importance of each covariate in explaining the occurrence of podoconiosis in Ethiopia. Four covariates (land cover, soil type, soil texture, urban rural classification) were excluded that showed little explanatory power (<1% of regression trees used the covariate) on the occurrence of podoconiosis. The retained covariates used to build the final model included annual precipitation, elevation, population density, enhanced vegetation index, terrain slope, distance to water bodies, silt fraction and clay fraction. In order to obtain a measurement of uncertainty for the generated model, we fitted an ensemble of 120 BRT submodels to predict sets of different risk maps (each at 1km x 1km resolution) and these were subsequently combined to produce a single mean ensemble map and the relative importance of predictor variables was quantified. These contributions are scaled to sum 100, with a higher number indicating a greater effect on the response. Marginal effect curves were plotted to visualize dependencies between the probability of podoconiosis occurrence and each of the covariates. To assess the association of covariates and high prevalence podoconiosis, the prevalence estimates were plotted against each environmental variable. This will help to identify the areas with very high prevalence and to prioritize interventions. BRT modelling and model visualization was carried out in R version 3.1.1 [287] using the packages Raster [288]and Dismo[289].

The resulting predictive map depicts environmental suitability for the occurrence of podoconiosis. In order to convert this continuous map into a binary map outlining the limits of podoconiosis occurrence, a threshold value of suitability was determined, above which the occurrence was assumed to be possible. Using the receiver operating characteristic (ROC) curve, a threshold value of environmental suitability was chosen such that sensitivity, specificity and proportion correctly classified (PCC) values were maximized. Finally, we estimated the number of individuals at risk by overlaying the binary raster dataset displaying the potential suitability for podoconiosis occurrence on a gridded population density map[281,282] and calculating the population in cells considered to be within the limits of podoconiosis occurrence. The 95% CI of the population at risk were calculated based on the uncertainty in environmental suitability.

The performance of each sub-model was evaluated using different statistics, including: proportion correctly classified [PCC], sensitivity, specificity, Kappa [κ] and area under the receiver operator characteristics curve (AUC). The mean and confidence intervals for each statistic were used to evaluate the predictive performance of the ensemble BRT model. In addition, an external validation was performed using historical data previously assembled [74]. The historical data included data from 96 data points conducted between 1969 and 2012 [7-14,35]. The AUC was used to assess the discriminatory performance of the predictive model, comparing the observed and predicted occurrence of podoconiosis at each historical survey. AUC values of <0.7 indicate poor discriminatory performance, 0.7–0.8 acceptable, 0.8–0.9 excellent and >0.9 outstanding discriminatory performance [113].

## 6.4 Results

Data were available for 141,238 individuals from 1,442 communities in 775 districts (*woredas*) from all regional states of Ethiopia. The mean number of individuals sampled per community was 97.6; the majority of communities (1,350, 93.6%) had more than 90 examined individuals, while 47 communities (3.3%) had less than 70 individuals.

Overall, 5,712 (4.0% lymphoedema positivity) podoconiosis cases were identified in 713 communities, with lymphoedema positivity rates ranging from 0.9 to 54.6% by community. **Figures 6.1B and 6.1C** display the distribution of podoconiosis at community and *woreda* level, respectively, and highlight marked regional variation. No cases of podoconiosis were found in Addis Ababa, Affar, Dire Dawa and Gambella regional states, whereas few cases were found in Tigray, Somali, Benishangul Gumuz and Harari regions (Table 6.1). Disease lymphoedema positivity rate was highest in the central highlands of Ethiopia, in Amhara, Oromia and Southern Nations, Nationalities and Peoples (SNNP) regional state (Table 6.2). A further four districts in Benishangul Gumuz and Tigray and 1 district in Somali were found to be endemic (**Figure 6.1D**).

**Table 6.0-1** The prevalence of podoconiosis among adults ≥15 years old in Ethiopia, by region. CI = confidence interval

| Region | Districts surveyed | Number of clusters | Population surveyed | Podoconiosis cases | Prevalence % (95% CI) |
|---|---|---|---|---|---|
| Addis Ababa | 4 | 8 | 800 | 0 | 0.00 |
| Affar | 32 | 64 | 6257 | 0 | 0.00 |
| Amhara | 144 | 285 | 28170 | 1097 | 3.89 (3.67- 4.12) |
| Benishangul Gumuz | 20 | 21 | 1737 | 8 | 0.46 (0.14-0.78) |
| DireDawa | 7 | 14 | 1400 | 0 | 0.00 |
| Gambella | 11 | 16 | 819 | 0 | 0.00 |
| Harari | 9 | 18 | 1801 | 1 | 0.06 (0.05- 0.16) |
| Oromia | 298 | 541 | 53647 | 2158 | 4.02 (3.86- 4.19) |
| SNNPR | 155 | 285 | 27860 | 2404 | 8.63 (8.30- 8.96) |
| Somali | 49 | 99 | 9583 | 14 | 0.15 (0.07- 0.22) |
| Tigray | 46 | 91 | 9164 | 30 | 0.33 (0.21-0.44) |
| Total | 775 | 1442 | 141,238 | 5712 | 4.04 (3.94-4.15) |

**Table 6.0-2** Classification of prevalence of podoconiosis among adults ≥15 years old in Ethiopia, by region

| | Podoconiosis prevalence category (%) | | | | | | Total | ≤1% | >1% |
|---|---|---|---|---|---|---|---|---|---|
| Region | 0 | 0.01-1 | 1.01-5 | 5.01-10 | 10.1-15 | >15 | | | |
| Addis Ababa | 4 | 0 | 0 | 0 | 0 | 0 | 4 | 4 | 0 |
| Affar | 32 | 0 | 0 | 0 | 0 | 0 | 32 | 32 | 0 |
| Amhara | 55 | 25 | 40 | 6 | 7 | 11 | 144 | 80 | 64 |
| Benishangul Gumuz | 16 | 1 | 3 | 1 | 0 | 0 | 21 | 17 | 4 |
| Dire Dawa | 7 | 0 | 0 | 0 | 0 | 0 | 7 | 7 | 0 |
| Gambella | 10 | 0 | 0 | 0 | 0 | 0 | 10 | 10 | 0 |
| Harari | 8 | 1 | 0 | 0 | 0 | 0 | 9 | 9 | 0 |
| Oromia | 104 | 50 | 76 | 32 | 15 | 21 | 298 | 154 | 144 |
| SNNPR | 21 | 6 | 39 | 40 | 24 | 25 | 155 | 27 | 128 |
| Somali | 38 | 10 | 1 | 0 | 0 | 0 | 49 | 48 | 1 |
| Tigray | 30 | 12 | 4 | 0 | 0 | 0 | 46 | 42 | 4 |
| Total | 325 | 105 | 163 | 79 | 46 | 57 | 775 | 430 | 345 |

### *6.4.1 Factors associated with podoconiosis occurrence*

**Figure 6.2** shows the marginal effect of each covariate on the predicted suitability of occurrence for podoconiosis, averaging across the effects of all other variables, and its relative contribution to the final BRT model. Major predictors of the occurrence of podoconiosis were annual precipitation (accounting for 30.7% of the variation explained by the model), elevation (22.6%), EVI (15.4%) and population density (12.7%). Slope only contributed 8.2% to the predicted occurrence. Annual precipitation causes an increase in probability of occurrence starting from precipitation values of around 1,000 millimeters (mm) per year. High suitability for podoconiosis is also positively associated with elevation, increasing between 1,000-2,000 m asl and then sharply declining after 2,000 m asl. EVI is linearly correlated to the risk of podoconiosis occurrence up to 0.5 and decline sharply thereafter. Population density is negatively correlated with the probability of podoconiosis occurrence, with population density greater than 10,000 population/ $km^2$ causing no effect on the probability of occurrence of podoconiosis. Although silt fraction and clay fraction contributed little to the final BRT model, the occurrence of podoconiosis was found to be associated with decreasing clay fraction and increasing silt fraction.

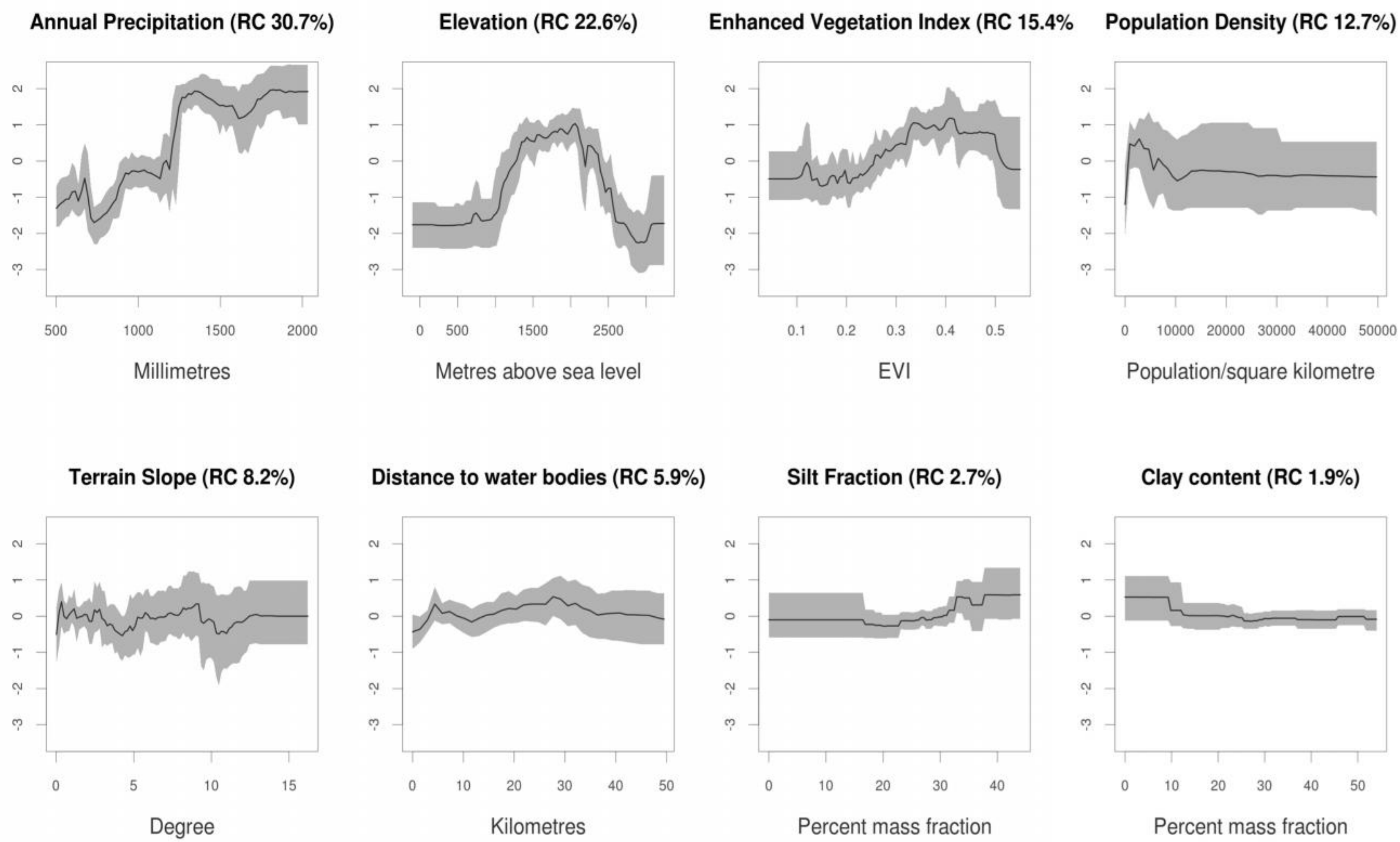


**Figure 6.2** Marginal effect curves for covariates included in 120 ensembles of boosted regression tree (BRT) models. The grey envelopes are the 95% bootstrap confidence intervals and the black line indicates the mean marginal effect. The figure in the parentheses indicates the relative contribution of each variable, which adds up to 100. The y-axis is the untransformed logit response and x-axis is the full range of covariate values.

### *6.4.2 Factors associated with the prevalence of podoconiosis*

Previous studies have indicated a relationship between the prevalence of podoconiosis and climate and environmental covariates (including rainfall, altitude, temperature and soil type), and have characterized high prevalence areas using certain environmental variables [19]. In order to assess this relationship in Ethiopia, **Figure 6.3** depicts the relationship between the environmental variables and the prevalence of podoconiosis. Thus, the distribution of podoconiosis is clearly bounded within an altitude range of 1,000-2,800 m asl EVI > 0.2 and annual precipitation >1,000 mm.

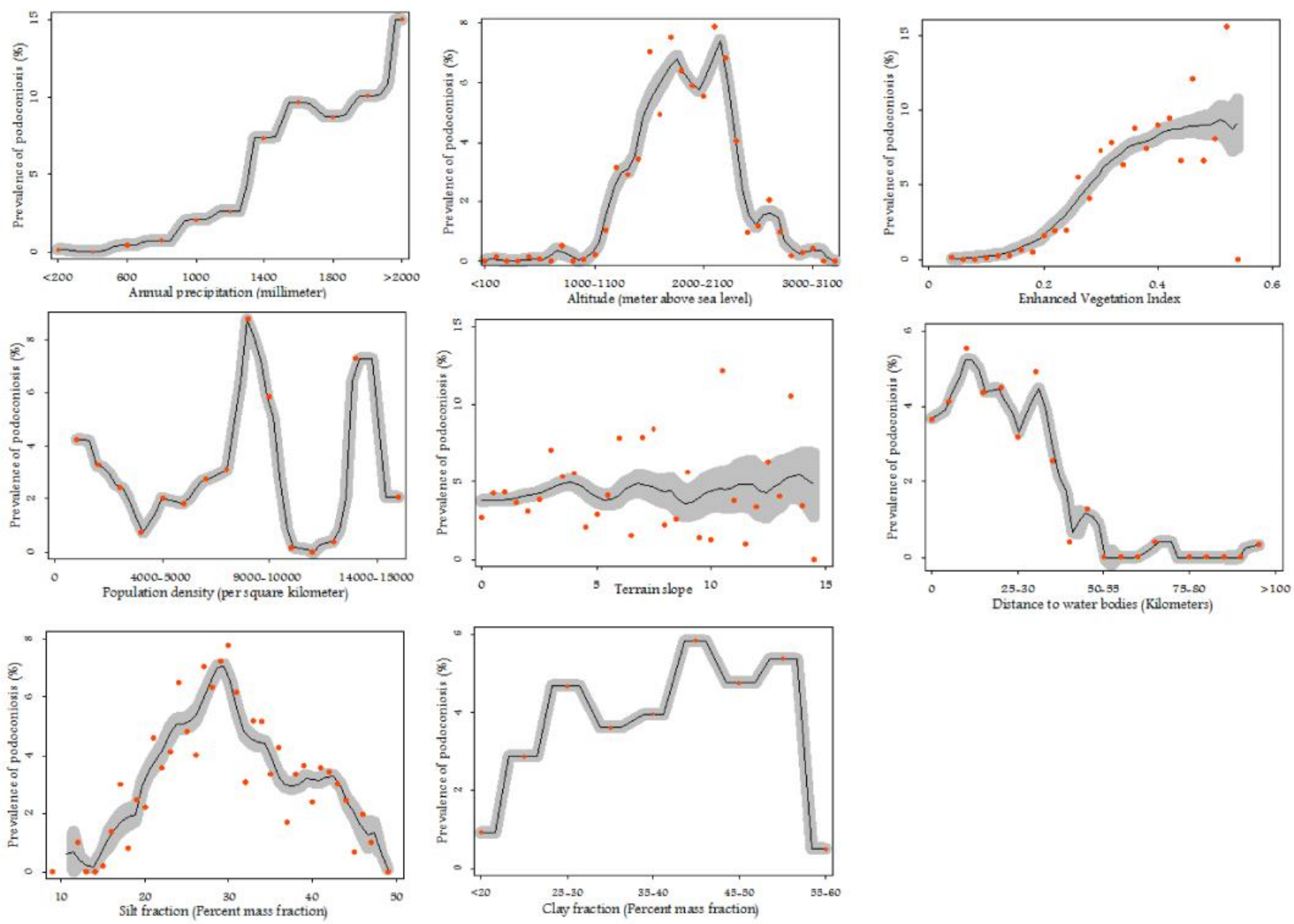

**Figure 6.3** Local polynomial smoothed line fitted to the prevalence of podoconiosis showing the relationship between environmental covariates and podoconiosis prevalence at village level. Lines represent the mean estimate, while shaded areas depict the associated 95% confidence intervals.

### *6.4.3 Environmental limits of podoconiosis in Ethiopia, based on BRT*

**Figure 6.4A** presents the map of environmental suitability for podoconiosis and suggests that suitability is greatest in the central highlands of Amhara, Oromia and SNNP regional states. Absence of podoconiosis is predicted in Affar, Gambella and Somali regional states. A suitability cut-off of 0.49 with a sensitivity of 0.77 and specificity 0.86 provided the best discrimination between presence and absence records in the training data, and therefore this threshold value was used to reclassify the predictive risk map into a binary map outlining the potential environmental limits of occurrence (**Figure 6.5**). Uncertainty was calculated as the range of the 95% confidence interval in predicted probability of occurrence for each pixel (**Figure 6.4B**) indicating high uncertainty in the eastern part of Somali regional state. Cross-validation in the BRT ensemble model indicated high predictive performance of the BRT ensemble model with an AUC value of 0.84 (95% confidence interval (CI): 0.84 – 0.85; standard deviation (sd): 0.016) (Table 6.3). External validation against historical data showed an excellent performance of the final fitted model to classify at-risk areas, with an AUC value of 0.89 (CI 95%: 0.81 – 0.97).

**Table 6.3 BRT prediction statistics**

| | Mean | Standard Deviation |
|---|---|---|
| Kappa | 0.63 | 0.10 |
| AUC | 0.84 | 0.06 |
| Sensitivity | 0.77 | 0.08 |
| Specificity | 0.86 | 0.07 |

| | | |
|---|---|---|
| Percent correctly classified | 0.82 | 0.05 |

### 6.4.4 *Estimating population at risk*

The national population living in areas environmentally suitable for podoconiosis is estimated to be over 34.9 (95% CI: 20.2-51.7) million, which corresponds to 43.8% of Ethiopia's population in 2010. The largest portions of the population at risk were found in SNNP (68.1%) Oromia (.48.0%) and Amhara (49.6%) (Table 6.4). We conducted a sensitivity analysis to determine the effect of the optimal suitability threshold (0.496) on the estimates of at-risk population. For that, we applied both a lower (0.3) and a higher (0.6) cut-off to dichotomize the final BRT model, and estimated the population living in suitable areas for podoconiosis based on these extreme thresholds. The total estimated population at risk would be 44.6 million (95%CI: 27.8 – 59.4) and 29.9 million (95%CI: 16.7 – 46.8) for the 0.3 and 0.6 cut-offs respectively.

**Table 6.4** Regional distribution of population at risk and surface area conducive to podoconiosis occurrence in Ethiopia

| Region | Population living in podoconiosis at risk area | Percentage of potentially exposed population | Landmass ($km^2$) environmentally suitable for occurrence of podoconiosis |
|---|---|---|---|
| Addis Ababa | 117,072 | 4.0 | 88 |
| Affar | 8,567 | 0.6 | 127 |
| Amhara | 9,122,394 | 49.6 | 60,692 |
| Benishangul Gumuz | 285,525 | 33.0 | 8,076 |
| Dire Dawa | 66 | 0.02 | 2 |
| Gambella | 1,736 | 0.5 | 155 |
| Harari | 6,624 | 3.3 | 42 |
| Oromia | 14,128,376 | 48.0 | 133,515 |

| | | | |
|---|---|---|---|
| SNNP | 10,995,913 | 68.1 | 55,840 |
| Somali | 26,826 | 0.6 | 1,458 |
| Tigray | 272,946 | 5.9 | 1,773 |
| Total | 34,966,046 | 43.8 | 261,768 |

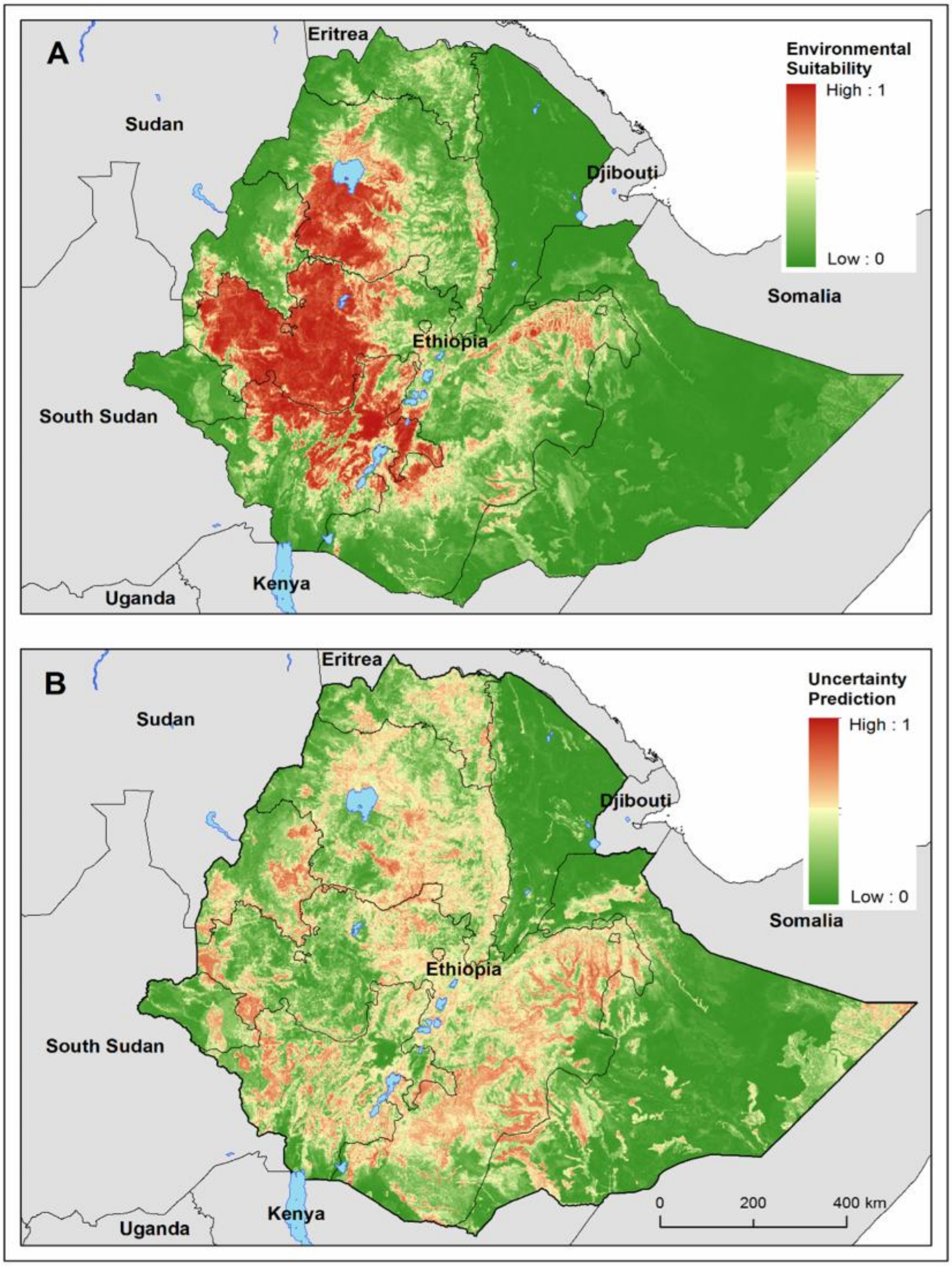


**Figure 6.4** Predicted (A) suitability of podoconiosis (B) Uncertainty associated with predicted suitability of podoconiosis in Figure 6.4 A. Uncertainty was calculated as the range of the 95% confidence interval in predicted probability of suitability for each pixel.

Regions of highest uncertainty are in red, with greener colour representing low uncertainty.

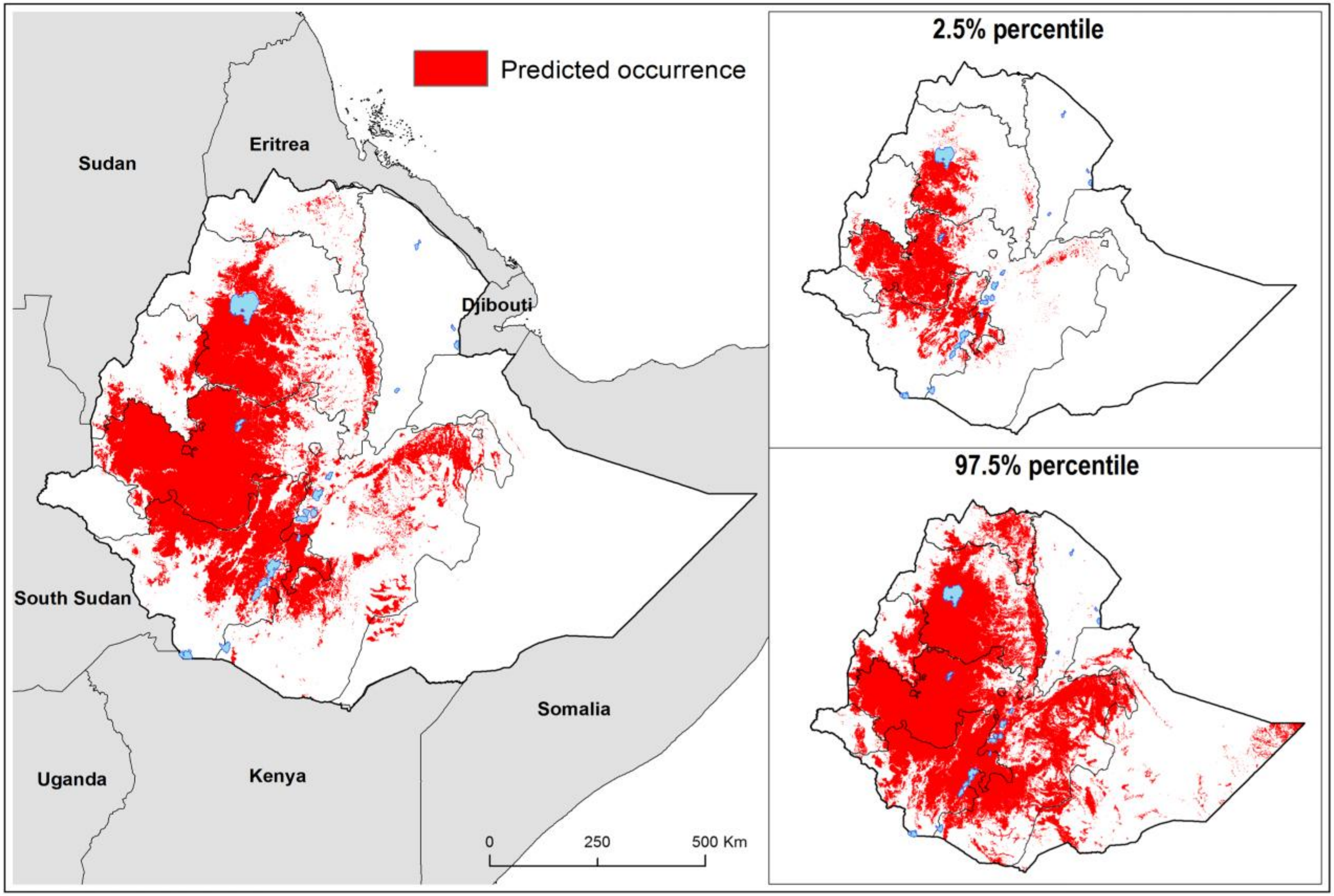


**Figure 6.5** Predicted occurrence of podoconiosis with the lower (2.5%) and upper (97.5%) bounds of the occurrence limits.

## 6.5 Discussion

Despite the growing global awareness of podoconiosis [222,290], national scale epidemiological data about the distribution of podoconiosis are lacking in all endemic countries. Understanding the geographical distribution and estimating the population at risk are important first steps to optimally use the resources allocated to podoconiosis [4,189]. To my knowledge, this is the first nationwide mapping of podoconiosis using a predefined clinical algorithm to diagnose podoconiosis. It is also the first attempt to develop a risk model of podoconiosis based on remotely sensed environmental data and robust statistical techniques. The study showed that podoconiosis is widely distributed in Ethiopia and covers substantial parts of the country. Besides, these results indicate that 43.8% of the Ethiopian population lives at risk of podoconiosis and a quarter of the landmass is conducive to podoconiosis occurrence. The mapping largely indicated high (close to 1) or low (close to 0) probability of occurrence of podoconiosis. This indicates the degree of certainty from the maps is very high for both presence and absence. Therefore, the findings here will help guide interventions and resource allocation and estimate the disease burden caused by podoconiosis.

In the current analysis, I identified specific environmental factors associated with the occurrence and prevalence of podoconiosis and used BRT modelling to delineate the environmental limits of podoconiosis in Ethiopia. The results show that the probability of podoconiosis occurrence and its prevalence increase with annual precipitation and elevation, and decrease with population density. Moreover, podoconiosis typically occurs in zones with silt-rich soils. Previously, it had been observed that altitude governs temperature and other climatic conditions conducive to generation of soil suitable for podoconiosis occurrence [19,60]. Rainfall is also important in the pathway of soil formation, and may also increase exposure to the soil components [19,28,60]. Studies have indicated that soils associated with podoconiosis are slippery and adhesive if allowed to dry [19,28,60].

The risk map, developed using BRT modelling, shows that the environmental conditions conducive to the occurrence of podoconiosis are found throughout the central highlands of Ethiopia, located in Amhara, Oromia and SNNP regional states. This distribution corresponds well with the historical distribution of podoconiosis in Ethiopia [74]. Furthermore, I was able to clearly identify environmental limits for the distribution and intensity of podoconiosis occurrence in Ethiopia. Podoconiosis occurred in areas where annul precipitation is >1000 mm, and elevation was between 1,000 and 2,800 m asl. In general, the high lymphoedema positivity rate (≥5%) districts were characterized by mean annual precipitation of 1,665 mm and altitude of 1,892 m asl.

Moreover, this work provides interesting insight into the regional distribution of podoconiosis in Ethiopia. Both the observed distribution (Figure 6.1 C) and the map of environmental limits (Figure 6.4 A) indicate a heterogeneous distribution within those regions most at risk of podoconiosis, namely Amhara, Oromia and SNNP. In Amhara, the highest environmental suitability is predicted in East Gojjam and West Gojjam, South Gondar and Awi zones, and similarly in the western part of Oromia including East Wollega, West Wollega and Kellem Wollega, Illubabor, Jimma, North and West Shoa zones. In SNNP, most of the zones are at a high risk of podoconiosis except Bench Maji and South Omo zones where LF is prevalent. These findings are in concordance with previous studies conducted at a lower scale in these three regional states [11,12,14,15], which almost exclusively cover the central highlands of Ethiopia where agrarian communities reside. Given the agriculture-led economy of the country, the findings here have several implications. First, podoconiosis is not only a health problem but may also be a constraint for economic development. To have a healthy and productive agrarian community, the government should prioritize prevention and control of podoconiosis in the most at-risk regions. The inclusion of podoconiosis into the national integrated NTD master plan was an important first step [26], but implementing this master plan will require resource mobilization and allocation.

The results here show that podoconiosis is more widely distributed in Ethiopia than previously thought. The population at risk and the landmass suitable for the occurrence of podoconiosis is considerably beyond previous estimates of 11-15 million people (or one fifth of the country's landmass) [21,189]. There are several reasons for these differences. First, previous estimates were limited to rural areas and zones historically known to be endemic for podoconiosis. Second, they relied on school and market surveys, which due to selection bias might have underestimated the geographical distribution of the disease [7,8,223], for these counts were only localized to areas in which markets or schools were present. For instance, these studies were conducted some 40 years ago when the school coverage in Ethiopia was fairly limited. In addition, population movement and settlement schemes may have contributed to the current increase in at-risk population [13].

Globally this is the first comprehensive mapping of podoconiosis. The work here included almost every district in Ethiopia and followed WHO recommendations for mapping LF [235]. I have used data from LF mapping in southwest Ethiopia [210], but only analysed data from non-endemic districts. The diagnostic criteria and sampling methods employed make both data sets comparable. Although the study has several strengths it is not without limitations. First, we used information from district offices to select study sites (mostly suspected endemic areas) within districts, which might have led to overestimation of prevalence. Second, although adult individuals were mobilized to central places for random selection, self-selection bias might have affected the findings, potentially overestimating occurrence. To minimize this, we mobilized the entire community prior to the survey using house to house visits by Health Extension Workers without mentioning the disease surveyed. Third, there is no definitive diagnostic test for podoconiosis to date, so I developed a clinical algorithm to diagnose podoconiosis[228]. The mapping excluded all other potential causes of lymphoedema using stringent criteria that might --if anything--result in underestimation rather than overestimation of podoconiosis. Fourth, no mapping approach for podoconiosis has yet been defined, consequently I adopted the mapping approach for LF. The assumptions valid for LF might not hold true for podoconiosis: for example, the prevalence estimates from two villages per district might not reflect the actual distribution in the district [235]. However, from previous observational studies, podoconiosis distribution has shown to be less focal than that of LF [19,90]. Fifth, lack of perfect temporal overlap of the outcome and covariate is another limitation of the data. Nonetheless I used the long term averages of environmental data for my analysis for a number of reasons. The weathering of rock to soil takes place over extended periods of time. Podoconiosis is a chronic disease and requires several years of exposure to irritant soil. The prevalent cases seen today may have been exposed for more than a decade to the putative causes. The various covariate data are available for differing time periods; I have however sought to use the available data which covers the largest time period. Finally, an important issue concerning the use of remote sensing data to identify ecological association between environment and podoconiosis is spatial scale [291,292]. The variables which affect the distribution of podoconiosis at small scale and large scale might differ. Although previous studies identified several soil characteristics to affect the risk of podoconiosis at small scale [18], such association was not maintained in the current analysis. Studies have identified different risk factors at different scales [293,294]. At small scale, the risk of podoconiosis might be affected by individual shoe wearing and hygiene practices which were not captured in the model due to lack of such data.

This work makes three important contributions to increasing the understanding of podoconiosis. First, I have defined the environmental limits of podoconiosis in Ethiopia, enabling estimation of population at risk. With further validation, this may lead to delineation of the global limits of podoconiosis occurrence. Second, I have identified environmental factors which are associated with the occurrence of podoconiosis in Ethiopia. If these environmental factors are found to be associated with the disease in other settings, a continental risk map of podoconiosis can be generated. Third, by narrowing the environmental limits of podoconiosis, the findings here will guide the identification of the exact mineral particles in the soil responsible for podoconiosis.

In addition to providing a predictive map of the risk of podoconiosis, the analyses also provide a map of uncertainty in these predictions, and an illustration of how that uncertainty relates to environmental variables in the marginal effect plots. By providing a map of where risk of occurrence is less predictable using the environmental variables considered here, I hope to better inform policy makers and researchers about where the main prediction map is likely to be most reliable. This map may also be used when deciding where to target future surveillance for the disease and where further studies could help elucidate its main drivers.

## 6.6 Conclusion

The geographical distribution and burden of podoconiosis is formidable in Ethiopia and represents an important challenge to national program planners and policy makers. Success in tackling this national problem is, in part, contingent on strengthening the evidence base on which control planning decisions and their impacts are evaluated. It is hoped that this mapping of contemporary distribution of podoconiosis will help to advance that goal. Empirical evidence has shown that podoconiosis morbidity management is effective in the early stages of the disease and improves clinical measures and the quality of life of patients [44]. If this morbidity management is found to be effective and cost-effective using more robust assessment, the next step will be scaling up interventions in all endemic districts. It is assumed that prioritizing those districts with high prevalence would be a cost-effective approach. Promoting consistent shoe wearing is also vital to help prevent podoconiosis. Studies in southern Ethiopia have identified cultural, financial and logistic barriers to shoe wearing [54,295], and have informed the development of a community messaging intervention to enhance prevention of podoconiosis[295]. This intervention requires testing and adaptation to other endemic districts, possibly in combination with the hygiene promotion package of the 16-package Health Extension Program[249,250].

In conclusion, the results here provide a detailed description of the geographical distribution and environmental limits of podoconiosis in Ethiopia. This will enable optimal allocation of the limited resources available for podoconiosis control and elimination, permit evaluation of the impact of interventions in the future, guide mapping of other potentially endemic countries and contribute to the global mapping of podoconiosis. The ultimate goal of mapping and scaling up interventions is the elimination of disease. Elimination as a concept is a motivating and appealing target, but it should be clearly defined and parameterized into measureable metrics in the context of podoconiosis. The next chapter will present the results of a Delphi exercise among experts to develop podoconiosis case definitions as they relate to case identification in the routine health care setting, district endemicity classifications (non-endemic, hypo-endemic, meso-endemic and hyper-endemic) and disease elimination targets.

# Chapter 7. Measuring elimination of podoconiosis, endemicity classifications and targets: An international Delphi exercise

## 7.1 Overview

The previous chapters discussed the historical and current distribution of podoconiosis in Ethiopia. Mapping results should be translated into practical implications for disease control so that they can be easily used by policy makers and program planners. Simplified messaging of prevalence results is important for decision-making. To present the mapping data in the form of action-oriented reports for decision makers, defining endemicity classification and elimination targets is critical. Categorizing areas based on endemicity class will allow prioritization of resources and interventions based on needs.

Historical accounts have suggested the potential for elimination of podoconiosis. The disease has been eliminated from northern African countries [2], due to socioeconomic development and secular changes in shoe wearing practices. With economic changes in endemic countries in addition to available interventions, eliminating podoconiosis within our lifetime is in our reach. The concept of elimination should be deconstructed to provide clearer metrics of measuring progress. This chapter focuses on describing the Delphi technique process used among experts in the field to define the key concepts of podoconiosis endemicity classifications and elimination targets to support a global strategy for the elimination of podoconiosis. The results presented here were published in 2015[296,297].

## 7.2 Introduction

The WHO identified podoconiosis as a NTD in 2011[222]. Although this inclusion was an important step forward, there is no clear global strategy for the elimination or control of podoconiosis to date. In 2012, Footwork, the International Podoconiosis Initiative (IPI), was established [222]. The vision of the IPI is to eliminate podoconiosis ("a world free of podoconiosis in our lifetimes"). This goal needs measurable indicators. Communities or countries need a pre-specified threshold to achieve the goal of elimination of podoconiosis as a public health problem. For other NTDs, elimination targets and endemicity classifications are often based on prevalence of the infective organism. This is not possible with podoconiosis, since the 'agent' is mineral rather than biological, so targets will rather be based on morbidity (lymphoedema) prevalence. For example, the target of global elimination of leprosy as a public health problem is the reduction of case prevalence to less than 1 per 10,000 population[298]. For lymphatic filariasis (LF), the target is the reduction of the cumulative incidence of 1 per 1000 in children, six to ten years old born after the initiation of the mass drug administration, and continued for at least five years [299,300](**Table 7.1**).

This information will be useful for public health policy and planning. Although residents of areas classified as hypo-endemic might not benefit from podoconiosis control programmes, these individuals would still be eligible for individual health facility-based treatment if diagnosed with podoconiosis. Similarly, there is a clear need for measurable targets for the elimination of podoconiosis to monitor progress. Equally, an endemicity threshold will help to identify areas considered endemic for podoconiosis and requiring interventions.

**Table 7.0-1** Neglected tropical diseases identified by WHO for elimination and their targets

| Diseases | Target year | Target | Threshold |
|---|---|---|---|
| Onchocerciasis | 2025 | Elimination of onchocerciasis as a disease of public health and socio-economic importance throughout Africa | Microfilaria in skin snips prevalence is less than 5% in all sample communities and 1% in 90% of sampled communities[301]. |
| Blinding trachoma | 2020 | The elimination of blinding trachoma as blinding disease. | The prevalence of active trachoma TF is less than 5 percent among children aged 1 to 9 years old and prevalence of trachoma trichiasis(TT) is less than 1 case per 1000 population[302]. |
| Leprosy | 2020 | Elimination as a public health problem in all countries. | Prevalence of, 1 case per 10,000 population in each country[303]. |
| Human African trypanosomiasis | 2020 | Eliminating human African trypanosomiasis as a public-health problem by 2020, | The detection of less than 1 case per 10,000 inhabitants in at least 90% of endemic foci in 2020, with the total number of cases reported annually at continental level to below 2000[304]. |
| Visceral leishmaniasis in Indian subcontinent | 2020 | To eliminate visceral leishmaniasis as a public health problem in the Indian subcontinent. | To reduce the annual incidence of kala-azar to less than one per 10 000 population in Indian subcontinent [107,305]. |
| Lymphatic filariasis | 2020 | Elimination as a public health problem and the interruption of transmission | Current working goal is five-year cumulative incidence of 1 per 1000 in children, six to ten years old born after the initiation of the mass drug administration, and continued for at least five years[306]. |

Here, I present the results of a Delphi assessment with experts working on podoconiosis and other NTDs. The objectives of this chapter are i) to describe a consensus among experts on the threshold by which an area is called endemic for podoconiosis, ii) to identify appropriate endemicity classes for podoconiosis (non-endemic, hypo, meso and hyper), iii) to identify thresholds and targets for elimination of podoconiosis from an endemic country, and iv) to produce case definitions of podoconiosis for surveillance.

## 7.3 Methods

### *7.3.1 Description of Delphi techniques*

The Delphi survey technique is an iterative email or web-based survey to reach a consensus among a group of experts who are familiar with a subject area [307]. The approach uses well-designed sequential surveys in which each round depends on the response from the previous round. Each round uses feedback from the previous rounds from the same group of experts. Once the experts are selected, they are asked to provide judgement on the concepts of the subject under consideration using open-ended questions[308]. The next phase asks the same panellists to rank the items based on a Likert scale, measuring their importance. Following that, several rounds may be needed until a consensus on each item has been achieved based on the results of the quantitative analysis[309].

### *7.3.2 Design and participants*

I used a Delphi method to define case definition, endemicity class, elimination targets and clinical outcomes of podoconiosis. I used a four-round Delphi method. In the first two rounds, small group of experts working on podoconiosis were involved in developing the tool. In the subsequent two rounds, a wider group of experts working on podoconiosis and other NTDs were involved. These later rounds were conducted from August to November 2014 (**Figure 7.1**).

The selection of experts for the Delphi process was done using a purposive sampling technique. For the first two rounds, experts with experience in podoconiosis research and programs were included. For the subsequent two rounds, the following eligibility criteria were used to select the experts: individuals working on NTDs at national or global level, individuals working on podoconiosis research or program management, senior podoconiosis professionals with in-depth knowledge and experience of control, and experts involved in developing indicators and targets for other NTDs.

During recruitment, potential experts were approached (initially via e-mail or by telephone) and provided with a detailed explanation of the study and its objectives. A total of 28 national and international experts participated in the Delphi process.

#### *7.3.3 Instrument*

I developed an instrument from a review of the literature and in consultation with experts in podoconiosis. The instrument included general information about the purpose of the study and the need for targets for podoconiosis control. A list of indicators, definitions and response categories was provided, and respondents were asked to justify their agreement or disagreement with each item and to provide alternative options for each (**Supplementary material 7.1**). A list of potential indicators and definitions was developed, using previous experience in arriving at elimination targets for other diseases and the range of podoconiosis prevalence estimates observed in different countries [7-9,11,12,14,15,33,74,251].

#### *7.1.1 Data collection and analysis*

The case definitions, endemicity classifications, elimination targets and monitoring indicators were developed in a series of four reiterative surveys between October 2012 and November 2014. In the first two rounds, experts who specialized in podoconiosis were selected. Feedback on each item was received and the questionnaire was modified. In the last two rounds, experts were asked to score items in terms of importance on a 9-point

Likert-type scale for each indicator ranging from 1 = ‘‘not important’’ to 9 = ‘‘extremely important’’.

For this study and in line with other related studies[310,311], I set the consensus level as follows: 1) Consensus of inclusion: >70% of participants scored the item ≥7; 2) Consensus of exclusion: > 70% subjects scored the item ≤5; 3) No consensus: item failed to meet either of the above criteria. The responses in the first-round survey were analyzed, using descriptive statistics, and the results were sent back to the experts for review and ratification. Items which were recommended for modification by the experts were revised and added to the second round questionnaire; new items suggested by the experts were also added to the second round questionnaire. In the second questionnaire, participants were asked to re-rank the items from the first round. Second Delphi responses that reached 70% consensus were determined to be appropriate items for assessing different aspects of podoconiosis elimination. The final results were presented to experts for discussion and final consensus, leading to the final targets and indicators.

Median and mode were used to describe the central tendency of expert responses. The coefficient of variation (CV) was used to describe the dispersals of expert responses. The CV is the ratio of the standard deviation of the responses of the experts on a specific item to its corresponding mean (average). Therefore, each survey item in each round yielded one CV [308,309].

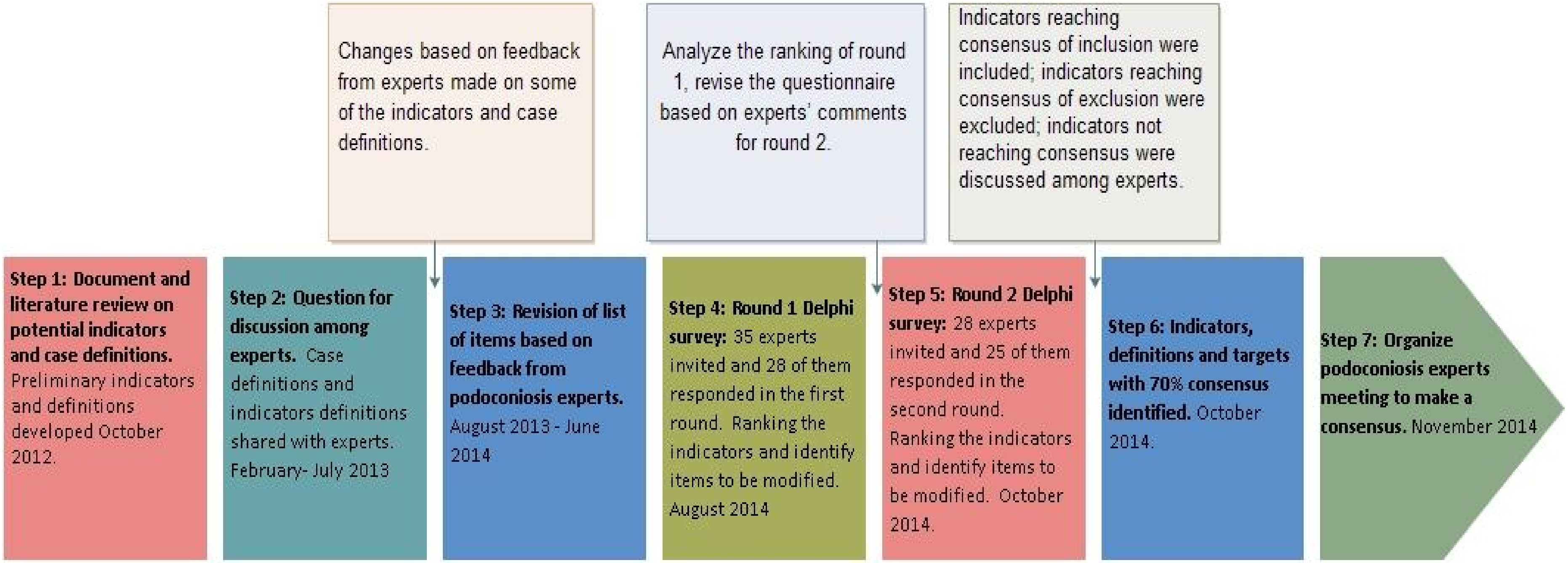


**Figure 7.1** Flowchart of the Delphi process for the development of case definitions, endemicity classifications and elimination targets.

## 7.2 Results

### *7.2.1 Characteristics of the experts*

During the first round of the Delphi survey, questionnaires were sent to 35 experts and 28 of them responded. The 28 experts were working at global and national levels based in six countries. All of them had Masters level education or above. Twenty five experts responded to the second round survey. Descriptive information on the experts is presented in Table 7.2.

**Table 7.0-2** Characteristics of experts involved in the survey

| Characteristics | | Number | Percentage |
|---|---|---|---|
| Age | <35 | 12 | 42.9 |
| | 35-45 | 10 | 35.7 |
| | 45-54 | 2 | 7.1 |
| | 55-64 | 3 | 10.7 |
| | >=65 | 1 | 3.6 |
| Sex | Female | 8 | 28.6 |
| | Male | 20 | 71.4 |
| Education | MSc/MA/MPH | 17 | 60.7 |
| | MD | 4 | 14.3 |
| | PhD | 7 | 25.9 |
| Work unit | Global | 8 | 28.6 |
| | National ( Endemic country) | 20 | 71.4 |
| Professional level | Middle | 8 | 28.6 |
| | Associate senior | 12 | 42.8 |
| | Senior | 8 | 28.6 |

### *7.2.2 Preparatory phase*

In two rounds, small groups of experts with extensive experience on podoconiosis were provided with an open ended questionnaire about potential case definitions, endemicity classifications and potential indicators for monitoring elimination and progress. The experts provided feedback and suggested a number of important indicators. Based on the first round feedback, a consolidated list of indicators and definitions was prepared and the questionnaire was sent to the same experts. In the second round, the comments given were mainly on rewording the indicators and refining them. After including the comments from the experts, a larger group of experts was sent a closed ended questionnaire with a Likert scale (Supplementary material 7.1).

### *7.2.3 Results of round 1 survey*

The results of the first round Delphi survey are shown in Table 7.3. Based on the findings the median score ranges from 6.5 to 9. Most of the items had CV of less than 0.3 indicating good central tendencies for expert scores.

**Table 7.0-3** Results of round 1 survey Delphi process for the development of case definitions, endemicity classifications and elimination targets

| | Median | Mode | CV | Consensus (% score of >7) |
|---|---|---|---|---|
| **SECTION 1:** Case definition | | | | |
| **Suspected case:** Any lymphoedema (swelling caused by the collection of fluid in tissue) of the lower limb of any duration. | 8.0 | 9.0 | 0.2 | 73.1 |
| **Probable case:** Any lymphoedema (swelling caused by the collection of fluid in tissue) of the lower limb present for more than 3 months in a resident of, or a long-term visitor to, an endemic area. | 7.5 | 8 | 0.3 | 57.7 |
| **Confirmed case:** Lymphoedema of the lower limb present for more than 3 months in a resident of, or long term visitor to an endemic area, for which other causes have been excluded (onchocerciasis, LF, leprosy, Milroy syndrome, heart or liver failure, etc). | 8.0 | 9 | 0.1 | 88.5 |
| **SECTION 2:** Endemicity classification | | | | |
| **Non endemic** <1% prevalence among adults ≥ 15 years old | 7.5 | 9 | 0.4 | 76.9 |
| **Hypo-endemic** ≥1to <3% prevalence among adults ≥ 15 years old | 8.0 | 9.0 | 0.3 | 76.9 |
| **Meso endemic** 3 to <10% prevalence among adults ≥ 15 years old | 8.0 | 9.0 | 0.3 | 76.9 |
| **Hyper endemic** ≥ 10% prevalence among adults ≥ 15 years old | 8.0 | 9.0 | 0.3 | 76.9 |
| **SECTION 3: Elimination** | | | | |
| ***Elimination of podoconiosis from a district*** | | | | |
| The prevalence is less than 1 percent (among individuals ≥15 years old) after 10 years of program implementation. AND | 8.0 | 9.0 | 0.3 | 73.1 |
| More than 90 percent of lymphoedema cases are treated adequately after 10 years of program implementation. | 6.5 | 9.0 | 0.3 | 50.0 |
| ***Elimination of podoconiosis from a country*** | | | | |
| Prevalence of untreated podoconiosis is maintained at less than 1 percent (among individuals >15 years old) in 100 percent of sample villages over a 10 year period. AND | 7.0 | 9.0 | 0.3 | 61.5 |
| Prevalence of early signs of podoconiosis among children 10-15 years | 8.0 | 9.0 | 0.3 | 70.8 |

| | | | | |
|---|---|---|---|---|
| after 10 years of control program implementation is less than 1 in 10,000. AND | | | | |
| Greater than 95 percent of population in endemic districts wears protective shoes. AND | 8.5 | 9.0 | 0.2 | 76.9 |
| Greater than 90 percent of lymphoedema cases are treated adequately. | 7.0 | 9.0 | 0.3 | 61.5 |
| *Key indicators for the podoconiosis elimination monitoring* | | | | |
| **Prevalence of podoconiosis (%)=**Number of old and new cases of podoconiosis in the implementation unit (≥15 years) divided by total population ≥15 years old in the same area, times 100 | 9.0 | 9.0 | 0.2 | 84.6 |
| **Case detection rate (%)=** Number of new cases of podoconiosis in the implementation unit divided by total population at risk in the same area, times 100 | 9.0 | 9.0 | 0.1 | 88.4 |
| **Treatment completion rate (%)**= Number of patients that completed the required duration of treatment divided by all new podoconiosis cases that started treatment in a given period, times 100 | 8.5 | 9.0 | 0.2 | 86.9 |
| **Coverage of shoe wearing (%)(point prevalence in sampled villages)=** Number of individuals wearing shoes (>1 years old) in implementation unit divided by total number of individuals >1 years old in the same area, times 100 | 9.0 | 9.0 | 0.2 | 84.6 |
| **SECTION 4: Monitoring clinical outcomes** | | | | |
| **Treatment completion:** A patient who has completed the full course of the initial treatment given at health facility/community level. | 9.0 | 9.0 | 0.2 | 92.3 |
| **Defaulter:** A patient who has been on treatment and whose treatment was interrupted for 2 or more consecutive months. | 8.0 | 9.0 | 0.3 | 73.1 |
| **Treatment Success:** Treatment is successful if an incapacitated patient can assume normal activities following treatment. | 8.0 | 9.0 | 0.3 | 69.2 |
| *Key indicators for monitoring progresses* | | | | |
| > 95% of population in endemic districts consistently wears protective shoes (measured for the last one year). | 8.0 | 9.0 | 0.2 | 80.8 |
| >90% of the population in the endemic districts practices proper foot hygiene* (measured for the last one year) (*proper foot hygiene is defined as washing once per day using soap and water over the period of one year) | 8.0 | 9.0 | 0.3 | 65.3 |

The experts suggested that the probable case definition should be modified. The experts did not recommend the deletion of any of the indicators. In the endemicity category, all the indicators had a median score of at least 7.5 and a mode of at least 9. In this category at least 70% of experts were in consensus on all the indicators, and apart from the non-endemic category, all had CVs of 0.3 or greater.

In the ‘elimination target’ category, of the ten indicators, nine had median ≥7 and mode of 9. Seven indicators had consensus of 70% or more of the experts. The three indicators with less than 70% agreement were related to lymphoedema management. The experts commented that "adequate treatment" should be clearly defined.

In the 'monitoring clinical outcome' category, of the five indicators, three reached consensus among >70% of the experts. The two indicators with less than 70% agreement were treatment success and measure of proper foot hygiene. The experts recommend that the term "incapacitated" mentioned in the treatment success definition should be further defined. The experts also indicated that the measurement of foot hygiene was poorly defined and a subjective measurement.

None of the indicators fulfilled the criteria of consensus of exclusion or >70% subjects scored the item ≤5. Therefore, none of the indicators was deleted from the third round of the survey. In the 'case definition' category, experts indicated that, given the chronic nature of podoconiosis lymphoedema, a three month duration period should not be considered in the case definition. Based on the recommendation, the case definitions were revised to reflect lymphoedema duration of at least 1 year. In addition, the experts recommended that long term visitors should not be included in the case definitions since podoconiosis requires an extended period of exposure to red clay soil to occur. Long term visits (defined as six months) would not be sufficient exposure for podoconiosis occurrence. Based on the experts' suggestions, the indicators were revised. For treatment of lymphoedema, the experts indicated that the 90% target was low and suggested it should be raised to 95%. The indicator was revised to reflect this recommendation.

#### *7.2.4 Results of round 2 survey*

According to the ranking of the second round of the survey, all the case definitions and indicators reached consensus among experts (>70% consensus). As shown in Table 7.4, the median or mode ranged between 8 and 9 and the CV was less than 0.3 for all the indicators and definitions. These results indicated that the ranking in the second round survey had good central tendency for almost all the definitions, classifications and indicators.

**Table 7.0-4** Results of round 2 survey of Delphi process for the development of case definitions, endemicity classifications and elimination targets

| | Median | Mode | CV | Consensus (% score of >7) |
|---|---|---|---|---|
| **SECTION 1:** Case definition | | | | |
| **Suspected case:** Any lymphoedema (swelling caused by the collection of fluid in tissue) of the lower limb of any duration. (At this stage we do not expect to make a differential diagnosis but need to record the actual numbers of people with lymphoedema, even if a medical diagnosis has not been confirmed.) | 9 | 9 | 0.1 | 92.0 |
| **Probable case:** Any lymphoedema (swelling caused by the collection of fluid in tissue) of the lower limb present for more than 1 year in a resident of an endemic area. | 8 | 9 | 0.3 | 76.0 |
| **Confirmed case:** Lymphoedema of the lower limb present for more than 1 year in a resident of an endemic area, for which other causes have been excluded (onchocerciasis, LF, leprosy, Milroy syndrome, heart or liver failure, etc). | 9 | 9 | 0.1 | 96.0 |
| **SECTION 2:** Endemicity classification | | | | |
| **Non endemic** <1% prevalence among adults ≥ 15 years old | 9 | 9 | 0.3 | 76.0 |
| **Hypo-endemic** ≥1to <3% prevalence among adults ≥ 15 years old | 8 | 8 | 0.2 | 84.0 |
| **Meso endemic** 3 to<10% prevalence among adults ≥ 15 years old | 8 | 8 | 0.2 | 84.0 |
| **Hyper endemic** ≥ 10% prevalence among adults ≥ 15 years old | 9 | 9 | 0.2 | 88.0 |
| **SECTION 3: Elimination** | | | | |
| ***Elimination of podoconiosis from a district*** | | | | |
| The prevalence is less than 1 percent (among individuals ≥15 years old) after 10 years of program implementation. AND | 8 | 9 | 0.2 | 92.0 |
| More than 95 percent of lymphoedema cases are treated adequately after 10 years of program implementation. | 9 | 9 | 0.1 | 88.0 |
| ***Elimination of podoconiosis from a country*** | | | | |
| Prevalence of untreated podoconiosis is maintained at less than 1 percent (among individuals >15 years old) in 100 percent of sample villages over a 10 year period. AND | 8 | 9 | 0.2 | 84.0 |
| Prevalence of early signs of podoconiosis among children 10-15 years after 10 years of control program implementation is less than 1 in 10,000. AND | 9 | 9 | 0.2 | 88.0 |
| Greater than 95 percent of population in endemic districts wears protective shoes. AND | 9 | 9 | 0.2 | 84.0 |
| Greater than 95 percent of lymphoedema cases are treated adequately. | 8 | 8 | 0.1 | 84.0 |
| *Key indicators for the podoconiosis elimination monitoring* | | | | |
| **Prevalence of podoconiosis (%)=**Number of old and new cases of podoconiosis in the implementation unit (≥15 years) divided by total population ≥15 years old in the same area, times 100 | 9 | 9 | 0.1 | 96.0 |

| | | | | |
|---|---|---|---|---|
| **Case detection rate (%)=** Number of new cases of podoconiosis in the implementation unit divided by total population at risk in the same area, times 100 | 9 | 9 | 0.1 | 100.0 |
| **Treatment completion rate (%)**= Number of patients that completed the required duration of treatment divided by all new podoconiosis cases that started treatment in a given period, times 100 | 9 | 9 | 0.1 | 100.0 |
| **Coverage of shoe wearing (%)(point prevalence in sampled villages)=** Number of individuals wearing shoes (>1 years old) in implementation unit divided by total number of individuals >1 years old in the same area, times 100 | 9 | 9 | 0.1 | 92.0 |
| **SECTION 4: Monitoring clinical outcomes** | | | | |
| **Treatment completion:** A patient who has completed the full course of the initial treatment given at health facility/community level. | 9 | 9 | 0.1 | 96.0 |
| **Defaulter:** A patient who has been on treatment and whose treatment was interrupted for 2 or more consecutive months. | 9 | 9 | 0.2 | 96.0 |
| **Treatment Success:** Treatment is successful if an incapacitated patient can assume normal activities following treatment. | 9 | 9 | 0.2 | 92.0 |
| *Key indicators for monitoring progresses* | | | | |
| > 95% of population in endemic districts consistently wears protective shoes (measured for the last one year). | 9 | 9 | 0.2 | 92.0 |
| >90% of the population in the endemic districts practices proper foot hygiene* (measured for the last one year) (*proper foot hygiene is defined as washing once per day using soap and water over the period of one year) | 9 | 9 | 0.1 | 96.0 |

#### *7.2.5 Case definition of podoconiosis for surveillance*

Currently, podoconiosis is a disease of clinical diagnosis through exclusion of other causes of lymphoedema[228]. The major causes of lymphoedema in the tropics are LF and podoconiosis. However, leprosy, onchocerciasis and other systemic and genetic diseases may also cause lymphoedema and be confused with podoconiosis. The diagnosis of podoconiosis is based on history of where the swelling started from, the age at which swelling started and the presence of any family member with similar conditions. Clinical examination for the presence of moss, intact sensation in the lower leg, and the absence of swelling in the groin area (hydrocele) is also important. In addition, podoconiosis patients must be negative for all possible tests for LF. A case of podoconiosis is defined as a person from an endemic area with lymphoedema of the lower limb of more than one year duration for which other causes have been excluded. Based on the current Delphi survey, case definitions are given in Table 7.5.

**Table7.0-5** Case definitions of podoconiosis

| Cases | Definitions |
|---|---|
| **Suspected cases** | Any lymphoedema (swelling caused by the collection of fluid in tissue) of the lower limb of any duration. (At this stage we do not expect to make a differential diagnosis but need to record the actual numbers of people with lymphoedema, even if a medical diagnosis has not been confirmed). |
| **Probable podoconiosis case** | Any lymphoedema (swelling caused by the collection of fluid in tissue) of the lower limb present for more than one year in a resident of an endemic area. |
| **Confirmed podoconiosis case** | Case in a resident of an endemic area, with lymphoedema of the lower limb present for more than one year and for which other causes have been excluded (onchocerciasis, LF, leprosy, Milroy syndrome, heart or liver failure, etc). |

### *7.2.6 Endemicity threshold*

Based on recent literature[7,9,11,12,14,32-34,70,74] concerning the experience of other NTDs and the observed distribution of podoconiosis prevalence **(Figure 7.2)**, the following definitions are considered: Districts or villages with prevalence of >1 percent of podoconiosis among individuals ≥15 years would be termed endemic for podoconiosis. Those districts with prevalence greater than zero but less than 1% would be addressed via routine health services without the need for control programs.

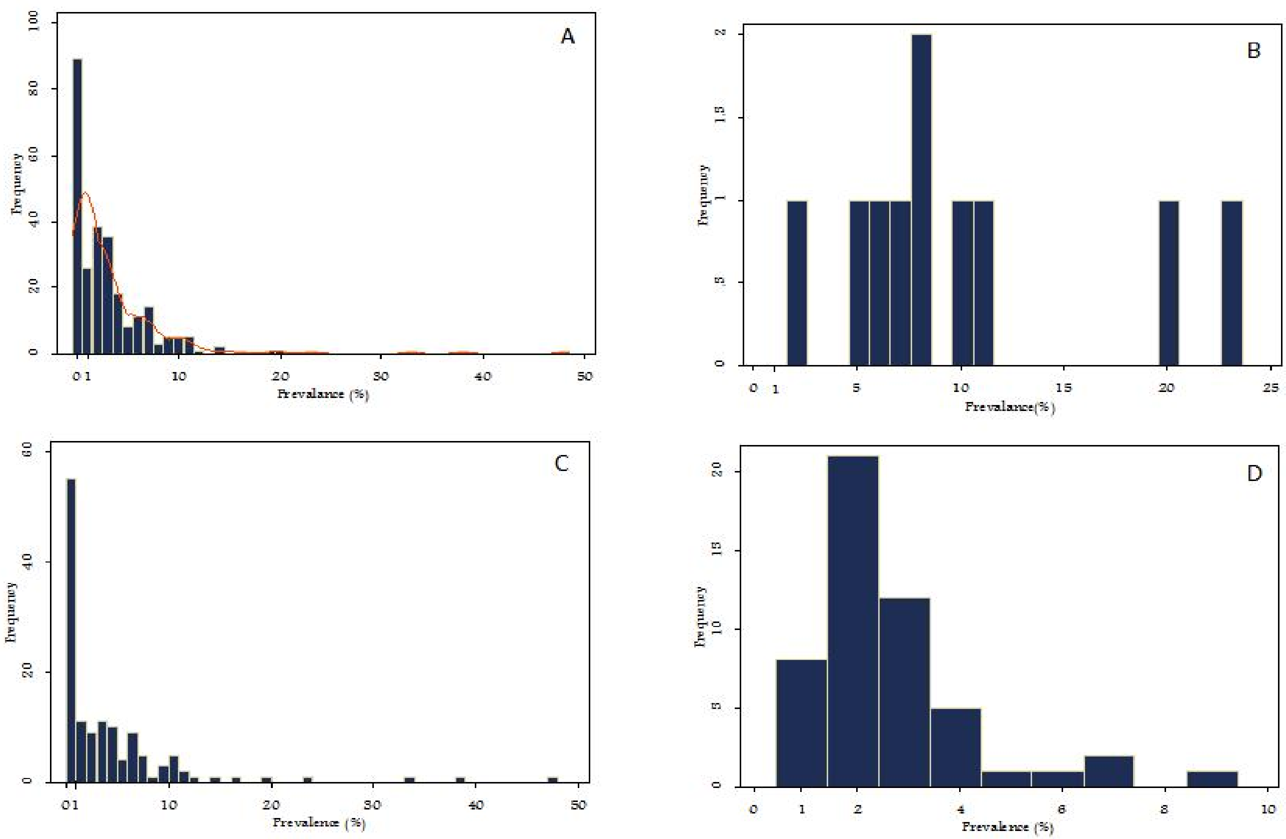


**Figure 7.2** Histogram of prevalence of podoconiosis using data from different countries with the bin width of 1 A) Overall histogram of prevalence data from 267 data points [7,9-15,32-34,70,74] B) data from Cameroon from 10 data points[33] C) Data from a large survey in Ethiopia prevalence data from 133 data points[74] D) Large survey from Ethiopia from 52 data points[7].

### *7.2.7 Endemicity classes for podoconiosis*

The sub-district prevalence of podoconiosis registered so far is 0-10%, with few observations greater than 10% **(Figure 7.2).** Therefore, the following classification (Table 7.4) is suggested based on data from different countries. The thresholds are meant more to prioritize endemic implementation units based on the overall prevalence, than to indicate any particular biological implications of disease occurrence. Mapping projects should still report the implementation unit prevalence.

### *7.2.8 Elimination targets*

It is proposed that podoconiosis is eliminated from an endemic district or implementation unit if the prevalence of untreated podoconiosis is less than 1% percent (among individuals ≥15 years old) and more than 95 percent of lymphoedema cases are treated adequately after 10 years of program implementation.

It is further proposed that podoconiosis is eliminated from a country when the following four targets are achieved:

1. Prevalence of untreated podoconiosis is maintained at less than 1 percent (among individuals≥15 years old) in 100 percent of sample villages over a 10 year period.
2. Prevalence of early signs of podoconiosis among children 10-15 years after 10 years of control program implementation is less than 1 in 10,000.
3. Greater than 95 percent of the population in endemic districts wears protective shoes.
4. Greater than 95 percent of lymphoedema cases are treated adequately.

Refer table 7.6 below on how each of the targets are measured.

The assumption here is that if the prevalence in an implementation unit is less than 1 percent, the formal health sector can manage patients reactively, provided the formal health sector is trained and equipped to do so, and prevention activities can be run by the health system, without the need for a control program.

### *7.2.9 Key indicators for podoconiosis elimination*

It is important for the global health community to recognize the disease burden, prevention and control of podoconiosis and its elimination target. Table 7.4 shows a proposed framework for countries based on the Delphi results to improve and accelerate their national podoconiosis programmes and promote neglected tropical disease and health system integration. This framework includes targets and indicators for actionable interventions for the prevention, treatment, and monitoring of podoconiosis control and elimination.

The target of podoconiosis elimination is to reduce the prevalence of podoconiosis in endemic districts to below 1%, to reduce the prevalence of early disease to less than 1 per 10,000 in children 10-15 years old, to treat 95% of lymphoedema cases and to increase shoe wearing practice to 95% in all endemic (sub) districts/implementation areas. Below are the important indicators and periods of measurement to monitor progress.

The first indicator is the case detection rate – tracking all new cases of podoconiosis in an area within a given year. These data can be obtained by including the case definition into the routine health management information system (HMIS) and the routine surveillance system. Alterative data sources include regular burden assessment surveys which list all cases of podoconiosis using house to house census. These surveys can be integrated with registration of individuals for Mass Drug Administration (MDA) for other NTDs.

The second indicator is the treatment completion rate. Unless people with podoconiosis adhere and complete their treatment, the backlog of lymphoedema will continue to be higher than the functional capacity of the routine health system. The target for treatment completion rate in any district should be above 90%. The third indicator is focused on prevention of podoconiosis i.e. proportion of individuals wearing protective shoes, which should be above 95%.

### *7.2.10 Monitoring clinical outcomes*

Measuring clinical outcomes of podoconiosis patients is a complex phenomenon. Although simple lymphoedema management for the cases exists, it is not properly evaluated or standardized. The duration of treatment, the follow-up frequency and duration are areas under research. Therefore, only three areas of clinical outcome areas are considered for definition, including treatment completion, defaulting treatment, and treatment success (Table 7.3). The rest will be defined once the ongoing randomized controlled trial (RCT) to test the effectiveness of 'standard' lymphoedema treatment is completed[45]. In addition, I provided the definitions and potential sources of the data in Table 7.6.

| Table 7.0-6 Indicators and sources of data | | |
|---|---|---|
| **Indicators** | **Measure** | **Data Source** |
| **SECTION 1:** Case definition | | |
| Number of suspected case | Number of suspected podoconiosis cases | Clinical record or HMIS |
| Number of probable case | Number of cases probable podoconiosis cases | Clinical record or HMIS |
| Number of confirmed case | Number of confirmed podoconiosis cases | Clinical record or HMIS |
| **SECTION 2:** Endemicity classification | | |
| Number of non-endemic implementation units | Number of non-endemic implementation units | Mapping and evaluation surveys |
| Number of hypo-endemic implementation units | Number of hypo-endemic implementation units | Mapping and evaluation surveys |
| Number of meso-endemic implementation units | Number of meso-endemic implementation units | Mapping and evaluation surveys |
| Number of hyper endemic implementation units | Number of hyper endemic implementation units | Mapping and evaluation surveys |
| **SECTION 3:** Elimination | | |
| ***Elimination of podoconiosis from an implementation unit*** | | |
| Prevalence of untreated podoconiosis (among individuals ≥15 years old) in endemic implementation unit | Prevalence of podoconiosis | Mapping and evaluation surveys |
| Percent of lymphoedema cases treated adequately | Percent of lymphoedema cases treated adequately | Evaluation surveys |
| Prevalence of early signs of podoconiosis among children 10-15 years in endemic implementation unit | Prevalence of early signs of podoconiosis | Mapping and evaluation surveys |
| Proportion of population in endemic implementation unit wearing protective shoes | Proportion of individuals wearing shoes. | Mapping and evaluation surveys |
| *Key indicators for podoconiosis elimination monitoring* | | |
| **Case detection rate:** Proportion of new cases of podoconiosis in the implementation unit | Proportion of new cases of podoconiosis in the implementation unit | Community based survey and Clinical record or HMIS |
| **Treatment completion rate:** Proportion of patients that completed the required duration of treatment divided by all new podoconiosis cases that started treatment in a given period | Proportion of patients that completed the required duration of treatment | Podoconiosis patient survey or Clinical record or HMIS |
| **SECTION 4:** Monitoring clinical outcomes | | |
| **Defaulter rate:** Percentage of patients with default treatment | Percentage of patients who experienced default treatment. | Podoconiosis patient survey and clinical record review or HMIS |
| **Treatment Success 1**: for advanced stage patients (podoconiosis clinical | Proportion of advanced stage patients who resumed normal | Podoconiosis patient survey and |

| | | |
|---|---|---|
| stage 3 or 4 or 5): proportion of advanced stage patient who can resume normal activities following treatment and maintained over a follow-up period of one year. | activities and maintained for 1 year period | clinical record review or HMIS |
| **Treatment Success 2**: for early stage patients (clinical stage 1 or 2): Proportion of patients with one stage decrease after completion of treatment and maintenance of this over a period of 1 year | Proportion of early stage patients who decreased one stage after completion of treatment and maintained for one year. | Podoconiosis patient survey and clinical record review or HMIS |
| *Key indicators for monitoring progresses* | | |
| Proportion of the population in the endemic districts practices proper foot hygiene (measured for the last one year). | Proportion of individuals who practice proper foot hygiene. | Community based survey |

## 7.3 Discussion

In a time of renewed global and national commitment to the elimination of podoconiosis, there are many things we still do not know. In 2011, WHO defined podoconiosis as one of the NTDs and included it under the ‘other conditions’ category[222]. While this is a step forward for the control of the disease, there were no clear targets or endemicity classifications. Such targets and definitions are important for the consolidated efforts to control podoconiosis. Historically, podoconiosis appears to have been eliminated from northern Africa due to socioeconomic development and widespread shoe-wearing practices[2].

Based on a Delphi technique, I defined the endemicity threshold for podoconiosis to be ≥1%, the underlying assumption being that in the absence of point of care diagnosis, overestimation of cases may occur. In areas where there is no podoconiosis or LF, the underlying prevalence of lymphoedema is approximately 0.1-0.5%[312]. Hence, a threshold of ≥1% will help account for residual lymphoedema cases. The second rationale for such a cut-off point is that even if the 1% cases are confirmed to be due to podoconiosis, the local health system can respond without the need for establishing a control program. Nonetheless, even in such cases, health providers working in the system should be given clear training and be equipped with the necessary supplies to provide care for podoconiosis-affected individuals. I have also classified the endemicity of podoconiosis. Evidence from national and small scale surveys indicates that the prevalence of podoconiosis ranges between 1-10% with few prevalence estimates >10% per district [32,33,74,251]. Classification into three endemicity classes will have several benefits; first, areas within the highest category will be prioritized for interventions; second, classes may serve as indicators for monitoring progress.

Based on the available prevalence data, I have produced an endemicity classification for podoconiosis. Areas with prevalence of podoconiosis <1% are considered to be non-endemic for podoconiosis. In these areas, treatment will be available in the routine health system without the need for a separate programme. Areas with prevalence of podoconiosis ≥1to <3% are considered to be hypo-endemic for podoconiosis, those with prevalence 3 to <10% meso-endemic and those with ≥10% to be hyper-endemic for podoconiosis. This classification was based on data available from several countries (Figure 7.2).

I have also produced strict (which address prevention of new cases and ensuring asses to prevalent cases) targets for monitoring the elimination of podoconiosis. Since there is no biological cause of podoconiosis, I could not assume transmission interruption. Thus, the focus was on access to preventive and treatment services. The combination of these criteria will avoid continued debates about the elimination targets such as those of leprosy. The target is comprehensive and addresses access to morbidity management for the backlog of cases and prevention of new disease (monitored through shoe wearing practice and new cases among children between 10-15 years of age). These stringent criteria will help to monitor progress while clearly addressing the existing needs for prevention and treatment. The evaluation of control and elimination programs was given a 10 year timeframe given the challenge of addressing the backlog of cases and addressing behavioural change with regard to preventive behaviours such as shoe wearing and regular foot hygiene practice. This will also enable monitoring of progress in reducing incident cases. Previous studies have indicated that at least 10 years is required for incident cases of podoconiosis to occur [13].

For the first time, I have developed a case definition for podoconiosis which can be used in the routine surveillance system. The sensitivity and specificity of the case definition must be evaluated in future studies. Nonetheless, with global movement towards integrated foot care services, identifying the specific causes of lymphoedema may not be necessary. Broad definitions will capture individuals with lymphoedema who may require foot care services to target health interventions. While the definition here is sufficient for surveillance purposes, those requiring identification of specific causes may conduct confirmatory tests to exclude other potential causes of lymphoedema, until podoconiosis-specific point-of-care diagnostic tools are developed.

Monitoring the clinical outcomes of podoconiosis is important. Clear end points for completion of treatment must be defined. Until the results of an ongoing randomized clinical trial are published, I have defined three outcomes based on current practices in the field. In Ethiopia, a patient is regarded as having completed treatment when he/she has followed supervised morbidity management for at least three months. Within these three months, if a patient misses two consecutive monthly clinical appointments, they are considered a defaulter. These end points are important in monitoring the success of morbidity management programs.

### 7.4 Looking ahead

WHO must take the lead in developing global strategy for the elimination of podoconiosis. This will help in advocacy, resource mobilization, political commitment and endemic country ownership. Such strategies must be based on the currently available evidence for both diagnosis and morbidity management services. A clearer case for investment must be provided for funding agencies and endemic country governments. The interventions for both prevention and treatment are simple, and short term goals such as restored function and improved quality of life can be achieved among lymphoedema cases after just three months of treatment [42,44]. Promotion of shoe wearing for podoconiosis prevention may have multiple health benefits.

Integrated morbidity management in the context of foot care may become an important approach to avoid duplication of efforts and to utilize the available resources efficiently. It is possible to integrate foot care services for podoconiosis with those for LF and leprosy. The continued challenge in providing morbidity management services at scale is the lack of skilled manpower in the health system. Most health providers in endemic counties lack knowledge and practical skills to address lymphoedema cases. Inclusion of morbidity management training in in-service and pre-service training curricula for health care providers will be important in scaling up and sustaining the services. Engaging national accreditation and credentialing bodies in efforts focused on the elimination of podoconiosis and inclusion of the subject in continued professional development are critical areas.

Access to treatment services for those in need is an important aspect of podoconiosis elimination. Currently the morbidity management services are provided by very few faith based organizations and NGOs in endemic countries[42,44]. Provision of free-of-charge or low-cost prevention and treatment through government programmes will be critical. Such approaches will support the ability of health workers to provide morbidity management services as a routine part of health service delivery, enabling universal access and sustainability. People with podoconiosis are often poor and marginalized due to their condition and introduction of user fees might hinder their access to the services.

Prevention of podoconiosis is an important component of its elimination. Promotion of shoe wearing as a health intervention should be advocated for. For those individuals who cannot afford shoes themselves, subsidized shoe distribution should be considered. This might be achieved through collaboration with shoe companies. A good example of such an initiative is the TOMS shoes approach, in which a pair of shoes is provided to a child at risk of podoconiosis for each pair sold elsewhere[313]. Extending similar collaborations to other shoe companies would be beneficial.

Finally, continued research should focus on identifying point-of-care diagnostic tools for podoconiosis to ascertain cases and verify elimination. At the start of elimination programs, definitive diagnosis may not be a priority, but as the 'end game' approaches, robust, sensitive and specific diagnostic tests will be required. In the earlier phases of elimination, a syndromic approach may suffice for the diagnosis of podoconiosis. In the long term, identification of biomarkers of podoconiosis will be vital.

## 7.5 Conclusion

Untreated lymphoedema due to podoconiosis causes significant deformity, disability, social and productivity loss in endemic countries. These disabilities are preventable with simple preventive measures (consistent shoe wearing and foot hygiene)[251,295] and early lymphoedema morbidity management[44]. These simple interventions can be integrated into the health system and delivered at low cost. It is time to capitalize on the experience of some endemic countries and provide the intervention sustainably and at scale. Therefore, I call for a global strategy for the elimination of podoconiosis, a clear case for investment potential to identify the resources needed to achieve podoconiosis elimination in endemic countries. Defining elimination targets and endemicity classification is critical for mobilizing communities and stakeholders and ensuring accountability in relation to elimination of podoconiosis. The indicators described here may serve as a starting point towards a global strategy for podoconiosis elimination.

# Chapter 8. Discussion

## 8.1 Overview

This thesis used existing data and generated new nationwide podoconiosis distribution data in Ethiopia to understand the individual and environmental risk factors of podoconiosis, to describe the geographical distribution of the disease, to estimate the population-at-risk and to define disease endemicity thresholds and elimination targets. The results of this thesis have already been used by the national podoconiosis control programme in Ethiopia. The national goal is to eliminate podoconiosis from Ethiopia by 2030[26]. The thesis findings have been used by the national NTD programme for the revision of Ethiopia's NTDs Master Plan (2016-2020), Health Sector Transformation Plan (2016-2020) and envisioning 2035 (Envisioning Ethiopia's Path Towards Universal Health Coverage Through Strengthening Primary Health Care). The results identified endemic districts requiring intervention and estimated the population-at–risk, which is the basis for planning interventions and monitoring future control activities. The resulting maps give an accurate description of the observed distribution of podoconiosis in Ethiopia and provide decision-makers with the information that can be used to prioritise districts for targeted podoconiosis control activities and resource allocation. In this chapter, the principal findings of the thesis will be synthesised and their interpretation discussed. The implications of the findings for future mapping will be presented with recommendations and alternative approaches. Finally, recommendations for the future direction of this work as it relates to research and practice in Ethiopia and more widely will be described.

## 8.2 Principal findings

In Chapter 2, a review of NTDs and their control in Ethiopia was conducted. The review showed that NTDs are a significant public health problem in Ethiopia. Ethiopia has the highest number of NTD cases in sub-Saharan Africa following Nigeria and the Democratic Republic of Congo. Ethiopia is estimated to have the highest burden of trachoma, podoconiosis and cutaneous leishmaniasis in sub-Saharan Africa, the second highest burden of ascariasis, leprosy and visceral leishmaniasis, and the third highest burden of hookworm. Infections such as schistosomiasis, trichuriasis, lymphatic filariasis (LF) and rabies are also common. A third of Ethiopians are infected with *Ascaris lumbricoides*, one quarter are infected with trichuriasis and one in eight Ethiopians lives with hookworm or are infected with trachoma. Despite the high burden of these infections, the control of most NTDs in Ethiopia was still limited in 2012. There were no national deworming school programmes for school-aged children, trachoma interventions were mostly limited to three Regional States[114], and there was no schistosomiasis control programme [314]. Mapping of most NTDs had not yet been conducted. Nonetheless, there were some disease-specific successes Ethiopia reached the leprosy elimination target of 1 case/10,000 population in 1999. No cases of human African trypanosomiasis had been reported since 1984. Guinea worm eradication is in its final phase. The Onchocerciasis Control Programme has been making steady progress since 2001. A national blindness survey was conducted in 2006 and the trachoma programme has started in some regions. Some small scale surveys of LF and podoconiosis had been conducted but mostly focused on suspected endemic foci; thus, there was a need for national level mapping of both diseases.

Chapter 3 presented a spatial analysis of available data on the prevalence and distribution of podoconiosis in Ethiopia, based on a systematic review of the published and unpublished literature. The results highlighted both the paucity of available data and the marked regional variation in the distribution of podoconiosis. The data points are concentrated in areas potentially thought to be endemic for podoconiosis, which has implications for prediction models. The analysis identified significant associations between a high prevalence of podoconiosis and a range of environmental factors, including mean annual air temperature, mean annual precipitation, topography of the land and fine soil texture. Although the collated data provided important information on the historical distribution of podoconiosis, most of the data used were collected approximately 40 years ago and may not represent the contemporary distribution of podoconiosis. Thus, there was a need for well-designed contemporary nationwide mapping data of podoconiosis in Ethiopia.

To overcome the lack of data, I led the design, conduct and analysis of an integrated nationwide mapping of podoconiosis and lymphatic filariasis. Chapter 4 described the methods used and documented important lessons for future similar mappings. The integrated mapping of 1,315 communities across Ethiopia was accomplished in a short period of time (June 2013 to October 2013). Within these communities, 129,959 individuals provided blood samples that were tested for circulating *Wuchereria bancrofti* antigen using immunochromatographic card tests (ICT). A clinical algorithm was used to reliably diagnose podoconiosis by excluding other potential causes of lymphoedema of the lower limb. A total of 8,110 individuals with leg swelling were interviewed and underwent physical examination. Smartphones linked to a central database were used to collect data, which facilitated real-time data entry and reduced costs compared to a traditional paper-based data collection approach; their inbuilt GPS function enabled simultaneous capture of geographical coordinates. This integrated approach led to an efficient use of resources and rapid mapping of an enormous geographical area. It was well received by survey staff and collaborators. The experience of the survey showed that mobile-based technology is a valuable tool for such large-scale studies and can be used in resource-constrained settings such as Ethiopia, with minimal challenges.

Using the collected survey data, chapter 5 explored individual and cluster level risk factors of podoconiosis which were associated with the underlying distribution of podoconiosis. I used Bayesian multilevel models to identify individual and environmental risk factors. Overall, 8,110 (6.2%; 95% confidence interval [CI] 6.1-6.4%) surveyed individuals were identified with lymphoedema of the lower limb, of whom 5,253 (4.0%; 95% CI 3.9-4.1%) were confirmed to be podoconiosis cases. In a multivariable analysis, being female, older, unmarried, washing the feet less frequently than daily, and being semi-skilled or unemployed were significantly associated with an increased risk of podoconiosis. Attending formal education and living in a house with a covered floor were associated with a decreased risk of podoconiosis. Podoconiosis exhibits marked geographical variation across Ethiopia, with variation in risk associated with variation in rainfall, enhanced vegetation index and altitude. These findings confirmed the variation of podoconiosis risks related to both individual and environmental factors. These associations suggest that individual and environmental factors could be used to extrapolate existing data and target those with increased risks of the diseases.

Chapter 6 combined data from two surveys: integrated mapping of podoconiosis and LF conducted in 2013, and an earlier mapping of LF in western Ethiopia from 2008-2010. The data included 1,442 communities in 775 districts from all nine regional states and two city administrations in Ethiopia. In 41.9% of surveyed districts, no cases of podoconiosis were identified, including districts in Affar, Dire Dawa, Somali and Gambella regional states. The disease was most common, with lymphoedema positivity rate exceeding 5%, in the central highlands of Ethiopia, in Amhara, Oromia and Southern Nations, Nationalities and Peoples regional states. Boosted regression tree (BRT) modelling indicated that the probability of podoconiosis occurrence increased with increasing altitude, precipitation and silt fraction of soil and decreased with population density and clay content. Based on the BRT model, we estimated that 34.9 (95% CI: 20.2-51.7) million people (i.e. 43.8%; 95% CI: 25.3-64.8% of Ethiopia's national population) lived in areas environmentally suitable for the occurrence of podoconiosis in 2010. Podoconiosis is more widespread in Ethiopia than previously estimated, but it occurs in distinct geographical regions that are tied to identifiable environmental factors. The resultant maps can be used to guide programme planning and implementation and estimate disease burden in Ethiopia. This work provides a framework with which the geographical limits of podoconiosis could be delineated at a continental scale, and deserves more careful attention.

Chapter 7 described a Delphi technique used among 28 experts to develop a case definition of podoconiosis, endemicity classifications and elimination targets. A questionnaire outlining possible case definitions, endemicity classifications and elimination targets was provided to participants in the Delphi panel. The resultant work lead to potential indicators for monitoring elimination, clinical outcomes and endemicity classifications for this disabling disease. A case definition for podoconiosis was developed for the first time. Defining elimination targets and endemicity classifications is critical for mobilizing communities and stakeholders and ensuring accountability in relation to the elimination of podoconiosis.

### 8.3 Limitations of the studies

Chapter 3 presented retrospective studies including market- and school-based surveys with large sample sizes. The market-based survey has several limitations: first, patients with the condition might not present themselves to the market either because of fear of stigma or lack of mobility as compared to healthy individuals. In addition, there could be measurement error in the diagnosis of podoconiosis since the included historical papers were conducted using observation of any leg swelling which could lead to an overestimated number of podoconiosis cases.

In our subsequent mapping study, we targeted a large sample size in most districts in Ethiopia. The purpose of the survey was to study the geographical distribution of podoconiosis rather than to estimate its prevalence at the district level. We used a pre-tested data collection format for the survey in addition to well-trained data collectors and supervisors. The diagnosis of podoconiosis was based on a panel approach including history, physical examination and ICT test. We used health providers to collect the data and smartphones were used for data collection to reduce error. Possible limitations of this mapping exercise include the non-random selection of included communities leading to potential selection bias. We purposively selected high-risk communities to participate in the study. However, this type of community selection was used due to practical and methodological considerations. The WHO guidelines for the mapping of LF recommends selection of one community purposively for mapping[235]. The other potential bias is self-selection bias because individuals were mobilized to gather at the central location of the village for systematic random sampling. This could introduce selection bias if individuals with any illness self-select themselves to the central place in anticipation of getting treatment, such as patients with lymphoedema. However, we blinded the participants to the purpose of the study during mobilization to avoid such a bias. Confounding is a mixing of the true effect due to a third factor – a confounder which is associated both with the exposure and the outcome. Therefore, potential confounders need to be controlled for. We used multivariate techniques to address this issue. For instance, the effect of environmental factors was controlled for numerous individual factors and the underlying spatial structure. There might be other potentially confounding factors which were unaccounted for in our model, such as genetic susceptibility.

## 8.4 Future directions

The availability of historical data on podoconiosis is low. Nonetheless, where data are available, they provide important information and are consistent with more contemporary data. The historical data found in Ethiopia reflect findings in contemporary surveys. This highlights the potential utility of historical data. However, such historical data arose from geographically limited areas, so there was a need for generating new data to map the distribution of podoconiosis in other endemic countries.

In the current study, we have identified both individual and environmental risk factors of podoconiosis. Evaluation of podoconiosis risk factors in different contexts will be important to understand the universality of these risk factors. While this thesis identified risk factors in much of Ethiopia, characterising the distribution of podoconiosis within a given district remains important. Risk factors might differ at different scales, and identifying risk factors at the district level (behavioural and socioeconomic factors) could help to better target high-risk communities and identify appropriate interventions.

Future research is needed to build on the findings of this thesis in three important areas. First, the global mapping of podoconiosis is a prerequisite for the scaling up of podoconiosis control and elimination efforts. The contemporary global distribution of the disease is not well understood. Except for Ethiopia[276] and Rwanda (Umulisa I, personal communication, Malaria and Other Parasitic Diseases Division, Rwanda Biomedical Center Kigali, Rwanda), where nationwide mapping had been conducted in 2013, no other endemic country has conducted a nationwide survey. The three-pronged approach to mapping and defining the distribution of podoconiosis in Ethiopia could be replicated at a global scale. We started by searching for the available literature and defining the historical distribution and limits of the disease in the country. Next, we used empirical data to identify districts endemic for podoconiosis and finally, we used a predictive model driven by data to delineate the environmental limits of the disease and to estimate the population-at-risk. Future mapping activities could potentially be guided by environmental factors predictive of podoconiosis and developed risk maps. Validating the environmental drivers of podoconiosis found in Ethiopia would be the first step to extending the findings beyond Ethiopia. If similar environmental drivers are found in other countries, this supports the potential for predictive mapping of podoconiosis in other endemic countries.

Second, estimating the burden of podoconiosis is another area in which to focus future research. Burden of disease estimates provide comparable indicators across diseases and injuries, based on standardized summary measures [101]. The recent inclusion of podoconiosis in the Global Burden of Diseases 2015 estimation is a major step forward. Future work should generate disability weight measurements for sequelae of podoconiosis which will enable estimation of Disability Adjusted Life Years. This work needs to be based on data on the global distribution of podoconiosis, which can be collected using the mapping approaches developed in this thesis.

Third, efforts to define elimination targets may lead to investment in podoconiosis elimination efforts. Elimination is an appealing goal, but careful consideration of the cost and feasibility of such efforts is important. There is a need for objective measurements to monitor the elimination of podoconiosis. Comprehensive evaluations of the feasibility of elimination for malaria[315,316] and STH[317] could be adapted for use in the case of podoconiosis. The capacity of endemic countries for elimination of podoconiosis can be assessed using important interventions and delivery capacity at the country level. The cost-effectiveness of elimination should also be evaluated in economic terms for both advocacy, policy and planning purposes.

## 8.5 Conclusion

This thesis has provided a systematic and detailed investigation of the spatial epidemiology and individual and environmental risk factors of podoconiosis in Ethiopia. Podoconiosis is widely distributed in Ethiopia and poses a significant disease burden, more than previously estimated. There is variation in the risk among individuals. The distribution of the disease is tied to certain environmental characteristics. The findings of this thesis identified endemic districts for targeted interventions and quantified the population-at-risk to inform planning, monitoring and evaluation of podoconiosis control programmes in Ethiopia. The resulting maps provide a sound epidemiological basis for guiding the country's investment in podoconiosis control and elimination efforts. Our predictive model and environmental factors identified in this study can form a framework for risk mapping of podoconiosis in other suspected endemic countries. The elimination targets can serve as an initial point for the global strategy of podoconiosis elimination. There continues to be a great need for further investigation of the spatial variation of the disease within a district, and of risk factors in smaller areas or different contexts to understand the universality of these risk factor findings.  Global elimination efforts need to be preceded by mapping the global distribution of podoconiosis and evaluation of cost-effectiveness of elimination.

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# Supplementary materials

**Supplementary material 4.1**

**Mapping of Podoconiosis in Ethiopia Field Protocol, 2013**

***Summary***

Lymphatic filariasis (LF) and podoconiosis are Neglected Tropical Diseases, these two cause tropical lymphoedema that results in range of temporary and permanent disabilities. Both of the diseases are associated with the disfigurement of grossly swollen limbs and results in stigma for people suffered from it.

Early 2012 International Podoconiosis Initiative was launched with the vision of "elimination of podoconiosis in our life time". In Ethiopia prevention of the disease through promotion and distribution of shoe for school age children and simple lymphoedema managements are showing promising results. To kickoff a global elimination of podoconiosis identifying endemic countries and mapping the distribution of the disease is a pre requisite.

While efforts to control of podoconiosis are continuing, none of podoconiosis endemic countries completed mapping.  Podoconiosis are endemic in Ethiopia and were recently included in the National Master Plan (2012-2015) for NTDs, yet control of the disease at national or sub national level is still at its infancy. The Ethiopian Federal Ministry of Health (FMoH) has recognized podoconiosis as priorities for control, and indicated that a nationwide mapping is the first step. So, this survey aims to generate a complete map of podoconiosis distribution in Ethiopia.

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## 1. Introduction

There are two principal causes of elephantiasis, or lymphedema, in the tropics [1]. The most common cause and a significant public health problem is lymphatic filariasis due to the parasitic nematode Wuchereria bancrofti (and, in Asia, Brugia malayi and B. timori), which is transmitted by mosquitoes [2]. The second principal cause is podoconiosis: a form of elephantiasis arising in barefoot subsistence farmers who are in long term contact with irritant red clay soil of volcanic origins [3].

Podoconiosis (endemic non-filarial elephantiasis) is a non-infectious geochemical disease arising in barefoot subsistence farmers who are in long-term contact with irritant red clay soil of volcanic origins. The disease causes progressive bilateral swelling of the lower legs. Mineral particles absorbed through skin are taken up into macrophages into the lymphatic system and result in an inflammatory process leading to fibrosis and obstruction of the vessels. This leads initially to swelling of the foot and the lower leg, which progresses to elephantiasis: gross lymphoedema with mossy and nodular changes of the skin [4]. Podoconiosis affects some 4 million people in Africa, Latin America, and a few areas of Asia. It is found in more than ten countries across tropical Africa where irritant soils have been generated by environmental conditions of high altitude (>1,000m) and high annual rainfall (>1,000mm), and are farmed by very poor people who cannot afford shoes or water [4].

Podoconiosis has significant economic impact, according to a study in Ethiopia it was found out that the disease results in productivity loss. Total direct costs of podoconiosis amounted to the equivalent of US$ 143 per patient per year. Total productivity loss for a patient amounted to 45% of total working days per year, and in a zone of 1.5 million people, the total overall annual cost of podoconiosis was calculated to exceed US$ 16

**Table S4.1.1** Podoconiosis prevalence surveys conducted in Ethiopia between 1969 and 2012

| Publication year | Place of study | Number of individuals | Data points | Type of survey |
|---|---|---|---|---|

million per year [5]. In addition the disease is known to be stigmatized with significant social exclusion[6].

| | | **sampled (prevalence)** | | |
|---|---|---|---|---|
| 1969 [7] | Multiple sites | 247,908(2.72%) | 56 | Market survey( visible leg swelling) |
| 1973 [8] | Multiple sites | 13,138(2.77%) | 26 | School enquiry |
| 1987 [9] | Ocholo, Southwest Ethiopia | 2689(5.4%) | 1 | Community based( physical examination) |
| 1992 [10] | Gera & Didessa, Western Ethiopia | 416(7.5%) | 2 | Community based(Physical examination) |
| 1997 [11] | Pawe Northwest Ethiopia | 1,900(7%) | 1 | Community based( Physical examination and microscopic examination of midnight sample) |
| 2003 [12] | Wolita zone, Southern Ethiopia | 33,678(5.46%) | 7 | Community based( physical examination) |
| 2011 [13] | Gulisso west Ethiopia | 38,420(5.2%) | 1 | Community based(physical examination) |
| 2012 [14] | Midakegni | 1,656(7.4%) | 1 | Community based(physical examination) |
| 2012 [15] | Debre Elias and Dembecha Northern Ethiopia | 50,620(3.3%) | 2 | Community based(physical examination) |
| 2012 [16] | Western Ethiopia in 112 Woredas | 11,249(4.6%) | 133 | Community based(ICT card) |
| Total | | 401,646(3.4%) | 229 | |

It is estimated that Ethiopia bears one fourth (1million) of podoconiosis cases in the world [3]. According to a recent review the prevalence of podoconiosis stands at 3.4 %( predominantly data from high prevalence areas) in the country with varying prevalence ranging from 0 to 48%. The disease is widely distributed in the highlands of Ethiopia extending from north to south of the country. High prevalence areas are characterized by mean altitude >1500masl, temperature between 19-21°C, mean annual rain fall >1500mm and mean annual precipitation >130mm [17].

GIS and Remote Sensing is becoming very important for capturing landscape epidemiology in cost effective and efficient manner, because it enables high order analysis of environmental variables related to the diseases incidence. Disease mapping has been greatly enhanced by the use of geographical information systems (GIS) and remote sensing (RS) over the past two decades. GIS has enabled data to be georeferenced, stored, extracted, integrated in new ways and displayed by the user [18]. The availability of accurate and current maps with clear geographical distribution will leads to cost-effective interventions [19].

## 2. The Need for Mapping

Podoconiosis is preventable if shoes are consistently worn, and early stages can be successfully treated using a simple lymphoedema regimen [20]. While one million people are estimated to be affected with podoconiosis in Ethiopia, and a further 19.2 million at risk[21], control efforts are hampered by a lack of information on geographical distribution – aside from recent isolated studies, the only previous mapping of this disease was based on podoconiosis cases from market and school surveys in 1970s [21].

Mapping distribution of podoconiosis is crucial for a number of reasons. Areas without risk of the two diseases need to be identified, while endemic areas need to be delineated and integrated into the elimination and control program. It is also important to define the size of the population at risk of podoconiosis in the country, both enabling effective planning and careful use of scarce resources.

## 3. Objective of the Study

The objective of the survey are

- To map the distribution of podoconiosis in Ethiopia.
- To develop a endemicity map of podoconiosis in Ethiopia
- To estimate the population at risk for podoconiosis in Ethiopia

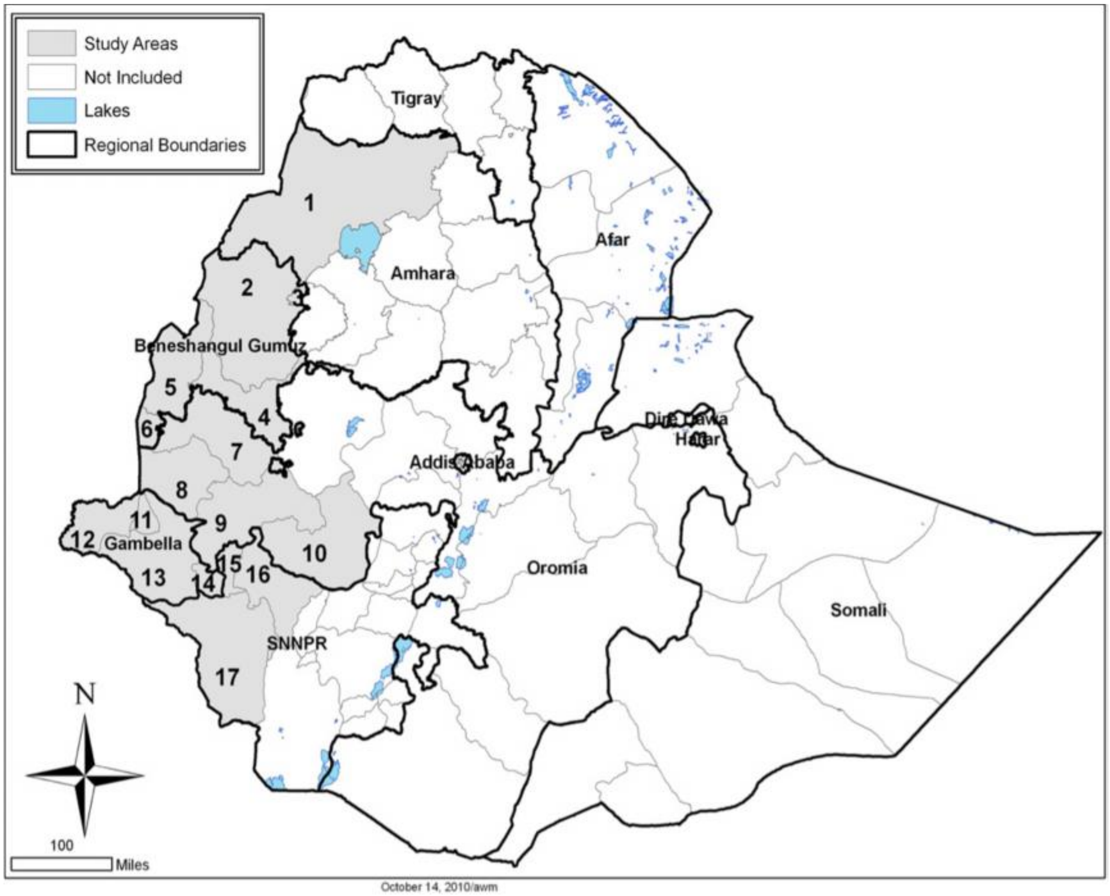


**Figure S4.1.1** District level administrative division and status of LF mapping in Ethiopia [16].

## 4. Materials and Methods

### 4.1 Study area and period

This study aims to complete the already started mapping of LF in Ethiopia. The study will cover Afar, Amhara, Tigray, Oromia, Somali, Dire Dawa, SNNPR and Harari regions of Ethiopia. The study will be conducted from January – June 2013.

The study will cover those unmapped woredas (districts) indicated in the map below **(Figure S5.1.1).** Ethiopia has a federal system of administration with nine regional states and two city administration councils. The Regional states/city administrations are sub divided into Zones, districts (Woredas) and kebeles (subdistrict) hierarchically. In total there are 817 woredas in Ethiopia. A woreda/district is the country's basic decentralized administrative unit and has an administrative council composed of elected members. The 817 woredas are further divided into about 16,253 *kebeles*. There are three broad ecologic zones in Ethiopia, that follow the topography: the "kola" or hot low lands are found approximately below 1500 meters, the "weyna dega" between 1500-1750 meters and the "dega" or the cool temperate highlands above 1750 meters. It is estimated that about 75% of the land in Ethiopia is malarious and 65% of the population is living in this area.

112 woredas were mapped for LF in 2008 and the results are shown in the map below. 13 districts are planned to be mapped by Addis Ababa University.

**Table S4.1.2.** The woredas and Zones of Ethiopia and the number of woredas mapped for lymphatic filariasis

| **Study zones** | **Number of Woredas** | **No of Woredas mapped** | **Remark** |
|---|---|---|---|
| **Tigray** | **47** | **0** | |
| North Western | 8 | 0 | |
| Central Tigray | 13 | 0 | |
| Eastern Tigray | 9 | 0 | |
| Southern Tigray | 11 | 0 | |
| Western Tigray | 4 | 0 | |
| Mekele Special | 2 | 0 | |
| **Afar Region** | **33** | **0** | |
| Zone 1 | 8 | 0 | |
| Zone 2 | 8 | 0 | |
| Zone 3 | 7 | 0 | |
| Zone 4 | 5 | 0 | |
| Zone 5 | 5 | 0 | |

**Table S4.1.2.** The woredas and Zones of Ethiopia and the number of woredas mapped for lymphatic filariasis

| Study zones | Number of Woredas | No of Woredas mapped | Remark |
|---|---|---|---|
| **Amhara Region** | **153** | | 4 woredas were mapped (Metema, Quara, Tacharmach ihoo and West Armachiho) |
| North Gonder | 23 | 4 | |
| South Gonder | 12 | 0 | |
| North Wello | 12 | 0 | |
| South Wello | 22 | 0 | |
| North Shewa | 24 | 0 | |
| East Gojam | 18 | 0 | |
| West Gojam | 15 | 0 | |
| Waghimra | 7 | 0 | |
| Awi | 11 | 0 | |
| Oromia | 7 | 0 | |
| Bahir Dar Special | 1 | 0 | |
| Argoba Special Woreda | 1 | 0 | |
| **Oromia Region** | **308** | **54** | |
| East Wollega | 18 | 0 | |
| Ilubabor | 24 | 19 | 19 woredas were mapped |
| Jimma | 19 | 13 | 13 woredas were mapped |
| West Shewa | 19 | 0 | |
| North Shewa | 15 | 0 | |
| East Shewa | 15 | 0 | |
| Arsi | 26 | 0 | |
| West Harerge | 16 | 0 | |
| East Harerge | 22 | 0 | |
| Bale | 20 | 0 | |
| Borena | 14 | 0 | |
| South West Shewa | 13 | 0 | |
| Guji | 15 | 0 | |
| Adama Special Zone | 1 | 0 | |
| Jima Special Zone | 1 | 0 | |
| West Arsi | 14 | 0 | |
| KelemWollega | 11 | 10 | 10 woredas were mapped |
| Horogudru | 10 | 0 | |
| Finfine Zuriya | 14 | 0 | |
| West Willega | 21 | 12 | 12 woredas were mapped |
| **Somali Region** | **72** | | |

**Table S4.1.2.** The woredas and Zones of Ethiopia and the number of woredas mapped for lymphatic filariasis

| Study zones | Number of Woredas | No of Woredas mapped | Remark |
|---|---|---|---|
| Shinile | 7 | 0 | |
| Jijiga | 8 | 0 | |
| Gegehabur | 10 | 0 | |
| Warder | 5 | 0 | |
| Korahe | 6 | 0 | |
| Fik | 10 | 0 | |
| Gode | 10 | 0 | |
| Afder | 10 | 0 | |
| Liben | 6 | 0 | |
| **Benshangul G Region** | **21** | **17** | |
| Metekel | 7 | 4 | 4 woredas were mapped |
| Assosa | 8 | 7 | 7 woredas were mapped |
| Kamashi | 5 | 5 | all woredas were mapped |
| Mao Komo special wereda | 1 | 1 | one/only woreda was mapped |
| **SNNPR** | **158** | **26** | |
| Gurage | 15 | 0 | |
| Hadiya | 11 | 0 | |
| Kembata | 8 | 0 | |
| Sidama | 22 | 0 | |
| Gedeo | 8 | 0 | |
| Wolayita | 15 | 0 | |
| South Omo | 9 | 0 | |
| Sheka | 5 | 5 | all woredas were mapped |
| Keffa | 11 | 10 | 10 woredas were mapped |
| Gamogofa | 17 | 0 | |
| Bench Maji | 11 | 11 | all woredas were mapped |
| Special woredas | 5 | 0 | |
| Dawro | 6 | 0 | |
| Silti | 9 | 0 | |
| Hawassa city | 1 | 0 | |
| Segen | 5 | 0 | |
| **Gambella Region** | **13** | **11** | |
| Agnewak | 6 | 5 | 5 woredas were mapped |
| Nuwer | 5 | 5 | all woredas were mapped |
| Mezenger | 2 | 0 | |
| Etang Woreda | 1 | 1 | one/only woreda was |

**Table S4.1.2.** The woredas and Zones of Ethiopia and the number of woredas mapped for lymphatic filariasis

| Study zones | Number of Woredas | No of Woredas mapped | Remark |
|---|---|---|---|
| | | | mapped |
| **Harari All Woreda** | **9** | **0** | |
| **Dire Dawa** | **8** | **0** | |
| **Addis Ababa** | **10** | **0** | |
| **Total** | **833** | **112** | |

## 4.2 Study design

The survey is a population based cluster cross sectional study.

## 4.3 Source population

The source population constitutes all individuals living in the selected woredas/districts of Ethiopia.

## 4.4 Study population

Individuals > 15 years old randomly selected from the residents in the selected village will be the study population.

## 4.5 Inclusion and exclusion criteria for study subjects

4.5.1 **Inclusion criteria:** To be included in the sample, people should have lived in the area for at least ten years, and be greater than or equal to 15 years old

4.5.2 **Exclusion Criteria:** individuals who lived in the area for less than 10 years, or who left the area for at least 6 months will be excluded from the study. The following will be excluded from the study:

- Terminally ill patients who cannot respond for the interview.
- Patients with a mental health condition that makes interview difficult
- Severely sick (eg. high fever)

## 4.6 Sampling strategy

All woredas that have not been mapped previously or planned to be mapped will be included in the study. In total 692 woredas will be mapped.

The methods that are going to be applied for the project will be composed of two broad categories. Namely: data collection phase and data analysis phase.

## 4.7 Data collection

All districts (Woreda) that have not been mapped before will be included making a total of 692. From each woreda, 2 kebeles will be selected. The selection of the kebeles will be guided by the health care facilities based on the presence of clinical cases (hydrocele or lymphoedema) from the selected Kebeles; communities (gotts) will be selected based on the previous knowledge clinical cases. Sensitization training will be given to the *gott* representatives and health extension workers for the selected gotts. At least 2 communities will be selected in each Woreda. 100 volunteers will be included (50 women and 50 men) older than 15 years old. 100 participants will be tested using ICT-Card in each gott. When conducting the survey if 20 positives are found after testing the first 50 individuals the survey can stop and the gott will be consider to be endemic.

In some *woreda*s, the *Woreda* Health Office may have additional information, such as frequent reports of hydrocoeles or lymphoedema that strongly suggests that filariasis or podoconiosis is endemic in specific villages. Before undertaking the survey, the survey team will visit the *Woreda* Health Office and seek information, if available, on the villages which are most likely to be endemic. The 2 villages most likely to be endemic according to the *Woreda* Health Office will be selected. Initially we thought adaptation of the WHO 2000 mapping guideline through selection of one village randomly and the other as a check village, however through discussion with experts from WHO and we opted to select two villages with anecdotal cases of hydrocoeles or lymphoedema. This method will increase the yield of detecting high-risk communities for both LF and podoconiosis.

**Table S.4.1.3** Administrative structures and numbers in Ethiopia

| SN | Regions | Number of Zones | Number of Woredas | Number of Woredas Mapped for LF | Woredas not map*ped* |
|---|---|---|---|---|---|
| *1.* | Addis A*baba* | *1* | 10 | 0 | 10 |
| 2. | Afar | 5 | 33 | 0 | 33 |
| 3. | Amhara | 11 | 153 | 4 | 149 |
| 4. | BenishangulGumuz | 3 | 21 | 17 | 4 |
| 5. | Dire Dawa | 2 | 8 | 0 | 8 |
| 6. | Gambella | 3 | 13 | 11 | 2 |
| 7. | Harari | 1 | 9 | 0 | 9 |
| 8. | Oromia | 18 | 308 | 54 | 254 |
| 9. | SNNPR | 15 | 158 (5sp) | 26 | 132 |
| 10. | Somali | 9 | 72 | 0 | 72 |
| 11. | Tigray | 5 | 47 | 0 | 47 |
| | Total | 70* | 833** | 112 | 721 |

* *Rec*ently, most of the large cities in the country have been delineated as special zones, increasing the total number of zones in the country to 94.

** Some woredas ha*ve rec*ently split, leading to a slight increase in total number of woredas from 817 in official reports in 2011

For podoconiosis, Ethiopia will be divided into three strata: high risk, medium risk and no information (low risk). To detect a prevalence of 0.5% with 0.25% precision (i.e. to produce a 95% confidence interval between 0.25% and 0.75%) with 80% power, and assuming a design effect of 2 and 10% non-response rate, we calculated that in each stratum, 6,728 individuals from 135 villages should be included, thus a total of 20,184 individuals from 405 villages will be included in the survey. Based on this sample size, the LF sampling will also be sufficient to address the objectives of podoconiosis mapping.

## 4.8 Study participants

After explaining the purpose of the study to the village leaders and obtaining their permission, all resident adults of the village (over 15 years old) will be asked to gather at a convenient point. The study will be explained in local language, and those willing to participate will be asked to form two lines, one o males and another of females. Fifty individuals will be randomly selected from each line using systematic sampling, resulting in an overall sample of 50 males and 50 females. Data will be recorded on the data sheets as soon as the participant is selected. Data sheets have been developed by CNTD for this activity.

### 4.9 Identification of participants

A simple questionnaire will be used to record age, sex, education, occupation, place of residence and the test result of ICT of all individuals involved in the study. For those individuals with lymphoedema, a simple checklist will be used to examine for possible differential diagnosis of podoconiosis. In those clinically confirmed to have podoconiosis, duration of illness, shoe wearing practice and disease stage will be recorded. The tool will assess the progression of the swelling, and check for a history of rheumatic heart disease. In addition, information from physical examination including preservation of sensation in the toes, clinical signs of leprosy or onchocerciasis, and groin involvement will be recorded. Screening of the study population for the main signs and symptoms of LF, i.e. elephantiasis or lymphoedema in both sexes and hydrocele in men, will be performed in a health facility setting (health center/health post) by trained nurses. All men who reported having genital symptoms of LF and agreeing to genital examination will be assessed by a nurse.

### 4.10 Diagnosis of *W. bancrofti* infection

#### 4.10.1 ICT-Card

On arrival of the ICT cards in Ethiopia the stock will be tested using LF antigen. After obtaining informed consent from the participant, the test will be performed by trained laboratory technicians, according to the manufacturer's instructions (SOP in annex). The patient's third or fourth finger will be cleaned with 70% alcohol and punctured using a sterile lancet. The initial sample of blood will be removed using a cotton swab, and sufficient fresh blood will be obtained to fill a 100-µl capillary tube. The blood will be transferred from the capillary tube to the pad on an immuno-chromatographic test (ICT) card and the card will be sealed. The result of each ICT card will be read at 10 minutes exactly, not before, and not after. A positive result shows two pink lines which appear in the card's window, and a negative result will show a single line. The test will be repeated if the control line is not shown and if both the control and test line show color other than pink. Test results with the individual's ID number will be recorded both on the card, and on each individual's data sheet.

### 4.11 Diagnosis of podoconiosis

In areas where there is at least one positive immuno-chromatographic test (ICT), all patients with lymphedema but a negative immuno-chromatographic test (ICT) will be asked to provide 5ml of blood for antifilarial antibody (Wb123 assay) testing according to the suppliers instruction using ELISA. In total, a maximum of 3000 lymphedema cases are estimated to require this additional diagnostic test. Those lymphedema cases with negative antifilarial antibody assay will undergo further physical examination and history. In addition, information from physical examination including preservation of sensation in the toes, bilateral/unilateral, clinical signs of leprosy or onchocerciasis, and groin involvement will be recorded. History of rheumatic heart disease will also be asked.

### 4.12 GPS data:

Community GPS coordinates will be collected using Handheld Global Positioning System Geographical Positioning System (GPS-GarmineeTrex®).GPS coordinates will put in to a map using GIS software, to display the distribution of LF in Ethiopia.

### 4.13 Data collection and management

After the training, a pre-test of field procedures will be conducted. This research project will be managed by a team from EPHI, BSMS, AHRI and LSTM. An assigned person will be responsible for overall technical leadership, management and liaison, as well as the overall compliance of the project. The team will identify key personnel and form teams at zonal and regional level. Designated regional coordinators will be responsible for the regional level coordination and zonal coordinators will be responsible for locating the identified clusters and making the necessary pre-survey arrangements including community sensitization and mobilization. The logistics aspect of the project will be coordinated by the field logistics coordinator: these include transport, laboratory tests, and other supplies. A training manual will be prepared by the team. Training on survey methods, interview techniques, the rapid diagnostic test for LF and the use of portable Geographical Positioning System (GPS-Garmin eTrex®) devices will be given to all members of the survey team. Initial training will be given in Addis Ababa with the aim of sensitizing regional leaders, explaining the objectives of the survey, and identifying and training potential survey team members. After the training, a pre-test of field procedures, including use of portable GPS devices, the LF rapid diagnostic test and podoconiosis disease staging, will be conducted. Based on the pre-test results, problems will be identified and corrected. In addition, the training will help the regional coordinators to select and make initial plans with the zonal coordinators. Following this, regional and zonal coordinators will organize training for data collectors in their respective areas. The standard training guide will be the source document for all training.

The actual field data collection date will be selected with input from regional and zonal coordinators, taking into account the heavy rainy season that can potentially hamper data collection and make some remote clusters inaccessible. The teams, consisting of the zonal coordinator, the interviewer and the village guide, will visit each cluster before the actual day of the survey to accomplish the following tasks: to inform local leaders and community representatives about the objectives of survey and get permission; to identify individuals to be included in the survey as per the protocol, to record geo-coordinates using a GPS device, to select a suitable day for the survey in consultation with the community members, and to record travel time and directions to the villages. The team will supervise data collection region by region, ensuring adherence to protocol and responding rapidly to problems encountered. There will be continuous communication with regional and zonal coordinators through mobile phones, so that problems arising during data collection are communicated for prompt action.

All forms completed at the field level will be received at the survey coordination office, manually checked for completeness and then systematically filed by village. Data from the village forms, individual questionnaires, and LF examinations will be entered onto computer by experienced data entry clerks using Microsoft Access. Skip patterns and error checking will be integrated in the data entry forms. A regular backup system will be created in order to ensure no loss of data during the data entry process. By linking the village number (three digits), and individual code (English alphabet from A to P) a unique identification number for each individual in the survey will be established to facilitate data analysis. Data entry will be supervised routinely by an experienced data manager and regularly by the investigators.

The team will work closely with the Ministry of Health throughout the project, which will benefit from use of resources including vehicles and personnel from regional and zonal health offices. To establish smooth implementation of the research project, the national Neglected Tropical Disease lead at the Federal Ministry of Health will be involved during the planning and implementation of the survey.

**4.14 Data entry and analysis:**

Each completed data sheet will be checked by the field coordinator at field level. The collected data will be double entered in Access Data Base. The data manager will verify, clean the data and prepare the analysis plan with the PIs. Data verification, cleaning and analysis will be done using SPSS and STATA statistical Software and ARC- GIS software packages.

**4.15 Ethical considerations:**

Ethical approval need to be obtained from EPHI and national Ethical board. Appropriate support letters will be obtained from responsible administrative bodies and informed consent will be sought from participants. Confidentiality will be maintained using ID codes. Names of participants will not be recorded. Individual informed consent will be obtained from each participant (≥18 years of age). Additionally and for those 15 to 18 years old consent will be obtained from their parents/guardian (see attached document) and the participant themselves will provide informed assent (15-18 years old). Patient information sheet and assent and consent forms will be in Amharic languages, but as the need arises, these forms will be translated to local language of the specific population and/or ethnic group. Forms are prepared in Amharic and English.

The confirmed *W. bancrofti* infection will be treated by co-administration of one tablet of albendazole 400mg and the required dose of ivermectin, as indicated by a dose-pole according to WHO recommendations. Furthermore if any positives are found in the village the entire district will be consider endemic and all eligible population will receive annual MDA for at least 5 years until LF is eliminated. The population will receive information on that.

Ethical approval was obtained from Liverpool School of Tropical Medicine for the LF mapping and from the School of Public Health, Addis Ababa, and the Research Governance & Ethics Committee of Brighton & Sussex Medical School (BSMS) for podoconiosis mapping.

As part of the LF and Podoconiosis elimination programs, Ethiopia will put in place a morbidity management and disability prevention plan that will include provision of care for the patients suffering from lymphoedema and hydrocele.

### 4.16 Expected output of the Study

1. Develop a distribution map of Podoconiosis (the endemicity classification will be defined based on international consensus among experts in the field).
2. Give an estimate of population at risk for podoconiosis in Ethiopia.

### 4.17 Dissemination of Results and Ensuring the Implementation

The operational research outlined in the proposal will provide important data to provide key knowledge and fills the information gaps that are crucial for the development of LF elimination strategies and Podoconiosis control in Ethiopia. After completion of the analysis of the intended study, the results will be disseminated to all partners in a workshop that would be organized at national level. All inputs and comments from potential partners (Federal Mministry of Health, Regional Health Bureau and local communities) will be taken care of and the study results will be refined and distributed to all Stakeholders and international scientific communities through publications.

### 4.18 Monitoring/Evaluation of the studies and Action plan with Time.

The following Monitoring and Evaluation Plans are to measure the progress of the proposed activities. Deliverables and activities will be used as milestones to monitor and evaluate the study progress and achievements. See Annex I for the details of the activities)

**Table S4.1.4** Time table for the mapping of podoconiosis

| S. No | Major Activities | Deliverables | Time frame | Responsible |
|---|---|---|---|---|
| 1 | Establish Partnership & Coordination | Finalize the study protocol with the participation of in-country stakeholders | Month 1 | Partners |
| 2 | | Micro-planning workshop will be conducted before kickoff | | |
| 3 | Capacity Building | training workshop in LF and Podoconiosis mapping, survey implementation and study protocol will be conducted for project staff | Months 1 | Partners |
| 4 | Implementati on Research Activities | LF and Podoconiosis map project completion as per study protocol: collection of data and data entry into study database as well as analysis | Months 2-10 | FMoH, RHB & participant investigator s |

| | | | | |
|---|---|---|---|---|
| 5 | Interim report and evaluation | Evaluation of project results and interim reporting | Months 11 | Stakeholders and invited experts |
| 6 | report for Stakeholders | Submission of Draft report to stakeholder | Months 11 | FMoH/Funding agency |
| 7 | Dissemination of LF and Podoconiosis Operational Research Results | Dissemination workshop (for stakeholders and publishing in peer-reviewed Journals. | Months 12-18 | Partners |

### 4.19 Research Team

**Team composition:**

- **From central level**

1 Nurse for a bleeding and clinical data recording.

1 Nurse for podoconiosis

1 Lab technician for reading ICT cards and record results.

1 Coordinator to organize the activity and collect the GPS coordinates and provide informed consent to the community

- **From local level**

2 local data recorder (data form, stick ID number)

1 local translator in some place

1 local community kebele leader for social mobilization

**Table S4.1.5**

| No | Professionals required | Condition |
|---|---|---|
| 1 | Nurse | bleeding and clinical data recording |
| 2 | Nurse | Podoconiosis |

| | | |
|---|---|---|
| 3 | Lab technician | reading ICT cards and record results |
| 4 | Coordinator | organize the activity and collect the GPS coordinates and provide informed consent to the community |
| 4 | Translator | |
| 5 | Data recorder | data form, stick ID number |
| 6 | Social mobilizer | |

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**Table S4.1.6 Time line and deliverables**

| **Activities** | 2012 | | 2013 | | | | | | | | | | | | 2014 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Nov** | **Dec** | **Jan** | **Feb** | **Mar** | **Apr** | **May** | **Jun** | **Jul** | **Aug** | **Sep** | **Oct** | **Nov** | **Dec** | **Jan** | **Feb** | **Mar** |
| Identify stakeholders & partners that are either sources of data or technically important | ■ | ■ | | | | | | | | | | | | | | | |
| Establish working group that involves in the project day to day activities & administrative links | ■ | ■ | | | | | | | | | | | | | | | |
| Development of working protocol | ■ | ■ | | | | | | | | | | | | | | | |
| Preparation of SOP for fieldwork | | | ■ | | | | | | | | | | | | | | |
| Procure supplies for mapping | | | ■ | | | | | | | | | | | | | | |
| Sign MOUs among partners | | | | ■ | | | | | | | | | | | | | |
| Identify data collectors and team leaders | | | | ■ | | | | | | | | | | | | | |
| Training of Trainers | | | | | ■ | | | | | | | | | | | | |
| Training of project staffs | | | | | ■ | | | | | | | | | | | | |
| Field data collection | | | | | | ■ | ■ | ■ | ■ | | | | | | | | |
| Data entry | | | | | | ■ | ■ | ■ | ■ | ■ | | | | | | | |
| Development of geo-data base | | | | | | | ■ | ■ | ■ | ■ | | | | | | | |
| Carryout spatial analysis | | | | | | | | | | | ■ | ■ | | | | | |
| Producing LF Map | | | | | | | | | | | | | ■ | | | | |
| Interim report and evaluation | | | | | | | | | | | | | ■ | | | | |
| Consolidation of map | | | | | | | | | | | | | | ■ | ■ | ■ | |
| Final validation base on expert group comments | | | | | | | | | | | | | | ■ | ■ | ■ | |
| Dissemination of the final result to wider group | | | | | | | | | | | | | | | | | ■ |
| Drafting and submitting for publication | | | | | | | | | | | | | | | | | ■ |

**Information sheet**

**Title of Project: Mapping Podoconiosis in Ethiopia**

**Lay Title: Mapping of Podoconiosis in Ethiopia**

**Name of Investigators:**

**Information Sheet**

My name is ………………., and I am working with Addis Ababa University, BSMS, EPHI and AHRI. You are invited to take part in this research study, which we hope will yield valuable information on geographical distribution of elephantiasis. Before you decide whether to take part it is important for you to understand why we are collecting this information and what it will involve. Please take time to read this paper carefully and discuss it with friends and relatives if you wish to. Ask us if there is anything that is not clear or if you would like more information.

**Background to the study.**

We are mapping elephantiasis in Ethiopia. Through this study we identify the geographical distribution of the disease and environmental factors affecting the distribution. We hope that this will help us in scaling up prevention and treatment of elephantiasis throughout the country. With your permission, we intend to:

1. Ask you a series of questions about you and your family, the way you live and work, and in particular, the contact you have with the red soil. If you have elephantiasis, we will also ask questions related to the disease and how you have managed it.

2. We would like to take a sample of blood. For this we prick your finger lightly with a fine needle and take a drop of blood. The blood sample will help to see if either of you have LF

or not. The samples will be analysed here onsite. We will not test for any other diseases with this blood sample.

3. In areas in which LF is discovered, if you have elephantiasis, we would like to double check the fingerprick test by taking a second sample of blood into a small tube. The amount of blood is small (about 5ml or what is held on a small teaspoon). We will store this so we can do further checks to distinguish the type of elephantiasis you have." And "If I have elephantiasis, I understand that the investigators will take samples of blood to distinguish which elephantiasis it is.

**Possible harms.** We do not anticipate any harm to you from asking the questions or collecting the blood samples. The questions will take a maximum of 30 minutes of your time.

**Benefits.** At the end of the questions, we will explain to you more about the condition and how to prevent and treat it. If appropriate, we will put you in touch with a treatment site if there is one nearby.

**Confidentiality.** All information which is collected about you during the course of the research will be kept on a password protected database and is strictly confidential. Any information about you which leaves the research unit will have your name and address removed so that you cannot be recognized from it.

**Autonomy.** If you wish to discontinue the questionnaire or the sample collection at any time, you may, however, all the information you give us is highly valuable to the study. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. If you decide not to participate, the treatment you or your family receives in future at government or NGO treatment sites will not be affected.

**If something goes wrong.** If a problem arises, you can report it to one of the project staff, your *kebele* head, or the study coordinators at the address given below.

**What will happen to the research?** We anticipate that the results of this immediate study will be available next year, and we hope to publish the results. You will not be identifiable in any publication.

**Who is organizing and funding the research?** The research has been funded by the Wellcome Trust and DFID, a UK-based funding bodies dedicated to improving human and animal health through research. The research is organized jointly by researchers in Addis Ababa and the UK. The research has been reviewed by the Institutional Review Board of the Faculty of Medicine, Addis Ababa University and the National Ethical Review Committee in Ethiopia, and by Brighton & Sussex Medical School Ethics Committee and Liverpool School of Tropical Medicine.

Contact Address:________________ or ________________

Cell Phone: __________________ ________________

Thank you in advance for considering taking part in this additional study!

**Healthy volunteer consent form**

Reference ID Number

| | | | |
|---|---|---|---|
| | | | |

Title of Project: **Mapping of Lymphatic Filariasis and Podoconiosis in Ethiopia**

**Name of Investigators:**

**Healthy Volunteer's Consent Form**

Please read this form and sign it once the above named or their designated representative, has explained fully the aims and procedures of the study to you

- I voluntarily agree to take part in this study.
- I confirm that I have been given a full explanation by the above named and that I have read and understand the information sheet given to me which is attached.
- I understand that the investigators will ask a series of questions about me and my work.
- I understand that the investigators will take samples of blood to test for LF.
- I have been given the opportunity to ask questions and discuss the study with one of the above investigators or their deputies on all aspects of the study and have understood the advice and information given as a result.
- I agree to comply with the reasonable instructions of the supervising investigator and will notify him immediately of any unexpected unusual symptoms or deterioration of health.
- I authorize the investigators to disclose the results of my participation in the study but not my name.

- I understand that information about me recorded during the study will be kept in a secure database. If data is transferred to others it will be made anonymous. Data will be kept for 7 years after the results of this study have been published.
- I understand that I can ask for further instructions or explanations at any time.
- I understand that I am free to withdraw from the study at any time, without having to give a reason.
- I confirm that I have disclosed relevant medical information before the study.
- I understand that if something goes wrong I can report it to one of the project staff or the study coordinators at the address given below.

**Name:** ………………………………………………………………………………………

**Address:** ……………………………………………………………………………………..

**Telephone number**: ……………………………………………………………………….

**Signature:** …………………………………………. **Date:** ……………………………….

I confirm that I have fully explained the purpose of the study and what is involved to:

……………………………………………………………………………………………………….

I have given the above named a copy of this form together with the information sheet.

**Investigators Signature:** ……………………….. **Name**: ………………………………

**Questionnaire**

**Podoconiosis mapping study questionnaire**

| | | | | |
|---|---|---|---|---|
| Date | *(DD-MMM-YYYY)* | \|__\|__\|-\|__\|__\|__\|-\|__\|__\|__\|__\| | Record Taker's Initials | \|__\|__\|__\| |
| Name of Community | | | Community Code | \|__\|__\|__\| |
| Participant Identification number | \|__\|__\|-\|__\|__\|__\|-\|__\|__\|__\| | | | |

| SN | Questions and Filters | Response & Coding Categories | Skip |
|---|---|---|---|
| **Section I Demographic and Socioeconomic Information** | | | |
| 101 | Region name | | |
| 102 | Zone Name | | |
| 103 | Woreda code | | |
| 104 | Kebele Code | | |
| 105 | Community Code | | |
| 106 | Sex Check box (✓) | ☐ 1 = Male ☐ 2 = Female | |
| 107 | How old are you?( years) | >15 years of age | |
| 108 | Religion | ☐ 1 = Muslim☐ 2 = Christian ☐ 3 = Animist ☐ 4 = Other | |
| 109 | Ethnic group | ____________ | |
| 110 | Where is your permanent residence? | ☐ 1 = Rural ☐ 2 = Urban | |
| 111 | How long you lived in the current location? | | |
| 112 | What is your major occupation currently?<br>(Whatever you do to earn money)? | ☐ 1 = Employed<br>☐ 2 = Businessman/women<br>☐ 3 = Farmer<br>☐ 4 = Housewife<br>☐ 5 = Daily laborer<br>☐ 6 = Student<br>☐ 7 = Have no Job<br>☐9 = Other specify __________ | |
| 113 | Are you able to read and write in any language? | ☐ 1 = Yes ☐ 2 = No<br>Grade completed ______ | |
| 114 | What is the monthly income (on average) of your household including your own? | Birr/month________________ | |
| 115 | What type of floor does your house have? | ☐1=Mud/earth ☐2=Wood ☐3=Cement<br>☐9=Other | |
| 116 | What is your current marital status?<br>Check box (✓) | ☐1=Single ☐2= Married<br>☐3 = Divorced ☐4 = Widowed | |
| **Section II Shoe wearing and foot care practice** | | | |
| 20 | Have you ever worn shoes? | ☐ 1 = Yes | |

| | | | |
|---|---|---|---|
| 1 | | ☐ 2 = No → | Go to Q206 |
| 202 | How old were you when you first got shoes? | | |
| 203 | Is the person wearing shoes at the time of the interview? | ☐ 1 = Yes →<br>☐ 2 = No | Go to Q205 |
| 204 | Describe the shoes the person is wearing. | ☐1= Hard plastic ☐2= Open sandal<br>☐ 3=Leather ☐ 4=Shera<br>☐ 5=other | |
| 205 | When do you wear shoes?( multiple answers possible) | ☐1= At home<br>☐ 2=During rainy season<br>☐3= On market days<br>☐4= On the field<br>☐5= On Sundays<br>☐ 6=When walking far | |
| 206 | How long (in min) does it take you to go to the nearest water source? | | |
| 207 | When do you wash your feet? | ☐1=Whenever they are dirty<br>☐2=Before sleeping<br>☐3=Before prayer<br>☐9=Other (specify )______ | |
| 208 | How often do you wash your feet very carefully so that they are very clean? | ☐1= More often than once a day<br>☐2= Daily<br>☐ 3=Less often than daily, but more often than weekly<br>☐4= Weekly or less often | |
| **Section III Leg swelling history ICT Card Results and physical examination** | | | |
| 301 | Do you have leg swelling? | ☐ 0 = No →<br>☐ 1= Yes (verify by observation) | End the interview |
| 302 | Do you have any family member (living or dead) with history of leg swelling? | ☐ 0 = No →<br>☐ 1 = Yes | Go to Q 304 |
| 303 | How many people in your family (living or dead) have leg swelling? | | |
| 304 | How old were you when you first noticed this swollen leg? | | |
| 305 | Where did the swelling start from? | ☐1= from high up<br>☐2= From the foot or lower leg | |
| 306 | Do you have history of rheumatic heart disease? | ☐ 0 = No<br>☐ 1 = Yes | |
| 307 | Do you have swelling in the groin area? | ☐ 0 = No<br>☐ 1 = Yes | |

| | | | |
|---|---|---|---|
| 308 | Are you diagnosed as a leprosy patient? | ☐ 0 = No<br>☐ 1 = Yes | |
| 309 | Is there preservation of sensation in the toes? (Physical examination) | ☐ 0 = No<br>☐ 1 = Yes | |
| 310 | Podoconiosis diagnosis established | ☐ 0 = No<br>☐ 1 = Yes | |
| 311 | Podoconiosis disease stage | ☐ 1 = Stage 1<br>☐ 2 = Stage 2<br>☐ 3 = Stage 3<br>☐ 4 = Stage 4<br>☐ 5 = Stage 5 | |
| 312 | Antifilarial antibody test blood sample collected? | ☐ 0 = No<br>☐ 1 = Yes | |

The end! Thank you for giving us your time and answers to many questions. We hope this will help the work in the future.

The end!

Thank you for giving us your time and answers to many questions. We hope this will help the work in the future.

# Training manual for Podoconiosis mapping in Ethiopia

## I. Background

Podoconiosis (endemic non-filarial elephantiasis) is a non-infectious geochemical disease arising in barefoot subsistence farmers who are in long-term contact with irritant red clay soil of volcanic origins. The disease causes progressive bilateral swelling of the lower legs. Mineral particles absorbed through skin are taken up into macrophages into the lymphatic system and result in an inflammatory process leading to fibrosis and obstruction of the vessels. This leads initially to swelling of the foot and the lower leg, which progresses to elephantiasis: gross lymphoedema with mossy and nodular changes of the skin. Podoconiosis affects some 4 million people in Africa, Latin America, and a few areas of Asia. It is found in more than ten countries across tropical Africa where irritant soils have been generated by environmental conditions of high altitude (>1,000m) and high annual rainfall (>1,000mm), and are farmed by very poor people who cannot afford shoes or water.

The current control strategy for podoconiosis consists of integrated approach prevention among school age children through promotion and distribution of protective shoe and lymphedema management. The main challenge in facing podoconiosis is lack of adequate data to inform policy makers, program planners and donors about the distribution of podoconiosis. Therefore this project was planned to generate distribution map of podoconiosis in Ethiopia. The output would help to target resources, monitor progress, and advocate for investment in podoconiosis prevention control and ultimately elimination.

## 1. <u>Introduction</u>

**Elephantiasis:** Elephantiasis is a term commonly used to describe lymphedema affecting a limb so that it becomes swollen, resembling that of an elephant. Lymphedema is a condition in which sections of the lymphatic system malfunction and block proper drainage of lymph. This in turn results in tissue inflammation and enlargement of the affected limb or area. Elephantiasis is very uncomfortable and disfiguring. In the tropics, there are two major types of elephantiasis, and, while the diseases do have some similarities, there are also significant differences.

**Lymphatic Filariasis (LF):** The first type is Lymphatic filariasis (LF). This is the type of elephantiasis that first comes to most people's minds when confronted with a swollen leg in the tropics. Lymphatic filariasis is a communicable disease transmitted between persons by mosquitoes that transmit filarial parasites. The parasites cause inflammation and subsequent malfunction of the lymphatic system, blocking normal lymph drainage. This blockage results in a vast enlargement of the affected limb. LF can occur in various body parts and most commonly occurs in the affected individual's feet, legs, arms, scrotum, vulva, or breasts.

**Non- Filarial Elephantiasis (Podoconiosis):** The second type of elephantiasis is Non-Filarial Elephantiasis or podoconiosis. In lay terms, the disease is also called Mossy Foot because of the moss-like skin changes that often occur on the feet. Podoconiosis is a non-communicable disease that is acquired through prolonged exposure to red clay soils of volcanic origins when tiny silica crystals appear to be absorbed through the feet. The disease occurs primarily where these red clay soils are found in areas of high altitude (over

1000m), high seasonal rainfall (over 1000mm per year), where most people are subsistence farmers.

Podoconiosis has been described in ten countries across tropical Africa, and has also been reported in tropical areas of Central America and Northern India. The exact global burden is still to be measured, but it is estimated that at least 4 million people are affected worldwide.

Not only is the causal agent of podoconiosis different from that of LF, but it also differs in several other ways. The limb swelling is almost always restricted to the feet and lower legs below the knees. The first signs of disease are often in the foot, with lymph nodes in the groin affected later (in LF groin involvement is earlier). Podoconiosis is preventable through the proper regular use of footwear and simple foot hygiene. Although, there is no "cure" for podoconiosis, it can be controlled and reversed through a variety of simple means to be discussed later. If continually treated properly, podoconiosis patients are able to return to a normal way of life.

The disease typically manifests itself between the ages of 10 and 30, but individuals as young as 5 may experience early symptoms. In addition, genetic studies show high heritability of the trait that causes podoconiosis. Podoconiosis is typically observed in rural subsistence farmers whose trade, culture, and economic circumstance often make it uncomfortable, against cultural norms, or a financial burden to wear shoes. Further, there is often stigma associated with podoconiosis sufferers. They are often excluded from religious meetings, government meetings, school, and other community gatherings.

Sufferers and/or sufferers' siblings are often barred from marrying into unaffected families.

Podoconiosis has significant economic impact; according to a study in Ethiopia it was found out that the disease results in productivity loss. It is estimated that 1 million cases are found in Ethiopia and 11 million people are at risk, living in 18% of the land of Ethiopia. Total direct costs of podoconiosis amounted to the equivalent of US$ 143 per patient per year. Total productivity loss for a patient amounted to 45% of total working days per year, and in a zone of 1.5 million people, the total overall annual cost of podoconiosis was calculated to exceed US$ 16. million per year. In addition the disease is known to be stigmatized with significant social exclusion. Podoconiosis is widely distributed in three continents; Africa, Central America and Asia particularly India. In Africa, at least 10 countries with the disease have been identified. Previous studies have documented the association of the disease with irritant red clay soils, which are generated in areas at >1500 metres above sea level (masl), with >1000 mm annual rainfall.

In Ethiopia, prevalence estimates from 56 market counts ranged from 0.42% to 3.73% these rates are probably underestimates because podoconiosis is a stigmatized disease that may keep affected people from attending public gatherings and the debility the disease causes reduces their mobility. More recent studies in Ethiopia estimated a prevalence of 5.46% in Southern Ethiopia, 5.2% in western Ethiopia, 7.4% in central Ethiopia and 3.3% in northern Ethiopia.

## 2. Prevention

- Education and Communication of Information
- Shoes for prevention among children

## 3. Treatment

Basic Podoconiosis Treatment
There are six components to treatment of podoconiosis. These are:

| SN | Treatment | Description |
|---|---|---|
| 1 | Foot hygiene | Foot hygiene is important because it removes soil particles from the foot, reduces bacterial load and restores the function of the skin. It is important that the feet are thoroughly washed and dried daily. The first step is to soak the feet for 15-20 minutes in a basin with cool, clean water and diluted antiseptic. |
| 2 | Skin care | After washing and drying the foot and leg, it is essential to rub the skin with local oil or ointment to keep it supple. In Wolaita, the MFTPA uses Whitfield ointment which is relatively inexpensive and easily attainable from Addis Ababa. In some other areas locally acquired, clean cooking oil with eucalyptus or neem extract is used. |
| 3 | Bandaging; | The leg should be bandaged from the toes towards the knee, ideally when the leg is elevated. The foot should be wrapped using a "V" shaped design and then bandaging continued in a spiral up the leg to 5cm above the upper limit of swelling, overlapping the previous layer by 50% each full turn around the leg. In Wolaita, MFTPA provides patients with two bandages per affected leg so that one may be washed while the other bandage is in use. |
| 4 | Socks and shoes | Socks and shoes are vital for both treatment and prevention of podoconiosis. |
| 5 | Elevation and movement | Movement or exercise and elevation of the leg can help improve lymph circulation and reduce swelling. Ankle circles and calf raises are recommended but should be suspended if they cause pain. |
| 6 | Surgery | Surgery is becoming increasingly uncommon among podoconiosis patients, since the vast majority of patients benefit from the simple treatment above. Very few patients benefit from surgery, which should be limited to removal of discrete nodules that are preventing the patient wearing shoes. Nodule removal may be followed by limited skin grafting. |

## 4. Clinical Staging of podoconiosis

Clinical staging is important for several reasons. First, it allows program planners to assess the burden of disease in an area. It also gives patients feedback during self-treatment, allowing a patient to see his or her progress. Staging also offers a means for health professionals to record the effectiveness of the treatment, and for researchers to document the effectiveness of an intervention or program.

There are several key words to define and understand before discussing the different stages of podoconiosis. For the sake of staging, these key words are defined as follows:

- Swelling a general increase in the size of the foot or leg.
- Knob/bump a discrete hard lump seen or felt to protrude.
- Moss tiny, rough lesions around the base of the foot that resemble moss.
- Ankle the level of the two ankle bones when standing.
- Knee the level of the top of the knee cap when standing.
- Circumference the greatest below the knee measurement in centimeters.

Staging of podoconiosis was developed from the Dreyer system for staging LF. The Dreyer system of staging did not fit the clinical picture of podoconiosis perfectly, thus the following system was developed to stage podoconiosis and is used widely in Ethiopia. The stages are:

- Stage 0 No disease is present.
- Stage 1 Swelling of the limb is reversible overnight. Swelling is not present when the patient first wakes up but sets in as the day progresses.
- Stage 2 Persistent below-the-knee swelling that is not reversible overnight. If present, knobs and/or bumps are below the ankle only.

Stage 3 Persistent below-the-knee swelling that is not reversible overnight. Knobs/bumps are now present above the ankle.

- Stage 4 Persistent above-knee swelling. Knobs/ bumps are present anywhere on the foot or leg.

- Stage 5 Joint fixation and swelling at any place on the leg. The ankle and toe joints are fixed and difficult for the patient to flex.

Generally each leg is staged independently of the other. First, the clinical stage of the leg is recorded using the above system. Next, presence or absence of moss is documented, using 'M+' if moss is present, or 'M-' if absent. Wounds are checked for, and the observation is recorded as follows: 'W+' if present and 'W-' if not. Finally, a flexible tape measure is used to measure the circumference of the largest point of swelling below the knee.

A patient with stage 3 podoconiosis, moss, no wound, and a 34cm greatest below the knee circumference would be recorded in the following way: 3, M+, W-, 34.

## 5. **Differential Diagnosis**

When diagnosing and treating podoconiosis, there are several other diseases causing swollen legs that must be considered:

| SN | Disease | How to differentiate? |
|---|---|---|
| 1 | Filarial lymphoedema (LF); | Where is the patient from? LF only occurs at altitudes of less than 1000 meters, where the mosquitoes that transmit it can survive. It cannot be transmitted at higher altitudes (dega and woina dega) where podoconiosis occurs.<br>Where did the swelling start? The swelling of podoconiosis starts in the feet and proceeds up the leg; that of LF starts at the groin and proceeds down the leg. |
| 2 | Leprosy; | Leprosy is frequently found in podoconiosis areas, and one of the consequences of long-term leprosy may be leg or foot swelling. The most important way of distinguishing the two conditions is to test for sensation in the foot. The leprosy disease process causes decreased sensation in addition to swelling, whereas in podoconiosis, sensation remains intact. If examination for skin depigmentation and thickened nerves suggests leprosy, the patient must be referred for anti-leprotic therapy. |
| 3 | Onchocerciasis; | May sometimes be found in areas in which podoconiosis is also endemic. Skin changes (itchy skin rash and 1-2cm nodules or bumps) on the trunk and arms are common in onchocerciasis. In some countries, eye changes are common in onchocerciasis, but these changes are rare in Ethiopia. Patients suspected to have onchocerciasis must be referred on. |
| 4 | Malnutrition in children; | May present with swollen feet, and malnourished children have at times been brought to podoconiosis clinics. Other signs of malnutrition include 'rusty' hair discolouration, swollen belly, shiny taut skin and lack of energy. Malnourished children require referral for specialist management. |
| 5 | Rheumatic heart disease; | Rheumatic heart disease is a condition in which permanent damage to heart valves is caused by rheumatic fever. The heart valve is damaged by a disease process that generally begins with a strep throat caused by bacteria called Streptococcus, and may eventually cause rheumatic fever. Joint inflammation - including swelling, tenderness, and redness over multiple joints. The joints affected are usually the larger joints in the knees or ankles. The inflammation |

| | | |
|---|---|---|
| | | "moves" from one joint to another over several days. |
| 6 | Post surgery; and | |
| 7 | Milroy's disease. | Milroy's disease is a familial disease characterised by lymphedema, commonly in the legs, caused by congenital abnormalities in the lymphatic system. Disruption of the normal drainage of lymph leads to fluid accumulation and hypertrophy of soft tissues. The defect in Milroy's disease is present from birth and symptoms are usually first experienced in childhood. The most common problem is one-sided leg swelling, unilateral edema, which is progressive and can affect both legs. |

## II. Purpose of the mapping

The FMoH is looking to control and eliminate podoconiosis from Ethiopia. In order to initiate the control and elimination programme, the first step is to identify areas where the disease exists. This is assessed by mapping the disease distribution using different diagnostic tools and identifying physical signs and symptoms. Once this information has been collected, the second step is to deliver treatment to all podoconiosis patients in areas endemic for the disease. Currently the treatment is free and will consist of six components as described above.

This project aimed at mapping the distribution of podoconiosis in districts which were not mapped for LF. In the study a total of 692 districts will be covered. From each districts two Kebeles will be selected and 200 individuals involved in the study. The two villages will be selected according to WHO protocol. The study will involve individuals >=15 years of age, who lived in the area for at least 10 years and didn't leave the area for more than 6 months. People who have serious acute or chronic illnesses should be excluded from the study.

## III. Guidelines for field mapping activities

Mapping will include collection of a variety of information including; community information, socio-demographic data, signs and symptoms caused by podoconiosis, disease stage, shoe wearing practice and housing conditions.

### Equipment

The mapping surveys require minimal equipment and aim to be rapid. Each mapping team will be provided with the following items for field surveys:

- Immuno-chromatographic test(ICT) cards
- Single Use Sterile Disposable Safety Lancets
- Alcohol
- Cotton
- Gloves
- Immuno-chromatographic test(ICT) cards
- Single Use Sterile Disposable Safety Lancets
- Syringe with needle
- Hand sanitizers
- Soap
- Bleach
- Insecticide
- Safety Box
- Plastic waste bags
- Plastic sheet
- Nunc tube
- Cold box
- Nunc tub rack
- Vacutainner
- Stationary
- Mobile Phones for Data Collection
- Informed Consent Forms

### Method

In each district, the mapping survey will be conducted in two sites that are selected by the FIELD TEAM based on the district/Woreda health data and reports on lymphodemas. In EACH OF THESE SELECTED SITES, information must be collected for a total of 100 RANDOMLY SELECTED INDIVIDUALS (50 Female and 50 Male), aged 15 years or above.

For true representation of the disease within the community and ethical reasons, not all individuals are eligible to participate in the mapping survey and it is important to adhere to the exclusion criteria below:

- Does not meet the minimum age requirements
- Has not lived in the community for a minimum of 10 years (as the individual may not be representative of the local population)
- Travelled out for greater than 6 months
- Has not provided consent
- Is severely sick

To collect the data, the field teams will be given mobile phones with a set of questions that the data collection members (Team Leader and Nurses) will have to enter information on.

**Community and Demographic Information**

COMMUNITY INFORMATION: This should be collected prior to the start of the field surveys by the Team Leader. This will collect basic information of the community in the following areas; such as the GPS location of the site, community name, population size etc. The unique coding and ID system used in these forms will be pre-set and provided to the Team Leader by FMOH.

DEMOGRAPHIC INFORMATION: This should be collected during the field survey by the Podo nurses. Each individual participating in the survey will be asked a number of questions about themselves such as gender, occupation, shoe wearing, foot hygiene practice and physical signs of Podo.

Please refer to the Data Collection Using Mobile Phones section for more information regarding all data collection and entry.

**Diagnostics – Podoconiosis**

Presence of the LF parasite within individuals will be determined by using the ICT card, which is a rapid diagnostic tool, used commonly in LF elimination programmes. The test will be conducted by the Laboratory Technician within the field team and the results entered into the phone by the Nurses.

In this study all lymphoedema cases are suspects for podoconiosis. Therefore different history, physical examination and diagnostic test will be conducted to exclude other causes and reach into the diagnosis of podoconiosis. First they will be tested for ICT and if found negative in areas where at least one ICT positive case is found additional blood sample will be taken for antibody test. Leprosy, onchocerciasis and rheumatic heart disease will be excluded as indicated above.

**Ethical considerations**

- Participation in the survey is VOLUNTARY and it is imperative that nobody within the community feels forced to take part or concerned that not participating may affect any future health benefits they receive.
- Selection of individuals to take part in the survey must be RANDOM and there should be no bias in selecting one individual over another.

- To ensure ANONYMITY, individuals will be identified by a unique identity number only and personal details such as name or address must not be requested during the mapping process.
- It is important to get written approval from the community leaders prior to starting the field surveys. This will confirm that they are informed about the survey happy for it to be conducted.
- All participants will be requested to provide WRITTEN CONSENT that they understand the purpose of the survey and voluntarily are happy to take part in the survey. Individuals who are under the age of 18 years, they will require additional consent from their parents or legal guardian.
- Individuals who are positive should be provided TREATMENT. Treatment will not be administered as part of the mapping survey and participants, who are tested positive, will be advised to visit their local health facility, where they will receive medications for free. The national programme will also distribute drugs through the MDA strategy shortly after the mapping results have been analysed.

**Additional Notes:**

(Write below any additional notes from the facilitator)

……………………………………………………………………………………………………………………………
……………………………………………………………………………………………………………………………
……………………………………………………………………………………………………………………………
…………………………………………………………………

**Field Teams**

As an integral member of a small field team for conducting the mapping surveys, team work and coordination is essential. Field teams will be composed of individuals with a variety of skill sets each of who have specific responsibilities as outlined below:

| **Team Member** | **Quantity** | **Key Responsibilities for podoconiosis Mapping** |
|---|---|---|
| Team Leader | 1 | Community<br>• Communicate with community leaders to obtain support and consent for mapping<br>• Communicate with community members to answer questions regarding LF, mapping and the LF elimination programme<br>• Point of contact for community during mapping<br>Field Team<br>• Lead the field team to conduct mapping surveys<br>• Oversee surveys and supervise field team activities, ensuring all team members are following the mapping protocol<br>• Point of contact for EPHI/FMOH<br>• Monitor all field data collection<br>• Manage time of field activities and time spent on each mapping site<br>Data Collection<br>• Collect GPS points for mapping site<br>• Record LF community form information<br>• Responsible for safe keeping of mobile phones and data at all times<br>• Inform participant of ICT result and record data into data collection form for result<br>Other<br>• Advise on treatment and answer further questions regarding ICT result<br>• Have knowledge on how to conduct all aspects of the mapping survey, including the ICT card<br>• Activities associated with mapping e.g. assisting other field team members<br>• Ensure local health facilities have drugs available for treatment referral or inform where FMOH where treatment cannot be provided |
| Nurse | 2 | Communication<br>• Communicating with members of the community regarding LF, mapping and the LF elimination programme<br>• Conducting physical examination of individuals participating in the mapping<br>Data Collection<br>• Enter all information accurately into data collection systems using mobile phones<br>Other |

| Team Member | Quantity | Key Responsibilities for podoconiosis Mapping |
|---|---|---|
| | | • Activities associated with mapping e.g. assisting other field team members<br>*(One nurse will focus on conducting the LF mapping, whist the other will focus on podoconiosis mapping.)*<br>*Podo nurse:*<br>• Collect blood sample from ICT negative lymphodema cases where the LF prevalence ≥1% using vacutainer<br>• Separate serum from the whole blood after one hour of collection<br>• Label using patient Worerd Village- individual ID number.<br>• Store in a cold box. |
| Laboratory Technician | 1 | Data Collection<br>• Prepare field lab for conducting LF diagnosis (ICT card)<br>• Collect blood sample from participant<br>• Ensuring correct allocation of ID number for participant and test<br>• Conduct ICT card test and determine ICT result<br>• Time management so ICT cards are read within the required time according to ICT card instructions<br>• Deliver ICT card results to LF Nurse and ensure capture correctly in data collection form<br>• Ensure good health and safety practices are followed for sample collection and disposal of all ICT card test material.<br>• Inform participant how the test will be conducted, what samples will be taken and what the result will show.<br>• Answer any questions associated with LF, mapping, the LF elimination programme and the ICT card test<br>Other<br>• Activities associated with mapping e.g. assisting other field team members |
| Translator | 1 | Communication<br>• Sensitise and inform the local community about LF, the mapping survey and the FMOH LF elimination programme<br>• Translate communication by mapping team member<br>• Translate communication by participant<br>• Ensure communication is sensitive to local cultural and behavioural settings<br>Other<br>• Activities associated with mapping e.g. assisting other field team members |
| Field Worker | 2 | Communication |

| Team Member | Quantity | Key Responsibilities for podoconiosis Mapping |
|---|---|---|
| (Local) | | • Obtain written consent from participant<br>• Sensitise and inform the local community about LF, the mapping survey and the FMOH LF elimination programme<br>• Motivate community members to participate in the survey<br>• Allocate identification (ID) number for participant<br>• Time slot allocation to ensure participants are not waiting for long periods of time unnecessarily<br>Other<br>• Activities associated with mapping e.g. assisting other field team members |
| Driver | 1 | • Safely transport all field team members and equipment from between mapping sites<br>Other<br>• Activities associated with mapping e.g. assisting other field team members |

## IV. On the day activities

Generally it is expected that mapping surveys for one site should take no longer than 1.5 days. On day 1, it is anticipated that there will be no field work and main activities will include sensitising community leaders and obtaining written approval that the survey can take place - this should be half a day's work. Field work should usually be conducted on day 2; participant recruitment, data collection and diagnostic testing.

**AT EACH NEW DISTRICT/WOREDA**, the field team will need to visit the district/Woreda level health centre first to obtain health records and review lymphedema and hydrocele information; to identify **TWO** suitable sites for conducting the mapping survey.

**Day 1**

Activities require: **Team Leader, Translator, Field Workers** and **Driver**

1. Team members travel to site within district
2. Meet with Community Leaders and introduce team
3. Team leader to discuss with community leaders the following areas;
    a. **LF:** What Podoconiosis is and how it is caused?
    b. **FMOH Plans:** Initiation of national LF elimination programme
    c. **Mapping Podo Distribution:** Aim and purpose of mapping, methodology, information collected, diagnostics used, benefits from participation, ethics and time required to conduct mapping
    d. **Treatment for Podoconiosis:** If individuals are positive what they should do? What treatment should they seek?
    e. **Result of Podoconiosis Mapping:** What will happen next? Analysis of results, findings translated into treatment strategy for national elimination programme
    f. **Consent to Map:** Discuss conducting the mapping survey in their community and obtain written consent that the mapping survey can be conducted there
    g. **Location for Mapping:** Discuss where the mapping survey can be conducted (central meeting point)
    h. **Community Involvement:** Request and motivate leaders to conduct **Community Sensitisation And Social Mobilisation**; to inform their community to participate in the mapping survey and requirements from local health facilities
    i. **Time:** Discuss time schedule of mapping survey
    j. **Other:** Any further site specific requirements

4. Team to identify location for conducting the mapping with Community Leader
5. Team Leader to collect Community information on mobile
6. Team to inform local health facilities of mapping survey
    a. If no drugs are available the Team Leader should contact FMOH and inform them that treatment is required for individuals who are positive in the specific mapping site.
7. Put up sensitisation material in places where community will see to inform them of upcoming survey (e.g. schools, local health facilities and community meeting place)
8. Return to rest of field team and prepare for mapping survey the next day

***Additional Notes:***

(Write below any additional notes from the facilitator)

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**Day 2**

Activities require **ALL MEMBERS OF THE FIELD TEAM**

1. Team members travel to site within district
2. Team meet with community leader and introduce team
3. Team members go to selected location and set up field mapping laboratory
    a. **Laboratory Technician** to set up LF diagnosis station
    b. **Nurses** to set up for data collection stations for LF and podoconiosis

4. **Community Leaders** assisted by local **Field Workers** round up community members to mapping laboratory
    a. **Community Leaders** must lead the social mobilisation and community sensitisation showing their support of the mapping survey in the community and to highlight the benefits of participating in the survey
    b. **Field Workers** should provide specific sensitisation on:
        i. LF – what it is and how it is transmitted
        ii. Aim and purpose of mapping
        iii. Methodology and information collected
        iv. Diagnostics used
        v. Benefits from participation (including availability of treatment from local health facility)
        vi. Ethical considerations and selection criteria
        vii. Time required to conduct mapping
    c. Answer questions from community with support from **Team Leader, Translator**
    d. Recruit and direct participants who voluntarily agree to take part to field laboratory
        i. It may be time efficient to allocate time slots for individuals to come

***TIME SLOTS:*** *Participants are divided in 25 people groups. Eachgroup is given a time slot for when the participants should to return to the mapping survey laboratory.*
*The first group should be individuals who are not requested to return but will be tested there and then. In the time slots below, 9am should be regarded as the group that are not requested to come back later.*

- **Group 1 – 9am**
- **Group 2 – 11am**
- **Group 3 – 1pm**
- **Group 4 – 3pm**

back to the mapping survey laboratory rather than waiting to be tested. **An example** of how the grouping system could work can be seen below:

5. Conduct Mapping Survey (testing 100 eligible individuals)
6. End mapping
7. Inform community leaders that the mapping has been completed (if required)

***Additional Notes:***

(Write below any additional notes from the facilitator)

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## V. Mapping Survey

After the initial community sensitisation, the **Team Leader**, **Translator** and one **Field Worker** should return to the field laboratory to carry out their duties during the mapping survey.

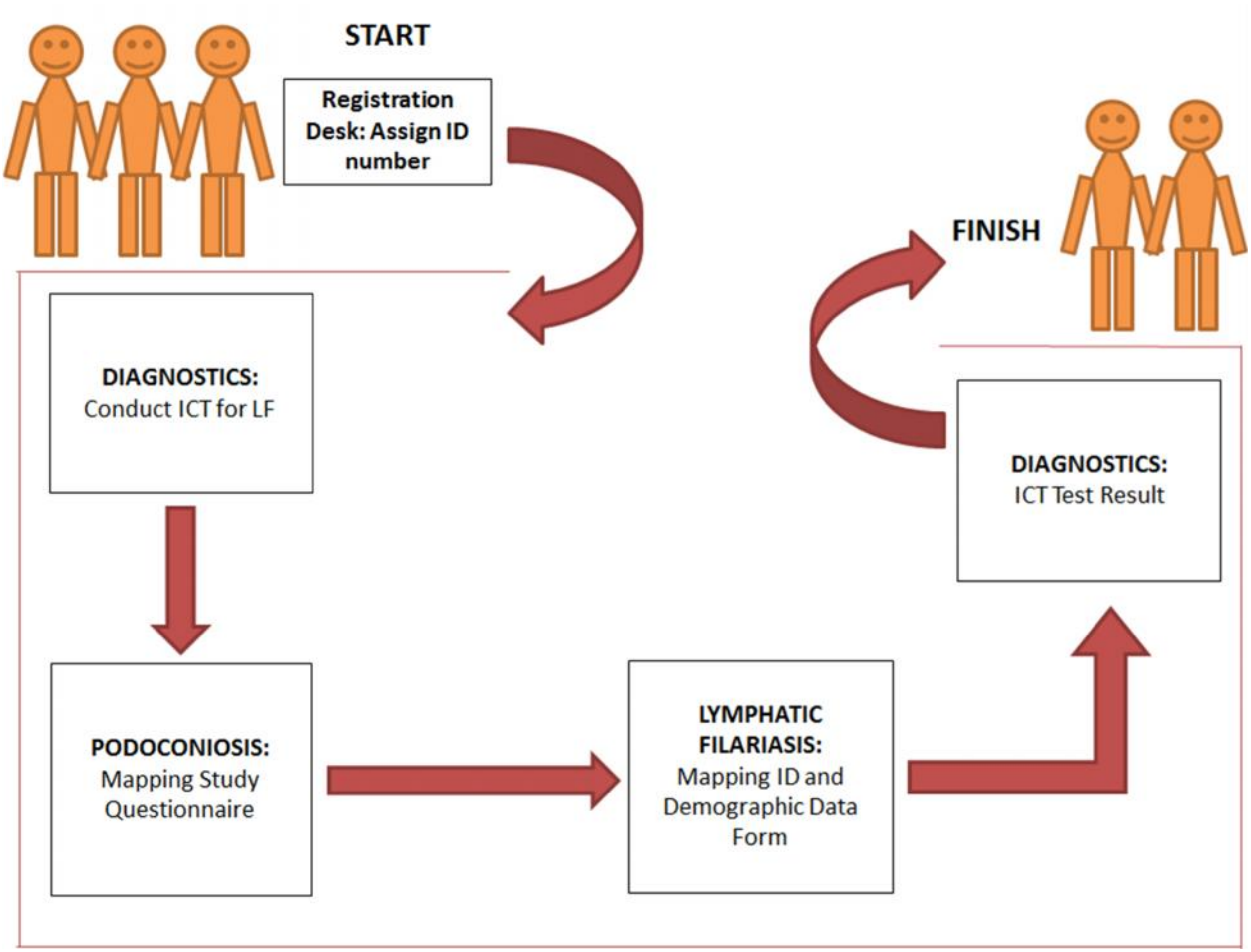


Figure 1: How the Mapping Survey should be set up

1. One **Field Worker** must be stationed at the registration desk as the first point of contact during the mapping survey.

   Their main role will be to ensure participants;

   - Meet the eligibility criteria
   - Are able to provide full signed consent (adult/ adult + assent)
   - Are allocated a unique id number
     - The last three numbers of the ID number should be on a piece of paper or the participant's hand for them to keep hold of and present at each data collection point (ICT card, LF mapping survey and podoconiosis survey)

- Further questions regarding the mapping are answered fully

N.B. Participants should wait at registration until they are able to proceed in the mapping process. It is advisable not to register too many participants at once as this can increase the potential for errors in data collection. The second **Field Worker** should try to recruit individuals and encourage them to be patient whilst waiting to be seen.

2. After registration, the participants will visit the **Laboratory Technician**.

   It is essential that the following steps are followed:

   - Provide an overview of what the test is and how it will be conducted, showing all equipment that will be used to conduct the test
   - Answer any questions regarding the test or the survey (participants will be fully informed about the survey prior to reaching the ICT card stage so general questions are not expected)
   - Follow the standard operating procedure for ICT cards to collect the blood sample and conduct the test
   - Write the ID number of the participant on the ICT card
   - Provide a cotton wool to apply pressure on the puncture site (if required/requested by participant) after the blood has been collected
   - Write on the ICT card the time when the test is started (when the blood reaches the pink part of the test). The test will be ready to be inspected after 10 minutes
   - Inform the participant that they will be told the result by the **Team Leader**and it will take 10 minutes for the result to become clear

3. Participants will then move onto the**LF Nurse** to answer a series of pre-set questions. The Nurse must also conduct a physical assessment of the individual to detect physical signs and symptoms of LF.

4. Following the LF survey, the participant will move to the **podoconiosis Nurse** to answer a further series of pre-set questions. *(Further details on this section of the survey will be provided in the podoconiosis training).*

5. The ICT card result requires 10 minutes and it is anticipated that the test results will be available after **BOTH** questionnaires are complete. The **Laboratory Technician** conducting ICT cards should write the result of the test on the ICT card as soon as 10 minutes have passed. The **Team Leader** should collect the results and speak to all participants individually to deliver the results.

6. The **Team Leader** will discuss the results of the diagnostic test and provide further information if the test is positive.
    - Individuals who are **POSITIVE** should be given a standard letter which states their result. They should be directed to the local health facility where they can receive free treatment, upon presenting the letter.

- Individuals who are **NEGATIVE** will require no further medical attention or treatment and are free to leave the mapping survey laboratory.

***IN ABSENCE OF TREATMENT IN SITE:*** *If the local health centre does not have any treatment available for individuals who test positive, then the team leader must speak with the person in charge of the health centre to ensure individuals can be treated at a later date. The health centre will be requested to collect participants' names to ensure that treatment is allocated appropriately. If participants are not happy to provide their names, they should then be advised to bring the letter provided by the mapping survey team when they come to the health centre at a later date.*

*The Team Leader should contact the LF Programme Manager at FMOH immediately and inform them that treatment is not available at the health centre and there are individuals who have tested positive by ICT card (Treatment is required if a minimum of 1 out of 100 people are found to be positive). The FMOH will be responsible for arranging transportation of drugs to the health facility and the individual in-charge of the health centre should be contacted by FMOH with further information regarding delivery.*

*The Team Leader must ensure the following information is provided to the FMOH LF Programme Manager:*

- *Name of the Health Centre*
- *Province, Woreda and Kebele of the Health Centre*
- *Name of person in charge of the Health Centre*
- *Contact details of the person in charge of the Health Centre*

7. Once the participant knows their ICT card result, they are free to leave the mapping survey laboratory as their assessment has been complete.

Participants may have questions at any stage of the survey and all field team members must be prepared to answer them fully. If they do not know the answer, then the participant should be referred to the **Team Leader** who will be able to answer it.The **Team Leader** must also oversee all activities taking part in the mapping, ensuring the mapping protocol is followed and results are accurately captured.

The **Translator** must assist in all parts of the data collection where there is a language barrier. They may be required to translate disease specific information which must be translated accurately whilst remaining sensitive to cultural and language differences.

The **Field Workers** should work together; one bringing people from the community into the mapping survey laboratory, whilst the other registers them to conduct the testing. These roles are interchangeable and Field Workers may consider changing positions during the mapping.

***Additional Notes:***

(write below any additional notes from the facilitator)

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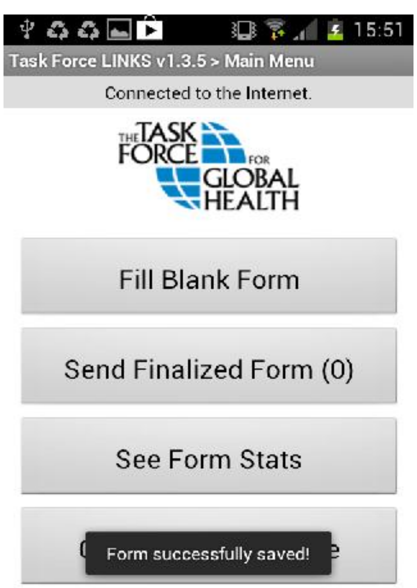
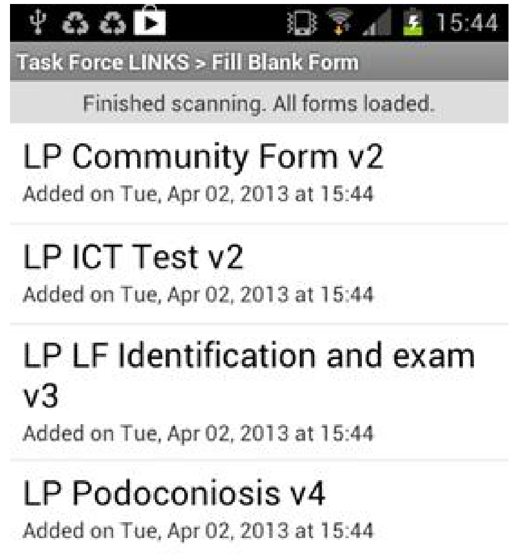
## VI. Data Collection using mobile Phones

### Selecting Forms

To fill in each form the team leader/nurse will open the Task Force LINKS app on the android phone and click on the **'Fill Blank Form'** option and then the correct form; the community form, LF form, Podoconiosis form or the ICT result form.






**LP Podoconiosis V4**

The 'LP podoconiosis V4" is used to collect all the relevant information pertaining to the mapping of podoconiosis throughout the county. This form will be filled in by one of the nurse on the field team and must be done for each participant.

To fill in this form the nurse will open the Task Force LINKS app on the android phone and click on the **'Fill Blank Form'** option and then the **'**LP podoconiosis V4**'**. This will open the LP podoconiosis V4**'** form

The following fields will appear in order as the record collector enters the information and used the navigational arrows:

1. **Record Taker's Name:**
    - o The record taker needs to type in their Name into the provided field

ie: **John Smith** would type in **John Smith** into the provided field

2. **Woreda Code (001-692)**
   - Enter the 3 digit code used to identify the District/Woreda; ensure that you enter the 0 or 00 prior to the district number if it is needed; districts 1-9 require 00 before the number while districts 10-99 require 0 before the district number.

     ie: the district code for first district is **001**

3. **Community Code (0001-1384)**
   - Enter the 4 digit code used to identify the Community; ensure that you enter the 0 or 00 prior to the community number if it is needed; communities 1-9 require 00 before the number while communities 10-99 require 0 before the district number.

     ie: the community code for first district is **0001**

4. **Individual ID Number (001-100)**
   - Record the individual's personal identification number; this should be found written on their hand.

5. **Age (15-100)**
   - Record the age of the individual in years

6. **Gender**
   - Select the correct gender for the participant; Male or Female

7. **Religion**

- Select the correct religion for the participant: Muslim, Christian, Animist or Other

8. **Ethnic Group**
    - Select the correct ethnic group that the individual belongs to from the provided list
        - Oromo, Amhara, Somali, Tigre, Afar or Other
- **If Other selected:** type in response

9. **Current occupation (Whatever the person does to earn money)?**
    - Select the correct occupation from the provided list
        - Employed, business man/woman, farmer, housewife etc
- **If Other selected:** type in response

10. **How long have you lived at your current location?**
    - Record the amount of time the individual has lived in location (in years)

11. **Years of School Completed**
    - Record the number of years that the participant went to school

12. **What is the monthly income (on average) of your household including your own?**
    - Write the monthly income of the household in Birr.

13. **What type of floor does your house have?**
    - Select the correct response
        - Mud/earth, Wood, Cement , Other
- **If Other selected:** type in response

**14. Current marital status?**

- o Select the correct response
    - ▪ Single, married , divorced, widowed

**15. Have you ever worn shoes?**

- o Select the correct answer to the question: yes or no

**16. How old were you when you first got shoes?**

- o Write age in years

**17. Is the person wearing shoes at the time of the interview?**

- o Select the correct answer to the question: yes or no

**18. Describe the shoes the person is wearing.**

- Select the correct answer to the question: hard plastic, open sandal , Leather, Shera , other
    - o **If Other selected:** type in response

**19.** When do you wear shoes?

- o Select the correct answer to the question: yes or no

- At home**:**
    - o Select the correct answer to the question: yes or no
- During rainy
    - o season Select the correct answer to the question: yes or no
- On market days
    - o Select the correct answer to the question: yes or no
- On the field
    - o Select the correct answer to the question: yes or no

- On Sundays
    - Select the correct answer to the question: yes or no
- When walking far
    - Select the correct answer to the question: yes or no

**20. How long (in min) does it take you to go to the nearest water source?**

- Write distance in minutes

**21. When do you wash your feet?**

- Select the correct answer to the question: whenever they are dirty, before sleeping, before prayer , Other
- Select the correct answer to the question: yes or no
    - **If Other selected:** type in response

**22. How often do you wash your feet very carefully so that they are very clean?**

- Select the correct answer to the question: more often than once a day , daily, less often than daily, but more often than weekly, weekly or less often.

**23. Do you have leg swelling?**

- Select the correct answer to the question: yes or no

**24. Do you have any family member (living or dead) with history of leg swelling?**

- Select the correct answer to the question: yes or no

**25. How many people in your family (living or dead) have leg swelling?**

- Write in number

**26. How old were you when you first noticed this swollen leg?**

- Write in number

**27. Where did the swelling start from?**

- Select the correct answer to the question:  from high up, from the foot or lower leg

**28. Do you have history of rheumatic heart disease?**

- Select the correct answer to the question: yes or no

**29. Do you have swelling in the groin area?**

- Select the correct answer to the question: yes or no

**30. Are you diagnosed as a leprosy patient?**

- Select the correct answer to the question: yes or no

**31. Is there preservation of sensation in the toes? (Physical examination)**

- Select the correct answer to the question: yes or no

**32. Podoconiosis diagnosis established**

**33. Podoconiosis disease stage**

- Select the correct answer to the question:Stage 1, Stage 2, Stage 3 , Stage 4**,** Stage 5

**34. Antifilarial antibody test blood sample collected?**

- Select the correct answer to the question: yes or no

Once all the information has been filled out a summary page will appear were you can double check all the information.  If all the information is correct click the **'Save and Send Form'** button.  This will finalize the form and return you to the home screen.

## VII. Standard operating procedure for collecting blood sample

In areas where at least a case of ICT positive is found individuals with leg swelling will give 5 ml of blood for antibody test.

Universal precautions – handle all specimens as if they are capable of transmitting infectious agents.

Explain the procedure to the person and obtain informed consent.

**Materials needed for blood sampling**

- Disinfectant for skin (eg alcohol wipe)
- Sterile syringe and needle.
- Cotton wool or gauze
- vacutainers
- Nunc Tube
- Glove
- Micropipette and tip

**Paperwork**

1. Label the vacutainers with the individuals ID, Village ID and District ID. Use a ballpoint pen or other permanent marker directly on the nunk tube.

**Sample collection**

- Put on gloves, select the site of blood collection clean the selected area of skin with a skin disinfectant swab and allow to dry for 30 seconds.
- Using syringe and needle collect 5ml of blood.
- Filled the blood collection vacutainers should sit upright after the blood is filled at room temperature for a minimum of 30 to a maximum of 60 minutes to allow the clot to form.

- Use pipette to transfer the serum (Recommendation: do not pour!). Pipette serum into the labeled Nunck tube, filling the vials in sequential order. Close the caps on the vials tightly. This process should be completed within 1 hour of centrifugation.
- Store the serum in deep freezer.

## VIII. Standard Operating procedure for ICT Cards

The ICT card test is a widely used sensitive tool for the detection of *W.bancrofti*antigen.

These tests are simple to use but require training to reduce the variability between observers and any misreading of the cards resulting in false positive results.

**For the purpose of this mapping survey, only the Laboratory Technician in the field team will be conducting the LF diagnostic tests.**

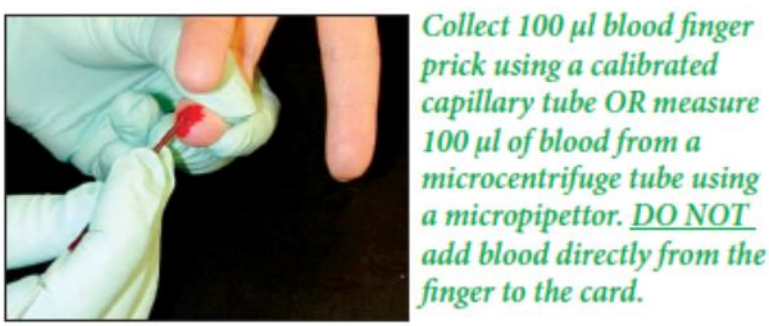
### Guidelines

### Storage and Transportation

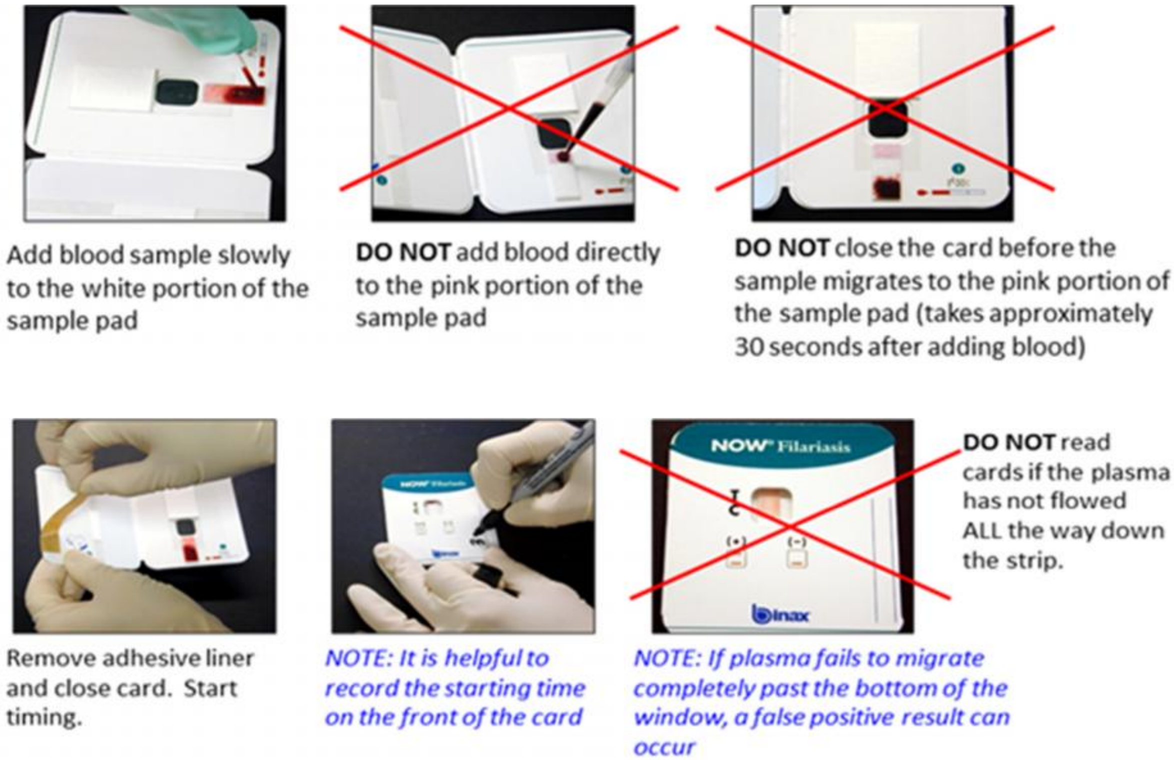
1. At optimal storage conditions ($4^0$C), cards have an approximate shelf life of 9 months. However when stored at $30^0$C the shelf life decreases to 3– 6 months.
2. When transporting cards to the study locations, it is advisable not to expose them to extreme heat for prolonged periods of time as this will rapidly decrease the shelf life.

**Sample Collection**

1. Put on a fresh pair of gloves.
2. Clean the site of the finger prick on the participant using a disinfectant wipe.
3. Using a lancet to prick the participant's finger, draw a small volume of blood.
4. From this prick, collect 100μL of blood using a capillary tube (supplied with ICT card).



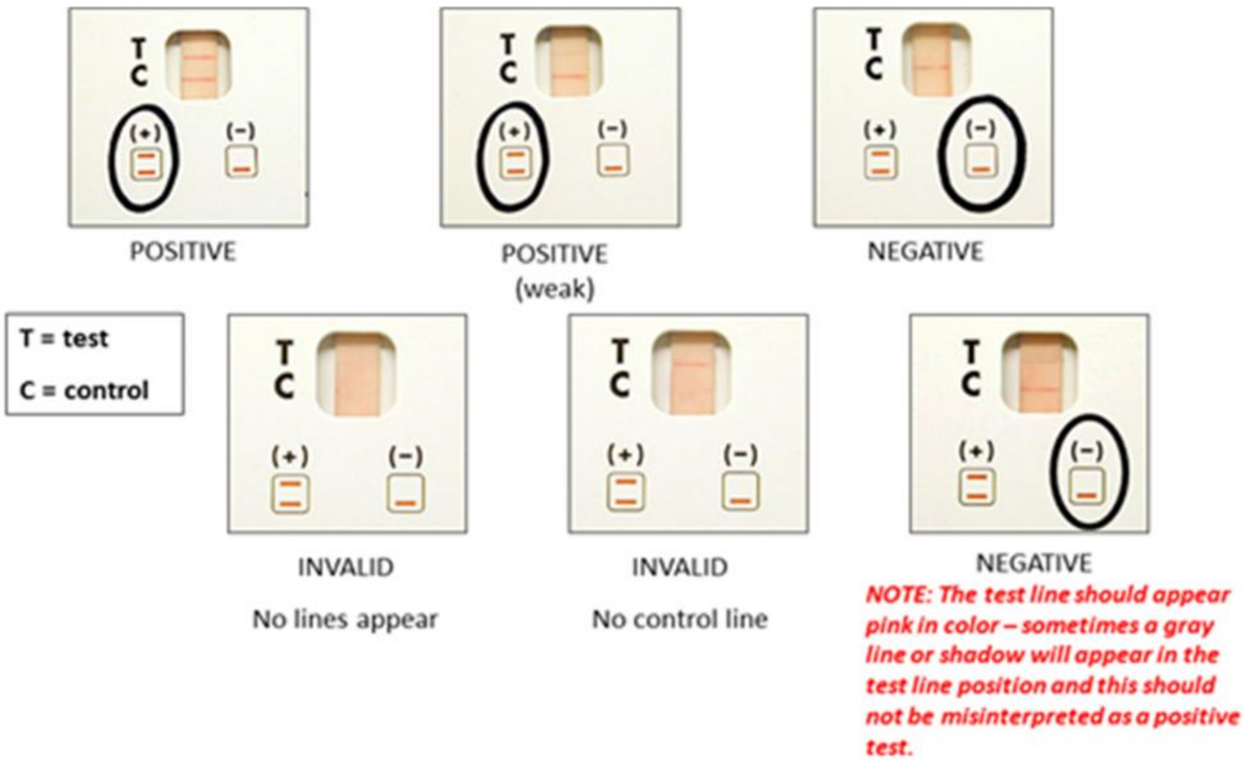

5. Add the collected blood sample to the white portion of the sample pad.
   - DO NOT add blood directly to the pink portion.
   - DO NOT close the card before the sample migrates to the pink portion; takes roughly 30 seconds.
   - Record the time when the blood reaches the pink portion on the card.
     - The test takes 10 minutes, starting from when the blood reaches the pink portion.




6. Read the results after 10 minutes and record the result by marking the card as positive or negative
    - DO NOT read the results at any other time as it can increase the chance of false positives
    - Ensure cards are read in a well-lit location, faint lines can be difficult to read if lighting is poor.
7. Safely dispose of the ICT card, capillary tube with any remaining blood found in the capillary tube
    - ICT card: ICT waste bag
    - Capillary Tube with any remaining blood: Sharps bin

**Examples:**

Below are example results from ICT cards showing the various results that can be seen on the card.




**Reference:**

World Health Organization, **2011**; *Global Programme to Eliminate Lymphatic Filariasis: Monitoring and Epidemiological Assessment of Mass Drug Administration*

## IX. Checklist for Conducting survey

For each participant, it is essential to ensure the following:

ID Number – General

1. Allocate the ID number to each participant at the beginning

2. Ensure no name and/or address is collected at any point and matched with an ID number
3. The ID number should be written on ICT card prior to conducting test
4. ID number on ICT card must correspond to ID number on forms for podoconiosis and LF
5. Participant's ICT result must be entered onto participant's corresponding forms for podoconiosis and LF
6. ID numbers on podoconiosis form and LF form for one participant must identical

Laboratory Technician – Health & Safety

1. Ensure the work bench is cleaned with bleach periodically to keep the work area clean
2. Alcohol swabs after single use must be discarded in the general waste bag
3. Lancets, once used, must be discarded in the sharps bin
4. ICT cards, once results have been recorded, must be discarded in a waste bag specific for ICT cards
5. Capillary tubes, used to conduct ICT cards, must be discarded in sharps bins once used, irrespective of whether there is still blood in the tubes or not.
6. Broken capillary tubes must not be used and discarded in the sharps bins
7. Gloves must be worn at all times when conducting diagnostic tests
8. Ripped/torn gloves must be replaced immediately
9. Gloves should be replaced regularly throughout the testing

10. Use hand sanitizers regularly and use soap to wash hands before and after conducting ICT cards
11. Waste bins for biological samples should not be mixed with any other waste
12. Cotton wool balls should be provided to participants when requested, or when the wound is still bleeding
13. Biological samples in the waste bags must be incinerated before leaving the site
14. Sharps bins should be used until they are full. Once full they should be closed and stored until returning to central level for safe disposal

Laboratory Technician – Laboratory Procedures

1. Follow standard operating procedures for conducting ICT cards
2. Write the time when the blood reaches the pink portion of the test onto the card
3. Read ICT card after 10 minutes and write result on the test immediately
4. Results should only be shown/discussed to the Team Leader and not discussed with any participants in the survey

Nurses –Laboratory Procedures, Health & Safety

1. Answer all questions in the questionnaire
2. Ensure ID number entered accurately into mobile devices
3. Use hand sanitizers regularly
4. Wash hands with soap before and after examining patients for physical signs or symptoms of LF
5. Record ICT card result before storing data and moving onto the next participant

## Supplementary material 5.1

### 5.1.1 Background to selection of environmental variables

Podoconiosis is caused by long term barefoot exposure to red clay soil of volcanic origin [1], thus, understanding how soil is formed is an important entry point in linking podoconiosis occurrence, the environment and climate. There are five classic factors for soil formation: climate, topography, parent material, time and organisms (flora and fauna) [2-4]. Soil varies depending on a range of climatic conditions [5]: temperature and precipitation influence the degree of weathering and leaching [3]. Seasonal and daily variability of temperature affects chemical reactions, moisture, biological activity and vegetation type, through influences on weathering [6]. The aridity of an area plays an important role, and winds in arid zones may redistribute sands and other soil particles.

Topography of the land, both altitude and slope, affects weathering. Altitude governs temperature, rainfall and vegetation of an area. Areas with steep slopes facing the sun are warmer, in addition, soils on slopes may more easily be eroded than soils on level ground. Plants, animals, microorganisms and human beings affect soil weathering [3]. Human activities such as erosion and deforestation have significant impact on soil formation [7]. Few soils weather directly from the underlying rock, and may therefore have completely different chemical and physical properties, making underlying rock a poor predictor of overlying soil type [6]. Fine particles have been linked to podoconiosis occurrence [8,9], and are thought to easily penetrate the skin and enter the body. Other factors such as distance to surface water are likely to be relevant to preventive behaviors such as foot hygiene, and so were included, as was urban-rural variation.

### 5.1.2 Multicollinearity

Most of the climate and environmental variables showed multicollinearity. To deal with these challenges, we used exploratory principal components analysis. Exploratory principal component analysis is used to replace correlated variables with a smaller number of uncorrelated variables which explain most of the variation [10]. PCA is often used as a pre-processing step for subsequent analyses [11].

As a rule of thumb, it is recommended to select the first k components which explain 70-80% of the variation[10], and to retain components with eigen values >0.7[12]. In the next step, the extracted factors were interpreted for their loadings, using the recommended cut-offs for factor loadings (coefficients) as follows: variables with loadings ≥0.60 were considered to be heavily loaded, those with loadings 0.40-0.59 to be moderately loaded, and those with coefficient 0.3-0.39 to be modestly loaded[13]. The selection of variables from each component was based on the PCA loading and the literature. Altitude was selected as a base variable since it appeared to be an important component of soil formation pathways and determines many of the climate variables [14,15]. In addition, it was consistently found to be associated with the occurrence of podoconiosis. PCA analysis was conducted using 11 climate and environmental variables. The majority (92.7%) of the total variation was explained by the first two principal components, which had eigenvalues greater than one and were below the elbow of the scree plot. The first principal component explained 78.4% of the variance and two contrasting groups of variables emerged. Most of the variables had similar loading. The first group was related to temperature including land surface temperature, annual mean, minimum and maximum temperature, mean temperature in the coldest and warmest quarters and annual potential evapotranspiration.

Altitude, aridity index and rainfall were the contrasting variables. Mean annual temperature was selected among from the first group based on the loading and literature. From the contrasting group, altitude was selected since it was found to be associated with podoconiosis. Annual precipitation, aridity index and EVI showed the highest load in the second principal component, which explained 13.6% of the variation. From the first component, EVI and annual rainfall were selected since both of them had the highest loading.

**Table S5.1.1.** Correlation matrix of environmental and climate variables

| Variable | Mean Annual Rainfall | LST | Annual maximum Temperature | Mean Annual Temperature | Annual minimum Temperature | APE | Mean temperature in the warmest quarter | Mean temperature in the coldest quarter | Altitude | Aridity Index | EVI |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mean Annual Rainfall | 1 | | | | | | | | | | |
| LST | -0.7058 | 1 | | | | | | | | | |
| Annual Maximum Temperature | -0.553 | 0.7813 | 1 | | | | | | | | |
| Mean Annual Temperature | -0.5545 | 0.7661 | 0.9839 | 1 | | | | | | | |
| Annual Minimum Temperature | -0.546 | 0.7371 | 0.9454 | 0.9829 | 1 | | | | | | |
| APE | -0.5154 | 0.7469 | 0.971 | 0.9191 | 0.8453 | 1 | | | | | |
| Mean temperature in the warmest quarter | -0.5624 | 0.7895 | 0.9792 | 0.9868 | 0.9717 | 0.9143 | 1 | | | | |
| Mean temperature in the coldest quarter | -0.5132 | 0.7178 | 0.9693 | 0.9807 | 0.9703 | 0.9087 | 0.9556 | 1 | | | |
| Altitude | 0.5414 | -0.7341 | -0.9541 | -0.9749 | -0.9737 | -0.8845 | -0.9563 | -0.9709 | 1 | | |
| Aridity Index | 0.9687 | -0.7751 | -0.7006 | -0.6843 | -0.6537 | -0.6818 | -0.6905 | -0.6458 | 0.6662 | 1 | |
| EVI | 0.6579 | -0.7866 | -0.4447 | -0.4146 | -0.3812 | -0.4343 | -0.4584 | -0.3519 | 0.3578 | 0.6576 | 1 |

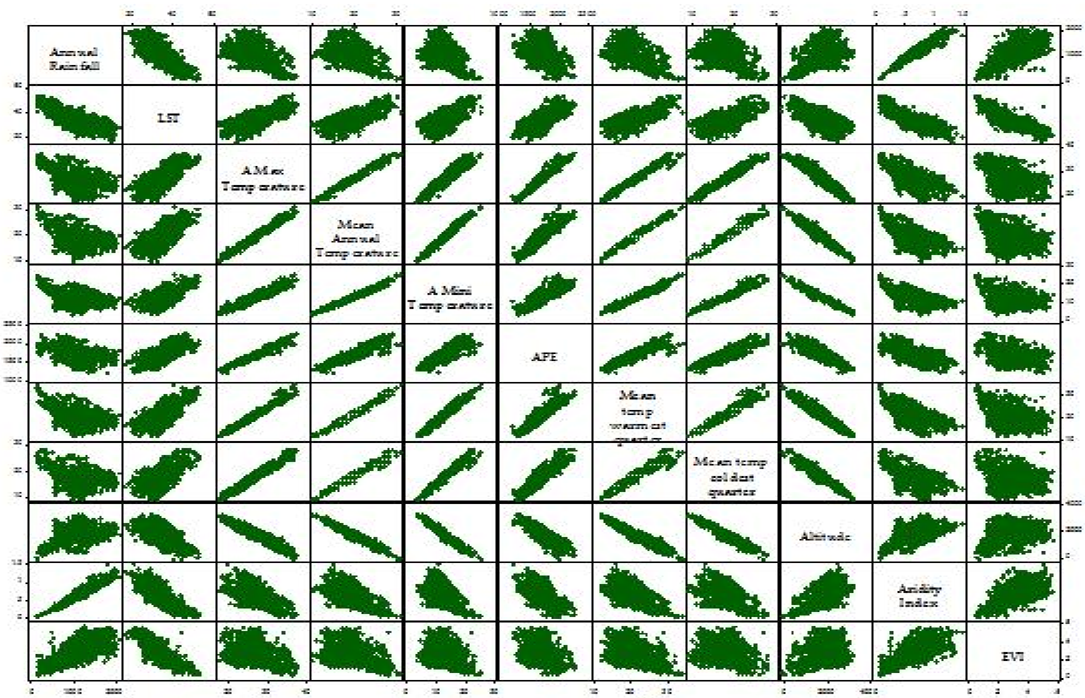



**Figure S.5.1.1** Scatter matrix of climatic and environmental variables showing correlation of variables.

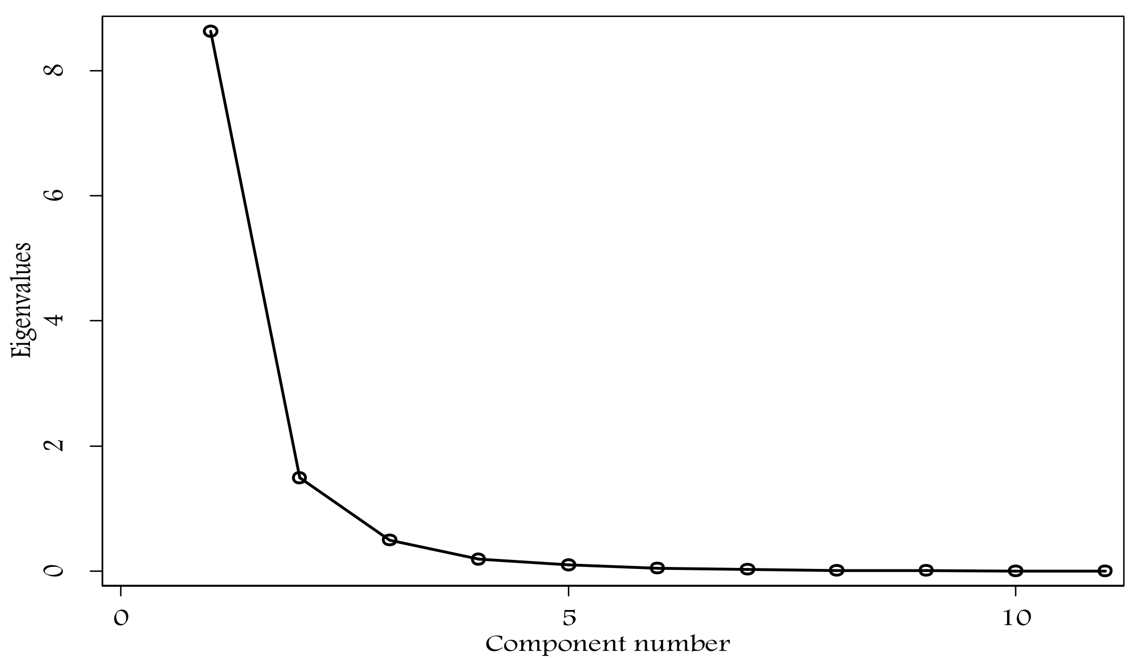



**Figure S.5.1.2** Scree plot of the variances of the principal components. Only the two comports have eigenvalue >1. The elbow of the plot appears near the third component, suggesting the first two components explain most of the variations.

**Table S 5.1.2** Eigenvalues proportions explained by each components and loadings of the principal components. As indicated below the first two components explained 92% of the variation and variables were selected from these two components. The highlighted variables were selected from the two components based on previous literature and loading values.

| Variable | Comp1 | Comp2 | Comp3 | Comp4 | Comp5 | Comp6 | Comp7 | Comp8 | Comp9 | Comp10 | Comp11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mean Annual Rainfall | -0.2409 | 0.4874 | 0.5304 | 0.0914 | 0.0223 | -0.0314 | -0.0963 | -0.6179 | 0.1088 | 0.0829 | 0.058 |
| LST | 0.2955 | -0.2625 | 0.3782 | -0.1136 | 0.8236 | -0.0023 | 0.0976 | 0.0012 | 0.0035 | -0.0005 | 0.0036 |
| Annual Maximum Temperature | 0.3311 | 0.1598 | 0.0572 | 0.2562 | -0.0615 | 0.1173 | 0.0559 | 0.0272 | 0.0603 | 0.219 | -0.8503 |
| Mean Annual Temperature | 0.3304 | 0.1832 | 0.0051 | -0.0995 | -0.0904 | 0.1586 | 0.0933 | 0.0275 | 0.68 | -0.5811 | 0.0674 |
| Annual Minimum Temperature | 0.3222 | 0.1972 | -0.0413 | -0.4607 | -0.1123 | 0.1373 | 0.1148 | 0.054 | 0.2261 | 0.6936 | 0.252 |
| APE | 0.3144 | 0.1397 | 0.091 | 0.7661 | 0.0012 | -0.0605 | -0.0677 | 0.2609 | 0.0334 | 0.1658 | 0.4262 |
| Mean temperature in the warmest quarter | 0.3302 | 0.1493 | 0.0673 | -0.0923 | -0.0924 | 0.6588 | -0.155 | -0.0973 | -0.5604 | -0.2261 | 0.1196 |
| Mean temperature in the coldest quarter | 0.3221 | 0.2312 | -0.0362 | -0.0759 | -0.1099 | -0.4923 | 0.6256 | -0.146 | -0.3666 | -0.1784 | 0.0481 |
| Altitude | -0.3227 | -0.2071 | 0.0737 | 0.2256 | -0.0381 | 0.4956 | 0.7257 | -0.0459 | 0.098 | 0.09 | 0.0558 |
| Aridity Index | -0.2787 | 0.385 | 0.4434 | -0.1861 | -0.0163 | -0.0076 | 0.0789 | 0.7159 | -0.1082 | -0.0884 | -0.0646 |
| EVI | -0.1964 | 0.5561 | -0.5954 | 0.0655 | 0.5237 | 0.1245 | 0.0571 | 0.0146 | -0.0093 | -0.0025 | -0.01 |
| Eigenvalues | 8.63 | 1.49 | 0.49 | 0.19 | 0.103 | 0.042 | 0.026 | 0.008 | 0.006 | 0.003 | 0.001 |
| Cumulative proportion of variance | 0.78 | 0.92 | 0.96 | 0.98 | 0.99 | 0.996 | 0.998 | 0.999 | 0.999 | 0.999 | 1.000 |

**Table S.5.1.3** Univariate multilevel mixed-effects logistic regression model developed using a likelihood-based approach, with random intercepts for village and woreda for podoconiosis among individuals ≥15 years old in Ethiopia

| Variable | Category | Non-cases | Podoconiosis cases | Univariate |
|---|---|---|---|---|
| | | Number (%) | Number (%) | |
| Sex | Male | 62650 (96.4) | 2208 (3.4) | 1.0 |
| | Female | 62056 (95.3) | 3045 (4.7) | 1.5(1.4-1.6) |
| Age in years | Mean(SD) | 36.1 (15.3) | 44.4 (16.6) | 1.02(1.01-1.02) |
| Education | No formal education | 73262 (94.6) | 4162 (5.4) | 1.0 |
| | Primary1-8 | 33444 (97.4) | 910 (2.6) | 0.4(0.4-0.5) |
| | Secondary 9-12 | 13765 (98.8) | 166 (1.2) | 0.2 (0.2-0.3) |
| | Post-secondary >12 | 4235 (99.7) | 15 (0.3) | 0.1 (0.04-0.1) |
| Marital status | Married | 91912 (96.1) | 3722 (3.9) | 1.0 |
| | Unmarried ¥ | 32794 (95.5) | 1531 (4.5) | 1.4(1.3-1.5) |
| Religion | Muslim | 44074 (98.3) | 752 (1.7) | 1.0 |
| | Other | 80632 (94.7) | 4501 (5.3) | 1.4 (1.2-1.6) |
| Type of floor | Mud/earth | 115354 (92.5) | 5145 (4.3) | 1.0 |
| | Cement/wood/plastic | 9352 (98.9) | 108 (1.1) | 0.4 (0.3-0.5) |
| Wore shoes before age 12? | Yes | 76725 (98.4) | 1286 (1.6) | 1.0 |
| | No | 47981 (92.4) | 3967 (7.6) | 2.9 (2.7-3.1) |
| How often do you wash your legs? | Daily or more often | 86533 (95.9) | 3754 (4.1) | 1.0 |
| | Two-Three times a week | 37379 (96.6) | 1325 (3.4) | 1.1 (1.0-1.2) |
| | Weekly or less often | 794 (82.0) | 174 (18.0) | 4.2 (3.3-5.3) |
| Occupation: | Professional | 8988 (99.3) | 68 (0.7) | 1.0 |
| | Semi-skilled | 77366 (95.7) | 3488 (4.3) | 3.9 (3.0-5.0) |
| | Unemployed | 38352 (95.8) | 1705 (4.2) | 4.4 (3.4-5.7) |

| Variables | | Non-cases | Podoconiosis cases | Mean difference |
|---|---|---|---|---|
| Age in years | Mean (SD) | 36.1 (15.3) | 44.4 (16.6) | -8.6 |
| Monthly household income | Mean (IQR) | 615.9 (200-700) | 322.8 (100-430) | N/A |
| Age at first shoe wearing | Mean (SD) | 11.4 (9.2) | 21.4 (14.5) | -9.9 |
| Shoe wearing duration in years | Mean (SD) | 24.2 (13.7) | 22.4 (14.8) | 1.8 |
| Environmental Variables | Categories | | | Univariate |
| EVI | <0.2 | | | 1.0 |
| | 0.2- 0.4 | | | 2.3(1.6-3.4) |
| | >0.4 | | | 5.1(2.9-9.1) |
| Rainfall | <1000 | | | 1.0 |
| | >=1000 | | | 3.3(2.5-4.3) |
| Altitude | <1000 | | | 1.0 |
| | 1000-2800 | | | 4.5(2.2-9.5) |
| | >2800 | | | 0.4(0.1-1.1) |

### 5.1.3 Semivariogram analyses

To test for the presence of spatial autocorrelation of podoconiosis prevalence, semi-variogram analysis was employed. This analysis estimates the spatial autocorrelation structure of a variable by defining semi-variance (a measure of expected dissimilarity between a given pair of observations made at different locations in space) as a function of lag (the distance separating the observation locations). If spatial autocorrelation is evident, semivariance typically rises with distance; eventually plateauing to a maximum value termed the sill. The separation distance at which the sill is reached is termed the range and represents the maximum distance over which values are autocorrelated, with larger separation distances implying spatial independence. Details of semi-variogram use are described very well elsewhere [16,17]. Empirical semivariograms were developed from the raw data. Semivariogram analyses were run from R version 3.0.2.

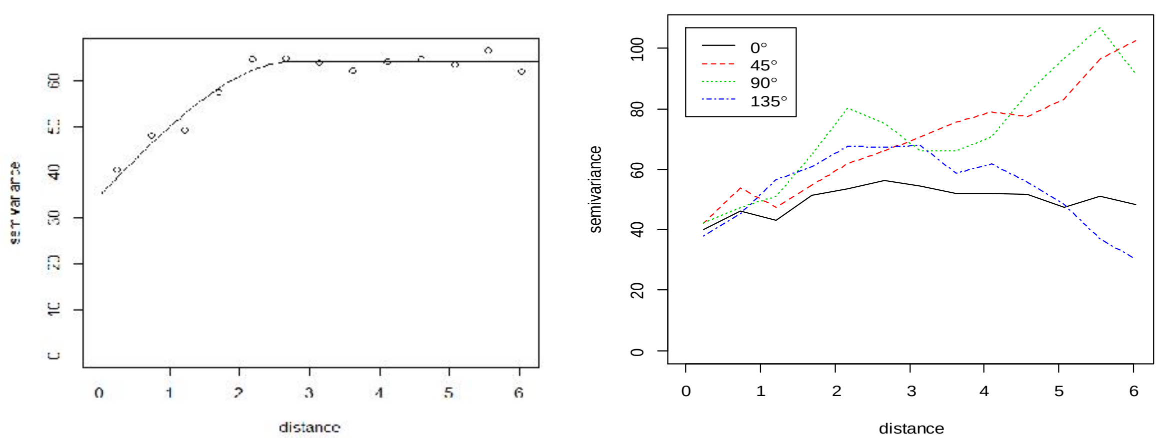



**Figure W4.** Empirical semivariograms model of the spatial dependency of podoconiosis in Ethiopia and best-fitted lines of spherical spatial raw prevalence data. From 1315 villages, among adults >=15 years old in Ethiopia. Parameter values fitted were range=2.795998, sill=58.3286, nugget=36.88.

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**Supplementary material 6.1**

**Background**

Identifying the geographical limits of a disease is central to predictive mapping. Once the areas outside these limits are identified, they will be excluded from further mapping and prediction. A wide range of approaches have been developed for empirical modelling of disease distribution given the availability of data on point observations of occurrence [1,2]. The Boosted Regression Tree (BRT) method was found to be one of the best performing models when compared to 16 other models [1,2]. BRT models can accommodate continuous and categorical variables, can model complex interactions between these variable and gives easily interpretable results [3]. Briefly, BRTs combine regression or decision trees and boosting. Regression trees use binary recursive partitioning to iteratively split the data into partitions. The model uses the data (in this case presence and absence of podoconiosis) and, in a series of steps, identifies the threshold of each input variable that results in either the presence or the absence of podoconiosis. It allows the input of continuous and categorical variables and different scales of measurement amongst the predicting variables. Boosting is described as machine-learning that increases a model's accuracy iteratively, and is based on the idea that it is easier to find and average many rough 'rules of thumb', than to find a single highly accurate prediction rule [1-3]. Given the many unknowns regarding the factors affecting the distribution of podoconiosis, the BRT model is well suited for the purpose. Using the limited evidence, including factors affecting soil formation, and covariates which increase individuals' exposure and affect preventive behavior, we selected variables which potentially affect the distribution of podoconiosis.

**Climate and environmental covariates selection**

Since podoconiosis mostly occurs in red clay soil areas [4], understanding how soil is formed is an important entry point in linking podoconiosis occurrence, the environment and climate. There are five classic factors for soil formation; climate, topography, parent material, time and organisms (flora and fauna) [5-7]. Soil varies depending on a range of climatic conditions [8]: temperature and precipitation influence the degree of weathering and leaching [6]. Seasonal and daily variability of temperature affects chemical reactions, moisture, biological activity and vegetation type, through influence on weathering [9]. Sixteen covariates were initially selected and eight of them were retained after conducting a multicollinearity analysis and simplification of the model (Figure S1). Below, we briefly describe the environmental and climate variables used in this study.

1. **Precipitation**

Precipitation may play an important role in podoconiosis occurrence; previous studies have indicated the potential association of rainfall and podoconiosis [10-12]. First, precipitation is one of the climatic factors which govern the generation of soil. Second, precipitation may play an important role in exposure to the putative mineral particles, by producing sticky mud which increases the contact time with the soil. Previous studies have indicated that soils associated with podoconiosis are slippery and adhesive if allowed to dry. Such occlusive adhesion encourages absorption of the particles by increasing exposure time [12]. A gridded interpolated surface for annual precipitation was obtained from the WorldClim database (www.wordclim.org). WorldClim database consists of a freely available set of global climate data at a 1 $km^2$ resolution which was compiled using weather data collected from world-wide weather stations. The data spans the period 1950-2000 and describes monthly averages of precipitation during this period. From these data, interpolated global climate surfaces were produced using ANUSPLIN-SPLINA software package [13].

**2. Aridity Index**

Aridity is usually expressed as a generalized function of precipitation, temperature, and/or potential evapo-transpiration (PET). It can be used to quantify precipitation availability over atmospheric water demand. The global aridity index has been modelled using the data available at the WorldClim database, and is calculated dividing the mean annual precipitation by the mean annual potential evapo-transpiration. The latter is a measure of the ability of the atmosphere to remove water through evapo-transpiration processes. A raster layer on a spatial resolution of 1 $km^2$ displaying the global aridity index was obtained from the Consortium for Spatial Information (CGIAR-CSI)[14,15].

**3. Altitude**

The topography of the land affects weathering and soil formation. Altitude governs temperature, rainfall and vegetation of an area, all of which play an important role in weathering and soil formation in an area. Previous studies indicated the potential association of podoconiosis and altitude, suggesting that podoconiosis was common in areas with altitude >1000 meters above sea level [16]. Elevation layer at 1 $km^2$ resolution was also downloaded from the CGIAR-CSI[17], which freely provides processed and resampled gridded digital elevation models (DEM) derived from the original 30-arcsecond DEM produced by the Shuttle Radar Topography Mission (SRTM) [18].

**4. Population density and urbanization**

Human activity is an important factor for soil generation. Studies have indicated that human activities affect soil formation, through deforestation, erosion etc. Previous observations indicate that podoconiosis is common in highly populated areas [12]. The WorldPop (www.worldpop.org.uk) project provides gridded maps of population density at country (100 m resolution) and continental scale (1 km resolution), among other demographic-related data (i.e. urbanization, poverty index). The dataset is formed by combining contemporary population count data with detailed satellite-derived settlement extents to map population distributions across the world at a finer spatial resolution. This repository of spatial data provides gridded population datasets for 2010 and also projections for 2015 [19]. The population density surface for 2010 was used to roughly estimate urban, peri-urban and rural areas based on the assumption that urban extents (UE) exhibit a population density >1,000 inhab/km$^2$, peri-urban >250 inhab/km$^2$ within a 15 km distance from UE edge, and rural <250 inhab/km$^2$ and/or >15 km from the UE edge[20].

**5. Enhanced Vegetation Index**

There is often a close association between local moisture supplies and vegetation canopy. Moisture is an important factor in the pathway of soil formation. We assumed that this vegetation characteristic might influence the distribution of podoconiosis. In a previous work we have demonstrated that more vegetated areas had lower risk of podoconiosis; this may be associated with decreased exposure to the mineral particles linked to podoconiosis in areas with high vegetation cover [21]. Averaged long-term enhanced vegetation index (EVI) for the period 2000 to 2012 was obtained from the Africa Soil Information Service (AfSIS). This vegetation index is collected at a 16-day basis by the *Moderate Resolution Imaging Spectrorariometer* (MODIS) sensor and delivered in monthly average raster datasets at 250 m resolution by the Columbia University International Research Institute for Climate and Society (IRI)[22].

6. **Distance from water body in kilometres**

One of the means of primary prevention of podoconiosis is regular feet hygiene. In a previous study, we found out that foot washing is associated with decreased risk of podoconiosis [21]. Access to water, indirectly measured by distance to water bodies, is likely to be an important factor in determining individual practice. Those who are closer to water bodies can presumably maintain better personal hygiene (e.g. wash their legs), and hence decreased risk of podoconiosis. Straight line distance to water bodies was calculated using the data layers of water bodies produced by the SRTM at 250 m resolution [18].

7. **Slope**

Areas with steep slopes facing the sun are warmer. In addition soils on slopes may more easily be eroded than soils on level ground. A raster layer of slope in degrees was created from the DEM at 1 $km^2$ resolution downloaded from the SRTM [18].

8. **Soil properties: silt, clay, sand and pH content, soil type and texture.**

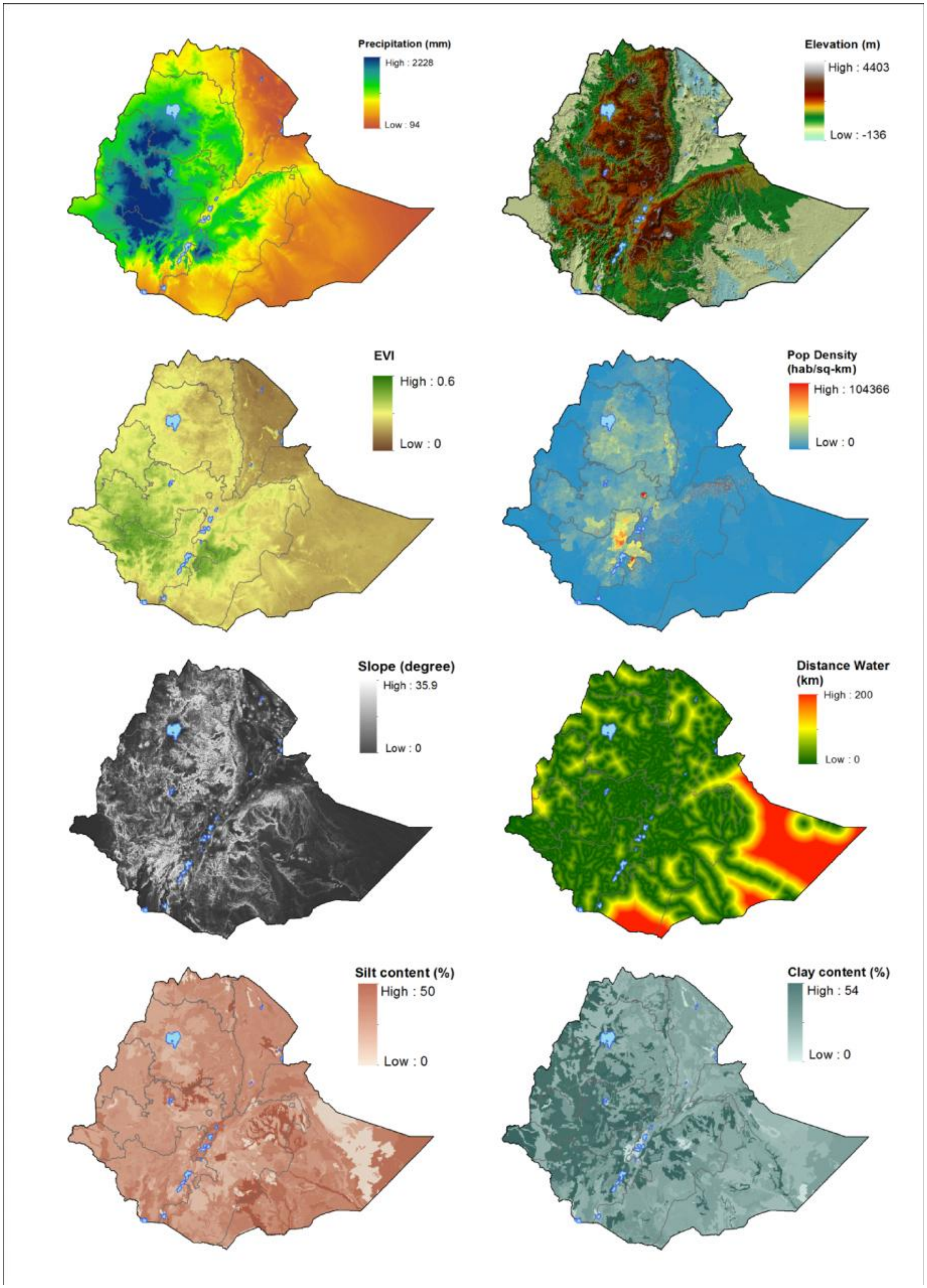
The physical and chemical composition of the soil is an important factor in determining the occurrence of podoconiosis. Previous studies have documented that podoconiosis is associated with red clay soil. The association was attributed to the characteristics and particle size of the soil. Smaller particles can easily penetrate the skin barrier and get into the body. The pH of the soil may play an important role in either through the possible irritant effect of more acidic soil, permitting passage of the trigger minerals, or may reflect the soil content. A previous study found out that podoconiosis was prevalent in areas where the pH was between 5.6 and 6.8 [12].

Gridded continuous surface of clay, silt and sand content, soil texture and pH at 1 $km^2$ resolution were obtained from the AfSIS, which is developing continent-wide digital soil maps for sub-Saharan African using new types of soil analysis and statistical methods [23]. The database is produced by using prediction models using major international soil profile databases and global environmental covariates representing soil forming factors and using automated mapping [24]. We extracted the dominant soil types and soil texture (fine, coarse and medium) from the Harmonized World Soil Database (HWSD, Ver1.1) which is a high resolution database also available at the AfSIS site [23]. The database combines updates and existing soil information globally. The data is available at 1 km by 1 km spatial resolution [25].

**9. Land cover**

The type of land cover might be related to the occurrence of podoconiosis in different ways. First, only certain types of vegetation can tolerate acid red clay soils, which have been found to be associated with the presence of podoconiosis. Second, the type of the land cover in an area determines the types of organisms which live in an area which will in turn affects the type of soil generated. Land cover data were downloaded from the GlobCover project at the European Space Agency [26]. This global land cover map is derived by an automatic and regionally-tuned classification of a 300-m MERIS FR time series (19 months) and comprises 22 land cover classes according to the UN Land Cover Classification System (LCCS)[27]. We grouped the 22 land cover classes into 7 major groups; agricultural lands, forest areas, shrubland, grasslands and woodlands, bare soil, urban areas, snow/ice and water areas.

**Figure S6.1.1.** Covariates selected to build the final BRT model



**Multicollinearity**

Multicollinearity between the predictor variables was explored in order to avoid unstable parameter estimates and inflated standard errors on estimates when modelling podoconiosis distribution. Multicollinearity suggests that several of the independent variables are closely linked in some way. Coefficient of linear correlation can help us identify collinearity effect between pairs of predictors. As a rule of thumb, collinearity is considered when correlation coefficient |r| is greater than 0.7. Having obtained pairwise correlation coefficients between all our linear predictors, we considered for spatial modelling that combination of covariates which did not exhibit linear correlation between them. As Table 1 shows, annual precipitation was correlated with aridity index and soil pH, sand fraction was correlated with clay and silt fraction, and altitude was correlated with mean annual temperature. Therefore, based on previous studies and the importance of the covariates, soil pH, sand fraction, aridity index and mean annual temperature were excluded from further analysis.

**Table S.6.1.1** Correlation matrix of environmental and climate variables*

| Covariates | Aridity index | Clay fraction | Annual precipitation | Altitude | Population density | EVI | Distance to water bodies | Mean annual temperature | Slope | pH $H_2O$ in soil | Silt fraction | Sand fraction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Aridity Index | 1 | | | | | | | | | | | |
| Clay fraction | 0.2959 | 1 | | | | | | | | | | |
| Annual Precipitation | 0.9616 | 0.2607 | 1 | | | | | | | | | |
| Altitude | 0.5026 | 0.2598 | 0.3156 | 1 | | | | | | | | |
| Population density | -0.0201 | 0.0259 | -0.0233 | 0.0198 | 1 | | | | | | | |
| EVI | 0.6304 | -0.0252 | 0.6451 | 0.1092 | -0.0316 | 1 | | | | | | |
| Distance to water bodies | 0.0797 | 0.1697 | 0.0695 | 0.0779 | 0.0008 | 0.0357 | 1 | | | | | |
| Mean annual temperature | -0.5318 | -0.2038 | -0.3415 | -0.9688 | -0.028 | -0.1815 | -0.0414 | 1 | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Slope | 0.1461 | -0.0186 | 0.128 | 0.1635 | -0.0403 | 0.1334 | 0.0395 | -0.1496 | 1 | | | |
| pH $H_2O$ in soil | -0.7357 | -0.1184 | -0.724 | -0.4012 | 0.013 | -0.6366 | 0.0426 | 0.4213 | -0.1601 | 1 | | |
| Silt fraction | 0.139 | 0.1793 | 0.0902 | 0.4269 | 0.0255 | -0.072 | 0.1392 | -0.3798 | 0.1175 | 0.1558 | 1 | |
| Sand fraction | -0.2784 | -0.7456 | -0.2232 | -0.4498 | -0.0341 | 0.064 | -0.197 | 0.383 | -0.0671 | -0.0317 | -0.7874 | 1 |

Four categorical covariates (land cover, soil type, soil texture and urban rural classification) were not include in the matrix.

***Evaluation statistics***

To evaluate the BRT model, the predictive performance of different statistical tests was assessed. Deviance, correlation, discrimination area under the receiver operator characteristics curve (AUC) and Kappa summary statistics were calculated to accompany each map combining classic accuracy metrics. Sensitivity: a value between 0 and 1, the proportion of presences correctly identified, Specificity: a value between 0 and 1, the proportion of absences correctly identified, proportion correctly classified (PCC): a value between 0 and 1 giving the proportion of presences and absences correctly classified, the details and interpretation of each statistics is provided in detail elsewhere [3].

**Model building**

**Simplifying the predictor set.**

A total of 12 covariates were included in the model. As indicated in supplemental table 2, the last four variables explained only a small amount of the variation. The elimination of non-informative variables involves simplifying the model by dropping the least important predictors as described in Elith *et al* [2].

**Table S 6.1.2** Relative influence of the pre-selected environmental and climate covariates

| **Variable** | **Relative influence percent** |
|---|---|
| Annual mean precipitation (mm) | 40.00 |
| Elevation (masl) | 26.40 |
| Population density (population/km$^2$) | 11.18 |
| EVI | 9.65 |
| Slope | 5.01 |
| Distance from water body (Kilometers) | 3.05 |
| Silt content (% mass fraction) | 1.86 |
| Clay content (% mass fraction) | 1.36 |
| Land cover | 0.84 |
| Soil type | 0.62 |
| Soil texture | 0.03 |

| | |
|---|---|
| Urban rural | 0.01 |

masl: meters above sea level

The last four variables showed an influence lower than 1% each and were excluded from the final BRT model assembled. Supplemental table 3 shows the mean relative contribution and confidence intervals for the covariates used to perform the final fitted BRT model, which was obtained from an ensemble of 120 BRT submodels.

**Table S6.1.3** Relative influence of the environmental and climate covariates selected to build the final BRT model

| **Variable** | **Relative influence** | | |
|---|---|---|---|
| | **mean** | **2.50%** | **97.50%** |
| Annual mean precipitation (mm) | 30.7 | 25.3 | 36.0 |
| Elevation (masl) | 22.6 | 18.9 | 26.7 |
| EVI | 15.4 | 12.0 | 20.0 |
| Population density (population/km$^2$) | 12.7 | 10.2 | 15.7 |
| Slope | 8.2 | 6.6 | 9.9 |
| Distance from water body (Kilometers) | 5.9 | 4.6 | 7.1 |
| Silt content (% mass fraction) | 2.7 | 1.8 | 3.7 |
| Clay content (% mass fraction) | 1.9 | 1.3 | 2.7 |

**Model performance**

Validation statistics indicated high predictive performance of the BRT ensemble model with area under the receiver operating characteristic (AUC) of 0.81 (CI95%: 0.78 – 0.83; sd: 0.01). AUC values of <0.7 indicate poor discriminatory performance, 0.7–0.8 acceptable, 0.8–0.9 excellent and >0.9 outstanding discriminatory performance) [28]. The receiver operating curve and validation statistics for predicting occurrence of podoconiosis are shown in Table S4. The AUC value indicated excellent predictive performance, based on an optimal probability threshold of 0.496. This threshold value was subsequently used to classify the probability map into a binary classification of occurrence. The BRT model at a cut-off 0.496 has excellent performance with area under the receiver operator curve (AUC) (0.84 and the kappa agreement of 0.63. The model was highly sensitive (0.86) with good specificity (0.77).

### Data abstraction from 2008-2010 survey

The 2008-2010 survey included 116 districts located in five Regional States in western Ethiopia, conducted by a team from Addis Ababa University. Thirty-seven of the 116 districts were found to be endemic for LF. All districts found to be endemic for LF were excluded for further consideration to avoid misclassification of cases. From districts which were non-endemic for LF, individuals who have lymphedema, with ICT negative results and without signs or symptoms of potential differential diagnoses were considered as podoconiosis [10,29,30]. Combined, the two surveys contributed 1,442 clusters from 775 districts of Ethiopia.

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**Supplementary material 7.1**

**Defining indicators exercise**

**Defining elimination targets and endemicity classification of podoconiosis**

**2nd round**

**INSTRUCTIONS: HOW TO COMPLETE THE QUESTIONNAIRE**

Podoconiosis (endemic non-filarial elephantiasis) is a non-infectious geochemical disease often found in barefoot subsistence farmers who are in long-term contact with irritant red clay soil of volcanic origins. The disease causes progressive bilateral swelling of the lower legs1.

As plans for the mapping of podoconiosis continue to progress, it is imperative to have targets for elimination and a threshold for endemicity. An endemicity threshold would help to identify areas which are endemic for podoconiosis and require interventions. This information would be useful for public health policy and planning. For example, districts/villages with a lymphedema prevalence of greater than 1% could be classified as endemic for podoconiosis. This could be further classified using endemicity classes (ie. hypo, meso and hyper) to show which areas may need high priority. Although residents of areas classified as hypo-endemic might not have podoconiosis treatment sites, these individuals would still be eligible for individual health facility-based treatment if they are diagnosed with podoconiosis.

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The vision of the International Podoconiosis Initiative is to eliminate podoconiosis ("world free of podoconiosis in our lifetimes"). Therefore, this goal needs to have a measurable indicator. Communities or countries should have a pre-specified threshold to achieve the goal of elimination of podoconiosis as a public health problem. For other NTDs, elimination targets and endemicity classifications are often based on prevalence of the infective organism. This is not possible with podoconiosis, so targets will rather be based on morbidity (lymphedema) prevalence. For example, the target of global elimination of leprosy as a public health problem is the reduction of cases to less than 1 per 10,000 population. For lymphatic filariasis (LF), the target is the reduction of microfilaraemia rate to below 1% in previously endemic districts. Similarly, there is a clear need for measurable targets for the elimination of podoconiosis.

**Assumptions:** The prevalence of lymphedema in areas where LF and podoconiosis are not endemic ranges 1-5 per 1000. Therefore the cut-off is reduced to 1% to accommodate this figures in case of any misclassification. In a district were the prevalence is <1% the cases will be treated in the formal health sector without the need for additional control program.

The prevalence of podoconiosis ranges between 0-10% with some areas having prevalence >10% based on studies from Ethiopia, Rwanda, Burundi, Cameroon and Uganda.

The current treatment practice is lymphedema management of 3 months. But there is an ongoing RCT which determines adequate treatment of podoconiosis. Therefore adequate will be defined up on completion of the study.

Population at risk is defined as the total number of individuals living in an endemic district.

Methods

Objectives

The objectives are as follows:

- To decide on a threshold by which an area is called endemic for podoconiosis.
- To identify appropriate endemicity classes for podoconiosis (non-endemic, hypo, meso and hyper).
- To identify the target for elimination of podoconiosis from a country.

We are aiming to reach agreement among a range of professional groups on the key components of endemicity classification and elimination target. We need your help in identifying the issues that are of importance. Please now score the items listed below. The questionnaire is divided into four sections:

**SECTION 1:** Case definition

**SECTION 2:** Endemicity classification

**SECTION 3:** Elimination targets

**SECTION 4:** Monitoring indicators

You are asked to <u>score the importance</u> of potential issues using the following grading:

**A 9-point scale with the anchors "not important" at 1 and "extremely important" at 9**

Please **circle the most appropriate score** in the **column next to each statement.**

Rest assured we will treat your responses in confidence.

**We would be grateful if you could complete the form as thoroughly as possible, but you are not obliged to complete all sections.**

If you have any comments, please use the space provided.

**Scoring: A 9-point scale with the anchors "not important" at 1 and "extremely important" at 9**

| **SECTION 1**<br>**Statement:** ***"The following definition is important to develop case definition for podoconiosis surveillance -----*** | | | | |
|---|---|---|---|---|
| | Median score Round 1 | Mode score Round 1 | % agreement Round 1 for scores 7,8 & 9 | **Your score Round 2** |
| **Suspected case:** any lymphoedema of the lower limb of any duration. (At this stage we do not expect to make a differential diagnosis but need to record the actual numbers of people with lymphoedema, even if a medical diagnosis has not been confirmed.) | 8.0 | 9.0 | 73.1% | **1 2 3 4 5 6 7 8 9** |
| **Probable case:** Any lymphoedema of the lower limb present for more than one year in a resident of, or a long-term visitor to, an endemic area. | 7.5 | 8 | 57.7% | **1 2 3 4 5 6 7 8 9** |
| **Confirmed case:** Lymphoedema of the lower limb present for more than one year in a resident of, or long term visitor to an endemic area, for which other causes have been excluded (onchocerciasis, LF, leprosy, | 8.0 | 9 | 88.5% | **1 2 3 4 5 6 7 8 9** |

| | | | | |
|---|---|---|---|---|
| Milroy syndrome, heart or liver failure, etc). | | | | |
| **SECTION 2**<br>**Statement “ *The following endemicity classification for podoconiosis is important for prioritization*** | | | | |
| **Non-endemic** <1% prevalence among adults ≥ 15 years old<br>AND | 7.5 | 9.0 | 76.9% | 1 2 3 4 5 6 7 8 9 |
| **Hypo-endemic** ≥1to <3% prevalence among adults ≥ 15 years old<br>AND | 8.0 | 9.0 | 76.9% | 1 2 3 4 5 6 7 8 9 |
| **Meso-endemic** 3 to<10% prevalence among adults ≥ 15 years old<br>AND | 8.0 | 9.0 | 76.9% | 1 2 3 4 5 6 7 8 9 |
| **Hyper-endemic** ≥ 10% prevalence among adults ≥ 15 years old | 8.0 | 9.0 | 76.9% | 1 2 3 4 5 6 7 8 9 |
| **SECTION 3**<br>**Statement “ *Podoconiosis is eliminated from a district if …*** | | | | |
| The prevalence of untreated podoconiosis is less than 1 percent (among individuals ≥15 years old after 10 years of program implementation.<br>AND | 8.0 | 9.0 | 73.1% | **1 2 3 4 5 6 7 8 9** |
| More than 95 percent of lymphoedema cases are treated adequately after 10 years of program implementation. | 6.5 | 9.0 | 50.0% | **1 2 3 4 5 6 7 8 9** |
| *Statement “Podoconiosis is eliminated from a* ***country*** *when* | | | | |
| Prevalence of untreated podoconiosis is maintained at less than 1 percent (among individuals >15 years old) in 100 percent of sample villages over a 10 year period. | 7.0 | 9.0 | 61.5% | **1 2 3 4 5 6 7 8 9** |
| Prevalence of early signs of podoconiosis among children 10-15 years after 10 years of control program implementation is less than 1 in 10,000. | 8.0 | 9.0 | 70.8% | **1 2 3 4 5 6 7 8 9** |
| Greater than 95 percent of population in endemic districts wears protective shoes. | 8.5 | 9.0 | 76.9% | **1 2 3 4 5 6 7 8 9** |
| Greater than 90 percent of lymphoedema cases are treated adequately. | 7.0 | 9.0 | 61.5% | **1 2 3 4 5 6 7 8 9** |
| Statement “ *The following key indicators for the podoconiosis elimination are important to be monitored* | | | | |
| **Prevalence of podoconiosis (%) =** Number of old and new cases of podoconiosis in the implementation unit (≥15 Years) divided by total population of ≥15 years old in the same area times 100 | 9.0 | 9.0 | 84.6% | **1 2 3 4 5 6 7 8 9** |

| | | | | |
|---|---|---|---|---|
| **Case detection rate (%)=** Number of new cases of podoconiosis in the implementation unit in a year divided by total population at risk in the same area times 100 | 9.0 | 9.0 | 88.4% | **1 2 3 4 5 6 7 8 9** |
| **Treatment completion rate** (%)= Number of patients that took completed the required duration of treatment divided by all new podoconiosis cases that started treatment in a given period times 100 | 8.5 | 9.0 | 86.9% | **1 2 3 4 5 6 7 8 9** |
| **Coverage of shoe wearing (%)(point prevalence in sampled villages)=** Number of individuals wearing shoes (>1 years old) in implementation unit divided by total number of individuals >1 years old in the same area times 100 | 9.0 | 9.0 | 84.6% | **1 2 3 4 5 6 7 8 9** |
| **SECTION 4:** Statement *" The following key indicators are important for monitoring clinical outcomes* | | | | |
| **Treatment completion:** A patient who has completed the full course of the initial treatment given at health facility/community level. | 9.0 | 9.0 | 92.3% | **1 2 3 4 5 6 7 8 9** |
| **Defaulter:** A patient who has been on treatment and whose treatment was interrupted for 2 or more consecutive months. | 8.0 | 9.0 | 73.1% | **1 2 3 4 5 6 7 8 9** |
| **Treatment Success:** Treatment is successful if an incapacitated patient can assume normal activities following treatment. | 8.0 | 9.0 | 69.2% | **1 2 3 4 5 6 7 8 9** |
| Statement *" The following key indicators are important for monitoring progresses* | | | | |
| > 95% of population in endemic districts consistently wears protective shoes (measured for the last one year). | 8.0 | 9.0 | 80.8% | **1 2 3 4 5 6 7 8 9** |
| >90% of the population in the endemic districts practices proper foot hygiene* (measured for the last one year).(proper foot hygiene is defined as washing once per day using soap and water over the period of one year) | 8.0 | 9.0 | 65.3% | **1 2 3 4 5 6 7 8 9** |

**We are very grateful for your help with this defining indicators exercise.**